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Editors’ Perspectives

Mining for Hirschprung’s disease in the overflowing stream

When comparing the year 1993 with the year 2001, Gary Freed and colleagues demonstrated that there has been an increase in the proportion of care provided by both pediatrician generalists and pediatric specialists for patients with constipation (Freed et al J Pediatr 2005;146:14-9). This trend reflects growth in the market share of pediatricians relative to nonpediatrician providers as well as an increase in the overall number of physician visits for constipation. This “backlog” of patients presents the clinician with a diagnostic dilemma – although in the vast majority of infants and children with constipation no organic disease is present, Hirschprung’s disease must at least be considered and, in a small subset, excluded.

The “gold standard” for diagnosis of Hirschprung’s disease—full thickness biopsy (FTB)—is invasive and requires general anesthesia. There is no easy path to the gold! Therefore, deLorijn et al asked whether other tests could replace FTB. They compared the diagnostic accuracy of three tests considered to be useful for the detection of Hirschprung’s disease—contrast enema (CE), anorectal manometry (ARM), and rectal suction biopsy (RSB). Of 111 consecutive patients with severe constipation, Hirschprung’s disease was confirmed by FTB or from the operative specimen in 28. Of the other tests, RSB had the highest sensitivity (93%) and specificity (100%) compared to CE (sensitivity = 76%; specificity = 97%) and ARM (sensitivity = 83%; specificity = 93%). These differences were not statistically significant; however, the study may have been underpowered to detect such a difference. Test results were inconclusive in 8 infants via CE, in 15 via ARM, and in 2 via RSB. These results support the concept that, short of FTB, a properly obtained RSB is the most accurate and conclusive test to diagnose Hirschprung’s disease.

—William F. Balistreri, MD

Tissue from patients with NEC can be informative

Necrotizing enterocolitis (NEC) remains an enigmatic disease associated primarily with prematurity. Hypotheses related to feeding, infection, and vascular perfusion abnormalities have been proposed as contributing to the pathophysiology of NEC. Coagulation necrosis of the intestine at resection or autopsy is diagnostic of NEC but provides few clues to pathogenesis. While vasoactive and inflammatory mediators are increased in the circulation of infants with NEC, their importance to the tissue of interest—the gut—is never clear. Nowicki et al hypothesized that the potent vasoconstrictor endothelin-1 contributed to the gut injury. They assayed endothelin-1 concentrations in resected gut from NEC patients and compared levels in necrotic gut, gut adjacent to the necrosis, and gut that appeared normal at the margin of resection. Endothelin-1 was increased in the gut tissue adjacent to the necrosis. They then made innovative measurements of arteriolar responses to endothelin 1 receptor antagonists using tissue recovered at surgery. Subserosal arterioles from gut adjacent to the necrosis vasodilated in response to an endothelin-1 receptor antagonist while arterioles from the more normal gut from NEC patients and gut from control patients did not. The use of resected gut from NEC patients to evaluate pathogenesis may be a very helpful experimental strategy.

—Alan H. Jobe, MD, PhD

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Does increasing physical activity really make a difference? Show me the evidence

In this issue of The Journal, Strong et al review what is known about the effects of physical activity on the health and behavior of school-aged children. A Consensus Conference was held in 1993 that resulted in the recommendation that adolescents should engage in three or more sessions per week of activities that last 20 minutes or more and require moderate to vigorous levels of exertion. What have we learned in 10 years?

The information obtained from this extensive literature review was shared with individuals representing several organizations and agencies, and after vigorous debate and based on this evidence–based approach, the authors recommend that school-aged youth should participate in 60 minutes of vigorous physical activity on a daily basis.

It appears that this amount of activity will have a positive effect on the academic performance and musculoskeletal development of children. It will also have a positive effect on the adiposity in the overweight child, will decrease blood pressure in the children with hypertension, and will have a beneficial effect on lipids if they are elevated. Increasing physical activity will have no detrimental effect on safety and well-being based on the literature available to date.

Armed with this information, the practitioner can, without reservation, now recommend vigorous daily physical activity in all school-aged youth. Further research is needed to continue to document the benefits of regular, vigorous physical activity in children.

—Reginald L. Washington, MD

Bone mineral density with children with cerebral palsy

Children significantly involved with cerebral palsy are well-known to have osteopenia and to be at risk for pathologic fractures. The natural history of this phenomenon is not well understood. In the current issue of The Journal, Henderson et al at the University of North Carolina report a longitudinal study of 69 children to examine bone mineral density (BMD) compared to a number of measures of disease severity, growth, and nutrition.

As expected, BMD correlated negatively with severity of cerebral palsy. Overall, there was an increase in BMD with time, but, in spite of this, z-scores for BMD in the distal femur actually fell. The suggestion was that these children were not so much losing bone mineral as not gaining it at the rate to be expected in typical children. This information will be very valuable for those designing interventions.

—Thomas R. Welch, MD

A biomarker in meconium for fetal exposure to alcohol

Alcohol exposure of the fetus is the largest preventable cause of mental retardation, and maternal histories of alcohol exposure are notoriously unreliable. The identification of which infant will be adversely affected by alcohol remains problematic because maternal metabolism of alcohol (based on genetic differences in enzymatic activities), drinking quantity and pattern, maternal age, and no doubt other factors contribute to the fetal risk. Furthermore, physical examination of infants at birth will miss a great majority of infants negatively impacted by fetal alcohol exposure. Bearer et al report the further development of biomarkers in meconium as indicators of amount of fetal exposure to alcohol. They find that the fatty acid ester ethyl linoleate, a non-oxidative metabolite of ethanol, is potentially useful for identifying fetal alcohol exposure. Such biomarkers should be helpful for epidemiologic and interventional studies of this intractable problem.

—Alan H. Jobe, MD, PhD

Dealing with the density of bone mineral content studies

Even the casual reader of The Journal must be aware of the increasing number of studies we have been publishing addressing bone mineral density (BMD) in children. These studies are beginning to use a vocabulary which may be confusing to those not current with the literature, such as the differences between BMD and bone mineral content (BMC). Readers will also see differing methodologies employed in these studies, ranging from the more typical DXA to the more recent quantitative computed tomography and quantitative ultrasound (“speed of sound”). Each of these techniques provide different information, and are not directly comparable.

The editors decided that it was necessary to invite a Medical Progress article to summarize this information succinctly for the practitioner. In the current issue of The Journal, Bonny Specker, PhD, does this very nicely. The information provided in this review is not available in such an accessible, clinically-relevant form anywhere else. Dr. Specker proceeds to discuss situations in pediatrics in which measurement of BMD (or BMC) is appropriate.

—Thomas R. Welch, MD
Follow-up studies of RVT

Neonatal renal vein thrombosis (better called renal “venous” thrombosis, recognizing that the problem usually begins in the small vessels) is an unusual event, but one that busy newborn services confront periodically. In the current issue of The Journal, Marks et al present the results of the longest follow up study of a large cohort of children with neonatal renal venous thrombosis. There are two important points. The first of these is the high incidence of renal complications in these children, sometimes occurring years after the newborn period; fully one third of these children, for example, had persistent hypertension. The second point is the frequency of defined prothrombotic disorders in this group of children. Although not all children in the series underwent complete testing, nearly half of those who did had a definable abnormality such as Factor V Leiden. Interestingly, despite this finding, none of the children in the series had subsequent thrombotic events during the period of follow up.

— Thomas R. Welch, MD

A 40 year follow-up!

The current issue of The Journal includes a brief case report in which modern molecular genetics “catches up” with the original description of a syndrome. There are several overlapping disorders characterized by mutations in a gene now called WT-1. This gene encodes one of the zinc finger proteins, and WT-1 mutations are associated with a variety of defects in urogenital development, including, in some cases, Wilms tumor. Over 40 years ago, one of these disorders was described by Frasier and associates in the pages of this Journal (J Pediatr 1946;64:740-5). In the current issue, one of the patients from that original report was identified and her WT-1 mutation was determined. She has done very well since receiving a kidney transplant at age 13. The fact that she has not developed a Wilms tumor is consistent with the observation that the Frasier syndrome WT-1 mutation does not seem to predispose to this malignancy, as opposed to the related Denys-Drash syndrome.

— Thomas R. Welch, MD

Developmental disorders and overweight

It is well known that we have been experiencing an epidemic of obesity in the children and adolescents in the United States. It is less clear how this affects subgroups of children. In this issue of The Journal, Bandini et al evaluated the prevalence of overweight in children with developmental disorders using data from the National Health and Nutrition Examination Survey from 1999-2002. They found a higher prevalence of overweight in children with disabilities that limited physical activity. They also found that girls with learning disabilities had a higher prevalence of overweight than those without these disorders. This suggests that these are important groups of children for whom preventive strategies should be developed.

— Stephen R. Daniels, MD, PhD

Virus burden and sensorineural hearing loss from congenital CMV infection

Boppana et al from the University of Alabama report the results of a prospective study of 76 infants identified at birth with congenital CMV infection to assess relationship of virus burden, as measured by quantitative virus isolation from urine samples and DNA in peripheral blood, on outcome. The majority of children had asymptomatic infection at birth. Virus burden in these children was directly correlated with sensorineural hearing loss (SNHL).

These findings allow speculation on pathophysiology of neurologic sequelae and will be valuable in targeting subjects for studies of potential interventions.

— Sarah S. Long, MD
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June 2005

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July 2005


August 2005

Charles E. Culpeper Scholarships in Medical Science, Goldman Philanthropic Partnerships is currently accepting applications for its 2006 Charles E. Culpeper Scholarships in Medical Science Program designed to support the career development of academic physicians. Up to three awards of $108,000 per year for three years will be made to United States medical schools or equivalent United States educational institutions on behalf of candidates who are U.S. citizens or aliens who have been granted permanent U.S. residence (proof required), who have received their M.D. degree from a U.S. medical school or the equivalent of an M.D. degree from an educational institution equivalent to a United States medical school in 1997 or later, and who are judged worthy of support by virtue of the quality of their research proposals and their potential for successful careers in academic medicine. All scientific research relevant to human health is eligible for consideration; research that has relevance to cures for human disease is highly encouraged. No institution may nominate more than one candidate.

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Deadline for applications is Wednesday, August 17, 2005. Awards will be announced in January 2006, for activation on or about July 1, 2006. Application forms and instructions may be obtained on the Web at www.goldmanpartnerships.org or by contacting Amanda Morton, Charles E. Culpeper Program Manager, Goldman Philanthropic Partnerships, 155 North Pfingsten Road, Suite 109, Deerfield, IL, 60015, telephone: (847) 948-5512, fax: (847) 948-5516.

September 2005

World Congress of the World Society for Pediatric Infectious Diseases, “WSPID 2005,” Warsaw, Poland, September 1-4, 2005, Website: www.kenes.com/wspid, E-mail: wspid2005@kenes.com.
The most significant source of public funding that affects access to health care for children is the joint effort between states and the federal government in the Medicaid and State Children’s Health Insurance Program (SCHIP). Medicaid is the single largest children’s health insurance program in the country, currently providing health coverage to nearly one third of the children in the United States. Together with SCHIP, these programs provide health insurance to more than 30 million children nationwide. This commentary will discuss the ongoing national policy debate surrounding these programs and the potential effects on access to health care for children.

Medicaid was established in 1965, along with Medicare. Initially, Medicaid coverage was limited to families receiving welfare and cash assistance but has subsequently been delinked from these programs. From 4 million beneficiaries at its beginning, Medicaid has grown to serve more than 50 million individuals, including more than 27 million low-income children. Mandatory populations include children whose families meet statutory income criteria. All children (from birth through the 18th year of age) who are in families earning at or below 100% of the federal poverty level ($15,670 for a family of three in 2004) are guaranteed eligibility in the Medicaid program. The eligibility income level is expanded to, at, or below 133% of the federal poverty level ($20,893 for a family of three in 2004) for infants and children up to age 6 and pregnant women. States are given the option of providing coverage above the mandatory income levels. States are also given the option of allowing individuals to qualify as “medically needy” by “spending down” to the eligibility income level by subtracting the cost of their medical expenses from their income. All beneficiaries that are provided coverage in the program at a state’s option are termed “optional” populations.

In 1997, Congress established the SCHIP as part of the Balanced Budget Act. This program provides an enhanced federal match of funds to those states that choose to expand their public health insurance programs for children beyond mandatory Medicaid eligibility income levels. Interestingly, the SCHIP program emerged from a national policy debate concerning Medicaid and efforts to limit, or blockgrant, federal spending in Medicaid eligibility income levels. States are also given the option of providing coverage above the mandatory income levels. For states that opt to set up a separate or stand-alone program, SCHIP provides flexibility in designing the benefits package. For example, the Medicaid program includes a comprehensive benefits package, the Early and Periodic, Screening, Diagnosis, and Treatment (EPSDT) benefit. This ensures that children receive essential preventive benefits and coverage (diagnosis and treatment) of chronic health care conditions, which is not required to be provided to children in SCHIP. Benefits in stand-alone SCHIP can be designed according to an established benchmark in the private market. Should the private market benefits for children deteriorate, coverage protections for low-income children in SCHIP probably will also deteriorate. The differences between the mandatory benefits provided under Medicaid and the optional benefits under SCHIP could be of particular importance for children with special health care needs.

Employment-based and private insurance provides coverage for the majority (62%) of children in the United States. Medicaid, together with SCHIP, provides health insurance for more than one third of the children, and enrollment in these programs has grown during recent slow economic times. Despite substantial decreases in employment-based and private insurance coverage, the uninsured rates for children have remained stable as Medicaid and SCHIP fulfill their role as a child health safety net.

More than 9 million American children are currently uninsured. Although the majority (6.3 million) of these children meet eligibility guidelines for Medicaid or SCHIP programs, they are not enrolled. State policies that impede enrollment include complicated enrollment processes, strict eligibility verification requirements, and burdensome eligibility renewal requirements. Although some states have made efforts to institute policies that encouraged enrollment into the programs, the recent state fiscal crisis brought the return of many of these barriers. Because the

From the Washington Office, American Academy of Pediatrics; Washington, DC and Tulane University Health Sciences Center.
SCHIP statute permits it, states also instituted enrollment caps to limit costs.

An important element of the Medicaid policy debate is that governors are seeking greater flexibility from federal guidelines to manage their Medicaid programs. A key target for such flexibility is benefit design. For children, federal law provides a statutorily defined benefit package that has protected these beneficiaries. States must provide EPSDT to all children in Medicaid unless states are granted a waiver that permits them to provide less comprehensive benefits. The extent of Centers for Medicare and Medicaid Services authority to grant state waiver applications is being called into question. Legislation was introduced in the last Congress that clarified limits on the administrations’ authority, to protect essential components of the Medicaid program, including EPSDT for children. As states continue to develop new proposals to contain costs in the Medicaid program, including new health insurance models such as health savings accounts coupled with high deductible health insurance plans, the extent to which the Centers for Medicare and Medicaid Services holds states accountable to the benefit protections for children in the Medicaid law will certainly affect access to quality health care for children.

Inadequate Medicaid physician payment rates also threaten the ability of beneficiaries to access services. Payment rates vary from state to state, but the average office visits are paid at 68% of the amounts they would be paid under Medicare and only 56% of rates in the employer-based or private market. Specialty services are often paid at even lower rates. The Medicaid statute does require that state Medicaid plans ensure that payments are “sufficient to enlist enough providers so that care and services are available under the plan at least to the extent that such care and services are available to the general population in the geographic area.” The federal government has not actively enforced this provision, commonly known as the “equal access” provision. Providers have had some success in state lawsuits to enforce this provision, but they have been costly and labor-intensive.

The Bush administration and Congress have signaled their interest in reforming the Medicaid program. On February 7, President Bush released his fiscal year 2006 federal budget proposal that included $60 billion in cost savings, or cuts, to the Medicaid program over a period of 10 years. Although the proposal suggested that the majority of these cost savings be found by limiting states efforts to maximize federal matching funds through such mechanisms as intergovernmental transfers and provider taxes, there is real concern that the Medicaid program cannot sustain cuts of this magnitude without undermining coverage and beneficiary protections.

In recent years, similar efforts to cut the Medicaid program through the congressional budget process have been successfully stopped in the Senate. This may be more difficult this year. If Congress passes a budget with reconciliation instructions that include the President’s target of $60 billion in cuts to the Medicaid program, the House Energy and Commerce Committee and Senate Finance Committee will have to report out reform legislation that will result in a decrease of $60 billion in federal Medicaid spending. Preventing cuts to Medicaid funding in the budget will be the first hurdle in protecting the Medicaid program for children. Should such cuts move forward, efforts will be focused on protecting critical elements of the program that become vulnerable, including the entitlement nature of the program and the EPSDT benefit for children. Risks include reforms implementing a limit, or cap, on federal spending in Medicaid coupled with increased flexibility to the states to design and manage their Medicaid programs. In addition, the 108th Congress did not pass legislation to redistribute $1.1 billion in unspent 1998–2001 SCHIP funds, further limiting the availability of needed funding for those states that had fully utilized their blockgrant.

Even if efforts to prevent cuts in the fiscal year 2006 budget are successful, the program remains vulnerable. Although the entitlement to Medicaid coverage may remain intact for the “mandatory” population of children during this reform effort, benefit protections for optional beneficiaries (including many children with special health care needs) may be weakened. Currently, 48% of the children in the Medicaid/SCHIP program are “optional” beneficiaries.

The involvement of pediatricians in the Medicaid policy debate will be necessary to ensure that policymakers understand the implication of proposed reforms on children’s health in their community. Pediatric involvement will ensure that this policy debate will not simply be about cutting costs but that reforms are found that will sustain and improve these programs for the millions of children who are currently enrolled and the millions more who are eligible but uninsured.

Children represent more than 50% of enrollees in Medicaid, less than 25% of the utilization of funds, and account for less than 15% of recent spending growth. Caps or blockgrants in Medicaid will necessarily lead to a reduction in benefits, payment rates, or enrollment as the eligible population grows. Pediatricians need to be active advocates to see that state and national legislators are aware of the data and implications and do no harm to the availability and quality of health care for children. Although there is great risk in the current policy debate, there are gains to be made in the Medicaid program by improving outreach, enrollment, and retention policies to deliver high-quality services and providing a remedy for inadequate Medicaid payment rates for pediatric care.

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REFERENCES


The article by Strong et al1 in this issue of The Journal of Pediatrics presents recommendations for the amount of physical activity in youth necessary to improve health and behavioral outcomes. The recommendations were the product of a critical and extensive review of more than 300 articles conducted by an independent expert committee composed of both clinical and public health experts and funded by the Division of Nutrition and Physical Activity at the Centers for Disease Control and Prevention. The references alone provide a valuable resource. The committee’s recommendations agree with those of the Dietary Guidelines for Americans that school-age children participate daily in 60 minutes or more of moderate to vigorous physical activity.2 Because the expert committee included representatives of many groups with expertise or investment in physical activity, the likelihood that these recommendations will be widely accepted and disseminated is increased.

Although the intent of the review was to develop physical activity recommendations for youth, the gaps in knowledge identified by the review provide the basis for research for years to come. It seems likely that the type and dose of physical activity necessary to prevent an adverse health outcome will depend on the adverse health outcome in question. For example, the amount of physical activity necessary to prevent or reduce cardiovascular disease risk factors may differ from the amount necessary to prevent obesity. Weight-bearing activities are more likely than swimming to prevent osteoporosis of the lower extremities or spine. Examination of the impact of physical activity on outcomes such as musculoskeletal or cardiovascular health in representative populations would augment the data derived from intervention studies. The role of physical activity in the origin and course of obesity provides a particularly rich area for investigation. For example, no studies have yet prospectively defined the amount of physical activity necessary to prevent excessive weight gain in children or adolescents. Although a recent Institute of Medicine report suggested that 60 minutes of moderate physical activity was necessary to prevent weight gain in adults,3 these findings were based on the amount of physical activity necessary to move a sedentary individual to a level of moderate physical activity. However, the energy spent on activity by obese and nonobese adolescents is comparable,4 and studies of youth have failed to find that reduced energy expenditure at baseline predicted increased gains in fatness.5-7 Among youth,8 as among adults,9 increased physical activity appears to have a limited effect on weight loss. The dose of physical activity necessary to maintain weight after weight loss in children and adolescents has not been studied. Among adults, physical activity reduces or improves obesity-related comorbidities such as hypertension, dyslipidemia, and glucose intolerance.10 As the review points out, physical activity appears to have the same beneficial effects in children. Although physical activity could therefore be expected to reduce obesity-associated comorbidities without an effect on weight, this issue has not been carefully examined.

One of the most important challenges is how to achieve these recommendations. The first step is for medical and public health practitioners to recognize the importance of physical activity. Successful implementation of the recommendations will require the efforts of both groups. Effective counseling by clinicians will likely depend on their ability to help patients and their families learn how to solve the problems that limit opportunities for children to be physically active.11,12 Complementary strategies in schools and communities will also be required. Individual behavior change will be less likely if children live in environments that are unsafe or lack playgrounds or other recreational facilities. The Guide for Community Preventive Services, an evidence-based review of community interventions, recommends a variety of strategies to increase physical activity, such as physical education, community-wide campaigns, and access to and promotion of recreational facilities.13 One of the most important barriers to increased physical activity of youth is the recent reduction in physical education programs in schools. This trend might well be reversed if studies demonstrate that physical activity improves classroom behavior and performance. The importance of access to recreational facilities suggests that providing resource lists for local facilities that offer opportunities for physical activity may be an important adjunct to counseling to increase physical activity. The committee that produced these recommendations has made a major contribution to the field of physical activity in youth. In doing so, they have reminded us how much more there remains to do.
I am grateful to Bill Kohl and Janet Fulton for their thoughts on the content of this editorial.

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STATISTICAL PROCESS CONTROL AND CALCINEURIN INHIBITOR MANAGEMENT

One wonders whether the article in this issue of The Journal by Bucuvulas et al is a sneak preview of a wave of change that is about to transform medicine. In approaching the problem of better managing critical immunosuppressive drugs in children after liver transplantation, they have applied the principles of statistical process control with some success. This approach, now common in industry, was developed by Walter Shewart to control quality at Bell Laboratories in the 1920s. Our need to have outcomes drive change in medicine is extremely relevant to this approach. As of yet, our understanding of how to apply this powerful tool to improving medical care is rudimentary.

Transplantation of the liver in children has become an everyday event. More than 500 transplantations occur annually, and the success rates are excellent. However, the average recipient is 5 years old and faces a life of immunosuppressive medication. The calcineurin inhibitors, which form the foundation for successful transplantation, are toxic to the kidney. However, without these medicines, rejection of the transplanted organ leads to graft failure and patient death. Keeping medication in a narrow therapeutic range is not easy under ideal circumstances, and the circumstances are hardly ideal. Challenges include inadequate information regarding pharmacokinetics in children, absence of a simple reliable marker of drug exposure, frequent failures in medicine adherence, and the myriad of drug protocols and combinations currently in use.

Bucuvulas et al have made a very important step forward in how to manage these important medications. Their work differs from prior efforts to improve our use of these drugs. In the past, exquisite management of the individual and their problems has been the most important characteristic of success in solid organ transplantation. The Cincinnati Liver Transplant Group has taken on the management of a critical drug in an entire class of patients, and it may have profound implications.

The background for this effort is worth retelling. While attending a conference on changing medical management using the principles of statistical process control, the authors realized that there could be an immediate application to their work in liver transplantation, particularly the management of calcineurin inhibitor level variability. They used the principles of statistical process control to design a change cycle that would lead to an increased proportion of calcineurin inhibitor drug levels within the target range. Testing their process on a small group of patients, they were able to prove the validity of their concept and then expand the process to the large group of patients whom they monitor. At the onset of this change cycle, only 50% of patients were within the target range. Currently, 85% are in the target range.

See related article, p 744.

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range, and variability of calcineurin inhibitor levels has diminished.

One might not understand the profound importance of this accomplishment if the context was not first understood. From early on in the discovery of cyclosporine, nephrotoxicity was known to be a problem. At one point, the only way to manage the individual patient was to increase the drug dosing to the point of nephrotoxicity and then decrease it again, having established the ceiling of drug dosing. One did not want to experience the other clinical endpoint, rejection, when the drug levels were too low. From those rather blind and difficult beginnings, the management has made significant progress. Crucial to management of the drug has been establishment of an effective test for monitoring drug levels and a better understanding of pharmacokinetics. Unfortunately, what we know of pharmacokinetics is not comforting. Intrapatient and interpatient variability is relatively large, absorption and metabolism are dynamic, and an easy and reliable biological marker of drug effectiveness or drug exposure does not exist. Current practice uses drug trough levels for both tacrolimus and cyclosporine, but for the latter in particular, these levels have no correlation with drug exposure. Nevertheless, control of drug exposure by standardizing interventions in a well-controlled setting is a great step forward. As the authors state, “A defined process to regulate blood levels of CNIs [calcineurin inhibitors] is not only critical to maintain allograft function but will improve quality by promoting safety and increasing the efficiency and effectiveness of care.”

But using the statistical process control as the tool for change is very different than our usual method of testing and intervention in medicine. This is no randomized, double-blind, crossover study. This is targeted intervention through a change cycle that continues to change until the target is achieved. The important steps in that change process are clear. The authors defined target drug levels using medical literature. They identified a timetable for blood levels and used a uniform method for assessing those levels. They identified uniform interventions to adjust medication dosing, and they measured their outcomes. During the change cycle, they recognized that the process itself needed additional revision. They implemented a work flow sheet, and they ultimately gave patients and practitioners access to blood levels and medication-dosing information through a web-based application. More patients and their doctors now have better information and control of a critical drug. Ultimately, this is perhaps less about science than it is about success. The changes focus less on identifying what is wrong and more on fixing it. Right now, there is much in medicine that needs fixing; the Institute of Medicine has made that perfectly clear.

What is not clear about this work is that improving the reliability of trough levels is the critical step in improving transplantation outcomes. Although they achieved an important step, Bucuvalas et al were not able to show improvement in rejection rates. Measurement of glomerular filtration rates might have revealed changes in renal function in this study. Clearly, the change cycle is not complete. The real goal of improving medicine has not yet been achieved.

The practice of medicine is ripe for application of the statistical process control approach to improving practice. Bucuvalas et al have taken an important step that will benefit the more than 500 children each year who will receive a liver transplant. Their methodology will become part of standard care, upon which further progress will be made. Of more importance is the recognition that this successful effort is one of the first fruits of the profound change medicine will realize as statistical process control gains widespread acceptance and application.

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SCREENING FOR ABNORMALITIES OF CARBOHYDRATE METABOLISM IN TEENS

The epidemic of childhood overweight has led to what is believed to be an explosion of abnormalities of glucose regulation in children and youth. These abnormalities progress in those with genetic susceptibility from overweight to insulin resistance to pre-diabetes and culminate with the diagnosis of type 2 diabetes.1 Presently, the numbers of children affected with abnormalities of glucose metabolism and the interplay of puberty, ethnicity/race, adiposity, fitness and socioecononimc status are not known because sufficient population-based studies have not been performed.

| BMI | Body mass index |
| OGGT | Oral glucose tolerance test |
Addressing the need to perform population-based assessments of glucose abnormalities, Dolan et al2 studied a large cohort (n = 2501) of non-Hispanic white and black students in grades 5-12 in the Princeton School District in Cincinnati, Ohio. Students were screened with weight and fasting plasma glucose and insulin. An oral glucose tolerance test (OGTT) was performed for those with (1) body mass index (BMI) > 85th percentile for age and sex, (2) fasting plasma insulin > 2 SD above the mean of the participants of the same race, sex, and stage of sexual development, or (3) fasting plasma glucose ≥110 mg/dL. More than one third, 39.66% (992/2501), of the students met criteria to be evaluated with an OGTT, and 887 actually had an OGTT performed. The results of the OGTT were used to place the students in one of 4 categories: (1) normoglycemic (fasting glucose < 110 mg/dL and 2-hour glucose < 140 mg/dL), (2) carbohydrate intolerant (either a fasting glucose ≥110 mg/dL and < 126 mg/dL and 2-hour glucose ≤140 mg/dL, or fasting glucose < 110 mg/dL and 2-hour ≥140 but < 200 mg/dL), (3) pre-diabetic (one fasting glucose ≥126 mg/dL and/or 2-hour glucose ≥200 mg/dL), or (4) diabetic (both fasting glucose values >126 mg/dL). Those students found to have diabetes were assessed with regard to whether they had type 1 or type 2 diabetes.

Dolan et al found a surprisingly low rate of abnormalities of glucose metabolism for the entire student group. Carbohydrate intolerance was found in only 2.48% (2.0% with impaired fasting glucose only, 0.4% with impaired glucose tolerance only, and 0.1% with both), pre-diabetes in 0.28% and diabetes in 0.36%, with only one third of the subjects with diabetes appearing to have type 2 disease. Even in the high-risk group of 887 subjects, 9 had impaired glucose tolerance, 3 had both impaired glucose tolerance and impaired fasting glucose, and 7 had pre-diabetes. The percentage of high-risk students with carbohydrate intolerance in Dolan et al’s large population-based study was dramatically lower than what has been found in studies in high-risk populations in the clinical setting. In the context of clinical studies in high-risk subjects, reports of impaired glucose tolerance have been at least 10-fold higher. For example, Sinha et al3 found impaired glucose tolerance (defined only a 2-hour glucose value ≥140 mg/dL and < 200 mg/dL) in 25% of overweight children 4-10 years of age and in 21% of overweight adolescents 11-18 years of age referred to their center for evaluation of obesity. Similarly, Goran et al4 reported that impaired glucose tolerance was found in 28% of a select group of overweight Hispanic youth with a positive family history of type 2 diabetes. Gomez-Diaz et al5 reported fasting plasma glucose levels > 110 mg/dL in 6.2% of 4-17 year old overweight children; 13.3% had fasting plasma glucose values >100 mg/dL cutoff, and 14.8% had impaired glucose tolerance. This would suggest that even with almost 50% ethnic/racial minority students, a high percentage with a BMI > 85th percentile (34.9%) and the majority of subjects in or completing puberty (88%), screening a population of “normal” children, and then further evaluating a group believed to be at high risk, does not yield a cohort of subjects with glucoregulatory abnormalities comparable to what is found in clinic-based studies.

The fact that the authors altered established definitions of carbohydrate intolerance and pre-diabetes may lead to difficulties in interpreting this study. The authors lumped impaired fasting glucose and impaired glucose tolerance into their definition of carbohydrate intolerant. Both have been previously defined as pre-diabetes by the American Diabetes Association.6 In addition, the authors used pre-diabetic to refer to glucose values, either fasting or during the oral glucose tolerance test that were in the diabetic range. By altering definitions, the authors have added to potential confusion with regard to how their results will be compared to past and future studies.

A Consensus Panel convened by the American Diabetes Association in 20007 recommended that testing for type 2 diabetes be performed in “at-risk youth.” Diabetes screening was recommended for children and youth with obesity and a positive family history of type 2 diabetes, those belonging to certain race/ethnic groups such as American Indian/Native American, black, Hispanic, Asian/Pacific Islander, and those having evidence of insulin resistance with hypertension, acanthosis nigricans, dyslipidemia, or polycystic ovarian disease. This recommendation to screen for type 2 diabetes was made, in the absence of sufficient data concerning the natural history of type 2 diabetes in pediatric subjects, because of the following: 1. It was presumed the disease was common among the general population, as well as among easily identifiable high-risk groups; 2. The disease was serious in terms of morbidity and mortality; 3. The disease had a prolonged latency period during which time there were no symptoms; 4. The screening test was adequately sensitive and specific; and 5. Intervention was available to prevent or delay disease onset or treat at an early stage. Screening was recommended in pediatric subjects because of a concern that the longer duration of diabetes would lead to an excess of both microvascular and macrovascular complications and to increased medical costs.

The results of the very low rate of undiagnosed diabetes in students in the Princeton School District, coupled with prior Third National Health and Nutrition Examination Survey8 findings of a very low rate of undiagnosed diabetes in children and youth, call into question when screening for type 2 diabetes in children should be done. This study suggests that screening all children for abnormalities of glucose metabolism is not indicated because of the very low yield. At this time, screening children and youth for diabetes should not be brought to community and school settings. Screening high-risk children might be indicated, but it appears that using BMI, fasting glucose and insulin levels does not identify a cohort of children with sufficient risk to justify screening. Further analysis and studies need to be done to better define high-risk children who would benefit from having an OGTT performed to diagnose where they fall on the spectrum of glucose abnormalities.

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THE CHANGING APPROACH TO MULTICYSTIC DYSPLASTIC KIDNEY IN CHILDREN

In this issue of The Journal, Ismaili and associates in Belgium have advanced our understanding of multicystic dysplastic kidney (MCDK), and they have made an important observation that should change practice significantly. To appreciate the importance of the Ismaili study, and to place it into perspective, some background must be reviewed.

MCDK, although “cystic” in appearance, is not one of the inherited renal cystic diseases—autosomal dominant (“adult”) or autosomal recessive (“infantile”) polycystic disease. It is really a form of renal dysplasia, in which cystic elements are found along with immature, undifferentiated, primitive tissue. Embryologically, MCDK may result from abnormal renal morphogenesis, likely consequent to abnormalities of developmentally expressed genes. Some degree of ureteropelvic junction obstruction is generally present. MCDK, in addition to cystic elements, may show some hydronephrotic features.

MCDKs are usually unilateral and nonfunctional. In the rare circumstances in which MCDK is bilateral, the condition is generally lethal in the newborn period. The overwhelming majority of isolated MCDKs are sporadic anomalies, for which no genetic explanation is currently available. In other cases, however, MCDK is but one component of a generalized disorder such as the VATER (vertebral defects, imperforate anus, rachischephageal fistula, radial and renal dysplasia) association, Zellweger syndrome, or the BOR (branchio-oto-renal) syndrome.

Until the 1980s, MCDK was generally diagnosed in the course of urinary tract imaging that was being obtained for the investigation of problems such as an abdominal mass, urinary tract infection, or hypertension. Thus, virtually all children with MCDK, by definition, had a complication of the condition. Pediatric urology texts from this period and before portray MCDK as an unusual condition, generally symptomatic, often associated with other urinary tract anomalies, requiring further diagnostic study, and frequently necessitating nephrectomy. For example, Campbell, in his 1951 text, described an entity “congenital multilocular cysts” (clearly MCDK), which was “rare” and which could cause symptoms from pressure on adjacent organs or bowel obstruction. The condition was to be differentiated from renal tumors, and was treated by surgical removal.

Changes in obstetric practice have altered this situation considerably. Today, virtually all MCDKs are recognized prenatally by ultrasonography. Thus, the typical patient is no longer a child being investigated for a specific symptom. Rather, the usual situation today is an otherwise healthy baby with an abnormal prenatal ultrasonogram. Although reliable modern incidence figures are difficult to obtain, this diagnosis constitutes between 2% and 3% of new visits for outpatient consultation in the pediatric nephrology clinic at University Hospital in Syracuse. Our pediatric urology clinic experiences a slightly smaller rate.

With the changing epidemiology of MCDK, a shift in management also has occurred. Routine initial nephrectomy for MCDK, once...
widely practiced, is extremely rare today and is limited to situations in which a real complication of the disorder is occurring.10,11 The MCDK registry documented a significant drop in the frequency of nephrectomy over the 13 years in which it was collecting data.12 Previously accepted indications for “prophylactic” nephrectomy, such as concern regarding the development of malignancy or hypertension, have disappeared. Again in Syracuse, two nephrectomies for MCDK have been performed in the past 3 years, both because of increasing size of the kidney in older children.

Similarly, the diagnostic approach to the presumed MCDK has been evolving, mainly in the direction of a more conservative approach. At one point, for example, it was generally accepted that some type of functional imaging (ie, renal scan) was needed to differentiate between MCDK (which should be nonfunctioning) and significant ureteropelvic junction obstruction with hydrenephrosis, in which some residual function may be present. Today, most pediatric radiologists would agree that a high-quality renal ultrasonogram is usually sufficient to make the diagnosis of MCDK.9 Although this opinion may not be held by all pediatric urologists, it may actually depend on the experience and technical expertise of the sonographer.

The remaining imaging issue for the child with MCDK is the need for a voiding cystourethrogram (VCUG). Mainly because of concern for the presence of vesicoureteral reflux (VUR) in the contralateral kidney, this procedure continues to be recommended13-15 and performed, although a few studies have recently questioned the need for this.9

Interestingly, even studies suggesting the need for this additional imaging on close examination do not always make a compelling case. Flack and Bellinger,14 for example, reported the results of VCUGs in 29 children with MCDK; eight had contralateral VUR despite what were said to be normal ultrasonographic appearance. Most of this VUR, however, was low grade, and all children who had subsequent VCUGs had resolution before 2 years of age. Thus, it is arguable whether any benefit accrued to the children by the recognition of this VUR. One of these children was said to have grade IV VUR and underwent surgical repair. It would be surprising for such a finding to be missed using the protocol described by Ismaili et al.

It is into this context that the Ismaili et al study fits. These investigators had the advantage of working with a cohort of children, whose MCDK was ascertained by prenatal ultrasonography. A close collaboration with their center’s obstetric unit allowed early recognition of such children. Each child was subjected to a systematic series of imaging procedures, again uniform for the group. These studies included additional ultrasonograms, renal scans, and VCUGs. Follow-up was complete and comprehensive.

The important finding of this study was the sensitivity and specificity of two renal ultrasonograms, about 1 month apart, in detecting contralateral urinary tract problems. As in other published series, the authors detected a variety of contralateral anomalies in this cohort. On the other hand, virtually all of these anomalies were detected by one of the two renal ultrasonograms. There were, for example, only four children with contralateral VUR who had totally normal ultrasonograms. In each, the reflux was low grade, resolved spontaneously, and was likely inconsequential. The ultrasonography examinations also detected most of the lower urinary tract anomalies. There were only three lower tract anomalies not suspected by ultrasonography; again, none of these was likely to be important.

It must be stressed that all of these ultrasonography examinations were undertaken by highly experienced personnel, using optimal equipment. The studies included measurements such as the pelvic diameter, which may not be a part of routine renal ultrasonography in every center.

On the basis of this study, as well as some of the other studies cited, it is reasonable to draw conclusions about the investigation of infants with prenatal ultrasonograms that suggest MCDK. All of these children should have high-quality urinary tract ultrasonography studies in the first few days of life. The study should be repeated in about a month. These should be performed in an experienced center. No further imaging appears to be necessary if both of these studies show a kidney that has the ultrasonographic features of MCDK, as well as a normal bladder and contralateral kidney. An important caveat to this recommendation is the reminder that the imaging must be performed in a center with interest and expertise in the imaging of the infant’s urinary tract.

We typically obtain follow-up studies on such children every 6 to 12 months for the first few years, looking for involution of the MCDK as well as normal growth of the contralateral kidney. Admittedly, the evidence basis for these follow-up recommendations is not as strong as it is for the initial studies. Perhaps ongoing studies of this cohort by Ismaili and associates may answer this question as well.

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Over the past decade there have been an increasing number of published manuscripts dealing with pediatric bone mineral density (BMD). The reason for this interest is 2-fold. First, there is a belief that bone gained early in life is an important factor in determining the risk of osteoporosis later in life. Second, there is a desire to identify children who may benefit from drugs that are becoming available for use in treating osteopenia and osteoporosis. Despite the interest, there are several important issues with assessing BMD or the amount of bone (bone mineral content [BMC] or bone mass) that are unique to children that need to be recognized and are discussed in this review. Dual energy x-ray absorptiometry (DXA) is the most common method for assessing BMD and BMC, but other methods, including peripheral quantitative computed tomography (pQCT) and quantitative ultrasonography (QUS), may provide important additional information on bone size, geometry, and quality, and these methods also are discussed.

Approximately 90% of adult bone mass is gained in the first 2 decades of life. Optimizing peak bone mass and bone strength early in life and stabilizing it during young adulthood is believed to play a significant role in preventing osteoporosis and fracture later in life. Environmental factors important in determining whether children reach their genetic potential in achieving peak bone mass include adequate nutrition and activity levels. Pediatric diseases, or the therapeutic interventions used in their treatment, also may prevent children from reaching their genetic potential. Diseases or conditions known to affect bone density adversely include osteogenesis imperfecta, gastrointestinal illnesses (ie, inflammatory bowel disease, Crohn's disease), cystic fibrosis, juvenile rheumatoid arthritis, growth hormone deficiency, chronic steroid use, and history of previous fracture. Obese and less-active children also have been shown to have decreased BMD or bone mass compared with nonobese children of similar weight.1,2 Whether this decreased BMD among obese children is a direct effect of fat on bone or due to decreased muscle mass or reduced activity levels, or a combination of both of these factors, is not clear. However, the epidemic of childhood obesity may in part directly or indirectly explain the increase in childhood fracture incidence that has recently been reported.3 Identifying children with low bone mass early in life could be an important strategy for preventative or therapeutic efforts to optimize bone accrual and, consequently, bone strength.

**METHODS FOR ASSESSING BONE HEALTH AND ASSOCIATED PITFALLS DXA**

DXA is the most widely used densitometric method for diagnosing osteoporosis in adults. DXA was developed in the late 1980s for use primarily in postmenopausal women. Pediatric software became available in the early 1990s after improvements in algorithms for detecting bone edges in children with low bone density. The advantages of DXA are its wide availability, short scanning times, and relatively low radiation exposure.

DXA measures bone in 2 dimensions and provides estimates of the amount of BMC and bone area. BMD is then calculated as BMC/bone area (g/cm²). Because this is a 2-dimensional measurement and not a true volumetric density, measurements using DXA are often referred to as areal BMD (aBMD). Measurements of aBMD are influenced by bone size, with larger bones having artificially inflated aBMD measurements (Figure 1). This is an important problem in pediatric bone assessment because of the large differences in body size and bone size within and across different ages. Studies show that aBMD by DXA increases with age, but studies using computed tomography indicate that true volumetric BMD (vBMD) is relatively constant during childhood until puberty, at which time there is
a large increase in vBMD. BMC increases with age, and the increase in aBMD that is observed is likely the result of greater bone size.

Several mathematical methods have been proposed to adjust aBMD to either control for bone size differences or more closely reflect vBMD. These methods include the calculation of bone mineral apparent density (BMAD) that divides BMC by a calculated bone volume rather than by bone area. This method has been used for the spine and hip and assumes that the bone has a cuboidal or cylindrical shape, respectively. Other investigators have proposed including bone area and body size parameters in a multiple regression approach to calculate a size-adjusted BMC. Molgaard et al have proposed a logical approach to assessing bone accrual in children that includes a 3-step examination of growth and bone data: height-for-age, bone area-for-height, and BMC-for-bone area. This type of examination would help distinguish whether a child has “short” bones, “narrow” bones, or “light” bones. Unfortunately, normative pediatric curves for these relationships are not available as part of the DXA software. Some DXA machines have normative data for aBMD-for-age at some bone sites, but use of these curves for diagnosing low aBMD or BMC may not be appropriate, especially if the child has decreased stature. Although adult aBMD has been shown to be predictive of future fracture risk in longitudinal epidemiologic studies, there is no evidence in children indicating this is so, and even among adults the sensitivity of DXA for assessing vertebral fracture risk is relatively low (65% using World Health Organization criteria). The aBMD results are often presented as T and Z scores. The World Health Organization criteria for diagnosing osteoporosis in adults are based on BMD T scores (defined as the standard deviation [SD] score of the observed aBMD compared with that of a normal young adult). A T score of less than −1 SD indicates osteopenia, and a T score of less than −2.5 SD indicates osteoporosis.

Because T scores compare the observed aBMD with that of young adults, they are not appropriate for growing children and should never be used. Z scores, defined as the SD score based on age and gender-specific norms, are often used to determine how a child’s aBMD compares with other children’s. This is a more appropriate method of comparison of aBMD in pediatrics. As previously described, however, aBMD is highly correlated to body and bone size, and in children with chronic diseases there often is stunting of growth, and comparison of aBMD measurements to age-matched norms may not be appropriate.

In situations where a child’s growth is stunted, it may be more appropriate to determine whether the aBMD or BMC is appropriate for his or her body size by comparing their measurements with those of children of similar height or weight. However, if these reference databases are not available on the DXA software, they must be obtained from the pediatric literature on published normative values. When this is done it is important to realize that there are different DXA manufacturers, different models by the same manufacturer, and different software analyses that are available. As shown in Figure 2, there are significant differences in the relationships observed between total body BMC measurements and body weight depending on the DXA model and software that is used. There also are significant differences among published pediatric norms. Leonard et al have shown that there are inconsistencies in the diagnosis of osteopenia among children with chronic diseases depending on the reference database used.

Results of total-body and regional DXA scans are often reported in pediatric studies. Regional scans include lumbar spine, forearm, and hip scans. Within the hip scan, measures of the femoral neck, trochanter, and intertrochanter region, as well as the total hip are available. The bone sites that are measured are important because they vary in the proportion of trabecular and cortical bone. The spine, which is
predominantly trabecular bone, will be affected by different factors than the total body or forearm, which are predominantly cortical bone. Dietary calcium intake has been shown to affect primarily appendicular bone sites that are predominantly cortical bone,15 whereas hypogonadism and steroid use affect primarily axial bone sites or the ends of long bones, which are predominantly trabecular bone.16,17

Although regional DXA scans can measure BMD and BMC at sites that are predominantly trabecular or cortical bone, it is not possible to obtain separate cortical and trabecular BMD results using DXA. The aBMD assessed by DXA is a function of both the amount of bone within the periosteal envelope and the size of the bone.

Quantitative Computed Tomography

Quantitative computed tomography (QCT) assesses bone in 3 dimensions and allows for separation of cortical and trabecular bone. QCT also provides assessment of bone size and geometry, both of which are known to significantly influence bone strength.18 Volumetric BMD (vBMD) at both peripheral and axial bone sites can be measured with QCT scanners. However, the primary disadvantage is the high radiation doses, making it unsuitable for use in determining factors that influence bone in healthy children. Without normative pediatric databases for QCT, it is difficult to use this method clinically.

Peripheral QCT (pQCT) provides a 3-dimensional assessment of bone size and geometry of the appendicular skeleton with much lower radiation doses. Although the pQCT method is not routinely used currently in the United States for clinical purposes, its popularity has grown in Europe among pediatricians and pediatric bone researchers.

pQCT permits analysis of cortical and trabecular vBMD and derivation of specific geometric parameters of cortical bone from cross-sectional images (periosteal and endosteal circumferences, cortical thickness, cortical area, etc) (Figure 3). These measures provide important information not available using DXA.

The importance of bone size and geometry, in addition to bone mass, is apparent from an evolutionary viewpoint. If optimizing bone mass were of primary importance, then evolutionary processes would have led to the formation of bones with solid, not hollow, diaphyses. However, this did not occur, and the anatomic structure of bone suggests that bone development is set to attain peak bone strength by using as little material as possible. For a bone with a given structure, bone mass usually correlates with strength. However, structure strength will differ depending on the size of the structure and where the material or mass is located.

Architectural parameters have been developed that allow calculation of structural strength on the basis of the amount or size of the structure and the distribution of the material. Such parameters include the polar moment of inertia and the section modulus. The polar moment of inertia is a measure of the influence of bone size on moment of inertia and section modulus. The polar moment of inertia and the section modulus are used in bone biomechanical studies and have been found to be good indicators of bone strength19,20 and can be easily and precisely determined using pQCT.21

The material properties of the bone also play a role in determining bone strength. The elastic modulus, or stiffness,
and calcium intake on bone. In this study of 239 preschool children, calcium intake modified the leg size-adjusted BMC results were investigated (Figure 6). Gross motor activity, which included bone loading exercises, increased periosteal circumference, whereas calcium supplementation appeared to decrease the endosteal expansion that also occurred. Although DXA leg BMC did not appear to be influenced by physical activity among the children receiving placebo, the periosteal circumference was greater in the children participating in gross motor activities compared with fine motor activities.

In spite of the important information that can be obtained using pQCT, there are several problems with its use in pediatric populations. Pediatric reference databases have been published for the radius and the tibia but are not provided with the software. There are also numerous scan sites and analysis options that have been used in pediatrics reports, making comparison among studies difficult. Thresholds for defining cortical and trabecular bone need to be specified by the investigator, and the use of different thresholds will have a significant effect on the values that are obtained for cortical and trabecular bone area, as well as volumetric density. Problems specific to pediatrics include standardization of scan acquisition and analysis programs, including consensus on where to mark the end of the bone in young children with large growth plates. In addition, measurement of cortical BMD in bones less than 2 mm thick is problematic because of the partial volume effect, which is described in greater detail elsewhere.

### QUS

QUS assesses bone by measuring the speed of sound (SOS) of an ultrasound wave along the bone. The theory behind QUS is that the propagation of ultrasound waves through a medium and the attenuation of the signal strength are influenced by the physical properties of the medium. In the case of bone, the speed of propagation is influenced by the bone density, elasticity modulus, and the microstructure and macrostructure of bone. There is no uniform terminology of ultrasound velocity; the terms speed of sound, velocity of sound, and apparent velocity of ultrasound all refer to the same measure. When the ultrasound beam travels through material, energy is lost, in a phenomenon known as attenuation. In the range of frequencies used, total attenuation is linearly proportional to frequency. The slope of attenuation as a function of frequency in dB/MHz/cm has become known in clinical practice as broadband ultrasound attenuation. Different methods of measurement have been developed, including pulse-echo (reflection) and transmission techniques. QUS has been shown to be comparable to DXA in identifying adults with multiple vertebral fractures, and its use for pediatric populations is appealing due to the low cost, lack of radiation exposure, and portability. Fielding et al recently reported that calcaneus ultrasound measurements detected low bone mineral in young patients with fragility fractures, as well as DXA, and concluded that QUS is a viable screening tool for detecting children with osteopenia. However, interpretation of QUS measurements at other sites, especially tubular bones, may be more problematic and influenced by bone size and cortical thickness.

In summary, the use of QUS in pediatric populations is still in its infancy, and not all ultrasound devices are appropriate for use in pediatric populations because of inappropriate transducer sizes. In addition, adequate reference databases are not currently available for a large number of existing ultrasound devices. There is wide diversity in commercially available techniques, and there are minimal studies...
in Table II. It is important to recognize that these provide a solution to the problem of measuring aBMD in with bone and body size in interpreting the results, do not
to indicate that QUS can identify disease or be useful in longitudinal assessment of treatment success.

WHO SHOULD HAVE BONE MEASUREMENTS MADE?

There are currently no standard recommendations by either a U.S. pediatric or bone organization on who should have bone measurements for clinical purposes. The British Paediatric and Adolescent Bone Group recently published pediatric guidelines for the clinical use of DXA. They suggested that children with conditions that may increase their risk of low bone density and fracture should be considered for a DXA scan if they also present with low trauma or recurrent fractures, back pain, spinal deformity or loss of height, change in mobility status, or malnutrition. The list of conditions that place children at increased risk is given in Table I, along with some of the more rare conditions that also may be associated with decreased BMD. Because of the lack of pediatric reference databases, the variation between machines, and the different software analyses that are performed, it is important that clinicians consult with pediatric bone specialists before using DXA diagnostically or prescribing treatment on the basis of DXA methods.

The International Society of Clinical Densitometry recently published an official position paper on recommendations for performance and clinical application of bone density testing, which included recommendations specific for diagnosis in children. These recommendations are summarized in Table II. It is important to recognize that these recommendations, although they acknowledge the problems with bone and body size in interpreting the results, do not provide a solution to the problem of measuring aBMD in pediatric populations.

SUMMARY

Bone acquisition early in life is considered an important predictor of osteoporosis risk later in life. DXA is the most common method for assessing bone health in pediatric populations. There are, however, several problems with interpreting DXA scans in children that need to be considered by clinicians before therapeutic interventions are implemented on the basis of DXA results. PQCT is a promising method that is currently being used in pediatric bone research that may find its way into clinical use for assessing bone strength and fracture risk. Further research is needed to determine whether QUS could be used as a radiation-free alternative for assessing bone development clinically and in epidemiologic studies.

REFERENCES


<table>
<thead>
<tr>
<th>Table I. Conditions in which children may be at increased risk of low bone density and osteoporotic fracture</th>
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<tbody>
<tr>
<td>Chronic inflammatory disease</td>
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<tr>
<td>Systemic long term corticosteroids</td>
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<td>Hypogonadism</td>
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<td>Osteogenesis imperfecta</td>
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<td>Idiopathic juvenile osteoporosis</td>
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<td>Prolonged immobilisation</td>
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<td>Apparent osteopenia on x-ray</td>
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<tr>
<td>Examples of rare conditions where assessment by DXA may be indicated: congenital neutropenia, certain inborn errors of metabolism, Ehlers Danlos syndrome, fibrous dysplasia, hypophosphatasia</td>
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Modified from Fewtrell. 

<table>
<thead>
<tr>
<th>Table II. Position of the International Society for Clinical Densitometry (ISCD) on the Use of DXA in Diagnosis in Children (males or females less than 20 years of age)</th>
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<tbody>
<tr>
<td>The WHO classification (for defining osteopenia and osteoporosis) should not be used.</td>
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<tr>
<td>Z-scores should be used instead of T-scores in children.</td>
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<td>T-scores should not appear in reports or on DXA printouts for children.</td>
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<td>The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone.</td>
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<tr>
<td>Terminology such as “low bone density for chronological age” may be used if the Z-score is below –2.0.</td>
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<tr>
<td>Z-scores must be interpreted in light of the best available pediatric databases of age-matched controls. The reference database should be cited in the report.</td>
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<tr>
<td>Preferred skeletal sites for measurement are spine and total body.</td>
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<tr>
<td>The value of BMD to predict fractures in children is not clearly demonstrated.</td>
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<tr>
<td>Standards for adjusting BMD or bone mineral content (BMC) for factors such as bone size, pubertal stage, skeletal maturity, or body composition have not been agreed upon. Clearly state any adjustments in the report.</td>
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<tr>
<td>Successive BMD studies should be done using the same machine, scanning mode, software, and analysis when appropriate. Changes may be required with growth of the child.</td>
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<tr>
<td>Deviations from standard adult acquisition protocols, for example low-density software or any adjustment of ROI (region of interest), should be stated in the report.</td>
</tr>
<tr>
<td>The position of the International Society of Clinical Densitometry is based on the evidence currently available.</td>
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EVIDENCE BASED PHYSICAL ACTIVITY FOR SCHOOL-AGE YOUTH

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Objectives To review the effects of physical activity on health and behavior outcomes and develop evidence-based recommendations for physical activity in youth.

Study design A systematic literature review identified 850 articles; additional papers were identified by the expert panelists. Articles in the identified outcome areas were reviewed, evaluated and summarized by an expert panelist. The strength of the evidence, conclusions, key issues, and gaps in the evidence were abstracted in a standardized format and presented and discussed by panelists and organizational representatives.

Results Most intervention studies used supervised programs of moderate to vigorous physical activity of 30 to 45 minutes duration 3 to 5 days per week. The panel believed that a greater amount of physical activity would be necessary to achieve similar beneficial effects on health and behavioral outcomes in ordinary daily circumstances (typically intermittent and unsupervised activity).

Conclusion School-age youth should participate daily in 60 minutes or more of moderate to vigorous physical activity that is developmentally appropriate, enjoyable, and involves a variety of activities. (J Pediatr 2005;146:732-7)

Recommendations for appropriate amounts of physical activity for the US population, including school-age youth, have been developed by several organizations and agencies.1 Although recent reviews have summarized the benefits of regular physical activity on the health of youth and its potential for reducing the incidence of chronic diseases that are manifested in adulthood,1,2-5 a more systematic approach is indicated. This report presents results of a systematic evaluation of evidence dealing with the effects of regular physical activity on several health and behavioral outcomes in US school-age youth, with the goal of developing a recommendation for the amount of physical activity deemed appropriate to yield beneficial health and behavioral outcomes.

METHOD

Under a contract with the Divisions of Nutrition and Physical Activity and Adolescent and School Health of the Centers for Disease Control and Prevention and the Constella Group, an expert panel was convened to review and evaluate available evidence on the influence of physical activity on several health and behavioral outcomes in youth aged 6 to 18 years. The co-chairs of the panel selected panelists on the basis of expertise in specific areas: adiposity, cardiovascular health (lipids and lipoproteins, blood pressure, the metabolic syndrome, type 2 diabetes mellitus, cardiovascular reactivity, heart rate variability, inflammation, and cardiovascular fitness), asthma, several domains of mental health (self-concept, anxiety, depression), academic achievement, injury associated with physical activity, and musculoskeletal health (bone mineral, muscular strength, and endurance). The epidemiology and tracking of physical activity and overweight in youth

See editorial, p 719.
were also reviewed because of their public health implications, but are not included in this report.

Literature Search

Databases (PubMed, ERIC, PsycINFO, 1980 to the present) were searched for publications in English that were related to physical activity and specific outcomes in youth. Approximately 1220 abstracts were reviewed, and >850 articles were provided to the respective panelists. Articles not identified in the bibliographic searches were added by several panelists.

Evaluation of Articles

The panelists systematically evaluated and abstracted relevant articles for each outcome. This information was abstracted for each report: complete citation, study design, characteristics of the study population, measure of physical activity, statistical analyses, outcome measures, main findings, and evidence for dose–response effects. The co-chairs and panelists developed conceptual definitions and inclusion and exclusion criteria for each of the outcomes. On the basis of the review of reports, each expert provided a summary of the evidence for strength (strong [>60% of studies reviewed], moderate [30%-59% of studies], weak [<30% of studies]) and direction (positive, null, negative) of physical activity effects on each health and behavioral outcome.

Meeting Format

A meeting of the panel and representatives of major organizations and agencies with interests in physical activity and health of youth was convened in January 2004. The 2-day meeting was designed and convened for maximum input from the expert panelists and individuals representing the invited organizations and agencies (Appendix). Panel members gave presentations summarizing the evidence for an assigned outcome; each presentation was followed by an open discussion. The process of developing physical activity recommendations was then discussed among all participants. Subsequently, the co-chairs and panelists met to develop a recommendation for physical activity for school-age youth in the context of the strength of evidence available for each health and behavioral outcome.

RESULTS

Evidence pertaining to the influence of physical activity on each health and behavior outcome in youth is summarized in Table I; available online at http://www.us.elsevierhealth.com/jpeds.

Normal Weight, Overweight, and Obesity

Much of the evidence dealing with adiposity and cardiovascular outcomes is based on subjects classified as overweight or obese. Current criteria are based on age- and sex-specific cut-points of the body mass index (BMI, kg/m²). In the context of national US surveys, a BMI >85th and <95th percentile is defined as “risk of overweight,” and a BMI ≥95th percentile is defined as overweight. The labels “overweight” and “obesity,” respectively, are often used in the literature. A BMI >5th and ≤85th percentile is considered normal weight.

Criteria for overweight and obesity, however, varied among studies considered (eg, weight >20% of that expected for height [relative weight], estimated percent fat >25% in boys and >30% in girls, triceps skinfold >85th age- and sex-specific percentiles, and BMI >85th, >90th, or >95th age- and sex-specific percentiles). Subjects who were normal weight had weight, percent fat, skinfold thickness, or BMI below the cut-points. Designation of subjects as overweight/obese or normal weight was accepted as described in the respective reports.

Adiposity

Cross-sectional and longitudinal observational studies suggest that youth of both sexes who participate in relatively high levels of physical activity have less adiposity than less active youth.6-17 Experimental studies of overweight boys and girls involved in systematic physical activity interventions provide more specific information about the influence of physical activity on adiposity. Programs of moderately intense exercise 30 to 60 minutes in duration, 3 to 7 days per week lead to a reduction in total body and visceral adiposity in overweight children and adolescents.18-20 However, such programs do not influence the percentage of body fat in normal weight children and adolescents.20-24 Limited evidence indicates that more intensive and longer sessions (>80 minutes/day) are more successful in reducing percentage fatness in normal weight boys and girls.25 The results suggest that relatively greater amounts of vigorous physical activity may be needed to have a beneficial effect on adiposity in normal weight youth.

Cardiovascular Health

Many indicators of cardiovascular health cluster with overweight and adiposity, and this should be noted in evaluating potential effects of physical activity.

Metabolic syndrome. Many studies view the metabolic syndrome (MS) as a clustering of risk factors. A proposed definition of the MS for adolescents is based on abdominal obesity (waist circumference >90th percentile), triglycerides (≥110 mg/dL), blood pressure (>90th percentiles for age, sex, height), fasting glucose (≥110 mg/dL), and reduced high-density lipoprotein cholesterol level (HDL-C; ≤40 mg/dL).26 Few studies have evaluated the impact of physical activity on the MS in youth.

Obese adolescent boys with the MS have lower exercise performance (exercise duration with a multistage treadmill protocol) than obese boys without the MS.27 Adolescents with type 2 diabetes mellitus, in addition to being obese, report no or very little habitual physical activity.28 In overweight children, exercise successfully reduced triglyceride and insulin levels in a randomized trial,29 whereas a 40-minute program of
Lipids and Lipoproteins. Relationships between physical activity and total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels are generally weak in observational studies. The results suggest a beneficial effect of physical activity on HDL-C and triglyceride levels, but no consistent effect on total cholesterol or LDL-C levels. Studies, however, indicate a null effect of physical activity on lipid and lipoprotein levels.

The latter more likely applies to youth who entered a study with relatively normal values. Results of studies relating lipid and lipoprotein levels to cardiovascular (aerobic) fitness are inconsistent and do not indicate a significant association.

Intervention studies, including clinical or school-based trials (randomized and non-randomized), show a weak beneficial effect on HDL-C and triglyceride levels, but not on total cholesterol or LDL-C levels. School-based interventions have not been effective in improving lipid and lipoprotein levels.

Allowing for variation in the available data, it appears that a minimum of 40 minutes of activity per day, 5 days per week for 4 months is required to achieve improvement in lipid and lipoprotein levels, primarily increased HDL-C and decreased triglyceride levels. This implies the need for a sustained amount of moderate to vigorous physical activity on a regular basis to induce and maintain the beneficial effect. The role of weight loss in mediating the effect of activity on lipid and lipoprotein levels has not been studied in youth.

Blood Pressure. Little evidence supports the efficacy of or need for exercise training to reduce blood pressure in normotensive youth. A meta-analysis and comprehensive review indicate no clear association between physical activity and reduction of blood pressure in normotensive youth. Limited studies of youth with systolic hypertension show a beneficial effect of aerobic activity programs of 12 to 32 weeks duration on blood pressure. Strength training after an aerobic intervention prevents the return of blood pressure to pre-intervention levels in hypertensive adolescents.

However, an 8-week strength training program by itself has no influence on blood pressure in hypertensive youth. Overall, data suggest that a physical activity intervention with a duration (at least 30 minutes), frequency (3 times/week), and intensity sufficient to improve aerobic fitness (approximately 80% of maximal heart rate) can be in reducing blood pressure in youth with mild essential hypertension. Continued physical activity is necessary to maintain the beneficial effect.

Other Cardiovascular Variables. Studies of physical activity in relation to hemostasis (fibrinogen), inflammation (high sensitivity C-reactive protein), and endothelial function are inconclusive, but experimental studies indicate a beneficial effect of activity on cardiovascular autonomic tone.

Cardiovascular Fitness (Aerobic Fitness). Correlational studies indicate low-to-moderate positive relationships between physical activity and maximal and submaximal indicators of aerobic fitness. Comparisons of habitually active and less-active children and adolescents show better levels of aerobic fitness in the former. Successful programs ordinarily involve continuous vigorous activity (eg, 80% of maximal heart rate) for >30 minutes at least 3 days per week. Change with systematic training averages approximately 10% (3-4 mL/kg/min).

Asthma

Comparisons of population-based and convenience samples of youth with asthma give inconsistent results. Physical activity levels are higher, lower, or not different in asthmatic compared with non-asthmatic youth. However, higher levels of activity are associated with greater reporting of asthma or related symptoms (eg, whistling, wheezing) in asthmatic youth. Some, but not all, studies indicate lower levels of aerobic and anaerobic fitness in youth with asthma. Risk of developing asthma may be associated with overweight in boys and girls. Controlled aerobic programs (2-3 sessions/week for at least 6 weeks) result in improved aerobic and anaerobic fitness in youth with asthma, but are not associated with systematic improvements in pulmonary function or exercise-induced bronchoconstriction.

Mental Health

Indicators of mental health in youth were delimited to anxiety, depression, and self-concept. There are too few studies of physical activity and other important aspects of mental health, such as perceived stress, emotional distress, and perceived vigor or exhaustion. Moreover, the dearth of prospective population cohort studies and randomized controlled trials limits conclusions about causality in results that are derived mainly from cross-sectional and quasi-experimental studies.

Anxiety and Depression. Cross-sectional studies suggest weak positive associations between physical activity and lower scores on scales of anxiety and depression symptoms, whereas quasi-experimental studies show strong positive influences of physical activity and improvement on measures of anxiety and depression symptoms. The influence of physical activity on anxiety and depression symptoms varies with mode of activity.

Self-concept. Self-concept refers to the perception of self, whereas self-esteem refers to the value placed on one’s
self-concept. Self-concept comprises several domains—academic and non-academic, social and emotional, and physical (sport competence, strength or endurance, appearance). The structure of self-concept changes with age and becomes more clearly differentiated in the transition into puberty and during adolescence. Cross-sectional studies suggest a moderately positive association between physical activity and physical self-concept, but weak positive associations between physical activity and global, social, and academic self-concept.133,139,140,145,145,151-162 Quasi-experimental studies135,149,150,163-188 indicate strong positive effects of physical activity on physical (sport competence) and global self-concept and weaker positive effects on social and academic self-concept. The influence of physical activity on self-concept may be mediated by mode of activity, with beneficial effects associated with aerobicics, aerobics combined with strength/flexibility activities, dance, perceptual-motor, and cognitive behavioral modifications to augment physical activity. Although sport activities are positively associated with global self-concept, they have the potential for negative influence. Coaching and teaching styles are particularly relevant to the self-concept in organized sport189 and physical education.190

Academic Performance

Indicators of academic performance include grade point average, scores on standardized tests, and grades in specific courses; measures of concentration, memory, and classroom behaviors are indirect estimates. The addition of physical education to the curriculum results in small positive gains in academic performance.191-193 The quasi-experimental data also suggest that allocating more curricular time to programs of physical activity does not negatively affect academic achievement, even when time allocated to other subjects is reduced.194 Some results also support a relative increase in academic performance per unit of time.194,195 Cross-sectional observations show a positive association between academic performance and physical activity142,196-199 and physical fitness.200 Physical activity has a positive influence on concentration and memory201-209 and on classroom behavior.194 Mechanistic studies of cognitive function also suggest a positive effect of physical activity on intellectual performance.210

Injuries

Children and adolescents incur injury in physical activities associated with recreation, free play, organized and unorganized sport, and physical education. Most data are case series based on convenience samples from emergency departments or sports medicine clinics. Other data are from accident reports, insurance records, interviews, and retrospective questionnaires. Variation in definition of injury, inadequate exposure data, and lack of description of the population at risk limits the value of much of the published research in drawing valid conclusions about the risks of injury to children and adolescents associated with a given physical activity.211 Descriptive longitudinal studies of injury in several high school sports are an exception.212,213 These studies have a known denominator, relatively accurate exposure data, immediate access to treatment by an athletic trainer, and a well-designed data collection system.

Although limited, information on injuries related to physical education classes suggests that the injury rate is nearly 0 during 20-minute sessions held 3 times/week,214-217 whereas the prevalence of injury in a supervised after school program is low, 0.0016 per student hour.218

Musculoskeletal Health and Fitness

MUSCULAR STRENGTH AND ENDURANCE. Although muscular strength and endurance were not among the primary health outcomes initially examined, panel members recommended inclusion because they are important components of physical fitness. Correlational studies and cross-sectional comparisons give equivocal results relating physical activity to indicators of muscular strength and endurance.210,246-249 but longitudinal studies of adolescents indicate a positive influence of habitual physical activity on upper body muscular endurance.81,220,223 Experimental studies of resistance training 2 or 3 times per week (with a day of rest between training sessions) show improvements in muscular strength and endurance during childhood and adolescence.226-241 Most studies focus on pre-adolescent children, and strength gains are not associated with muscular hypertrophy.230,232,237,241 Muscular hypertrophy in association with gains in strength with resistance training occurs in adolescent boys,242 but data for adolescents of both sexes are limited.

BONE MINERAL. The tensile and compressive forces associated with muscular contractions during weight-bearing activities and specialized exercises such as strength/resistance training have a favorable influence on skeletal tissue. Case studies,243,244 correlational studies,245-252 retrospective studies of activity in childhood in relation to bone mass in adulthood,253-259 comparisons of habitually active and inactive children and adolescents,260-266 and comparisons of elite young athletes with less active youth267-281 indicate a beneficial effect of physical activity on skeletal health. The osteogenic influence of physical activity is generally site-specific and related to local mechanical strains. The benefits are reflected in bone mineral content, bone mineral density, and bone mineral apparent density. Prospective studies of children with varying levels of current or past physical activity,282-287 and experimental studies give similar results in pre-pubertal boys and in girls who were either prepubertal157,277,288-290 or in the early stages of puberty216,235-295. The experimental studies generally involve programs of 10 to 60 minutes duration of moderate to high-strain activity (impact, weight bearing) for 2 to 3 or more days per week. The benefits are not as clearly established for adolescents214,295,296 in later stages of puberty (primarily girls).
Recommendations

School-age youth should participate every day in 60 minutes or more of moderate to vigorous physical activity that is enjoyable and developmentally appropriate. Interventional studies indicate specific amounts of physical activity necessary for beneficial changes in the skeletal health, aerobic fitness, and muscular strength and endurance of youth, and in adiposity in youth who are overweight (Table). Activity protocols varied somewhat among studies, but most used programs of continuous moderate to vigorous activities for 30 to 45 minutes duration for 3 to 5 days per week. It is reasonable, however, to expect that the amount of physical activity necessary to achieve similar or greater beneficial effects in the context of ordinary daily activities, which are typically intermittent, would be substantially more than indicated in controlled experimental conditions. This is generally consistent with rationale for prior recommendations. Moreover, allowing for inter- and intra-individual differences in physical activity and in response to physical activity among free-living children and adolescents, 60 minutes or more of moderate to vigorous physical activity on a daily basis is consistent with desired health and behavioral outcomes.

Physical activities of children and adolescents vary with age, type of exercise, and setting. Physical activity begins in infancy with pushing up, turning, crawling, and eventually walking, and it progresses to more complex activities as neuromuscular control develops. Basic movement patterns develop during preschool ages and are the foundation for a wide range of physical activities at later ages. With growth, maturation, and experience, basic movements are integrated and coordinated into more specialized and complex movement skills that characterize the free play, games, sports, and other activities of school-age youth. Guided instruction and supervised practice, specifically by qualified teachers, coaches, and others who work with children, are important in learning movement skills. Types and contexts of activities are variable and change with age during childhood and adolescence. Activities of children aged 6 to 9 years are largely anaerobic (as in non-sustained activities or games such as “tag”), and they help the child learn basic and more specialized motor skills. As youth move into the pubertal transition (about age 10-14 years, earlier in girls than in boys), these skills are incorporated into a variety of individual and group activities and many organized sports. Mature structure and function are approached or attained in late adolescence (age 15-18 years), so that physical activity programs can be more structured.

Recommended priorities for physical activities during childhood and adolescence relative to the development of skills and to behavioral, health, and fitness benefits are schematically illustrated in the Figure. During the preschool and early school ages, general movement activities develop movement patterns and skills (dashed line in Figure). As these basic movements become established and skills improve, health, fitness, and behavioral components of physical activities increase in importance (solid line in Figure). Health-related activities include those that emphasize cardiovascular and muscular endurance and muscular strength and those that involve weight bearing. The setting of physical activity is especially important in achieving positive behavioral outcomes. Although there is less emphasis on the development of motor skills during adolescence, refinement of those skills is important and new movement skills can be learned and can contribute to a physically active lifestyle.

Activities are generally classified as low, moderate, and vigorous intensity on the basis of METs (metabolic activities of children and adolescents vary with age, type of exercise, and setting. Physical activity begins in infancy with pushing up, turning, crawling, and eventually walking, and it progresses to more complex activities as neuromuscular control develops. Basic movement patterns develop during preschool ages and are the foundation for a wide range of physical activities at later ages. With growth, maturation, and experience, basic movements are integrated and coordinated into more specialized and complex movement skills that characterize the free play, games, sports, and other activities of school-age youth. Guided instruction and supervised practice, specifically by qualified teachers, coaches, and others who work with children, are important in learning movement skills. Types and contexts of activities are variable and change with age during childhood and adolescence. Activities of children aged 6 to 9 years are largely anaerobic (as in non-sustained activities or games such as “tag”), and they help the child learn basic and more specialized motor skills. As youth move into the pubertal transition (about age 10-14 years, earlier in girls than in boys), these skills are incorporated into a variety of individual and group activities and many organized sports. Mature structure and function are approached or attained in late adolescence (age 15-18 years), so that physical activity programs can be more structured.

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Activities are generally classified as low, moderate, and vigorous intensity on the basis of METs (metabolic
equivalents for specific activities on the basis of the ratio of activity to resting energy expenditure). Tables of MET values for a variety of activities based largely on measurements in adults are available. Because exercise energy expenditure per unit of body mass is higher in children and adolescents than in adults, these MET values have limitations. Nevertheless, moderate-to-vigorous activities require about 5 to 8 METs, and such intensity is needed to derive most health benefits. Brisk walking, bicycling, and active outdoor playing ordinarily reach this criterion.

The recommended 60 minutes or more of physical activity can be achieved in a cumulative manner in school during physical education, recess, intramural sports, and before and after school programs. In this regard, the Centers for Disease Control recommends daily quality physical education from kindergarten through grade 12. Both physical education and recess afford opportunities to achieve the daily physical activity goal without any evidence of compromising academic performance. Opportunities to influence youth participation in physical activities are readily available at home and school, as well as in community and health care settings.

Physical inactivity is a strong contributor to overweight. Sedentary activities such as excessive television viewing, computer use, video games, and telephone conversations should be discouraged. Reducing sedentary behaviors to <2 hours per day is important to increasing physical activity and to health.

The decline in physical activity during adolescence is of special concern. Data from several European countries highlight the importance of involvement in community-based sport clubs during adolescence as an important predictor of physical activity in adolescence. Restoration of intramural sport programs and expansion of the school day for such programs in middle and high schools may provide opportunities for all students to be physically active.

For youth who have been physically inactive, an incremental approach to the 60-minute goal is recommended. Increasing activity by 10% per week, an approach used in athletic training, appears to be acceptable and achievable. Attempting to achieve too much too rapidly is often counterproductive and may lead to injury.

Risk of overweight and sedentary behavior are increasingly evident in children aged 2 to 5 years, which has implications for subsequent ages. It is important to promote physical activity and limit the amount of physical inactivity beginning with the preschool child. The family unit, the pediatric community, day care centers, and preschools are important contributors to encouraging healthy behaviors. Children live at home and receive their health care in a variety of settings, including a pediatrician or family practitioner’s office, clinics, and public health facilities. The child’s health care providers should routinely screen for overweight and inactivity and counsel parents and other caregivers about the health risks of overweight and the health benefits of physical activity, not only for the child, but also for the parents. At home, in day care, and in preschool, children should be regularly encouraged to be active and to explore. The amount of time that they are restrained from being active should be minimized. Two recent sets of guidelines for the promotion of physical activity among youth are excellent sources of information on this topic. Physicians are important in this process and should be strong advocates of a physically active lifestyle for youth at home and in schools and communities.

**CONCLUSIONS**

Increasing the level of habitual moderate- to vigorous-intensity physical activity in youth is a health promotion and a disease-prevention strategy. Sedentary youngsters should progress toward the recommended level of physical activity gradually. The recommendations are consistent with presently available scientific evidence and are also in general accord with recommendations promoted by governmental agencies and professional organizations.

**APPENDIX**

American Cancer Society; American Academy of Kinesiology and Physical Education; American Diabetes Association; American Heart Association; American College of Sports Medicine; American Academy of Pediatrics; Centers for Disease Control and Prevention, National Association for Sport and Physical Education; National Cancer Institute; National Heart, Lung and Blood Institute; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Institute of Child Health and Human Development; National Institute of Diabetes and Digestive and Kidney Diseases; National Center for Health Statistics; Robert Wood Johnson Foundation; US Department of Agriculture; US Department of Health and Human Services, Office of Public Health Science; and the US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, President’s Council on Physical Fitness and Sports.

References available online at [http://www.us.elsevierhealth.com/jpeds](http://www.us.elsevierhealth.com/jpeds).
PREVALENCE OF OVERWEIGHT IN CHILDREN WITH DEVELOPMENTAL DISORDERS IN THE CONTINUOUS NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 1999-2002

LINDA G. BANDINI, PhD, RD, CAROL CURTIN, MSW, CHARLES HAMAD, PhD, DAVID J. TYSOR, MS, MPH, AND AVIVA MUST, PhD

Objective To estimate the prevalence of overweight in children identified with developmental disorders on the basis of nationally representative survey data.

Study design We estimated the prevalence of overweight in children with developmental disorders on the basis of a recent large nationally representative survey. The continuous National Health and Nutrition Examination Survey (NHANES) 1999-2002 included 4 questions to identify children with developmental disorders. Height and weight were used to calculate body mass index (BMI). BMI percentiles were estimated relative to the age- and sex-specific Centers for Disease Control and Prevention growth reference. The 85th percentile BMI defined at-risk-for-overweight and the 95th percentile BMI defined overweight.

Results We found a higher prevalence of at-risk-for overweight and overweight among children with limitations in physical activity and a higher prevalence of overweight in girls with learning disabilities, compared with children without these conditions, after adjustment for age and race-ethnicity.

Conclusion To the extent that children with developmental disorders are included in large representative surveys, the data suggest that children with developmental disorders have a risk for overweight that is at least as great as that of typically developing children. (J Pediatr 2005;146:738-43)

The prevalence of overweight among US children has been escalating.1 Little has been done to determine the prevalence of and risk factors for obesity in children with developmental disorders, in this case, children who have physical limitations, learning disabilities, attention disorders, and those who receive special education services. The importance of this inquiry was underscored by a conference convened in 2001 by the Surgeon General that addressed the health needs of individuals with mental retardation (MR) and developmental disabilities.2 The conference report called for research and clinical intervention to address the specific health needs of persons with MR and to develop health promotion programs that seek to improve their overall health and wellness.

In this study, we used data derived from a recent nationally representative survey, the National Health and Nutrition Examination Survey (NHANES) 1999-2002, to estimate the prevalence of overweight in children with developmental disorders. Measured heights and weights from the NHANES 1999-2002 survey3 were used to estimate the prevalence of at-risk for overweight or overweight in children with developmental disorders. We hypothesized that children with developmental disorders would be at higher risk for overweight than their typically developing peers. The complex medical, physical, and psychosocial difficulties that these children encounter may put them at higher risk for obesity. For example, dietary factors such as the use of food as a behavioral reinforcer or mealtime behaviors that influence food choices or parental meal preparation may lead to an energy imbalance. Lack of participation in physical activity opportunities because of a lack of inclusion in team sports, poor coordination, and/or social isolation may contribute to positive energy balance and, in time, to increased weight gain. Furthermore, because of the numerous physiological, social, and educational demands and stresses associated with raising a child with a developmental disorder, weight control may not be a priority for the

BMI Body mass index
CDC Centers for Disease Control and Prevention
LD Learning disability
MR Mental retardation
NHANES National Health and Nutrition Examination Survey

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families of these children. In this report, we estimated the prevalence of overweight in children with physical limitations, children receiving special education or early intervention services, and children with attention deficit disorder or learning disabilities. We also explored whether the prevalence of overweight varied by age and sex.

METHODS

NHANES is a series of national examination studies conducted in the United States since 1970. After the NHANES III 1988-1994 survey, the periodic examination surveys became a “continuous” survey. Since 1999, data have been collected every 2 years from a representative sample of the US population; approximately 7000 subjects from different locations are sampled. In the basic protocol for all these surveys, randomly selected subjects are first interviewed in their homes, and information on demographics, socioeconomic status, diet, and health-related questions are obtained. In a mobile examination center, body weight and height are measured with a standard protocol. Weight is measured to 2 decimal places with an electronic-load cell scale in kilograms; height is measured with a fixed stadiometer. Children who are unable to stand are not weighed and therefore are not included in this analysis. Unfortunately, the number of children not weighed for this reason is not available from the public use dataset.

Survey items from the 1999–2002 NHANES identified children with developmental disorders. Because of the dearth of this information in comprehensive nationally representative surveys, we selected questions that would suggest that the child had a developmental disorder. We limited our analyses to children aged 6.0 to 17.9 years to reflect the school-age years. Although many children who receive special education services remain in high school until the age of 22 years, they were not included in our analysis because the data on reference children would not be comparable.

The NHANES 1999–2002 combined survey has an examination sample size of 19,759. Details of the sampling design and survey elements are available. In the continuing survey, we selected 4 questions that identified children with developmental disorders as follows: (1) children with physical limitations; (2) children receiving special education or early intervention services; (3) children with attention deficit disorder; and (4) children with learning disabilities. (Appendix; available online at http://www.us.elsevierhealth.com/jpeds). Items that identified children receiving special education services and children with a learning disability were asked only of children aged 6 to 14.9 years.

Criteria for Overweight

Body mass index (BMI) was calculated from measures of height and weight (kg/m²) and used to identify overweight. To provide a measure of relative weight, a BMI z-score was calculated for each BMI measure, with the reference to age- and sex-specific parameters provided by the Centers for Disease Control and Prevention (CDC) growth reference standards. We adopted CDC terminology to define at-risk-for-overweight and overweight. At-risk-for-overweight is defined as a BMI >85th percentile and overweight is defined as a BMI >95th percentile.

Statistical Analyses

For each survey, the analytic dataset consisted of all children with a measured height and weight whose parents responded to the identified survey items. Prevalence of at-risk-for-overweight and overweight were estimated for the entire population and for individuals with a positive response to the questions about developmental disorders. We tested the statistical significance of the differences in prevalence by group using chi-square tests.

Multivariate logistic regression analysis was undertaken to estimate the relative risk of at-risk-for overweight and overweight (and their 95% confidence limits) for children with developmental disorders compared to children not identified as having developmental disorders, after controlling for age, sex, and race-ethnicity. Racial-ethnic categories were constructed for non-Hispanic white, non-Hispanic black, Hispanic, and other. Interactions were tested between each condition and sex; when the interaction term was statistically significant, results were stratified by sex.

Data were analyzed using SAS software (version 8.02; SAS Institute, Cary, NC) and SUDAAN software (version 8.0, Research Triangle Institute, Cary, NC). We included 4-year sample weights to adjust for unequal selection probabilities and over-sampling in the complex samples. In the combined NHANES 1999-2002, masked variance units as pseudo-primary sampling units were used, as recommended. When the P value was <.05, results were deemed to be statistically significant.

RESULTS

In the NHANES 1999–2002 dataset, 4 questions identified 1128 children with developmental disorders. Specifically, items identified children with physical limitations, attention deficit disorder, learning disability, and those receiving special education or early intervention services. Of the 1128 children, 654 (57.9%) had 1 of these conditions, 327 (28.9%) had 2 of these conditions, 133 (11.8%) had 3 of these conditions, and 14 (1.2%) had all 4 of these conditions. The most frequent coexisting diagnoses were that 40.4% and 31.8% of children with learning disabilities and attention deficit disorder, respectively, also received special education services.

The percentage of children aged 6 to 17 years with health problems that limit their ability to walk play or run was 4.1% (SE, 0.38). Children with these physical activity limitations were significantly more likely to be at-risk-for-overweight than those without physical activity limitations (50.9% versus 30.6%, P < .001, Table I). These children were also more likely to be overweight (29.7% versus 15.7%, P < .01). In sex-specific analyses, girls with physical limitations had a significantly higher prevalence of at-risk-for-overweight...
(49.2% versus 29.5%, \( P < .01 \)) and overweight (28.1% versus 14.5%, \( P < .01 \)) than girls without physical limitations. Boys who had physical limitations also had higher prevalence of at-risk-for-overweight (52.5% versus 31.7%, \( P < .01 \)) and were also more likely to be overweight, but the difference was of borderline significance (31.3% versus 16.9%, \( P = .09 \)).

Approximately 11% of children (10.7%; SE, 0.62) aged 6 to 15 years were receiving special education or early intervention services. The prevalence of at-risk-for-overweight was not significantly higher in children receiving special education services than children who did not receive special services (33.4% versus 31.4%, Table II). There was also no significant difference in the prevalence of overweight between children receiving and not receiving services (17.4% versus 16.3%).

About 10% of respondents (9.6%; SE, 0.55) reported that a doctor or health professional had told them at some point that their child had attention deficit disorder. The prevalence of at-risk-for-overweight was not significantly higher in children with attention deficit disorder compared with children without attention deficit disorder (29.5% versus 31.6%, \( P = .58 \)). Also, the prevalence of overweight among children with attention deficit disorder was similar to that of children without attention deficit disorder (14.5% versus 15.7%).

### Table I. Prevalence of at-risk-for-overweight (85th percentile) and overweight (95th percentile) by sex, age and condition (%): NHANES 1999-2002

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (y)</th>
<th>With limitations</th>
<th>No limitations</th>
<th>With limitations</th>
<th>No limitations</th>
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<tbody>
<tr>
<td>Both</td>
<td>All</td>
<td>50.9</td>
<td>30.6*</td>
<td>29.7</td>
<td>15.7*</td>
</tr>
<tr>
<td>Male</td>
<td>All</td>
<td>52.5</td>
<td>31.7*</td>
<td>31.3</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>6-8</td>
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<td>31.7</td>
<td>56.3</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>9-11</td>
<td>52.7</td>
<td>31.7</td>
<td>24.0</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>12-14</td>
<td>50.3</td>
<td>30.6</td>
<td>27.3</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>32.2</td>
<td>32.9</td>
<td>24.7</td>
<td>18.9</td>
</tr>
<tr>
<td>Female</td>
<td>All</td>
<td>49.2</td>
<td>29.5*</td>
<td>28.1</td>
<td>14.5*</td>
</tr>
<tr>
<td></td>
<td>6-8</td>
<td>44.9</td>
<td>26.9</td>
<td>38.2</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>9-11</td>
<td>63.8</td>
<td>32.3*</td>
<td>38.8</td>
<td>16.0*</td>
</tr>
<tr>
<td></td>
<td>12-14</td>
<td>62.8</td>
<td>32.1*</td>
<td>24.5</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>24.7</td>
<td>26.8</td>
<td>22.0</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Significantly different prevalence of at-risk for overweight or overweight between children with and without the condition, by chi-square, \( p < 0.05 \).
However, the prevalence of overweight was lower in boys with attention deficit disorder (12.7% versus 18.2%, \( P < .03 \)). When stratified by sex and age group, a significantly lower prevalence of overweight was seen in boys aged 9 to 11 years (6.7% versus 18.6%, \( P < .02 \)) and boys aged 12 to 14 years (7.6% versus 18.3%, \( P < .01 \)). Also, in boys aged 12 to 14 years, there was a significantly lower prevalence of at-risk-for-overweight in boys with attention deficit disorder, compared with their peers (19.8% versus 33.9%, \( P < .04 \)).

There were no statistically significant differences in the prevalence of at-risk-for-overweight and overweight in girls with attention deficit/hyperactivity disorder compared with girls without the disorder.

Multivariate logistic regression analyses were undertaken to further characterize the observed relations (Table IV). In separate models, after adjustment for age, sex, and race-ethnicity, receiving special education or early intervention services did not elevate the risk of at-risk-for-overweight or overweight. In contrast, children with limitations in physical activity were more than twice as likely to be at-risk-for-overweight and overweight when compared to peers without limitations. Also, girls with a LD were more likely to be overweight compared with their peers without a LD. Boys with attention deficit disorder were less likely to be overweight than boys without attention deficit disorder, but these results were not significant (\( P < .11 \)).

**DISCUSSION**

The limited available literature on the prevalence of overweight in children with developmental disorders has been based on clinical observations and studies with small sample sizes. Although the high prevalence of overweight among children with genetically-related disabilities such as Prader-Willi syndrome,7 Down Syndrome,8,9 congenital disabilities such as spina bifida,10-12 and some types of cerebral palsy10 is well documented, there is a need for representative data for children with other types of developmental disorders. We found that the prevalence of at-risk-for-overweight or overweight in children with certain developmental disorders was as high or higher than in children without developmental disorders.

One of the difficulties in assessing the prevalence of overweight in children with developmental disorders is in the identification of these children, because of the broad variability in physical, developmental, and cognitive skills that characterize this population. In a previous analysis of the NHANES III survey, we restricted our analyses to 1 question, “Does your child have mental retardation?” We found that the prevalence of MR on the basis of this question was 0.38%,13 far less than estimates derived from other sources.14 Although we found no significant differences in the prevalence of overweight among children with and without MR, these findings were limited by the low prevalence of MR reported.13

In the NHANES 1999-2002 survey, 4% of children had physical limitations, 11% received special education or early

**Table III.** Prevalence of at-risk-for-overweight (85th percentile) and overweight (95th percentile) by sex, age and condition (%): NHANES 1999-2002

<table>
<thead>
<tr>
<th>Learning Disability</th>
<th>At-Risk-For- Overweight (%)</th>
<th>Overweight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Learning Disability</td>
<td>No Learning Disability</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35.4</td>
<td>31.1</td>
</tr>
<tr>
<td>6-8</td>
<td>31.1</td>
<td>32.2</td>
</tr>
<tr>
<td>9-11</td>
<td>39.2</td>
<td>32.9</td>
</tr>
<tr>
<td>12-14</td>
<td>32.4</td>
<td>32.5</td>
</tr>
<tr>
<td>15-17</td>
<td>27.9</td>
<td>32.4</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>42.7</td>
<td>30.1*</td>
</tr>
<tr>
<td>6-8</td>
<td>39.3</td>
<td>26.6</td>
</tr>
<tr>
<td>9-11</td>
<td>40.1</td>
<td>32.3</td>
</tr>
<tr>
<td>12-14</td>
<td>47.0</td>
<td>32.3</td>
</tr>
<tr>
<td>15-17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*significantly different prevalence of at-risk for overweight or overweight between children with and without the condition, by chi-square, \( p < 0.05 \).
intervention services, 10% had an attention deficit disorder, and 12% had a LD. Of interest is our observation that boys with attention deficit disorder have a lower prevalence of overweight and at-risk-for-overweight in comparison with boys without attention deficit disorder, especially before the age of 15 years. In contrast, the prevalence of at-risk-for-overweight and overweight for girls with attention deficit/hyperactivity disorder does not differ from girls without attention deficit/hyperactivity disorder. The difference in prevalence by sex among children with attention deficit/hyperactivity disorder may reflect the differences in medication usage or tendency of girls with the disorder to have the inattentive type of the disorder, whereas boys are more likely to have the hyperactive/impulsive or combined types. Girls identified with attention deficit disorder may be more sedentary than their more physically active male counterparts, an observation worthy of future focused research.

There are no earlier studies that have identified children with a LD as having a higher prevalence of overweight than typically developing children. In this study, we found a higher prevalence of both at-risk-for-overweight and overweight in girls with a LD. An explanation for why girls with a LD are at an increased risk for overweight is unclear. Learning disabilities represent a heterogeneous group of disorders, and within this sample there is no additional information with which these girls can be characterized. The finding that girls with a LD are more likely to be at risk for overweight than typically developing peers and that girls with attention deficit/hyperactivity disorder are at higher risk for overweight than their male counterparts may suggest that being overweight in girls may be related to decreased physical activity levels. This warrants further investigation.

Although a particular strength of the data summarized in this report derives from the representative nature of the source surveys, there are several limitations of our analyses that may undermine the validity of the prevalence estimates. The results in response to the question of overweight prevalence in children with limited activity need to be interpreted cautiously. Children with limitations in physical activity may have an altered body composition. This phenomenon has been observed among children with cerebral palsy and spinal bifida. The criteria for overweight used in this report were based on BMI, in accordance with current recommendations. Studies have not been conducted to establish the validity of BMI as a means of identifying overweight in children with physical disabilities. In addition, children who could not stand were not weighed, and therefore they are not included in the analysis. Thus, this category only represents children who are ambulatory, but have limitations that may interfere with movement. Therefore, children with severe physical limitations would not have been included in this analysis. These children are often underweight because of oral motor problems that affect feeding. Furthermore, children who have limitations in physical activity may not have developmental disorders (eg, children with acute medical problems). Thus, the findings that children with physical limitations are more likely to be overweight must be interpreted cautiously, because the sample may be heterogeneous and will not include all children who have physical limitations. Nevertheless, the findings suggest that in children who have the ability to stand, limitations in physical activity increase their risk for being overweight.

The NHANES 1999-2002 dataset begins to attempt to differentiate among groups of children with developmental disorders by querying about the specific problems of attention deficit disorder, special education, and a LD. However, these categories remain very broad, and important differences among children with different developmental disorders cannot be determined. Moreover, the prevalence of certain disorders, such as attention deficit/hyperactivity disorder, are reported to be higher than that reported in the literature, which may be caused by a reliance on parent report, or the question of whether the child had received a definitive diagnosis of attention deficit/hyperactivity disorder, or both. In addition, the pattern of significant results varies with age and may represent a true underlying phenomenon or random variation. Finally, parents of children with these limitations may decline participation in voluntary surveys like NHANES. Although children with developmental disorders are included in the volunteer sample, it is not clear whether special efforts are made to encourage families of children with disabilities to participate.
Children with developmental disorders share the same risks for the sequelae of being overweight, such as type II diabetes mellitus, cardiovascular disease, orthopedic problems, and sleep apnea, as typically developing children. To reduce the likelihood of developing obesity-related secondary health conditions, educational and healthcare providers need to include this group of children in active health promotion efforts, including the provision of anticipatory guidance and specific counseling about the health risks of being overweight and obesity and the benefits of balanced nutrition and physical exercise. The finding of a high prevalence of overweight in children with developmental disorders emphasizes the importance of developing health promotion efforts for this population.

Considerable research in this area is warranted for several reasons: (1) to better establish the prevalence of overweight in this population; (2) to elucidate the specific challenges that children with various developmental disorders face in the health promotion arena; and (3) to devise appropriate intervention strategies that take their particular needs into account.

**REFERENCES**

A NOVEL APPROACH TO MANAGING VARIATION: OUTPATIENT THERAPEUTIC MONITORING OF CALCINEURIN INHIBITOR BLOOD LEVELS IN LIVER TRANSPLANT RECIPIENTS

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Objective To apply the principles of statistical process control (SPC) to manage calcineurin inhibitor (CNI) blood levels. We hypothesized that the use of SPC would increase the proportion of CNI blood levels in the target range.

Study design The study population consisted of 217 patients more than 3 months after liver transplantation. After demonstration of proof of concept using the rapid cycle improvement process, SPC was applied to the entire population. The change package included definition of target ranges for CNI, implementation of a web-based tool that displayed CNI blood levels on a control chart, and implementation of a protocol and a checklist for management of CNI blood levels. The principal outcome measure was the proportion of CNI blood levels in the target range.

Results In the pilot study, the proportion of CNI blood levels in the target range increased from 50% to 85%. When the protocol was spread to the entire population, the proportion of drug levels in the target range increased to 77% from 50% (P <.001), whereas the range of CNI levels decreased. The rate of allograft rejection did not change.

Conclusions Utilization of SPC increased the proportion of CNI blood levels in target range. These observations may be applicable to the care of other chronic healthcare problems. (J Pediatr 2005;146:744-50)

The calcineurin inhibitors (CNIs) cyclosporin and tacrolimus have revolutionized solid organ transplantation by decreasing acute allograft rejection and early graft loss, increasing patient and graft survival.1-3 The pharmacokinetics of the CNIs are complex.1-2,4-12 Unacceptable variation around target levels of CNIs increase the risk of allograft rejection, the frequency of rehospitalization, and the risk of renal insufficiency.7,13,14 Blood levels of CNIs are influenced by meals and changes in gastrointestinal motility, exposure to medications that cause variation in the function of cytochrome P450, isoenzyme CYP3A4, and polymorphisms for genes involved in absorption and metabolism of CNIs.15-20 Consequently, there is poor correlation between dose and drug levels for the population and significant intra-individual variation.

Therapeutic drug monitoring (TDM) first requires specification of target ranges. The second component of TDM is measurement and interpretation of the drug levels or the biological response. When faced with interpretation of a drug level, the healthcare provider determines whether the drug level is within specifications and makes a decision regarding modification of dose. In other words, the healthcare provider must determine if variance of the drug levels reflects “noise” or a “signal.” Failure to distinguish noise from signal may decrease the effectiveness of the medication, increase the risk to the patient, and decrease the efficiency of the process. Even though the correlation between trough blood levels and drug exposure is inconsistent, particularly for cyclosporine, TDM is standard at most transplant centers, and most transplant physicians use TDM to define CNI dosing regimens for individual patients.21-24 A defined process to regulate blood levels of CNIs is not only critical to maintain allograft function but will improve quality by promoting safety and increasing the efficiency and effectiveness of care.

Our goal was to identify and implement a process that would increase the proportion of CNI blood levels in the target range. To do so, we applied the principles of statistical
process control (SPC) developed by Walter Shewhart in the 1920s and first applied to the manufacturing industry, specifically, the quality of telephones at Bell Laboratories. In health care, SPC has been used in pilot studies to adjust anticoagulation of patients treated with warafin sodium (Coumadin) and to manage the use of the bronchodilators in patients with asthma.25-29 Our aim was to test the hypothesis that the application of SPC would increase the proportion of CNI blood levels in the target range.

METHODS

Study Population

The study population consisted of all patients (n = 217) 0.5 to 21 years of age who are cared for at Cincinnati Children's Hospital and are more than 3 months after liver transplantation. We chose 90 days as an entry time because mortality risk decreases after the perioperative phase of care and transplant recipients enter a period of stability both with respect to allograft function and pharmacodynamics of CNIs.5 30 Since 1996, we have used tacrolimus as our primary immunosuppressive medication. Before 1996, the primary immunosuppression medication used was cyclosporine. This improvement effort was approved by the Institutional Review Board at Cincinnati Children’s Hospital.

Strategy for Change

The strategy for change employed five steps:

1. We obtained consensus on target levels for CNIs as a function of time since transplantation.31-34 The process involved transplant surgeons, hepatologists, nurse coordinators, and pharmacists who make up the clinical arm of the interdisciplinary liver transplantation care team at Cincinnati Children’s Hospital. The target range for tacrolimus was 8 to 12 ng/mL during the period of 3 to 6 months after transplantation, 6 to 10 ng/mL 6 months to 12 months after transplantation, and 3 to 8 ng/mL >12 months after transplantation. The target range for cyclosporine was 100 to 150 ng/mL >12 months after transplantation. All patients taking cyclosporine were >12 months after transplantation.

   To demonstrate proof of concept, we used the rapid cycle improvement process to test the use of SPC to manage tacrolimus levels in a subgroup of the 15 patients >12 months after transplantation over a 2-month period and then spread the change to the entire population of liver transplant recipients at our center. The PDSA (Plan, Do, Study, Act) cycle is used for rapid cycle improvement. The intervention is planned (P), conducted (D), and then the effects are summarized. It is the purpose of the S phase to identify new knowledge and to use the knowledge gained for a new action (A), in this case spread of the SPC methodology.

2. Our second test of change was to develop a protocol to guide management of CNI levels by the individual teams, which comprised of a hepatologist and a liver transplant nurse coordinator.

3. Our third test of change was to give health care providers point of care access to CNI drug levels depicted as an SPC chart. A web-based application, which was password protected was developed so as to provide online access of the charts to families and their providers at Cincinnati Children’s Hospital. The average level and control limits were determined as part of an integrated function of the database.

4. The final component of our change package was implementation of a workflow sheet (Table I) that was aligned with the guideline and served as a data retrieval form.

Construction of Statistical Control Charts

We depicted the target range and most recent 20 blood levels for CNIs for each patient as a function of time on a process control chart. The mean ± 1 and 2 standard deviations were depicted. The most recent 20 CNI blood levels were used to determine the mean and control chart limits.

Process of Care

CNIs were managed according to Cincinnati Children’s Hospital Medical Center protocol for managing immunosuppression: at least every 2 weeks for patients <3 months, at least every month for those 3 to 12 months after transplantation, and every 1 to 3 months for those <1 year after transplantation. Each of the care teams comprised a hepatologist and a liver transplant nurse coordinator, who met at least 3 times each week to review control charts of CNI blood levels and manage immunosuppression. Trough blood levels of tacrolimus and cyclosporine were measured according to standard techniques. The steps for management of blood levels of CNIs by the care teams are outlined below:

1. Determine if the present blood level is in a range in which toxicity is likely. Although this is individualized and patients may tolerate different levels of immunosuppression, tacrolimus trough level that exceeded 15 ng/mL or a cyclosporin trough level that exceeded 300 ng/mL were defined as levels that required further assessment.

2. Confirm if the target range for the patient is based on the protocol or modified because of recurrent allograft rejection, renal insufficiency, post-transplant lymphoproliferative disease, or opportunistic infection.

3. Determine if there is excessive variation of blood levels of the immunosuppressive medication. Situations in which the probability of a random blood level was <5% were identified as those with excessive variation. The control chart was examined for evidence of variation based on parameters to identify excessive variation. These parameters included:
   a. Trough CNI blood levels that exceed 2 SD from the mean.
   b. Three consecutive CNI blood levels exceeding 1 SD from the mean.
c. Five consecutive CNI blood levels that are above or below the mean.
d. Five consecutive increasing or decreasing CNI blood levels.

If excessive variation was detected, then the nurse coordinator contacted the family and proceeded with a structured interview to determine the cause. During the interview, the coordinator assessed dose and formulation of drug, assessed timing of blood draw and medication administration, the presence of intercurrent illness, or the administration of new medications including anticonvulsants, antihypertensives, antibiotics, or herbals and asked if the patient was taking the medication as prescribed.

4. Determine if the blood level is in an acceptable range defined by target level for the patient.

To ensure patient safety while not excessively tampering with the CNI dosing regimen, a dose change was made if the mean for the CNI blood levels for the last four blood levels was outside the target range and there was no evidence of excessive variation. Following a dose change, blood level were measured once each week over a 4-week period, the first level being 60 hours after the dose change (5 half-lives) to define the impact of the change. As part of standard practice and to ensure safety, we measured serum glutamic oxaloacetate transaminase (AST), glutamic pyruvic transaminase (ALT), total and conjugated bilirubin, and gamma-glutamyltransferase (GGT) with each blood draw. If significant changes in the liver profile were detected, then it was left to the discretion of the care team to deviate from the protocol and make dose changes.

**Measure of Improvement**

The principal outcome measure was the proportion of CNI trough blood levels in the target range defined as the number of tacrolimus and cyclosporin blood levels in the target range divided by the total number of blood levels. The outcome measure was determined at baseline and then monthly. As secondary measures, we determined the proportion of CNI blood levels in the toxic range and the range of blood levels before and after the intervention. The frequency of measurement of CNI blood levels for individual patients
varied from weekly to monthly, so that in any given month, a person may have had more than one blood level included in the outcome measurement. Blood levels measured during hospitalization were not included in the analysis because patients took additional medications, drug formulations were different, and diet changed, all of which might increase variation. As a balancing measure, we used the rate of late allograft rejection before and after the intervention.

**Analyses**

We used descriptive statistics to describe the population and the outcome measures. The calculations were performed using the Statistical Analysis Systems software, version 8.2 (SAS Institute Inc., Cary, NC). Chi-squared test was used to compare the proportion of CNI blood levels in the target range for the entire patient population before and after the introduction of SPC.

### RESULTS

#### Characteristics of the Study Population (Table II)

The mean age at transplantation was 5.1 years, and the average time since transplantation was 7.6 years, ranging from 0.5 to 17 years. Children with biliary atresia accounted for 48% of the study population. Forty-two percent of the study population received technical variant grafts, and 61% received tacrolimus as their primary immunosuppressive medication. Eighty-two percent of patients were white, and 41% were Medicaid recipients.

#### Baseline Characteristics and Pilot Study

We conducted a pilot study of 15 children who were >3 months after liver transplantation to determine if the methods of SPC were applicable to TDM of CNIs, in this case, tacrolimus. At baseline, approximately 50% of the tacrolimus levels were outside the target range (Figure 1). The box represents the target range for trough tacrolimus blood levels. The bars depict the frequency of the measured trough tacrolimus blood level. The line showing the cumulative percentage of trough tacrolimus levels blood levels is depicted by the shaded diamonds.

![Figure 1](image1.png)

**Figure 1.** Distribution of trough tacrolimus levels at baseline for patients who were >12 months after liver transplantation (n = 201). The box represents the target range for trough tacrolimus blood levels. The bars depict the frequency of the measured trough tacrolimus blood level. The line showing the cumulative percentage of trough tacrolimus levels blood levels is depicted by the shaded diamonds.

![Figure 2](image2.png)

**Figure 2.** Annotated run chart showing trough tacrolimus blood levels from an individual patient. The box represents the target range for trough tacrolimus blood levels. The arrows indicate dose changes. This figure is available in color online at http://www.us.elsevierhealth.com/jpeds.

Based on the pilot study, a protocol for managing CNI blood levels was established, and the method was spread to the entire patient population of children who were >3 months after liver transplantation. Using successive tests of change, we spread the method. Initially little progress was made (Figure 3), but with development of a workflow chart that paralleled the guideline, the proportion of drug levels in the target range increased to 77%. Concurrently, the proportion of drug levels in the toxic range decreased from 9.6% in
April 2003 before the spread of the intervention to 5.0% in July 2004 ($P < .05$). When the subset of patients who are >1 year after transplantation and who received tacrolimus was examined, the proportion of drug levels in the target range exceeded 85% ($P < .0001$; Figure 4). Compared with baseline data for the same population, the variance of drug levels decreased from 1 to 22 ng/mL before the intervention to 3 to 15 ng/mL after the intervention. The standard deviation for trough blood levels of tacrolimus in this subset of patients decreased from 3.8 to 2.9. The rate of allograft rejection defined as the proportion of patients with a rejection episode was determined quarterly and did not change over the time course of the study (8% vs 7%).

DISCUSSION

Management of CNI blood levels is a critical component of post-transplant care for solid organ transplant recipients. In the current proposal, we showed that application of the methods of SPC increased the proportion of CNI blood levels in the target range, whereas the proportion of blood levels in an undesirable or toxic range decreased.

We employed several steps to spread the innovation. First, Web-based technology was used to provide care teams with real-time data on blood levels of CNIs. Second, a protocol was developed to standardize the process of care of management levels. Each step of the protocol was based on a dimension of quality. The first step addresses toxicity or medication safety. If drug levels are found to be in a range at risk for complication, the rest of the steps of the guideline are aborted. The second step addresses specifications for the levels of CNIs. The specifications are dependent on knowledge available in the literature, and by standardizing processes, reliability is increased. The third step depends on SPC and is the core of the present work. Increased proportion of drug levels in the target range was demonstrated only after development of a workflow form aligned with the guideline.

Finally, the decision to change doses in the fourth step depends on an understanding of drug formulation and pharmacokinetics of CNIs. Although the results of the pilot study were compelling, the spread of the innovation was slow. This observation emphasizes that the rate of change is dependent on human factors that may be distinct from evidence supporting the innovation. Only when we implemented a workflow sheet that was aligned with the protocol were we able to spread and sustain the innovation.

Our goal was to increase the proportion of CNI levels in the target range, using SPC and a defined change package to decrease unnecessary variation related to decisions by health-care providers. Despite implementation of the change package, 15% to 20% of drug levels remain outside the target range. Previous work has suggested that patients who have increased variation in drug levels as defined by larger standard deviations are at increased risk for late allograft rejection and hospital admission.\textsuperscript{13} A proportion of such patients may be non-adherent to medical regimen. The change package described here does not address the issue of patient adherence. However, it may be possible to identify those patients who might best benefit from targeted psychosocial and behavioral interventions by using standard deviation of drug levels as a marker.

Despite the significant improvement, we recognize that the study has deficits. The results may have been subject to unrecognized bias that is minimized in a double-blinded randomized design. We did not use a double-blinded randomized control design to test our hypotheses. The study design was based on a change of care process. Consequently, the impact of the intervention was apparent to all involved because we used observable results (control chart) to guide therapy. If the improvement efforts had impacted outcome and we had a separate control population, providers might consciously or subconsciously used these methods for the control population.

To avoid putting a patient at unnecessary risk because of a toxic blood level, we used 2 standard deviations as control...
limits instead of the 3 standard deviations control limits used in the manufacturing industry. We did so because 2 standard deviations are approximately the same as the fifth percentile for a normal distribution, and in clinical studies, convention dictates significance as an event that has a probability of <.05. We recognized that by doing so we increased the chance of responding to a drug level that may reflect common cause variation (tampering or Type I error). However, by setting these limits, we decreased the risk of attributing variation to common cause variation and putting the patient at unnecessary risk (undercontrolling or Type II error). Even within these parameters, we recognize the inherent limitations of TDM for CNIs. Trough measurement of CNIs is flawed; improvement in control of trough level variation alone may not result in improvement in clinical care. However, if we used a TDM process that accurately reflected drug exposure and the patients were managed using the methods described here, the adverse events related to management of CNIs might be reduced.

This study was conducted at a single center. The information gained here may not be applicable to a center with different patient composition. However, we think the analysis will be applicable to the national population of pediatric liver transplant recipients because our patient population reflects the national registry for pediatric liver transplant recipients and our immunosuppression protocol reflects those at most liver transplant centers.

Finally, we used a surrogate measure, the proportion of CNI blood levels in the target range, as the principal outcome measure. For the most part, the specifications for CNI levels are based on observational studies and in this case, the Cincinnati Children’s Hospital Medical Center liver transplant immunosuppression protocols. Consequently, it is possible that we increased the proportion of CNI blood levels in the target range without affecting the rate of adverse events. In this case, we will have a process in control but an output that is not desired. The next steps might be to re-examine the specifications or modify the immunosuppression protocol.

The implementation of a change package, which included consensus on target for CNI blood levels, real-time access to drug levels via a web-base tool, and a protocol that incorporated the principles of SPC, effectively decreased variation and increased the proportion of CNI levels in target range for pediatric liver transplant recipients. Although SPC has widespread use in manufacturing and service-related industries, it has not been extensively used in clinical care. This failure to incorporate the concept remains despite the recommendations of health service researchers and quality improvement experts. The essential observation of the current work is that managing variation can improve quality of care. The observations here are not only applicable to TDM in other liver transplant centers and for other solid organ transplant recipients but may be used to manage variation, improve outcome, and decrease risk in the care of applicable chronic healthcare problems including diabetes, anticoagulation, seizure disorders, asthma, and hypertension.

We thank William Balistreri for his thoughtful review, Michael McKechnie and Yelena Rice for their advice regarding the use of SPC, Cynthia Wenkind and Tamara Hutson for their assistance in the development of the guideline and workflow sheet, and Julie Kremer, Kelly King, and Libby Cox for implementing the use of the protocol to manage calcineurin blood levels.

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19. Parasrampuria DA, Lantz MV, Birnbaum JL, Vincenti FG, Benet LZ. Effect of calcineurin inhibitor therapy on P-gp expression and function in


FREQUENCY OF ABNORMAL CARBOHYDRATE METABOLISM AND DIABETES IN A POPULATION-BASED SCREENING OF ADOLESCENTS

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Objective To document the frequency of glucose intolerance in adolescents in a population-based study of primarily African-American/Non-Hispanic whites in an urban-suburban school district.

Study design Measurement of fasting and 2-hour post-glucose load plasma glucose concentrations.

Results Carbohydrate intolerance (either impaired fasting glucose, impaired glucose tolerance, or both) was identified in 8.0%, near-diabetes (1 fasting glucose ≥126 mg/dL [7.0 mmol/L] and/or 2-hour glucose ≥200 mg/dL [11.1 mmol/L]) in 0.3%, and diabetes in 0.36% (type 1A = 0.24%; type 2 = 0.08%; undiagnosed type 2 = 0.04%). A model for abnormal carbohydrate metabolism was constructed with regression analysis in the Carbohydrate Intolerance (CI)/near-diabetes group and with logistic regression in the entire study population. Risk factors for the development of CI/near-diabetes included having a 1 unit increase in body mass index (BMI) z-score and either being non-Hispanic white or in the pubertal group. Increased fasting glucose correlated with having puberty and decreased BMI z-score, whereas 2-hour glucose correlated with increased BMI z-score. By using National Health and Nutrition Survey (NHANES) III (1988-1994) definitions, impaired fasting glucose was present in 2.0% in this study versus 1.7% (NHANES III).

Conclusion The prevalence of CI/near-diabetes was 8.3%. Undiagnosed diabetes mellitus was rare. One third of adolescents with diabetes mellitus could be classified as having type 2 diabetes mellitus. The adult model of the progression of insulin resistance to type 2 diabetes mellitus in adolescents may be valid. Despite the increase in the overweight population since NHANES III, abnormalities in glucose metabolism have not changed significantly. (J Pediatr 2005;146:751-8)

In adults, there is considerable evidence to support a model by which individuals at risk for the development of type 2 diabetes mellitus progress from normal carbohydrate metabolism to carbohydrate intolerance (CI) to undiagnosed diabetes mellitus before a clinical diagnosis is established.1-14 It is generally assumed that adolescents in whom type 2 diabetes mellitus develops progress through these same stages.

The National Health and Nutrition Survey (NHANES) III (1988-1994) was the last comprehensive population-based assessment of the prevalence of the stages of abnormal carbohydrate metabolism in 12- to 19-year-olds.15 By using a single fasting blood glucose value in adolescents, NHANES III documented that impaired fasting glucose occurred in 1.7%, undiagnosed diabetes mellitus occurred in 0.18%, and diagnosed diabetes mellitus occurred in 0.41%. However, since the completion of NHANES III, the frequency of being overweight in adolescents, a known risk factor for the development of abnormal carbohydrate metabolism, has increased from 10.5% to 15.5%.16 As a result, NHANES III may underestimate the present frequency of the stages of abnormal carbohydrate metabolism.

See editorial, p 721.

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CI Carbohydrate intolerance
ANOVA Analysis of variance
NHANES National Health and Nutrition Survey
PSD Princeton School District
BMI Body mass index
CV Coefficient of variation
RIA Radi immunoassay
OGT Oral glucose tolerance
IFG Impaired fasting glucose
IGT Impaired glucose tolerance
IAA Insulin autoantibodies
GAD Glutamic acid decarboxylase
ICA 512 Islet cell antibody 512
IR Insulin resistance
NHW Non-Hispanic whites
AA African Americans
The Princeton School District (PSD) study is a prospective, epidemiologic study of the development of type 2 diabetes mellitus in adolescents in a well-defined, racially integrated (African American, Non-Hispanic white), urban-suburban school district with a wide range of socioeconomic status in each ethnic group. We report a cross-sectional evaluation of this cohort and provide a current estimate of the prevalence of abnormalities in glucose metabolism in adolescents.

METHODS

Study Population

Students (2501 of 4273) in grades 5 through 12 of the PSD participated in the study; 1263 were Non-Hispanic white (NHW), 1117 were African American (AA), 48 were Hispanic, 37 were Asian, 32 were multiracial, and 4 were West Indian. Inclusion and exclusion criteria required a participant to have no known chronic disease and be taking no medication(s) known to affect carbohydrate metabolism. Pregnant female students were excluded.

The protocol was reviewed and approved by the institutional review board at Cincinnati Children’s Hospital (CCH), written informed consent was obtained from the parent/legal guardian, and assent was obtained from the participant.

Data Collection

After a 10-hour overnight fast, the following procedures were performed in a designated area at the student’s school: 1) confirmation of the length of the fast and completion of the medical history; 2) height, weight, and documentation of the stage of axillary hair; and 3) venipuncture for glucose, insulin, and estradiol or free testosterone concentrations. Parents and students completed a personal medical history for each participant, documenting chronic disease, medication use, and family history of diabetes mellitus. The blood samples were maintained on wet ice, transported to CCH, processed within 3 hours of venipuncture, and then frozen at −20 degrees. Samples were batched, and assays were performed weekly.

Participants meeting 1 or more of the following 3 criteria then underwent an oral glucose tolerance test (1.75 g/kg, maximum 75 g, of Glucola) after a 10-hour overnight fast with sampling of fasting and 2-hour glucose and insulin concentrations. Blood samples for the oral glucose loading test were obtained and processed in an identical manner to the initial fasting sample aforementioned. Criteria including: 1) being overweight (BMI >85th percentile for age and sex as defined in NHANES I); 2) being insulin resistant (IR; fasting insulin concentration >2 SD higher than the mean for participants of the same race, sex, and stage of sexual development who had a BMI ≤85th percentile for age and sex as defined in NHANES I); or 3) having an initial fasting glucose ≥110 mg/dL (6.1 mmol/L).

This protocol was designed and the data was collected before the publication of the 2004 criteria for impaired fasting glucose that lowered the glucose value from 110 mg/dL (6.1 mmol/L) to 100 mg/dL (5.5 mmol/L). Thus students who had an initial fasting glucose value between 100 and 109 mg/dL (5.5 mmol/L and 6.0 mmol/L) were not invited to have a 2-hour glucose load test. However, to ensure that the data in the study are presented with the most recent definition of impaired fasting glucose, the students with initial fasting glucose values of 100 to 109 mg/dL (5.5–6.0 mmol/L) are included in the impaired fasting glucose category.

The subjects were then re-classified with the results of the initial fasting glucose, the fasting glucose before glucose load, and the 2-hour post-load glucose tests. The four final classifications were based on the following criteria: 1) normoglycemic—both fasting glucose <100 mg/dL (5.5 mmol/L) and the 2-hour glucose <140 mg/dL (7.7 mmol/L); 2) carbohydrate intolerant (CI)—either impaired fasting glucose (IFG; 1 or both fasting glucose values ≥100 mg/dL [5.5mmol/L], but <126 mg/dL [7.0 mmol/L] and 2-hour glucose <140 mg/dL [7.7 mmol/L]), impaired glucose tolerance (IGT; both fasting glucose <100 mg/dL [5.5 mmol/L] and 2-hour glucose ≥140 mg/dL [7.7 mmol/L], but <200 mg/dL [11.1 mmol/L]), or both; 3) near-diabetes—1 fasting glucose ≥126 mg/dL (7.0 mmol/L), 2-hour glucose ≥200 mg/dL (11.1 mmol/L), or both; 4) diabetes—both fasting glucose ≥126 mg/dL (7.0 mmol/L).

Subjects with known or newly diagnosed diabetes mellitus also had islet cell antibody titers measured. Subjects with known diabetes mellitus had fasting plasma c-peptide levels measured. Subjects with newly diagnosed diabetes mellitus had plasma c-peptide levels measured after fasting and during a mixed meal challenge as described later.

History and Physical Examination

A family history of diabetes mellitus was defined as a self-report of a sibling, parent, or grandparent with diabetes. Height, weight, and waist circumference were measured with standard procedures and equipment as described previously.

Axillary hair was documented in all male participants as stage I (no axillary hair), stage II (presence of any axillary hair), or stage III (adult distribution of axillary hair). All research team members were trained to assess the axillary hair stage and then certified by direct comparison of blinded assessment of the stages of axillary hair to that of a board certified pediatric endocrinologist. All team members achieved a Kappa statistic of 0.8 before independently assessing the stages of axillary hair.

Pubertal status was assessed with serum estradiol concentration and the presence or absence of menarche for 2 years in female students and serum-free testosterone concentrations in male students. Estradiol concentration was measured in female students and free testosterone was measured in male students who underwent a physical examination and pubertal Tanner
Stage assessment as part of the National Growth and Health Study (females) or the Sex Hormone and Lipoprotein in Adolescent Males Study. The estradiol and free testosterone concentrations were grouped according to T staging: TI and TII to IV for female students (TI n = 24; TII-IV n = 60) and male students (TI n = 24; TII-IV n = 76), respectively. Receiver operating curves were generated to establish the estradiol and free testosterone concentrations that established the greatest sensitivity and specificity to identify female and male students who were in TI versus TII to IV.

Pubertal status (pre-pubertal, pubertal, and post-pubertal) was then assigned in the Princeton cohort by using the following definitions. In female students, pre-pubertal was defined as an estradiol level <11 pg/mL, pubertal was defined as an estradiol level >11 pg/mL without menarche or duration of menarche <2 years, and post-pubertal status was defined as the absence of menses for >2 years. In male students, pre-pubertal was defined as a free testosterone level <1.0 pg/mL, pubertal was defined as a free testosterone level >1.0 pg/mL and axillary hair stage III, and post-pubertal status was defined as a free testosterone level >1.0 pg/mL and axillary hair stage III.

A mixed meal challenge was performed in students with newly diagnosed diabetes mellitus by having the subjects ingest 6 mL/kg (maximum of 360 mL) of a liquid nutrient drink (BOOST, Meade Johnson, Evansville, Ind) after a 10-hour fast. Blood was sampled before and every 30 minutes after the meal for 2 hours, and plasma c-peptide concentrations were measured.

Laboratory Measurements

Plasma glucose was measured with a Hitachi model 704 automatic chemistry analyzer (glucose oxidase) with intra- and inter-assay coefficient of variations (CV) of 1.2% and 1.6%. Plasma insulin was measured by radioimmunoassay (RIA) using an anti-insulin serum raised in guinea pigs, 125I labeled insulin (Linco, St. Louis, Mo), and a double antibody method to separate bound from free tracer. The sensitivity of the insulin RIA is 2 pM, with intra- and inter-assay CVs of 5% and 7%. Plasma C-peptide was measured with RIA (Linco) with a sensitivity of 0.1 ng/mL and intra- and inter-assay CVs of 4% to 5%. Serum estradiol was measured with RIA (Diagnostic Systems Laboratories, Webster, Tex) with a sensitivity of 0.1 ng/mL and intra- and inter-assay CVs of 4% to 5%. Serum-free testosterone was measured with RIA (Diagnostic Systems Laboratories) with a sensitivity of 0.18 pg/mL and intra- and inter-assay CVs of 5% to 7%.

Table I. Characteristics of the study population: the distribution by sex, pubertal status and ethnicity in the study population and the carbohydrate intolerant and near-diabetes populations

<table>
<thead>
<tr>
<th>Study population (N = 2501)</th>
<th>Carbohydrate intolerance (N = 199)</th>
<th>Near-diabetes (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N = 1232)</td>
<td>Male (N = 119)</td>
<td>Male (N = 2)</td>
</tr>
<tr>
<td>Female (N = 1269)</td>
<td>Female (N = 80)</td>
<td>Female (N = 5)</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Pre-pubertal</td>
<td>215 17.5</td>
<td>22 18.5</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>120 9.7</td>
<td>14 11.8</td>
</tr>
<tr>
<td>African American</td>
<td>82 6.7</td>
<td>7 5.9</td>
</tr>
<tr>
<td>Other</td>
<td>13 1.1</td>
<td>1 0.8</td>
</tr>
<tr>
<td>Pubertal</td>
<td>494 40.1</td>
<td>58 48.7</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>275 22.3</td>
<td>33 27.7</td>
</tr>
<tr>
<td>African American</td>
<td>197 16.0</td>
<td>22 18.5</td>
</tr>
<tr>
<td>Other</td>
<td>22 1.8</td>
<td>3 2.5</td>
</tr>
<tr>
<td>Post-pubertal</td>
<td>518 42.0</td>
<td>38 31.9</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>247 20.0</td>
<td>20 16.8</td>
</tr>
<tr>
<td>African American</td>
<td>248 20.1</td>
<td>17 14.3</td>
</tr>
<tr>
<td>Other</td>
<td>23 1.9</td>
<td>1 0.8</td>
</tr>
<tr>
<td>Missing stage</td>
<td>5 0.4</td>
<td>1 0.8</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>3 0.2</td>
<td>0 0</td>
</tr>
<tr>
<td>African American</td>
<td>2 0.2</td>
<td>1 0.8</td>
</tr>
<tr>
<td>Other</td>
<td>0 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

Table II. Characteristics of the study population: demographic data

<table>
<thead>
<tr>
<th>Study population (N = 2501)</th>
<th>Carbohydrate intolerance (N = 199)</th>
<th>Near-diabetes (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Carbohydrate intolerance</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1 (5.9)</td>
<td>23.9 (6.6)</td>
</tr>
<tr>
<td>Z score for BMI</td>
<td>0.7 (1.0)</td>
<td>0.9 (1.1)</td>
</tr>
</tbody>
</table>
inter-assay CVs of 6% and 9%. Antibody titers for insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), and islet cell antibody 512 (ICA512) were performed at the Barbara Davis Center (Denver, Colo) as previously described, with interassay CVs of 10.3%, 6.5%, and 11.7%.26-28

Statistical Analysis

All results were conducted with SAS software, version 8.2 (SAS Institute, SAS/STAT User’s Guide, version 6, 3rd ed., Cary, NC: SAS Institute; 1990). Demographic characteristics of age, sex, and ethnicity of the students who participated in the study and those who did not were examined. Tables I and II give the characteristics of the students who participated. The prevalence of the types of diabetes mellitus and their 95% CIs were calculated. By using linear regression, initial fasting glucose and 2-hour glucose, within the CI/near-diabetic group were compared across sex, ethnicity, BMI z-score, age, and pubertal stage. Pubertal status was defined by using 2 centered variables to determine whether: 1) on average, pubertal and post-pubertal status differed from pre-pubertal status, 2) post-pubertal status differed from pubertal status. Family history of diabetes mellitus was controlled for in all model runs. The variables were examined separately. A model was then fit that included any main effects significant at the .05 level, covariates, and all possible 2-way interactions between significant main effects. Next, all non-significant interactions (P > .05) were dropped. The final model included all main effects previously defined as significant, covariates, and any interactions significant at the .05 level. Mean initial fasting glucose level, mean 2-hour glucose level, and the SDs are reported (Table III). To identify risk factors leading CI and near-diabetes, logistic regression was run for all students enrolled. The factors examined were sex, ethnicity, BMI z-score, age, and pubertal stage. A family history of diabetes mellitus was controlled for in all model runs. Pubertal stage was defined as 2 dummy variables, with the pre-pubertal students being the reference. The regression model was first run with all main effects, covariates, and all 2-way interactions between main effects. Then, a reduced model was fit that included the main effects that were statistically significant and those included in the significant interactions, covariates and only 2-way interactions that were statistically significant at the .05 level. The final model is presented in Table IV.

RESULTS

Tables I and II present the characteristics of the study population and the CI and near-diabetes populations. These data were examined with the demographic data of the non-participants. The mean age of both groups was 14 years. Although the sex distribution in the participant population was approximately 50%, a greater percentage of the total number of

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Table III. Frequency and glucose values in carbohydrate intolerant and near-diabetes subjects classified by type abnormality (N = 206)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency</th>
<th>Fasting glucose* (mg/dL)</th>
<th>Fasting glucose* (mg/dL)</th>
<th>2-hour glucose* (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial elevated fasting only</td>
<td>159 (77.2%)‡</td>
<td>107.4 (6.5)</td>
<td>84.5 (7.6)</td>
<td>92.2 (19.1)</td>
</tr>
<tr>
<td>OGT elevated fasting only</td>
<td>17 (8.3%)</td>
<td>89.37 (5.7)</td>
<td>106.2 (5.9)</td>
<td>92.3 (25.3)</td>
</tr>
<tr>
<td>Initial elevated fasting and OGT elevated fasting only</td>
<td>11 (5.3%)</td>
<td>107.4 (5.5)</td>
<td>103.9 (2.8)</td>
<td>101.3 (21.0)</td>
</tr>
<tr>
<td>OGT elevated 2-hour only</td>
<td>7 (3.4%)</td>
<td>88.6 (7.4)</td>
<td>89.5 (8.7)</td>
<td>154.2 (10.8)</td>
</tr>
<tr>
<td>Initial elevated fasting and OGT elevated 2-hour only</td>
<td>4 (1.9%)</td>
<td>113.4 (3.6)</td>
<td>89.6 (12.2)</td>
<td>155.5 (20.2)</td>
</tr>
<tr>
<td>Initial elevated fasting, OGT elevated fasting and OGT elevated 2-hour only</td>
<td>1 (0.5%)</td>
<td>104.8 (n/a)</td>
<td>108.4 (n/a)</td>
<td>165.2 (n/a)</td>
</tr>
<tr>
<td>Near-diabetes</td>
<td>7 (3.4%)</td>
<td>109.8 (24.3)</td>
<td>94.8 (5.8)</td>
<td>167.4 (82.6)</td>
</tr>
</tbody>
</table>

OGT = Oral Glucose Tolerance; n/a = not applicable.

*Mean (SD).
‡ For conversion to mmol/L, divide by 18.
§ Not all subjects were asked to return for follow-up visit because of changes in the definition of carbohydrate intolerance (see Data Collection in Methods section for details).

Table IV. Factors predicting carbohydrate intolerance and near-diabetes: interactions between ethnicity and z-score for body mass index and between pubertal stage and z-score for body mass index

<table>
<thead>
<tr>
<th>1-unit increase in z-score for BMI*</th>
<th>Adjusted odds ratio†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>1.000</td>
<td>Referent</td>
</tr>
<tr>
<td>White</td>
<td>1.435</td>
<td>1.057-1.946</td>
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<tr>
<td>Pre-pubertal</td>
<td>1.000</td>
<td>Referent</td>
</tr>
<tr>
<td>Pubertal</td>
<td>1.578</td>
<td>0.936-2.661</td>
</tr>
<tr>
<td>Post-pubertal</td>
<td>0.721</td>
<td>0.417-1.245</td>
</tr>
<tr>
<td>Post-pubertal</td>
<td>1.000</td>
<td>Referent</td>
</tr>
<tr>
<td>Pubertal</td>
<td>2.188</td>
<td>1.580-3.030</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex using CDC criteria.
† Adjusted for family history of diabetes mellitus.
female students (62.7%) in the school district than male students (54.7%) participated. When ethnicity was examined, the percent of AA students who enrolled was 58.3% of the total number in the district, 60.2% for NHW students, and 47.5% for other students. In addition, no large discrepancies in zip code distribution were seen. On the basis of these observations, the groups were not different in any meaningful way.

By using our criteria for pubertal status, 11.8% of the PSD subjects were pre-pubertal, 40.0% were pubertal, and 47.8% were post-pubertal. The prevalence of being overweight (BMI >85th% for NHANES I) was 34.9% and of insulin resistance was 15.2%.

On initial screening, IFG was found in 175 of the subjects. On the basis of the rates of being overweight, insulin resistance, and IFG on the initial blood draw, 39.7% (992/2501) of the population was defined as high risk and were asked to return for an oral glucose tolerance test (OGT). Of the 992 subjects asked to return, 890 underwent an OGT. Of these, 29 subjects had IFG detected before glucose load. In addition, 12 subjects had 2-hour post-load glucose values >140 mg/dL (>7.7 mmol/L). Seven subjects were asked to return for an oral glucose tolerance test (OGT). Of these, 29 subjects had IFG detected before glucose load. Of these, 29 subjects had IFG detected before glucose load. In addition, 12 subjects had 2-hour post-load glucose values >140 mg/dL (>7.7 mmol/L). Seven subjects were identified with near-diabetes.

CI was identified in 8.0% (199/2501) of the participants (Table III). These individuals were predominately male (59.8%) and NHW (58.8%). The means for BMI and BMI z-score among these individuals were 23.9 and 0.9, respectively. IFG only was found in 7.5% (187/2501), with 159 students having only an elevated initial fasting glucose level, 17 students having only an elevated fasting glucose level before glucose load, and 11 students having both elevated initial fasting glucose and fasting glucose before glucose load. IGT only was present in 0.3% of subjects (7/2501). Both IFG and IGT were present in 0.2% of subjects (5/2501).

Near-diabetes was identified in 0.3% (7/2501) of the participants. These individuals were predominately female (71.43%) and of AA/other ethnicity (71.43%; Table I). The mean BMI and BMI z-score in these individuals were 28.2 and 1.6, respectively.

A regression analysis was performed within the CI and near-diabetes population to identify factors that contribute to the fasting and 2-hour glucose values. For mean initial fasting glucose, the final model included ethnicity, BMI z-score, the 2 centered variables for pubertal stage, age, and history of diabetes mellitus. Decreased BMI z-score correlated with increased initial fasting glucose (P <.01). In addition, pubertal and post-pubertal individuals had significantly higher initial fasting glucose values than pre-pubertal individuals (P = .02). However, there was no significant difference between pubertal and post-pubertal subjects. For 2-hour glucose values, the final model included BMI z-score and family history of diabetes mellitus. Increased BMI z-score correlated with increased 2-hour glucose value (P <.01).

Logistic regression was run to identify risk factors of CI and near-diabetes (Table IV). Because the interaction between ethnicity and BMI z-score and the interaction between pubertal status and BMI z-score were statistically significant, BMI z-score must be considered when examining the risk factors of ethnicity and pubertal status. Table IV presents the odds ratios (OR) and 95% CI for these interaction terms. When examining a 1-unit increase in z-score for BMI, CI/near-diabetes was more likely to develop in NHW participants than in AA/other participants (OR, 1.435; 95% CI, 1.057–1.946). In addition, CI/near-diabetes was more likely to develop in pubertal students than in post-pubertal students (OR, 2.188; 95% CI, 1.580–3.030).

In those subjects with an elevated initial fasting glucose value, the initial fasting glucose value was higher than the fasting glucose value before glucose load (107.4 versus 83.4 mg/dL [5.9 versus 4.6 mmol/L], respectively). This pattern was also found in subjects with IGT, IFG and IGT, and pre-diabetes (Table II).

Previously undiagnosed diabetes mellitus was identified in a 16-year-old AA male student with negative GAD, ICA512, and IAA titers, a fasting c-peptide value of 2.5 ng/mL, and a peak simulated c-peptide value of 6.7 ng/mL, confirming a diagnosis of type 2 diabetes mellitus. In addition, 8 students with known diabetes mellitus participated in the study. Six of these 8 students had positive titers for either GAD or ICA512 and a fasting c-peptide value <0.3 ng/mL, consistent with type 1A diabetes mellitus. Two students had negative ICA titers and fasting c-peptide values of 3.5 and 4.4 ng/mL, consistent with type 2 diabetes mellitus. The frequency of all types of diabetes mellitus was 0.36%; the frequency of type 1A diabetes mellitus was 0.24%; the frequency of type 2 diabetes mellitus was 0.08%; and the frequency of undiagnosed type 2 diabetes mellitus was 0.04%.

**DISCUSSION**

This population-based study of 9- to 20-year-old students used initial fasting glucose and subsequent fasting and post 2-hour glucose load glucose values to define the frequency and characteristics of abnormal carbohydrate metabolism. The frequency of carbohydrate intolerance, near-diabetes, and diabetes mellitus was 8.0%, 0.3%, and 0.36%, respectively. Within the CI group, 7.5% had IFG only, 0.3% had IGT only, and 0.2% had both IFG and IGT. Of subjects with a clear diagnosis of diabetes mellitus, 0.24% had type 1A and 0.08% had type 2 diabetes mellitus, with 0.04% having previously undiagnosed type 2 diabetes mellitus. Risk factors for developing CI/near-diabetes include having a 1-unit increase in BMI z-score and being either NHW or pubertal. A higher initial fasting glucose value was found in pubertal and post-pubertal subjects, and a lower BMI z-score also correlated with a higher initial fasting glucose value. However, increased BMI z-score correlated with 2-hour post-glucose load glucose value. These findings provide population-based prevalence estimates of disordered carbohydrate metabolism in NHW and AA children and adolescents.

Previously, the most comprehensive estimate of abnormal carbohydrate metabolism in adolescents was NHANES III.15 In contrast to PSD, NHANES III was a national population-based analysis and included a greater sampling of Hispanic subjects. In NHANES III, classification of abnormal
glucose metabolism was based on a single fasting glucose value (≥110 but <126 mg/dL [≥6.1 but <7.0 mmol/L]) in 1083 of 2867 adolescents and self-report of insulin or oral hypoglycemic agent treatment to define diabetes type. In the PSD, measurements of fasting glucose value (≥100 but <126 mg/dL [≥5.5 but <7.0 mmol/L]) were also used as a first-order screening. Despite the passage of more than a decade, the frequencies of IFG by using the NHANES III definition in PSD and NHANES III populations were found to be 2.0% and 1.7%, respectively. These findings indicate that abnormalities in glucose metabolism, as reflected in fasting glucose levels, have not changed in the last decade. However, by using the most recent definition of IFG (≥100 but <126 mg/dL [≥5.5 but <7.0 mmol/L]), the frequency of IFG increased to 7.5%. Because comparable data from NHANES III are not available, it is not clear whether there has been a temporal change in the frequency of IFG in the range ≥100 but <110 mg/dL (≥5.5 but <6.1 mmol/L).

Since NHANES III (1988-1994), the percentage of overweight (as defined as a BMI ≥95th percentile by Centers for Disease Control criteria) 12- to 19-year-old individuals has increased from 10.5% to 15.5% (NHANES 1999-2000). This increase in being overweight accompanied the appearance of type 2 diabetes mellitus in adolescents. The frequency of overweight subjects in PSD was 19.4% (BMI ≥95th percentile by Centers for Disease Control criteria), suggesting that PSD subjects were as overweight as those in NHANES III. In this context, the stability in the prevalence of IFG (≥110 but <126 mg/dL [≥6.1 but <7.0 mmol/L]) is surprising. Although the constancy of normal fasting glucose values for the last 10 to 15 years is reassuring, it may be that single glucose values are not sufficiently sensitive to reflect overall glucose metabolism, a finding that is supported by the relatively low concordance of IFG and IGT in our subjects.

After screening with fasting glucose values, we performed 2-hour oral glucose tolerance tests in 890 subjects who were classified as high-risk for abnormalities in glucose metabolism (overweight, insulin resistance, abnormal initial fasting glucose value). In the high-risk group, 7 subjects (0.3% of all PSD subjects) had IGT but not IFG, 5 subjects (0.2%) had both IFG and IGT, and 7 subjects (0.3%) had near-diabetes. When added to the subjects that had IFG alone (n = 187), the overall prevalence of abnormal glucose metabolism in PSD was 8.3%. This rate may be an underestimate because we did not perform glucose loading in all subjects. However, we think that rate of IGT in the subjects not identified as high risk is very low because none of the 255 fifteen-year-old subjects in Chicago had a capillary glucose >140 mg/dL (>7.7 mmol/L) 90 to 120 minutes after a 100-g carbohydrate meal.

There was a similar prevalence of all types of diabetes mellitus (0.56% versus 0.41%), undiagnosed type 2 diabetes mellitus (0.04% versus 0.06%), and the percentage of all diabetes mellitus that is type 2 (33% versus 30%) in PSD versus NHANES III, respectively. Both studies identified a small number of subjects with silent type 2 diabetes mellitus. These data suggest that undiagnosed diabetes mellitus is very uncommon in adolescents and has not changed over the last decade. However, the frequency of CI and near-diabetes in PSD suggest that there are a number of adolescents who may be at risk for the development of diabetes mellitus as older adolescents or young adults.

Despite collecting and processing the initial and pre-glucose load blood samples with an identical protocol, we found a low frequency of reproducibility of IFG in PSD. One explanation is that the subjects were not fasting for the initial venipuncture. Although this possibility cannot be eliminated, all participants were mailed written instructions, received a phone call the night before, and were questioned by the research team on the morning of each venipuncture about adherence to the overnight fast. This process identified a number of subjects who were not fasting, and those subjects’ tests were rescheduled. Further evidence that the PSD participants were fasting is that a comparison of initial fasting glucose and fasting glucose values before glucose load revealed that initial fasting glucose values were higher in all groups (IFG only, IGT only, IFG and IGT, pre-diabetes). This finding in subjects with and without abnormal carbohydrate metabolism suggests that lack of reproducibility of fasting glucose may be caused by an as-yet-unexplained variability of fasting glucose concentration and not ingestion of food before the venipuncture.

Logistic regression in PSD demonstrated that with a 1-unit increase in BMI z-score, NHW subjects were at a greater risk than AA/other subjects for the development of CI/near-diabetes. In addition, CI/near-diabetes was more likely to develop in pubertal students than post-pubertal subjects. These findings are consistent with data documenting increased insulin resistance (IR) with increased BMI and the physiologic rise of IR with the onset of puberty. The second notable finding in our analysis was that NHW students were at a higher risk for the development of CI/near-diabetes than AA students. These data are in keeping with the greater prevalence of type 1A diabetes mellitus in the adolescent NHW population than in the AA/other ethnicity population.

An analysis of the components of CI/near-diabetes (fasting and 2-hour glucose) demonstrated that students with increased BMI z-score had higher mean 2-hour post-glucose load glucose values. Also, pubertal and post-pubertal students had a higher mean fasting glucose value than pre-pubertal subjects. These findings are consistent with data documenting that pubertal subjects and those with increased BMI are more IR than pre-pubertal subjects and subjects with lower BMI. An unexpected finding was the higher mean fasting glucose value associated with a decreased BMI z-score. This finding was caused in part by a subset of non-overweight NHW subjects who had non-reproducible increases in fasting glucose values.

An adult model of CI/pre-diabetes has been developed from longitudinal data collected in Pima Indians and cross-sectional data from different ethnic populations. These data suggest that increased BMI, ethnic minority, and age are predictors of progression from normal carbohydrate metabolism.
metabolism to CI to diabetes. In adolescents with CI or pre-diabetes, the finding of an association of mean 2-hour glucose value with increased BMI z-score is consistent with the adult model. These findings suggest that the development of CI and diabetes in adolescents and adults may follow similar routes and implies common inherent and environmental causes.

The authors gratefully acknowledge the work of the PSD research team: Tara Håmått, RN, Stacy Poe, MS, Amy Clins, RN, Elena Strickland, RN, Tara Schafer–Kalkhoff, Sang Sam, Michelle Hull, Julie Schwalkner, and the administration, staff, teachers, students, and parents of the Princeton School District.

REFERENCES


50 Years Ago in The Journal of Pediatrics

PSEUDOMONAS INFECTIONS IN INFANTS ASSOCIATED WITH HIGH-HUMIDITY ENVIRONMENTS


Pediatricians from Baltimore City Hospitals report the extraordinary occurrence of 13 cases of Pseudomonas aeruginosa infections in the premature infant nursery in a 1-year period after the implementation of the use of high-humidity atmosphere and mist in infant incubators. It was thought that such environments would be beneficial, especially in infants with a risk for or evidence of hyaline membrane disease. Infections included septicemia, noma (ulcerative necrosis) of the face, conjunctivitis, and omphalitis. Although Pseudomonas aeruginosa was not isolated from distilled water used to humidify, the ubiquity of the organism in the environment, its minimal requirements for growth, and its enhancement of growth in humid habitat probably account for high-density inoculation. Intrinsically limited and extrinsically violated skin barriers of the premature infant created the second half of the tragic story.

The downsides of recent “advances” in neonatology—such as the use of corticosteroids, indomethacin, topical petrolatum, central venous catheters, and potent broad-spectrum antibiotics—remind us how naive it is to assume that intended therapies won’t have unintended consequences.

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YMPD1445

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ROUTINE VOIDING CYSTOURETHROGRAPHY IS OF NO VALUE IN NEONATES WITH UNILATERAL MULTICYSTIC DYSPLASTIC KIDNEY

KHALID ISMAILI, MD, FRED E. AVNI, MD, PHD, MARC ALEXANDER, MD, CLAUDE SCHULMAN, MD, PHD, FRANK COLLIER, MD, AND MICHELLE HALL, MD

Objectives To determine if two successive ultrasound examinations could rule out the presence of clinically significant contralateral anomalies in neonates with multicystic dysplastic kidney (MCDK), thereby avoiding unnecessary voiding cystourethrography (VCUG).

Study design We followed 76 newborn infants with antenatally discovered MCDK. Two successive neonatal renal ultrasound examinations were performed, one within the first week and one at around 1 month of life. VCUG and isotopic studies were performed in all infants.

Results Urologic anomalies of the contralateral kidney were present in 19 of 76 children (25%): vesicoureteral reflux (VUR) in 16 (21%), ureteropelvic junction obstruction in 2 (3%), and renal duplex kidney in 1 (1%). Sixty-one infants (80% of total) had normal contralateral urinary tract on the 2 successive neonatal renal ultrasound scans. Among them, 4 of 61 (7%) infants presented with low-grade VUR on VCUG that had resolved spontaneously before 2 years of age. The sensitivity, specificity, positive predictive value, and negative predictive value of two successive ultrasound scans in the neonatal period to predict contralateral urological anomalies on VCUG were 75%, 95%, 80%, and 93%, respectively.

Conclusions In infants with antenatally diagnosed MCDK, two successive normal neonatal renal ultrasound scans will rule out clinically significant contralateral anomalies, thereby rendering the need for a neonatal VCUG unnecessary.

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See editorial, p 723.

MCDK Multicystic dysplastic kidney
SDS Standard deviation scores
UTI Urinary tract infection
VCUG Voiding cystourethrography
VUR Vesicoureteral reflux

A ntenatal diagnosis of fetal anomalies by obstetric ultrasound has led to the detection of an increasing number of uropathies, including multicystic dysplastic kidney (MCDK). MCDK may be associated with contralateral urinary tract abnormalities, including vesicoureteral reflux (VUR) and ureteropelvic junction obstruction. Contralateral VUR in association with MCDK may put the solitary functioning kidney at risk for pyelonephritic scarring. As a result, some studies have suggested that the treatment of all infants with antenatally diagnosed MCDK should include systematic voiding cystourethrography (VCUG) to allow early identification of clinically significant contralateral anomalies, including VUR, and initiation of prophylactic treatment. For those infants screened with VCUG, this technique may serve to lower the risk of a hypothetic urinary tract infection (UTI), albeit at the price of irradiation and painful procedures. As demonstrated in babies with antenatally diagnosed renal pelvis dilatation, it is possible to rely on neonatal ultrasound to select patients who should not undergo a VCUG. The aim of this study was to determine whether a normal–appearing urinary tract of the contralateral kidney in neonates with MCDK, as assessed by meticulous ultrasound examination, may coexist with clinically significant anomalies and whether a normal ultrasound examination can be used to exclude clinically significant contralateral anomalies, thereby avoiding unnecessary VCUG.
METHODS

Since 1990, we have maintained a registry of antenatally diagnosed urinary tract abnormalities, including MCDK, in collaboration with colleagues in obstetrics, radiology, urology, pathology, and genetics. During the last 12 years, we have followed and evaluated 76 consecutive newborn infants with an antenatally diagnosed unilateral MCDK in our department, using the same imaging protocol in a systematic manner.

At birth, a urine sample was collected and antibiotic prophylaxis using trimethoprim (2 mg/kg per day) was started immediately. Antibiotic prophylaxis was continued in all infants with VUR or significant hydronephrosis.

To avoid confusion, the term ipsilateral is used in this report to refer to the kidney or ureter on the same side as the MCDK; contralateral refers to the kidney or ureter on the side opposite the MCDK.

Two careful neonatal ultrasound examinations of the urinary tract were performed, one during the newborn infant's stay (after day 3) and the other at around 1 month. Diagnosis of MCDK was made according to the criteria of Stuck et al: multiple noncommunicating cysts of varying size and nonmedial location of the largest cyst, absence of normal renal sinus echoes, and absence of normal renal parenchyma.

The neonatal ultrasound criteria studied for abnormal contralateral kidney included pelvic anteroposterior diameter $\geq 7$ mm, calyceal or ureteral dilation, pelvic or ureteral wall thickening, absence of the corticomedullary differentiation, and signs of renal dysplasia (small kidney, thinned or hyperechoic cortex, and cortical cysts). Renal length of the contralateral kidney was defined according to Rosenbaum et al and expressed in standard deviation scores (SDS). Careful examination of the bladder was also performed to exclude associated structural abnormalities of the lower urinary tract.

All patients were followed by ultrasonography at the ages of 6 and 12 months and afterward at intervals of 1 year. The postnatal ultrasound scans were performed by the same trained pediatric radiologists using adapted equipment, with high-resolution curvilinear and linear transducers with settings optimized to pediatric patients.

All of the babies underwent a VCUG during the first month of life. The radiographic cystography technique consisted in filling the bladder by urethral catheterization in all infants. VUR was graded by means of the International Reflux Study Committee classification. Cystography was repeated in those children with VUR between 1 and 2 years of age.

Further assessment with $^{99m}$Tc-mercaptoacetyltriglycine renogram or $^{99m}$Tc-dimercaptosuccinic acid scintigraphy was performed in all patients to confirm the absence of function of the dysplastic kidney.

Statistical analysis was performed by means of the nonparametric Mann-Whitney test. A 2-sided $P$ value of <.05 was considered statistically significant.

RESULTS

There were 44 male (58%) and 32 female (42%) children with antenatally diagnosed MCDK. The MCDK was on the left side in 41 children (54%) and on the right side in 35 (46%).

<table>
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<th>No</th>
<th>MCDK</th>
<th>Sex</th>
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<th>D</th>
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</table>

MCDK, multicystic dysplastic kidney; VCUG1, first voiding cystourethrography (I to V grades of reflux); VCUG2, second voiding cystourethrography (−, normal); D, pelvic dilatation (mm); C, calyceal dilatation, (+, present); U, ureteral dilatation (+, present); PUW, pelvic or ureteral wall thickening (+, present); CMD, corticomedullary differentiation (+, absent); Dyspl, signs of dysplasia (+, present); R, right; L, left.
Unilateral Multicystic Dysplastic Kidney

Routine Voiding Cystourethrography Is Of No Value In Neonates With Unilateral Multicystic Dysplastic Kidney

Table II. Correlation between ultrasound and VCUG findings in all 76 infants with antenatally diagnosed MCDK

<table>
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<th>VCUG</th>
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</tr>
<tr>
<td>Abnormal ultrasound</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Normal ultrasound</td>
<td>4</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>60</td>
<td>76</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, positive predictive value, and negative predictive value of 2 successive US in the neonatal period to predict clinically significant contralateral anomalies on VCUG were 75%, 95%, 80%, and 93%, respectively.

Associated urologic anomalies of the contralateral kidney were present in 19 of 76 children (25%): primary VUR in 16 of 76 children (21%), ureteropelvic junction obstruction in 2 of 76 children (3%), and renal duplex kidney in 1 of 76 children (1%).

Associated lower urinary tract anomalies were present in 12 of 76 children (16%). Eleven of these 12 anomalies were ipsilateral to the MCDK. In 3 patients, the ipsilateral ureter ended in an obstructed single-system ureterocele. Two male patients had ipsilateral ectopic ureter inserted into the seminal vesicle and 1 female patient into the vagina. Three patients had ipsilateral residual blind ending ureter. The meticulous ultrasound assessment of the bladder and the genital system permitted us to diagnose or suspect all these anomalies except for 3 (2 bladder diverticuli and 1 urethral cyst).

The correlation between the sonographic and VCUG findings in the 16 children with contralateral VUR is presented in Table I. VUR occurred in the ipsilateral ureter in 2 patients; both children had bilateral reflux. In 13 of 16 infants (81%) with VUR, the reflux was of low grade (I to III). A second VCUG was performed in all these 16 children with VUR when they were younger than 2 years of age. Reflux had resolved spontaneously in 13 cases (81%).

Sixty-one infants (80% of total) had strictly normal-appearing contralateral urinary tract on the 2 successive neonatal renal ultrasound examinations. In this group, 4 of 61 (7%) infants presented with low-grade VUR (I or II) on VCUG that had resolved spontaneously before 2 years of age.

On the basis of these data, sensitivity, specificity, positive predictive value, and negative predictive value of 2 successive ultrasound scans in the neonatal period to predict urologic contralateral anomalies on VCUG in these children were 75%, 95%, 80%, and 93%, respectively (Table II).

The median SDS for renal length of the contralateral kidney at birth was 1.67 (range, −1.54 to 4.9) in normal kidneys and 1.67 (range, −0.58 to 3.2) in the refluxing units (P = .71). The median SDS for renal length of the contralateral kidney at 1 year of age was 1.42 (range, −0.39 to 3.1) in normal kidneys and 1.20 (range, 0 to 2.77) in the refluxing units (P = 0.77) (Table III).

DISCUSSION

The apparent incidence of MCDK is increasing because more cases are being detected with the use of antenatal ultrasound. Data collected by Liebeschuetz and Thomas put the prevalence at 1 in 2400 live births, which is far greater than previous older reports.

Management of MCDK has historically been varied and controversial. Until the late 1970s, the management of this disorder when discovered was surgical removal. Today, fewer children are undergoing nephrectomy, since many studies have reported frequent spontaneous involution of MCDK.

Controversy surrounds the management of the solitary functioning renal unit. When the diagnosis of MCDK has been made, accurate evaluation of the contralateral kidney takes on extreme importance during postnatal imaging studies because some reports found evidence of associated urologic anomalies in 39% of them. The most common abnormality was contralateral VUR. The incidence of VUR in newborn infants with antenatal diagnosis of MCDK varies from 20% to 30% in studies that have included VCUG at birth. Our study in which newborn infants have been investigated in a systematic manner confirms that there is a significant percentage of VUR in the contralateral kidney (21%).

VUR is currently central to the problems raised by the discovery of MCDK. Since it is thought that VUR in the contralateral kidney may be associated with renal scarring, especially if UTI occurs, many centers advocate obtaining VCUG on all patients with MCDK at the time of diagnosis. Some authors suggest that VUR cannot be suspected with any accuracy by ultrasound technique alone.

Table III. Median renal length in millimeters and SDS at birth and 1 year for refluxing and nonrefluxing contralateral solitary functioning kidneys in 76 infants with unilateral MCDK

<table>
<thead>
<tr>
<th></th>
<th>Reflexing kidney (n = 16)</th>
<th>Nonrefluxing kidney (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal length (mm) at birth</td>
<td>50 43/56</td>
<td>50 40/60</td>
</tr>
<tr>
<td>Renal length (SDS) at birth</td>
<td>1.67 −0.58/3.2</td>
<td>1.67 −1.54/4.9</td>
</tr>
<tr>
<td>Renal length (mm) at 1 year</td>
<td>70 62/80</td>
<td>71 60/82</td>
</tr>
<tr>
<td>Renal length (SDS) at 1 year</td>
<td>1.20 0/2.77</td>
<td>1.42 −0.39/3.09</td>
</tr>
</tbody>
</table>

P values

SDS, standard deviation score; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography; MCDK, multicystic dysplastic kidney.
in patients with MCDK. Flack and Bellinger have pointed out the importance of looking for reflux, even in the presence of a normal postnatal ultrasound scan: 6 of 8 children with VUR had normal ultrasound examinations and would not have undergone further radiographic study on the basis of ultrasound criteria alone. However, in their study, patient age at presentation was variable; from newborn to 2 years, and the ultrasound criteria used were not specified.

Other authors disagree with the statement that a VCUG should be performed in every patient with MCDK. They argue that VCUG is not indicated unless the ultrasound examination reveals abnormal findings on ultrasonography. Furthermore, it is not clear from the existing data whether undetected VUR leads to a higher frequency of UTI or places the contralateral kidney at higher risk for injury in children with MCDK.

In our study, when neonatal renal ultrasound performed within the first week and at 1 month of life showed one or more of the following anomalies (pelvic anteroposterior diameter ≥7 mm, calyceal or ureteral dilation, pelvic or ureteral wall thickening, absence of the corticomedullary differentiation, and signs of renal dysplasia), VCUG was abnormal in 80% of cases (positive predictive value).

In concordance with our results in infants with antenatally diagnosed renal pelvis dilatation, the current study demonstrates the ability of neonatal ultrasound to select patients who should not undergo a VCUG. Applying well-defined ultrasound criteria, we have shown that in 61 babies with completely normal-appearing contralateral urinary tract on ultrasound examinations, only 4 (7%) have had low-grade VUR (I or II) on VCUG.

Our study does not address the endless debate concerning the necessity of diagnosing all cases of VUR. Yet, it should be remembered that there is enough evidence that only patients with high-grade disease really challenge us clinically. Our experience is that VUR in infants with MCDK was of low grade in 81% of cases with a high rate of spontaneous resolution. Furthermore, all patients with high-grade reflux had hydrenephrosis and/or hydroureter visualized on postnatal ultrasound and would have been anyway the subject of more intensive investigation (Table I). Although occasional cases of VUR could be missed by this approach, it seems reasonable to consider that the risk of missing low-grade reflux would be outweighed by the benefit of avoiding unnecessary invasive examinations in the majority of healthy infants. Furthermore, increasing parental awareness of symptoms of urinary tract infection by pediatric nephrologists and urologists could result in prompt self-referral of “missed” cases. Therefore, we believe that VCUG should not be used routinely in patients with antenatally diagnosed MCDK who have normal contralateral kidney on 2 successive neonatal ultrasound examinations.

In addition, the meticulous ultrasound assessment of the bladder and the genital system allowed us to diagnose or to suspect the presence of the majority of associated lower urinary tract abnormalities. When screening with 2 neonatal ultrasound examinations was negative, subsequent VCUG did not increase the diagnostic yield. Abnormalities missed by ultrasonography were all benign in nature and had no prognostic implications.

In contrast to previous reports, we showed that VUR has no influence on contralateral renal length in infants with MCDK. In our series, there was no difference in the extent of compensatory hypertrophy among contralateral kidneys with and without VUR (Table III).

Finally, perhaps one of the most critical variables rarely mentioned by different authors are the experience and personal involvement of the pediatric radiologist in performing renal ultrasound under standardized conditions, combined with the permanent dialogue and communication between physicians who are implicated in neonatal childcare.

**REFERENCES**

Florman reports 3 cases of recurrent bacterial parotitis in preschool-age children cared for at Mount Sinai Hospital in New York. He collects current data and thoughts about the disorder, reviews anatomy of the gland, and speculates on pathophysiology. We have not advanced much since, except to note many fewer cases, almost certainly related to the removal by means of universal immunization of mumps virus as an important primary necrotizing event. Florman’s analogy of the abnormalities of cystic dilatations seen on sialograms to bronchiectasis seems valid.

The microbiology of acute and recurrent bacterial parotitis has not changed much in 50 years. *Staphylococcus aureus* is a typical pathogen, especially as the cause of suppurative parotitis in the first 2 months of life, which is thought to be related to inspissated secretions or dehydration. Many common respiratory tract viruses can cause acute parotitis as their uncommon manifestation of infection. Recurrent episodes of bacterial parotitis are likely secondary to impaired drainage, and the bacteriology predominantly is that of normal mouth flora. Chronic, low-grade, relatively non-tender parotid infections have been associated with both *Bartonella henselae* and human immunodeficiency virus.

Ultrasound or computed tomography scanning replace the sialogram for most diagnostic needs. Differential diagnosis of parotid enlargement is broad and includes anatomic, metabolic, and immunologic disorders. Treatment for recurrent bacterial parotitis without calculi is very different than 50 years ago when antibiotic instillation through Stensen duct or radiography treatment was popular. Orally administered antibiotics, hydration, and the use of sialagogues (such as chewing gum) usually lead to prompt remission.

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SPEED OF SOUND: RELATION TO GEOMETRIC CHARACTERISTICS OF BONE IN CHILDREN, ADOLESCENTS, AND ADULTS
OLIVER FRICKE, MD, BAERBEL TUTLEWSKI, BERND SCHWAHN, MD, AND ECKHARD SCHÖNAU, MD

Objectives To investigate the relation between volumetric bone mineral density (vBMD) and speed of sound (SOS).

Study design Total and trabecular vBMD were measured by peripheral quantitative computed tomography at the forearm in a population of 216 individuals of a pediatric outpatient clinic. Moreover, SOS was measured by a quantitative ultrasound device (QUS) at the thumb, patella, and os calcis.

Results Linear regression analysis revealed that the prediction of SOS by vBMD is relatively weak ($R^2 < 0.1$). Moreover, body height and measures of bone size have a stronger influence on SOS than vBMD. The influence of bone size on SOS also depends on the location of measurement (highest prediction of SOS by body height at patella with $R^2 = 0.56$). Anthropometric characteristics have a stronger influence on SOS than measures of bone mineral density at the thumb and patella in comparison to os calcis (body height predicts SOS at os calcis, with $R^2 = 0.03$).

Conclusions QUS is not a suitable method to assess bone density. If QUS is applied for the assessment of bone development and of bone fracture risk, the measurement should be performed with consideration of anthropometric measurements. (J Pediatr 2005;146:764-8)

A variety of noninvasive methods is available to assess characteristics of the skeleton. The most widely applied method is to measure the relative absorbed energy of electromagnetic waves propagated through bone. This is the principle in all devices that are based on the use of x-rays and are called densitometric methods. There are two types of densitometric measurement. Dual-energy x-ray absorptiometry (DXA) is the most frequently used device for planimetric measurements, whereas quantitative computed tomography (QCT) represents the volumetric assessment of bone density.

Measurements with QCT possess an advantage over DXA measurements because they provide geometric characteristics of bone. Furthermore, geometric measures influence the results of planimetric measurements and describe mechanical characteristics of the skeleton, which are essential for mechanical stability.

Assessment methods based on x-ray are associated with ionized radiation. Therefore, the substitution of safer methods is advantageous, especially in children and adolescents with chronic diseases. In contrast to x-rays, sound waves oscillate longitudinally. However, similar to electromagnetic waves, they also follow the process of attenuation while propagating through the organism. Therefore, absorption depends on the density of the material in which the waves propagate. The propagating wave loses energy by diffraction and scattering, whereas these parameters depend on the structure, the specific acoustic properties of the medium, and the wavelength of the ultrasound signal.\(^1\)\(^2\)

Ultrasound has been recently introduced as a diagnostic tool for bone diseases.\(^3\) For example, broadband ultrasonic attenuation and speed of sound (SOS) are measures that are based on principles described above.\(^4\) The current study investigates the influence of bone geometry on SOS in children and adolescents. Our study aimed to assess data from a sample representative of a German university children’s hospital.

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BMD Bone mineral density
DXA Dual-energy x-ray absorptiometry
PKU Phenylketonuria
PQCT Peripheral QCT
QCT Quantitative computed tomography
QUS Quantitative ultrasound
SOS Speed of sound
SSI Strength-strain index
vBMDtot Volumetric total BMD
vBMDtrab Volumetric trabecular BMD

See related articles, p 726, p 769, and p 776.
METHODS

Subjects

Bone measurements were evaluated by pQCT and quantitative ultrasound (QUS) in 216 children, adolescents, and adults who were admitted to the Children’s Hospital of the University of Cologne. The subjects were distributed into the following groups: Ullrich Turner syndrome (n = 23; mean age, 13.8 ± 5.7 years), cystic fibrosis (n = 25; 15 male subjects; 10 female subjects; mean age, 21.4 ± 8.5 years), anorexia nervosa (n = 38; 1 male subject; 37 female subjects; mean age, 19.7 ± 3.7 years), idiopathic short stature (n = 25; 13 male subjects; 12 female subjects; mean age, 10.5 ± 3.8 years), phenylketonuria (PKU) (n = 74; 28 male subjects; 46 female subjects; mean age, 14.8 ± 7.2 years), and galactosemia (n = 31; 14 male subjects; 17 female subjects; mean age, 11.7 ± 7.0 years). In the group of patients with PKU and patients with short stature, 3 and 2 individuals, respectively, contributed to the data two times with an interval >1 year. All other individuals contributed to the data once. None of the subjects had a previously known fracture of one of the bones studied. The anthropometric characteristics of the entire study population are described in Table I. The current study was approved by the ethics committee of the university, and informed consent was obtained from all subjects as well as from their parents when the subjects were younger than 18 years of age.

Measurement of Bone Density

Bone density on the nondominant side of each subject was measured by pQCT (XCT 900; Stratec Medizintechnik GmbH, Pforzheim, Germany). A single tomographic slice of 2.5-mm thickness was taken at the site of the radius, whose distance to the medial border of the distal radial articular cartilage corresponded to 4% of forearm length. Forearm length was measured as the distance between the ulnar styloid processus and the olecranon using a caliper. Cross-sectional area was calculated after detecting the outer bone contour at a threshold of 280 mg/cm². Volumetric total bone mineral density (vBMDtot) and volumetric trabecular bone mineral density (vBMDtrab) were automatically analyzed from the tomographic image, using the manufacturer’s software. vBMDtot is defined as the mean density of the total cross section. vBMDtrab was defined as the mean mineral density of the 45% core area of the bone cross section.

Measurement of SOS

The SOS through bone is defined by the ratio of the traversed distance to the transit time, and it is expressed in meters per second. For the measurement of SOS a QUS device was used with frequencies between 200 to 600 kHz (Minhorst, Wiesbaden, Germany). The ultrasound equipment consisted of a transmitter and a receiver that are placed on opposite sides of the bone of interest. The diameter of the transducer was 10 mm. The ultrasound wave produced by the transmitter crosses the bone and is received by the second transducer. The distance and transmission time was measured by the caliper of the transducer. SOS was measured at three different locations that were not assumed to be largely different in the thickness of adipose tissue and skin. The transducers were mounted horizontally at the distal end of the proximal phalanx of the thumb, at the point of maximal transverse diameter of the patella, and os calcis midway between the processus lateralis tali and the tuber calcanei. Measurements were performed on the nondominant side and followed previous descriptions.

Table I. Anthropometric characteristics of the entire study population (N = 216)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [y]</td>
<td>15.4</td>
<td>7.3</td>
<td>14.0</td>
<td>3.0-43.0</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>149.1</td>
<td>22.0</td>
<td>154.0</td>
<td>95.0-188.0</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>43.3</td>
<td>17.6</td>
<td>43.5</td>
<td>13.0-90.0</td>
</tr>
<tr>
<td>vBMDtot [mg/cm³]</td>
<td>254</td>
<td>56</td>
<td>246</td>
<td>115-624</td>
</tr>
<tr>
<td>vBMDtrab [mg/cm³]</td>
<td>138</td>
<td>40</td>
<td>135</td>
<td>54-291</td>
</tr>
<tr>
<td>SOS-T [m/s]</td>
<td>2079</td>
<td>107</td>
<td>2067</td>
<td>1827-2331</td>
</tr>
<tr>
<td>SOS-C [m/s]</td>
<td>1697</td>
<td>48</td>
<td>1691</td>
<td>1592-1980</td>
</tr>
<tr>
<td>SOS-P [m/s]</td>
<td>2003</td>
<td>163</td>
<td>2003</td>
<td>1642-2427</td>
</tr>
</tbody>
</table>

Statistical Analyses

Linear regression analyses were performed for the prediction of SOS due to auxologic and bone specific parameters. In addition, the predictions of SOS were investigated by multiple regression analyses to reveal interactions between independent variables for the prediction of SOS. Partial correlations between independent variables are presented to detect connections between independent variables in the regression analyses. Moreover, multiple regression analyses provided β values for the assessment of the absolute part of contribution to the prediction of the dependent variable SOS by an independent variable. Least linear correlation coefficients were determined for SOS values assessed at different locations. The capital letter R indicates regression coefficients and lower-case r indicates correlation coefficients. Significant differences were ascribed at a value of P < .05. Statistical analyses were performed with PC Statistics 4.0 (Hoffmann-Software, Giessen).

RESULTS

The linear regression models showed weak correlations, with $R^2 < 0.10$ for the relation between SOS and bone mineral density (the maximum was $R^2 = 0.09$ for the prediction of SOS at the os calcis by vBMDtot; Table II and Figure). Body height was the strongest influence on the prediction of SOS (the maximum was $R^2 = 0.56$ for the prediction of SOS at the patella by height; Table II and Figure). The lowest influence of auxologic parameters on SOS was calculated for the os calcis ($R^2 = 0.03$ for the prediction by height; Table II and Figure).

When the predictions of SOS were performed for each disease separately, multiple regression equations predicting
were not significant at all three locations of measurement in every group. Only for the thumb was the prediction of SOS significant in all groups. Moreover, the subgroup of individuals with PKU was the only group with significant predictions of SOS at all 3 different locations of the skeleton. β values of measures of bone density (vBMDtot and vBMDtrab) had equal or lower β values than auxologic variables in the prediction of SOS in all groups and the total group of patients (Table III). This result is emphasized by the calculation of partial correlations between independent variables and SOS values. Significant correlations of bone density to SOS with a higher correlation coefficient than for auxologic parameters were only calculated for the os calcis (Table IV). Thereby, vBMDtot had a higher coefficient in absolute values than did vBMDtrab. SOS-T and SOS-P had a high significant correlation to each other (r = 0.75). In contrast, each of both locations showed a low significant correlation to SOS-C (r = 0.26 for SOS-T; r = 0.31 for SOS-P).

**DISCUSSION**

Our data on the correlation of SOS with growth measures are consistent with other studies.\(^5\)\(^-\)\(^8\) In the present data, the thumb and patella have similar SOS, in contrast to the os calcis. The os calcis is the only bone that has a significant partial correlation between vBMDtot and SOS in the entire group of patients (Table IV; r = 0.22 for the relation between vBMDtot and SOS-C). The absence of significant correlations between SOS at the alternative locations (thumb and patella) and bone density indicate that the significant prediction (linear regressions) of SOS by bone density is caused by the dependence of vBMDtot on auxologic parameters (r = 0.28 to 0.32 for the correlations between auxologic parameters and vBMDtot in the entire patient group; data not shown). Therefore, the cross-correlations

---

**Table II. Linear regression analysis**

<table>
<thead>
<tr>
<th>Predicted Variable</th>
<th>Equation</th>
<th>SE</th>
<th>R²</th>
<th>Equation</th>
<th>SE</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X = vBMDtot</td>
<td></td>
<td></td>
<td>X = vBMDtrab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOS-T</td>
<td>0.47 X + 1958</td>
<td>104</td>
<td>0.05</td>
<td>P &gt; .05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOS-C</td>
<td>0.27 X + 1629</td>
<td>45</td>
<td>0.09</td>
<td>0.23 X + 1664</td>
<td>47</td>
<td>0.04</td>
</tr>
<tr>
<td>SOS-P</td>
<td>0.81 X + 1796</td>
<td>156</td>
<td>0.07</td>
<td>P &gt; .05</td>
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<td></td>
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</tbody>
</table>

**Linear regressions: prediction of SOS by auxologic parameters, N = 216**

<table>
<thead>
<tr>
<th>Predicted variable</th>
<th>Equation</th>
<th>SE</th>
<th>R²</th>
<th>Equation</th>
<th>SE</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X = Height</td>
<td></td>
<td></td>
<td>X = Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOS-T</td>
<td>0.36 X + 1539</td>
<td>71</td>
<td>0.49</td>
<td>3.61 X + 1923</td>
<td>86</td>
<td>0.34</td>
</tr>
<tr>
<td>SOS-C</td>
<td>0.43 X + 1633</td>
<td>47</td>
<td>0.03</td>
<td>P &gt; .05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOS-P</td>
<td>5.57 X + 1173</td>
<td>107</td>
<td>0.56</td>
<td>5.81 X + 1752</td>
<td>127</td>
<td>0.38</td>
</tr>
</tbody>
</table>

The presented regression equations are significant (p < .05).

**Figure.** Prediction of SOS by height and vBMDtot in the entire study group (n = 216). Three graphs on the left show the relation between height and SOS at three different locations of measurement (thumb, os calcis, and patella). Height predicts SOS, with a higher \(R^2\) at the locations thumb and patella than at the location os calcis. Three graphs demonstrate the relation between vBMDtot and SOS on the right side. vBMDtot predicts SOS, with \(R^2 < 0.1\) at all three locations of measurement. The regression equations for prediction are presented in Table II.
between vBMDtot and auxologic parameters mainly contribute to the significant relation between vBMDtot and SOS-values.

Wuensche et al\textsuperscript{9} and Lequin et al\textsuperscript{10} showed SOS to be independent of age in children and adolescents. However, our data revealed a dependence of SOS on age for SOS-T and SOS-P, which was nearly similar or lower than the dependence of SOS on height (Table IV). However, the dependence of SOS on age can be explained by the high correlation between age and height in our entire study population ($R^2 = 0.78$ for the prediction of height by age, data not shown). As described above, the lowest dependence of SOS on body height and no dependence on age were revealed at the os calcis in our data, which are in concordance to the conclusions of previously published studies. The reason for the close relation between body height and SOS can be explained by the rules of skeletal development in children and adolescents in regard to the physical laws describing the propagation of sound waves in bones.

A close relation between body height and the geometry of the bone exists because the biomechanical forces applied to the skeleton depend on body height. This adaptation of skeletal system to its biomechanical environment is called modeling and follows the cybernetic rules of the mechanostat theory.\textsuperscript{11} A bone tube with a larger diameter has a smaller curvature of the cortical shell than a bone with a lower diameter. Therefore, a bone with a smaller curvature needs a relatively higher cortical thickness to resist forces causing side strain.\textsuperscript{12} The resistance of bone to biomechanical forces can be described as the set point in the feedback loop adapting the skeletal system to its biomechanical environment. Measurements of bone density reveal that vBMDtot remains stable between 6 and 15 years of age and then increases in both sexes.\textsuperscript{13} This increase of vBMDtot is mainly due to an increase in the cortical thickness at the distal radius. Thereby, the material density remains unchanged as a material constant.\textsuperscript{14}

SOS depends on elasticity and density of the bone described by the equation

$$\text{SOS} = \frac{\text{modulus of elasticity}}{\text{material density}}$$

The material density of the bone does not change during childhood and adolescence. The mass of tubular bones is mainly due to cortical thickness, which is dependent on applied mechanical forces. Moreover, the amount of applied mechanical forces depends on bone size and therefore on body height. As a result of an increase of bone size, cortical thickness is augmented, and therefore sound waves propagate at a longer distance through the cortical bone in larger skeletal elements. This results in the dependence of SOS on growth measures.

The os calcis is not a tubular bone, which might explain the different behavior regarding SOS. Mechanical forces applied to the os calcis derive mainly from pressure and not from side strain. This fact explains the relatively small cortical thickness of the os calcis. Therefore, in comparison to tubular bones, cross-correlations between SOS and auxologic parameters are less at the os calcis, which might explain the significant partial correlation between vBMDtot and SOS-C.

The poor correlation between SOS values at different skeletal locations and bone density at the forearm indicates that QUS cannot replace the classic assessment of bone mineral density by the use of devices based on x-rays. QUS follows different physical laws and therefore sound waves are

| Table III. Multiple regression analysis for the prediction of SOS (N = 216) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Age Beta       | Height Beta     | Weight Beta    | vBMDtot Beta   | vBMDtrab Beta  | constant        | $R^2$ | SE  |
| SOS-T           | 7.26          | 0.49           | 2.84           | 0.58           | -1.70          | -0.27           | 0.09 | 0.04 | -0.08 | -0.03 | 1606            | 0.65 | 63           |
| SOS-C           | -0.88         | -0.13          | 0.85           | 0.39           | -0.59          | -0.21           | 0.29 | 0.33 | 0.04  | -0.03 | 1541            | 0.12 | 45           |
| SOS-P           | 8.10          | 0.36           | 4.31           | 0.58           | -1.24          | -0.13           | 0.00 | 0.00 | 0.29  | 0.07  | 1248            | 0.60 | 101          |

All regression equations are significant ($p < .05$). The beta values are presented in the right column to the independent parameters.

| Table IV. Correlation coefficients of partial correlations for the prediction of SOS |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | SOS-T           | SOS-C           | SOS-P           |
| Norm <18 y      | Age: 0.85       |                  |                |
| Norm >18 y      | Age: -0.45      | Age: -0.46      |                |
| UTS             | Age: 0.75       | Weight: 0.49    | vBMDtrab: 0.47  | Age: 0.64       |
| CF              | Age: 0.51       |                  |                |
| AN              |                  | Age: 0.39       | Height: 0.47   |
| Short stature   | Height: 0.50    | Weight: -0.53   |                |
| PKU             | Height: 0.50    | Weight: -0.25   | vBMDtot: 0.33   | Age: 0.30       |
| Galactosemia    | Height: 0.56    | Weight: -0.53   | vBMDtot: 0.33   | Age: 0.30       |
| Total collective| Age: 0.44       | Height: 0.19    | Age: 0.32      |
| of patients     | Height: 0.41    | vBMDtot: 0.22   | Height: 0.40   |

Correlation coefficients of independent parameters are presented for different locations of SOS. All correlations are significant ($p < .05$).
influenced by different aspects of the bone as compared with x-rays crossing skeletal elements. Nevertheless, the question remains unanswered, if SOS represents useful characteristic of bone, which have an obvious dependence on bone geometry. The strength-strain index (SSI) could be such a measure. Because the partial volume effect is relatively high at the classic location for the measurement of bone mineral density at the forearm (4% site), SSI cannot be accurately determined by our data. However, a study focused on the relation between SSI at a proximal location of the radius (65% site) and SOS could elucidate, if SOS is a much better instrument for the investigation of bone stability than it is for bone material density. In this case, QUS might be a useful instrument for the assessment of bone fracture risk.

SUMMARY

Body height and therefore bone size has a strong influence on SOS. The amount of influence on bone size depends on the location of measurement of SOS. When measurements are taken at the thumb and patella, the anthropometric characteristics of the individual have a stronger influence on the value of SOS than parameters describing bone density. The neglect of anthropometric characteristics might explain differences of SOS data in different study populations. This dependence on anthropometric characteristics is an important issue in pediatrics because many diseases in children and adolescents influence growth and body height. Therefore, when a QUS device is used for the assessment of bone density, the measurement should be performed under the consideration of anthropometric characteristics of the skeletal element.

REFERENCES

LONGITUDINAL CHANGES IN BONE DENSITY IN CHILDREN AND ADOLESCENTS WITH MODERATE TO SEVERE CEREBRAL PALSY

RICHARD C. HENDERSON, MD, PHD, JOHN A. KAIRALLA, BS, PH, JOHN W. BARRINGTON, MD, ALMAS ABBAS, BS, AND RICHARD D. STEVENSON, MD

Objective  To assess the natural history of “growth” in bone mineral density (BMD) in children and adolescents with moderate to severe cerebral palsy (CP).

Study design  A prospective, longitudinal, observational study of BMD in 69 subjects with moderate to severe spastic CP ages 2.0 to 17.7 years. Fifty-five subjects were observed for more than 2 years and 40 subjects for more than 3 years. Each evaluation also included assessments of growth, nutritional status, Tanner stage, general health, and various clinical features of CP.

Results  Lower BMD z-scores at the initial evaluation were associated with greater severity of CP as judged by gross motor function and feeding difficulty, and with poorer growth and nutrition as judged by weight z-scores. BMD increased an average of 2% to 5%/y in the distal femur and lumbar spine, but ranged widely from +42%/y to −31%. In spite of increases in BMD, distal femur BMD z-scores decrease with age in this population.

Conclusions  Children with severe CP develop over the course of their lives clinically significant osteopenia. Unlike elderly adults, this is not primarily from true losses in bone mineral, but from a rate of growth in bone mineral that is diminished relative to healthy children. The efficacy of interventions to increase BMD can truly be assessed only with a clear understanding of the expected changes in BMD without intervention. (J Pediatr 2005;146:769-75)
The North American Growth in Cerebral Palsy (NAGCeP) Project is a multi-center, observational study of multiple issues related to growth and nutrition in children and adolescents with CP. One dimension of growth under investigation has been BMD. The purpose of this report is to delineate our findings on the longitudinal changes in BMD observed in a cohort of skeletally immature subjects with moderate to severe CP. The relationships between “growth” in BMD and nutritional status, general health, pubertal status as judged by Tanner stage, other measures of growth, and various clinical features of CP are examined.

METHODS

The NAGCeP Project is a 6-center study of children and adolescents with moderate to severe spastic CP. Excluded were children with recognized chromosomal abnormalities and children who were normal until a specific event or injury that occurred after 12 months of age resulted in their impairment. As detailed elsewhere, the NAGCeP evaluation included a detailed anthropometric assessment, Tanner staging of pubertal maturation, the Children’s Health Status Questionnaire, and complete medical and surgical history. Informed consent approved by each site’s Institutional Review Board was obtained for all participants.

Because of their close proximity, the University of North Carolina and Duke University collaborated as a single site in the NAGCeP Project. At this site 143 subjects have been enrolled, including 115 who were willing and able to have dual energy x-ray absorptiometry (DXA) measures of BMD. The initial baseline measures of BMD for most of this study group are included in a previous report. This was a convenience sample, but as described in the initial report the identification and recruitment process included newspaper notices, hospital and clinic records, pediatric physical therapists, handicap equipment vendors, special education teachers in the local school systems, and regional United Cerebral Palsy newsletters as means of obtaining a broadly based sample.

An attempt was made to obtain follow-up evaluations on all subjects initially enrolled. Of the 115 subjects who had a baseline measure of BMD, this report focuses on the 69 for whom a follow-up evaluation that included another measure of BMD was obtained. The remaining 46 subjects included 17 who at the end of data collection for this report were being actively recruited to obtain a follow-up evaluation, 11 who had aged out of the project (>19 years), 8 who had died, 5 who had moved from the state, 4 who were treated with bisphosphonates, and 1 who declined to participate further in the project. Ages of the 69 subjects at the time of their first evaluation ranged from 2.0 to 17.7 years, with a mean (± standard deviation) of 9.0 ± 3.7 years. There were 40 males, and 47 subjects were white.

The interval between the initial and second evaluations ranged from 1.5 to 49.7 months (median 21.5 months). Forty-six subjects have had a third evaluation, 25 a fourth evaluation, and 10 have had 5 to 9 evaluations that included measures of BMD. Thus there were a total of 164 follow-up evaluations.

Overall observation intervals for the 69 subjects ranged from 5.6 to 57.9 months (median 39.5 months), with 55 subjects observed for more than 2 years and 40 subjects for more than 3 years. Follow-up evaluations were done at the convenience of the participants, generally at the time of visits to the medical center for assorted clinical care appointments. Therefore the time interval between evaluations was variable.

Severity of CP

The degree of neurologic impairment was assessed on 2 different scales of potential relevance to BMD. The Gross Motor Function Classification assessment (GMFC) focuses on gross motor skills, particularly weight-bearing ambulation. GMFC level 3 subjects (n = 7) achieve independent sitting and by 4 years of age are ambulatory with assistive mobility devices and/or aid from an adult. GMFC level 4 subjects (n = 18) are minimally ambulatory, even with assistance, and have some difficulty with sitting trunk control. GMFC level 5 subjects (n = 44) lack independent motor function even for basic antigravity postural control.

Difficulty feeding a child with CP because of oral-motor dysfunction relates to his/her nutritional status. The care provider reported feeding difficulty on a categorical scale developed for this population as none (n = 21), mild (n = 12), moderate (n = 6), or severe (n = 30). The scale is based on whether the child has no problems with a regular diet (none category); has slight difficulty swallowing or feeding and requires some modification of foods (mild category); has moderate feeding difficulties, some difficulty swallowing liquids and requires moistened, mashed, or chopped foods (moderate category); or has a diet limited to well moistened solid foods, thickened fluids, and/or tube feedings (severe category).

Calcium Intake

Dietary calcium intake was readily determined in those children who were fed through feeding tubes, because the volumes and calcium content of prepared formulas and supplements are known. In children fed orally, calcium intake was estimated by use of a calcium-focused food frequency questionnaire. Determination of dietary calcium intake also included calcium supplements if regularly given to the child.

Total calcium intake from all sources was categorized as <700 mg/d (n = 14), 700 to 1200 mg/d (n = 25), and >1200 mg/d (n = 30).

Calcium intake and all other results of each subject’s evaluation were shared with the care providers. A pamphlet describing means of increasing calcium intake was provided if calcium intake was low. This was the only intervention in this otherwise observational study, and it likely did have some impact. Calcium intake was found to be <700 mg/d at only 11 of the 164 follow-up evaluations, as compared with 14 of the 69 initial evaluations.

DXA Measures of BMD

Bone density was measured in the lumbar spine using standard techniques. Bone density was also measured in both distal femurs with the subject positioned in the lateral...
position, a scanning technique developed specifically to deal with the contractures common in this population.19,20 The distal femur is divided into 3 separate regions for analysis. Distal femur Region 1 is located within the metaphysis just proximal to the growth plate. Region 3 is the distal portion of the femoral diaphysis, and Region 2 is the region of transition between the broad metaphysis (Region 1) and narrow femoral shaft (Region 3). These regions are defined such that Region 1 is primarily cancellous bone, and Region 3 is primarily cortical bone. Corresponding left and right side measurements were averaged and the mean used for subsequent analyses. Measures of BMD were also converted to age, sex, and for lumbar spine BMD, race-normalized z-scores.1,20

The Hologic (Waltham, Mass) model 1000W scanner was used for 61 of the initial evaluations. Transition to the newer, faster fan-beam Delphi model scanner was made over the course of this project, and utilized for 8 of the initial evaluations and 102 of the 164 follow-up evaluations. Exchange of calibration spine phantoms and same-day scanning of subjects on both machines confirmed reliability of pooling results from the 2 scanners.

DXA measures of BMD are particularly difficult to obtain in this population because of contractures, metallic fixation devices, and motion artifact that result from involuntary muscle spasms and an inability to cooperate. For these reasons a reliable measure of lumbar spine BMD was not obtained on 23 of the 233 evaluations and was not obtained in the distal femur of either limb on 37 of the evaluations.

Statistical Analyses

Multiple variables related to growth, nutrition, CP, and general health are correlated with BMD z-scores observed at the initial evaluation (Table I). However, the primary outcome variable of interest in this study is the rate of change in BMD during an observation interval expressed as an annualized rate of percentage change (Table II):

\[
\% \Delta \text{BMD} = \frac{\text{Evaluation B BMD} - \text{Evaluation A BMD}}{\text{Evaluation A BMD}} - \frac{\text{Time between Evaluation A and B}}{\text{Year}}
\]

Considerable attention was given to the selection of observation intervals that were used in the analyses. The precision of duplicate measures is approximately 3% (personal observation) in this difficult-to-scan pediatric population. With small changes in BMD the imprecision in the measurement becomes a potentially more significant component of the apparent change. Further, with short observation intervals the calculation of annualized % Δ BMD involves dividing by time less than 1 year and effectively multiplies any potential error. Therefore in selecting the observation intervals for determination of % Δ BMD/y, we excluded observation intervals of <6 months, and intervals of 6 to 12 months were used only if longer intervals for that particular subject were not available. As examples, a subject with evaluations at times 0, 5 months, and 16 months had only the observation interval 0 to 16 months selected for the analyses. Similarly, a subject with evaluations at times 0, 13, 20, and 38 months had the 2 intervals of 0 to 13 months and 13 to 38 months included in the analyses. In this latter example the baseline evaluation for the second observation interval was also the follow-up evaluation for the first interval.

After this selection process, there were 97 observation intervals with reliable measures of lumbar spine BMD, and 90 intervals with reliable measures of distal femur BMD. The length of the individual observation intervals is shown in the scatter plot of % Δ BMD as a function of the observation interval (Figure). There is considerable evidence in adult and other pediatric populations that immobilization associated with fractures and/or surgical osteotomy procedures in the lower limbs significantly impacts on BMD.21-23 Therefore 13 distal femur BMD intervals (7 fracture and 6 femoral osteotomy events) in which this occurred either less than 6 months before or any time during the interval were removed from the data set.

Multiple variables related to growth, nutrition, CP, and general health were each correlated with the % Δ BMD/y using regression analyses (Table III). Whether the baseline measure of the particular variable, or the mean of the baseline and follow-up measures were used in the analyses did not affect the findings. Therefore results are presented using the baseline evaluation data. Also correlated with % Δ BMD/y

### Table I. Bone density z-scores at the initial evaluation

<table>
<thead>
<tr>
<th>Region</th>
<th>Distal femur* (Mean ± SE)</th>
<th>Lumbar spine (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 2.0 - 5.9 y</td>
<td>-2.4 ± 0.4</td>
<td>-2.8 ± 0.3</td>
</tr>
<tr>
<td>6.0 - 11.9 y</td>
<td>-3.0 ± 0.2</td>
<td>-1.7 ± 0.2</td>
</tr>
<tr>
<td>12.0 - 19.4 y</td>
<td>-3.4 ± 0.4</td>
<td>-2.3 ± 0.4</td>
</tr>
</tbody>
</table>

GMFC

<table>
<thead>
<tr>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 3</td>
<td>-1.4 ± 0.4</td>
<td>-1.2 ± 0.4</td>
</tr>
<tr>
<td>Level 4</td>
<td>-2.7 ± 0.3</td>
<td>-1.9 ± 0.3</td>
</tr>
<tr>
<td>Level 5</td>
<td>-3.4 ± 0.2</td>
<td>-2.4 ± 0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 3</td>
<td>0.0005</td>
</tr>
<tr>
<td>Level 4</td>
<td>0.0006</td>
</tr>
<tr>
<td>Level 5</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Feeding difficulty

<table>
<thead>
<tr>
<th>Level 1 or 2</th>
<th>Level 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 or 2</td>
<td>-2.3 ± 0.2</td>
</tr>
<tr>
<td>Level 3 or 4</td>
<td>-3.5 ± 0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>0.0006</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.13</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.02</td>
</tr>
<tr>
<td>Level 4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Level 5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Based on the mean of the 3 regions.
were changes in various measures of growth and nutrition that occurred over the observation interval (Table IV). All continuous variables were analyzed as such (*t* tests using the Pearson correlation coefficients), although they are categorically presented for clarity. Categorical variables were analyzed with the Jonckheere-Terpstra nonparametric trend test.

**RESULTS**

At their initial evaluation, BMD was generally quite low in this cohort of moderate to severely involved children and adolescents (Table I). Lower distal femur BMD *z*-scores were associated with greater severity of CP (GMFC level, feeding difficulty), poorer growth and nutrition (*weight* *z*-scores), and advancing age.

Rate of change in BMD over the multiple observation intervals was similar in the 4 measurement regions, with median increases of 2% to 5%/y. However, as shown in Table II, BMD *z*-scores in the 3 regions of the distal femur on average decreased in spite of the increases in BMD. This reflects that the increases in BMD observed in these children with CP were less than the increases expected in healthy children. Of note, the observed rates of change varied widely, ranging from an increase in BMD of 42%/y, to a loss of 31%/y (Figure, Table II). For two thirds of the subjects, however, the observed rate of change in BMD was between a loss of 1% to 7%/y and an increase of 10% to 13%/y.

No baseline variable was found to be a consistently strong predictor of subsequent change in BMD (Table III). The most significant variable was nutritional status as assessed by triceps skinfold *z*-scores. Better nutritional status was associated with greater %Δ*BMD*/y in the lumbar spine and distal femur Regions 2 and 3. Rate of change in BMD was not found to be statistically significantly related to age, sex, Tanner stage, use of anticonvulsants, GMFC level, difficulty feeding the child, height, weight, or general health as assessed by the Children’s Health Status Questionnaire (all *P* > .05).

Growth over the observation interval as measured by weight gain tended (*P* < .1) to be associated with greater gains in %Δ*BMD*/y (Table IV). Changes in BMD in the 3 regions of the distal femur were strongly associated with each other, but not with %Δ*BMD*/y in the lumbar spine. The correlation was greatest between Regions 2 and 3 (*r*² = 0.58, *P* < .0001) and weakest between Regions 1 and 3 (*r*² = 0.08, *P* = .01).

**DISCUSSION**

Only in recent years has the clinical problem of osteopenia received much attention in pediatrics. The tendency is to apply established concepts of osteopenia in adults to pediatrics. However, a longitudinal study such as this highlights one very significant difference between osteopenia in children and elderly adults. In the latter, the osteopenia develops because of a loss in BMD over time. In the former, it was found that although periods of true loss in BMD did occur, most often BMD is actually increasing. Osteopenia occurs primarily because the increases in BMD are less than in normal children.

It is therefore appropriate to view osteopenia in this population as one manifestation of a growth failure. The observed relationship between increases in weight and increases in BMD further substantiate this concept. It is well known
that poor nutrition contributes to diminished growth. In this study diminished growth in BMD was associated with poor nutritional status as reflected by triceps skinfolds and suggests a potential target for intervention.

When discussing bone density and growth, it is very important to recognize that BMD as measured with DXA is an areal density (gm/cm²) and not a true volumetric density (gm/cm³). Areal bone density may be diminished relative

<table>
<thead>
<tr>
<th>Table III. Rate of change in bone density vs various baseline measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualized % Change in BMD (%/year)</strong></td>
</tr>
<tr>
<td>(Distal femur)</td>
</tr>
<tr>
<td>Region 1 (mean ± SE)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>2.0 - 5.9 y</td>
</tr>
<tr>
<td>6.0 - 11.9 y</td>
</tr>
<tr>
<td>12.0 - 19.4 y</td>
</tr>
<tr>
<td>P = .02</td>
</tr>
</tbody>
</table>

| GMFC               |                         |                         |                         |
| Level 3 or 4       | 4.3% ± 1.5%            | 5.1% ± 1.4%            | 5.4% ± 1.5%            | 5.3% ± 1.2% |
| Level 5            | 0.8% ± 1.6%            | 4.1% ± 1.4%            | 3.4% ± 0.9%            | 4.1% ± 1.2% |
| P = .10            | P > .2                 | P > .2                 | P > .2                 |

| Feeding difficulty |                         |                         |                         |
| Level 1 or 2       | 3.9% ± 1.2%            | 4.2% ± 1.2%            | 4.4% ± 1.1%            | 5.4% ± 0.9% |
| Level 3 or 4       | 0.5% ± 1.9%            | 4.8% ± 1.7%            | 4.0% ± 1.2%            | 3.8% ± 1.5% |
| P = .07            | P > .2                 | P > .2                 | P > .2                 |

| Anticonvulsants    |                         |                         |                         |
| Yes                | 0.7% ± 1.8%            | 4.0% ± 1.7%            | 3.8% ± 1.1%            | 4.5% ± 1.6% |
| No                 | 3.7% ± 1.3%            | 5.0% ± 1.2%            | 4.6% ± 1.2%            | 4.8% ± 0.8% |
| P = .15            | P > .2                 | P > .2                 | P > .2                 |

| General health z-score |                         |                         |                         |
| < -1.5               | -2.1% ± 2.4%           | 5.0% ± 2.3%            | 6.0% ± 1.4%            | 5.5% ± 3.5% |
| -1.5 to 0            | 2.1% ± 1.9%            | 5.6% ± 1.5%            | 4.9% ± 1.2%            | 3.8% ± 1.2% |
| >0                   | 3.6% ± 3.3%            | 2.3% ± 2.0%            | 2.9% ± 1.3%            | 4.1% ± 1.2% |
| P = .11              | P > .2                 | P = .19                | P > .2                 |

| Triceps skinfold    |                         |                         |                         |
| <10%ile             | -0.7% ± 2.7%           | -0.8% ± 2.0%           | 0.0% ± 1.5%            | 2.5% ± 1.5% |
| 10 – 50%ile         | 5.2% ± 2.1%            | 6.1% ± 1.1%            | 5.1% ± 1.0%            | 4.6% ± 1.5% |
| >50%ile             | 1.5% ± 1.3%            | 6.8% ± 1.8%            | 6.3% ± 1.3%            | 6.8% ± 1.4% |
| P > .2               | P = .01                | P = .008               | P = .02                |

| Calcium intake      |                         |                         |                         |
| <700 mg/d           | 1.6% ± 4.1%            | 1.0% ± 2.8%            | 2.6% ± 2.5%            | 7.9% ± 3.1% |
| 700 – 1200 mg/d     | 0.2% ± 2.0%            | 6.5% ± 2.0%            | 4.7% ± 1.4%            | 4.6% ± 1.2% |
| >1200 mg/d          | 3.9% ± 1.4%            | 3.7% ± 1.2%            | 4.2% ± 1.1%            | 3.9% ± 1.2% |
| P = 0.11            | P > .2                 | P > .2                 | P > .2                 |

| Weight z-score      |                         |                         |                         |
| < -2.5              | 1.3% ± 2.4%            | 2.2% ± 1.6%            | 2.4% ± 1.3%            | 2.8% ± 1.4% |
| -2.5 to -1          | 3.2% ± 1.8%            | 6.0% ± 1.5%            | 5.8% ± 1.4%            | 6.6% ± 1.1% |
| >-1                 | 1.8% ± 1.6%            | 5.8% ± 2.3%            | 4.8% ± 1.5%            | 5.2% ± 1.1% |
| P > .2               | P = .18                | P > .2                 | P > .2                 |

| Distal femur BMD z-score |                         |                         |                         |
| < -3.5               | 3.7% ± 2.2%            | 8.1% ± 2.0%            | 5.0% ± 1.4%            | 4.1% ± 2.7% |
| -3.5 to -2.5         | 3.5% ± 2.4%            | 2.7% ± 1.5%            | 3.6% ± 1.1%            | 6.4% ± 1.5% |
| >-2.5                | -0.6% ± 1.3%           | 2.8% ± 1.7%            | 3.8% ± 1.6%            | 4.3% ± 1.7% |
| P > 0.2              | P = .05                | P > .2                 | P > .2                 |

*Based on the mean of the 3 regions.
to age-matched healthy children because of a true decrease in volumetric density, or because of differences in the 3-dimensional structure of the bone.\textsuperscript{24,25} A diminished outer diameter of the bone or thinning of the cortex will both result in diminished areal bone mineral density as measured with DXA. However, the diameter of a cylindrical bone and the thickness of the cortex are both important mechanical parameters that significantly impact on the ability of a bone to withstand loads without fracture. Clearly, the changes in bone “density” measured in these children involve more than just changes in true volumetric density.

Multiple factors including mobility (GMFC level), feeding dysfunction, nutritional status, and other measures of growth were found here and in other single observational studies to correlate with BMD z-scores in persons with CP.\textsuperscript{1,5,26,27} Yet none of these variables were found in the longitudinal portion of this study to have a statistically significant ($P < .05$) correlation with the observed $\% \Delta \text{BMD}/\text{y}$. Likely lack of statistical power accounts for the absence of more positive findings. For example, $\% \Delta \text{BMD}/\text{y}$ in the lumbar spine averaged 5.4%/y in children with little or no feeding dysfunction and 3.8%/y in those children with moderate or severe feeding dysfunction ($P > .05$, Table III). This is consistent with what one might predict, that significant feeding problems could impair growth in BMD. However, it would require an $n$ of roughly 400 in each group to find that this difference was statistically significant (power analysis with alpha = 0.05, power = 0.2). Factors such as immobility and feeding dysfunction do impact on BMD, and in a simple cross-sectional study the cumulative affect over the course of the child’s life is apparent (Table I). However, very considerable statistical power is required to detect these effects in an annual rate of change in BMD.

Osteopenia resulting in frequent fractures is a significant problem in children with physical disabilities, and there is increasing interest in developing treatment strategies. Bone density $z$-scores typically decrease with aging in persons with CP, in spite of increases in BMD that average 2%-5%/y. Wide variation is noted, however, and periods of true loss in BMD do occur. Researchers investigating the benefits of various interventions must recognize the considerable statistical power required to prove efficacy, even if the intervention improves BMD 3%-5%/y, a treatment effect generally considered to be of tremendous clinical value in elderly adult populations. Clinicians deciding whether to treat osteopenia in this or any other pediatric population should have a clear understanding of the changes likely to occur in bone density without intervention.

\textit{We thank Mark Conaway, PhD, University of Virginia Department of Health Evaluation Sciences for his guidance with the statistical analyses.}

### Table IV. Rate of change in bone density vs change in other measures

<table>
<thead>
<tr>
<th></th>
<th>Region 1 (mean ± SE)</th>
<th>Region 2 (mean ± SE)</th>
<th>Region 3 (mean ± SE)</th>
<th>Lumbar spine (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6%/y</td>
<td>1.2% ± 2.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6%-14%/y</td>
<td>1.4% ± 2.2%</td>
<td>3.1% ± 1.2%</td>
<td>3.1% ± 1.3%</td>
<td>4.2% ± 1.7%</td>
</tr>
<tr>
<td>&gt;14%/y</td>
<td>4.1% ± 1.7%</td>
<td>5.9% ± 2.1%</td>
<td>6.2% ± 1.7%</td>
<td>4.7% ± 1.4%</td>
</tr>
<tr>
<td><strong>Height change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm/y</td>
<td>2.7% ± 2.1%</td>
<td>4.4% ± 1.7%</td>
<td>3.7% ± 1.5%</td>
<td>6.1% ± 1.0%</td>
</tr>
<tr>
<td>2-4 cm/y</td>
<td>0.3% ± 2.4%</td>
<td>4.2% ± 1.5%</td>
<td>3.7% ± 1.3%</td>
<td>3.5% ± 1.6%</td>
</tr>
<tr>
<td>&gt;4 cm/y</td>
<td>3.2% ± 1.6%</td>
<td>4.8% ± 2.1%</td>
<td>4.8% ± 1.4%</td>
<td>4.8% ± 1.4%</td>
</tr>
<tr>
<td><strong>Triceps change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;0 mm/y</td>
<td>2.2% ± 2.4%</td>
<td>5.3% ± 1.4%</td>
<td>4.9% ± 1.7%</td>
<td>4.1% ± 1.9%</td>
</tr>
<tr>
<td>0-1.5 mm/y</td>
<td>0.6% ± 2.0%</td>
<td>3.6% ± 1.8%</td>
<td>3.5% ± 1.2%</td>
<td>2.6% ± 1.1%</td>
</tr>
<tr>
<td>&gt;1.5 mm/y</td>
<td>3.8% ± 1.8%</td>
<td>5.4% ± 2.2%</td>
<td>4.4% ± 1.4%</td>
<td>6.8% ± 1.1%</td>
</tr>
</tbody>
</table>

**REFERENCES**


BONE DENSITOMETRY IN PEDIATRIC POPULATIONS: DISCREPANCIES IN THE DIAGNOSIS OF OSTEOPOROSIS BY DXA AND CT

TISHYA A. L. WREN, PhD, XIAODONG LU, MD, PhD, PISIT PITUKCHEEWANONT, MD, AND VICENTE GILSANZ, MD, PhD

Objectives To test the hypothesis that because of errors associated with growth and development, osteoporosis is frequently overdiagnosed in children when using dual-energy x-ray absorptiometry (DXA). This study compared bone density values obtained by DXA with those from computed tomography (CT), which is not influenced by body or skeletal size.

Study design Vertebral bone density was measured by using both DXA and CT in 400 children (100 each, healthy and sick boys and girls). Regression analysis was used to compare DXA and CT Z scores, and the agreement between DXA and CT classifications of Z scores below -2.0 was examined.

Results DXA and CT Z scores were moderately related ($r^2 = 0.55$ after accounting for age and anthropometric measures). DXA Z scores predicted CT Z scores below -2.0 with reasonable sensitivity (72%), specificity (85%), and negative predictive value (98%), but positive predictive value was low (24%). Many more subjects were classified as having bone density lower by DXA (76/400) than by CT (25/400), particularly subjects below the 5th percentile of height and/or weight for age.

Conclusions The inability of DXA to account for the large variability in skeletal size and body composition in growing children greatly diminishes the accuracy of this projection technique for assessing bone acquisition and diagnosing osteoporosis in pediatric populations. (J Pediatr 2005;146:776-9)

Dual-energy x-ray absorptiometry (DXA) is the most widely used technique for measuring bone acquisition in children because of its low cost, minimal radiation exposure, accessibility, and ease of use. The availability of DXA has resulted in many large-scale studies of the genetic and environmental determinants of areal bone mineral density (aBMD) in healthy children. Although DXA studies in pediatrics have provided much information regarding changes in aBMD over time, there is still considerable confusion over the interpretation of DXA measures. Most growth-related increases in DXA aBMD values are due to increases in the size rather than the density of the bone, and sex differences in aBMD values are also largely the result of greater bone size in male subjects.

The confounding effect of skeletal geometry on DXA measures is gaining much recognition. Recently, it has been suggested that major errors in interpretation occur when using this technique in pediatric populations, leading to the overdiagnosis of osteoporosis in growing subjects. Indeed, several investigators have proposed that osteoporosis should not be diagnosed on the basis of DXA densitometry criteria alone. In addition, whereas in adults, DXA aBMD is a powerful predictor of fracture and is used to define osteoporosis, there is insufficient pediatric evidence to determine aBMD standard deviation criteria for osteopenia and osteoporosis, as indicated by the World Health Organization. Hence, it is recommended that when reporting DXA results in subjects younger than 20 years of age, it is more appropriate to define a Z score of less than -2.0 as low bone density rather than using the World Health Organization classification for osteoporosis.

In this study, we examined the relation between vertebral DXA measurements of aBMD and vertebral quantitative computed tomography (CT) values of volumetric bone density (vBD), which are not influenced by skeletal or body size, in a large cohort of healthy and sick children. We specifically examined the relation between DXA and CT Z scores, which are defined as the number of standard deviations the aBMD or vBD is above or below the mean for age-matched control subjects.

See related articles, p 726, p 764, and p 769.
METHODS

Study Subjects

During the past 5 years, many children and adolescents have had bone measurements through the use of both CT and DXA at Children’s Hospital Los Angeles. This retrospective review included the records from 100 healthy boys and 100 healthy girls who were participants in several studies on bone acquisition during growth and from 100 sick boys and 100 sick girls. For the purpose of this study, “sick” subjects were defined as patients being evaluated for bone mass deficiency. The protocol was approved by the institutional review board for clinical investigations at our institution. Written informed consent was obtained from all healthy subjects and their parents. Data from the sick subjects were reviewed retrospectively under a waiver of consent approved by the institutional review board.

All 400 subjects, ages 6 to 17 years, were enrolled in this study. Age, height, and weight were recorded for each. Measurements of total height were obtained to the nearest 0.1 cm, using the Harpenden stadiometer (Holtain Ltd, Crymmych, Wales), and measurements of weight were obtained to the nearest 0.1 kg, using the Scale-Tronix (Scale-Tronix, Inc, Wheaton, Ill). Height, weight, and body mass index (BMI) percentiles-for-age were determined by using the references provided by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion.

CT and DXA Assessments of Vertebral Bone

The technique for determining lumbar vertebral bone density by quantitative CT has been described in detail elsewhere. All CT studies were performed by the same radiology technologist, using the same scanner (CT-T 9800; General Electric Co, Milwaukee, WI) and the same mineral reference phantom (CT-T bone densitometry package; General Electric Co, Milwaukee, WI). Identification of the sites to be scanned was performed with lateral scout views, and the density of cancellous bone in the vertebral body was obtained from the 10-mm midportion of the L1, L2, and L3 vertebral bodies. The average density of L1-L3 was calculated aBMD for each vertebral body as well as Z score for the average L1-L4 aBMD (Z_{DXA}). The time required for the procedure was approximately 5 minutes, and the radiation exposure was negligible.

Statistical Analysis

Statistical analysis was carried out with the use of Statview (version 5.0.1; SAS Institute Inc, Cary, NC) and Stata (version 8.0; Stata Corp, College Station, TX). Linear regression was used to compare Z_{DXA} with Z_{CT}, both in simple regression and in multiple regression, including age, height, weight, BMI, height percentile, weight percentile, and BMI percentile as covariates. After the regression analysis, the ability of DXA Z scores to predict CT Z scores below −2.0 was examined. Sensitivity (proportion of subjects with CT Z scores below −2.0 who also had DXA Z scores below −2.0), specificity (proportion of subjects with CT Z scores above −2.0 who also had DXA Z scores above −2.0), positive predictive value (proportion of subjects with DXA Z scores below −2.0 who also had CT Z scores below −2.0), and negative predictive values (proportion of subjects with DXA Z scores above −2.0 who also had CT Z scores above −2.0) were calculated.

RESULTS

Table I summarizes the anthropometric measurements for all subjects.

A significant linear relation was observed between Z_{DXA} and Z_{CT} (r^2 = 0.39; P < .0001) (Figure). This relation was improved when age and anthropometric measures were included in the regression model (r^2 = 0.55). Results for subgroups divided by health status (healthy or sick) and sex were similar to the overall results (r^2 values of 0.27 to 0.48 for single regression, 0.51 to 0.65 for multiple regression).

When DXA Z scores were used to predict CT Z scores below −2.0, sensitivity and specificity were reasonable and negative predictive value was extremely high. However, positive predictive value was low (Table II). This was true whether all subjects were analyzed together or sick and healthy subjects were analyzed separately. For the subjects who were classified differently by CT and DXA, many more were identified as having bone density lower by DXA (58/400) than by CT (7/400). Of the 58 subjects who were identified by DXA only, most were small for their age (<5th percentile) in terms of height (30/58, 52%), weight (22/58, 38%), or both height and weight (17/58, 29%).

DISCUSSION

Currently, DXA is routinely used worldwide in children to diagnose osteoporosis, assess response to therapy, and study the determinants of bone accretion during growth. The results of the current study indicate, however, that DXA measures of aBMD underestimate bone accretion in children and adolescents. On average, 3 times as many subjects were determined to have low bone density (Z score < −2.0 for chronological age) by DXA than by CT; this was true for both healthy (2% vs 7%) and sick (10.5% vs 31%) children.

We found that whereas DXA and CT Z scores are related, almost 50% of the variability remains even after age...
and anthropometric measures are taken into account. When classifying low bone density based on a $Z$ score cutoff value of $-2.0$, DXA had a reasonable sensitivity and specificity in predicting CT classification, but positive predictive value was low. This is partly due to DXA underestimating bone density and overestimating osteoporosis in children who are small for their age (<5th percentile for height and/or weight), since bone size tends to increase with greater height and weight. The consequence is that DXA $Z$ scores $\geq -2$ have greater concordance with CT $Z$ scores than do DXA $Z$ scores $<-2$, which require further screening to confirm osteoporosis.

Since this study involved two specific bone densitometers, the findings may differ with equipment of other manufacturers. The systematic overreading of low bone mass by DXA may, in fact, be the result of the currently available Hologic reference data. When using values from the healthy children in the current study to calculate $Z$ scores for the sick children, the tendency of DXA to yield lower $Z$ scores than CT was greatly curtailed, although comparisons with this database did not strengthen the correlation between DXA and CT $Z$ scores. Although many children were identified as having low bone density by one modality but not the other, they were more evenly split with regard to which technique yielded the $<-2$ classification. Consequently, discrepancies probably will exist between DXA and CT assessments of low bone density regardless of the reference data used.

In addition, the discrepant results between DXA and CT classifications are, in part, due to the errors associated with the unknown composition of soft tissues adjacent to the axial skeleton. Because corrections for soft tissues are based on the assumption of a homogenous distribution of fat around the vertebrae, changes in DXA measurements are observed if fat is distributed inhomogeneously around the bone measured. It has been estimated that inhomogeneous fat distribution in soft tissues resulting in a difference of 2 cm of fat between the soft tissue and bone areas will influence DXA measurements by 10%. This disadvantage especially limits the use of DXA in studies of children with eating disorders, such as obesity and anorexia nervosa.

Last, the lack of a definable association between pediatric bone density values and a clinical outcome measure obfuscates the significance of these measurements in children.

The relation of bone measurements to pediatric fractures is, at
CONCLUSIONS

The interpretation of DXA measurements is considerably more challenging in children and adolescents than in adults because of the dynamic changes in body and skeletal size and configuration associated with growth and sexual development. The results of this study support the contention that current DXA bone determinations frequently underestimate the amount of bone in children regardless of age, sex, or whether they are healthy or sick. The immediate challenge is to obtain valid interpretations of DXA bone measurements in pediatrics so that a subclinical deficiency in bone accrual can be identified accurately in “at risk” children. To this end, greater understanding of the DXA errors associated with variations in growth and development and the methods to correct for size bias and soft tissue distribution is needed.

REFERENCES

Objectives  To compare neuropsychological and psychosocial function in children with a history of snoring, children with a history of behavioral sleep problems (BSP), children with both a history of snoring and BSP, and a group of control subjects.

Study design  Families awaiting consultation for “sick” visits in 5 general practice clinics completed the Sleep Disturbance Scale for Children. A subset of children were categorized into groups: Snorers (n = 11), BSP (n = 13), Snorers+BSP (n = 9), and controls (n = 31). Children underwent psychological (Wechsler Abbreviated Scale of Intelligence, Children’s Memory Scale; Test of Everyday Attention and Auditory Continuous Performance Test) and psychosocial assessment (Child Behavior Checklist).

Results  With analysis of variance, it was revealed that, compared with children in the BSP and control groups, those in the Snorers+BSP and Snorers groups showed reduced intelligence and attention scores. By contrast, compared with children in the Snorers and control groups, children in the Snorers+BSP and BSP groups reported reduced social competency, increased problematic behavior, and reduced memory scores. Children in the combination of Snorers+BSP group showed more deficits than children in all other groups.

Conclusion  In children, snoring and BSP, separately and together, are associated with impaired neuropsychological and psychosocial functioning. Furthermore, snoring and BSP are related to performance in disparate ways. Snoring was associated with intelligence and attention deficits, whereas BSP was associated with memory and behavioral deficits. (J Pediatr 2005;146:780-6)

The critical role of sleep and sleep disturbances in daytime functioning is becoming increasingly apparent. Of particular interest is the relationship between sleep disturbances and neuropsychological and psychosocial functioning. In adults, sleep disturbance caused by sleep disorders or experimental sleep fragmentation is associated with cognitive deficits and mood disturbances.1,2 In children, there is mounting evidence that insufficient sleep or sleep disruption results in similar deficits.3,4,5 The most abundant available information about the effects of pediatric sleep disturbance on daytime function is in children with sleep disordered breathing (SDB). The underlying pathophysiological mechanisms for these deficits include hypoxia caused by obstructive apneas/hypopneas and disrupted sleep architecture from frequent arousals during sleep.6-11

Neuropsychological and psychosocial dysfunction may result from sleep disturbances not associated with hypoxia, suggesting that disturbance of sleep architecture per se may be a significant contributor to daytime deficits. Children who snored but did not demonstrate hypoxia or demonstrable upper airway obstruction showed deficits in the Wilkinson Addition Test12 or improved their scores on the cognitive tests when snoring was treated.13 In a large study of snoring children (n = 851),14 a significant negative relationship was found between academic performance and snoring that was not mediated or affected by hypoxia. In addition, significant psychosocial dysfunction has also been reported in non-hypoxic snores.12 This implies that in children with non-hypoxic snoring, psychosocial and cognitive sequelae may ensue. It is unclear whether the same is true for non-hypoxic...
sleep disorders that disrupt sleep architecture, such as behavioral sleep problems (BSP). Children with a disruption of sleep architecture or whose sleep was experimentally restricted were reported to show daytime psychosocial dysfunction. One way to better understand the impact of sleep disruption on neuropsychological and psychosocial functioning in children is to compare groups of children with symptoms of common sleep problems that disrupt sleep architecture. Common sleep problems in children that disrupt sleep and have been reported to result in daytime sequelae are habitual snoring (reported in 8%-12% of children) and BSP (reported in 15%-41% of children). The aim of this study was to assess the neuropsychological and psychosocial function in children whose parents report varying levels of sleep disturbance: children who snore, children with BSP, children with both snoring and BSP, and control subjects.

METHODS

Subjects

As part of a larger 8 month study, 19 parents of children aged 0 to 16 years who were awaiting consultation for “sick” visits were asked by medical staff at 5 demographically similar general practices in South Australia to complete the Sleep Disorders Scale for Children (SDSC). As estimated with clinic records of average weekly attendance, the percentage of all visiting parent/child pairs who actually completed the survey at the 5 general practices ranged from 19% to 34% (mean, 26.4%). This figure was limited by the availability of busy reception staff to approach parent/child pairs. Although exact figures were not available, on the basis of approximations of reception staff and returned questionnaires, we estimate that 90% of attendees participated. From the total sample (n = 645), school-aged children aged 6 to 16 years (n = 361) who matched our inclusion criteria (n = 166) were invited to participate in neuropsychological and psychosocial assessment. Inclusion was based on the parent’s responses (with the child’s response when age appropriate) on the SDSC at the time of consultation to the snoring item (see question 1) and items from the Disorders of Initiating and Maintaining Sleep factor (referred to as BSP; see questions 2-8): 1) Does your child snore? 2) How many hours does your child sleep on most nights? 3) How long after going to bed does your child get to sleep? 4) Does your child go to bed reluctantly? 5) Does your child have difficulty getting to sleep? 6) Does your child feel anxious or disturbed when falling asleep? 7) Does your child wake up more than twice per night? and 8) After waking up at night, does your child have difficulty in falling back to sleep? Response options for questions 1 and 4 through 8 were on a Likert scale (1 = never, 2 = occasionally, 3 = sometimes, 4 = often, 5 = always). Items 2 through 8 were summed to formulate a BSP raw score, which was converted to a T-score on the basis of normative data.

Exclusion Criteria

Children whose parents answered yes to the question, “Does your child have any illness or disability (either physical or mental)” were excluded, because of potential confounders with cognitive functioning or behavior. Sixteen children could not be contacted, 28 withdrew before testing, and 14 did not attend the testing session. These 58 children were of the same age range and from the same demographic area as the participating sample. To ensure that the final subject sample would only include children who were displaying chronic sleep problems that were persistent during the study period, we excluded children whose parents reported different SDSC scores at initial completion from those completed at the time of testing from the data set (n = 5; mean [SD] test – retest time = 153 [76.5] days; range, 15-300 days). To maximize comparison effects, 23 children with BSP and snoring scores in the borderline ranges (according to normative data) were excluded. Specifically, for BSP, T scores < 60 were classified as non-BSP, T-scores > 67 were classified as BSP, and children with T scores from 60 to 67 were excluded (n = 6). Similarly for snoring, children who snored never or occasionally (≤ 1-2 times a month) were classified as non-snorers, children who snored often or always (≥ 3-5 times per week) were considered snorers, whereas children who snored sometimes (1-2 times per week) were excluded (n = 8). The final sample (n = 64) was divided in 4 groups (Table I) and had a mean age (± SD) of 10.4 ± 3.0 years (range, 6.2-16.8 years).

Apparatus

An abbreviated test battery was selected to minimize task demands on children while still testing areas of functioning that have been reported to show deficits in children with sleep disorders. The test battery was administered by a trained psychologist.

The Wechsler Abbreviated Scale of Intelligence was used to test intelligence (IQ), with 4 subtests measuring verbal, performance, and global IQ. These measures have a mean of 100 (SD = 15).

The Children’s Memory Scale word pairs and numbers subtests were used to test verbal and nonverbal short- and long-term memory. Children were required to remember lists of words or numbers and repeat them back during 3 trials. This gave a learning score. Word pairs was also re-tested after a 20 minutes, giving both a short- and longer-term memory score. Word pairs learning and short-term recall were summed to give a word pairs total score. The Children’s Memory Scale numbers subtest is thought to measure short-term working nonverbal memory. All memory subtests have a mean of 10 (SD = 3).

The Auditory Continuous Performance Test (ACPT) and the Test of Everyday Attention in Children (TEA-Ch) code transmission subtest were used to test attention. The ACPT measures auditory selective and sustained attention and impulsivity by listening for a target word among many distracter words. A basic hearing test was undertaken before testing to determine at what auditory level the ACPT tape
Table I. Subject groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (±SD) Age (Range) in years</th>
<th>n</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snorers + BSP</td>
<td>9.5 ± 3.3 (6.2-16.8)</td>
<td>9</td>
<td>Children who reported snoring ≥3 to 5 times a week (often or always) and who reported a BSP T-score &gt; 67</td>
</tr>
<tr>
<td>Snorers</td>
<td>10.5 ± 1.6 (6.4-11.9)</td>
<td>11</td>
<td>Children who reported snoring ≥3 to 5 times a week (often or always) and reported a BSP T-score &lt; 60</td>
</tr>
<tr>
<td>BSP</td>
<td>10.6 ± 2.5 (6.9-14.8)</td>
<td>13</td>
<td>Children who snored ≤1 to 2 times per month (never or occasionally), but who reported a BSP T-score &gt; 67</td>
</tr>
<tr>
<td>Controls</td>
<td>11.3 ± 3.2 (6.2-15.9)</td>
<td>31</td>
<td>Children who snored ≤1 to 2 times per month (never or occasionally) and reported a BSP T-score &lt; 60</td>
</tr>
</tbody>
</table>

NB classification was based on SDSC scores at the time of testing.

should be played. Higher scores on all 3 ACPT subscales are indicative of increased errors. Because normative data in the ACPT is limited to children <12 years old, raw scores were used in analyses. Because the code transmission subtest from the TEA-Ch is standardized in children 6 to 16 years old, it was used as an additional measure of auditory sustained attention in which children were to identify a number before 2 target numbers. Lower TEA-Ch scores are indicative of reduced attention capacity. TEA-Ch subtests have a mean of 10 (SD = 3).

The Child Behaviour Checklist (CBCL) was used to measure competent behavior and also internalized, externalized, and other behaviors, which combine into a total problem behavior score. Scores are based on responses to 20 competency items and 118 problematic items. Behavior scores were transformed into T-scores with a mean (±SD) of 50 ± 10.

Protocol

The neuropsychological tests were administered in a 1-hour session in this order: ACPT, word pairs, numbers, Wechsler Abbreviated Scale of Intelligence, and Code Transmission. During the testing session, parents completed the CBCL and a second SDSC and gave demographic information (address, schooling [private or state], occupation, and level of education). Although efforts were made to test children before school or on non-school days, parental availability limited this to 32 of the 64 children. All children except 4 were tested between 9:00 a.m. and 2:00 p.m. or 3:30 and 5:00 p.m.

The study was approved by the ethics committee of the University of South Australia, and parents signed consent forms before study participation.

Statistical Analyses

Chi-square analyses were used to test for group differences in demographic and test condition parameters. A series of one-way analysis of variance tests were used to explore the effect of group on neuropsychological and psychosocial parameters and Fisher Planned Least Significant Difference (PLSD) post-hoc tests to test for significance and main effects. The relationships between variables were explored with the Pearson r correlations with the Fisher r-z transformations to test for significance. A series of multiple regression analyses were undertaken to further explore the relative contribution of snoring and BSP to the variance in neuropsychological and psychosocial scores. Statistical significance was set at a P value of .05. Because of the exploratory nature of the data, no corrections were made for multiple comparisons. Data were analyzed with a commercially available statistical software package (Statview 1992-98, SAS Institute).

RESULTS

Subject Demographics

Of the total sample (n = 64), 59% were girls. Chi-square analyses revealed no significant group differences in paternal or maternal education or occupation, school type (state or private), sex distribution, or time of testing among groups (all P > .05). Analysis of variance revealed no significant between group differences for age (F [3,60] = 2.6, not significant).

Between-group Differences

The mean (±SD) SDSC sleep parameter, neuropsychological, and psychosocial scores are reported in Table II. In summary, questionnaire responses for sleep confirmed group classification, with parents of children in the Snorers and Snorers + BSP groups reporting higher snoring scores and parents of children in the BSP and Snorers + BSP groups reporting higher BSP scores. For neuropsychological function, with 1 exception, children in the Snorers + BSP group, followed by children in the Snorers group, performed the poorest on all IQ and attention tests, compared with children in the BSP and Controls groups. The 1 exception was for memory, in which children in the Snorers + BSP and BSP groups performed worse than children in the Snorers group, followed by the Controls group, although these differences did not reach significance. For behavior, parents of the children in the Snorers + BSP and BSP groups reported more problematic behavior and lower competency than parents of children in the Snorers and Controls groups, who reported generally comparable scores. Except for 1 case, post hoc analyses of specific CBCL subscales confirmed that for all subscales of the CBCL, parents of children in the Snorers + BSP and BSP groups reported significantly more problematic and less...
competent behavior than parents of children in the Snorers and Controls groups. The 1 exception was that children in the BSP group showed worse somatic behaviors than children in all other groups.

To indicate the clinical significance of cognitive and behavioral findings, qualitative analyses were performed by comparing scores to normative data for each test (data not shown). Inspection of the distribution revealed that children in the Snoring+BSP group, Snorers group, or both had the highest percentage of scores indicative of poor performance in memory and attentional capacity, less competent behavior, and increased problematic behavior (Table III). Higher BSP scores were moderately correlated to impaired short term/working non-verbal memory, less competent behavior, and increased problematic behavior. Overall, snoring showed a stronger relationship with IQ and attention, whereas BSP showed a stronger relationship with memory and behavior.

To test predictive contributions, a stepwise regression was conducted on the whole sample (n = 83) using parameters of snoring and BSP as independent variables and neuropsychological function and psychosocial measures as dependent variables. The analyses were restricted to the key composite neuropsychological and psychosocial parameters. Only regression results that were significant are reported (Table IV). Overall, the analysis revealed that snoring made a BSP raw score in the borderline range (n = 6), and those whose snoring scores changed significantly between initial questionnaire completion and completion of the SDSC at time of testing (n = 5) were included. Overall, higher snoring scores were moderately related to lower IQ scores, poorer attentional capacity, less competent behavior, and increased problematic behaviour (Table III). Higher BSP scores were moderately correlated to impaired short term/working non-verbal memory, less competent behavior, and increased problematic behavior. Overall, snoring showed a stronger relationship with IQ and attention, whereas BSP showed a stronger relationship with memory and behavior.
small predictive contributions to global IQ, attention, impulsivity, competent behavior, and total problematic behavior. By contrast, BSP did not significantly predict IQ or ACPT selective attention scores, but made small but significant, predictive contributions to sustained attention and memory and stronger predictive contributions to internalized, externalized, and total problematic behavior.

## DISCUSSION

This study found that snoring was significantly associated with reduced IQ and attentional capacity, but not with reduced memory, and only moderately with problematic behavior. In contrast to snoring, BSP were associated with increased problematic behavior and impaired nonverbal memory, but less with reduced intelligence and attention. When snoring and BSP occur in combination, they have a significantly greater impact on daytime function than when they occur separately.

Previous studies support the findings that snoring is associated with reduced IQ and attention in children who snore and who have SDB. Although this evidence suggests that children with upper airway obstruction associated with hypoxia during sleep are more likely to have reduced IQ and attentional capacity, similar findings have also been reported in children with non-hypoxic snoring, which was previously thought to be innocuous. Guilleminault et al. reported reduced mathematical skills in 5 children with non-hypoxic snoring, whereas Ali et al. reported an improvement in cognitive function in 11 non-hypoxic snorers after amelioration of snoring. Similar findings have been reported in a large sample of snorers, in which children who snored but did not have hypoxia had reduced academic performance compared with that of control subjects (n = 851). Although this study did not assess the presence of hypoxia and we cannot therefore discount the fact that some of these snorers had obstructive sleep apnea syndrome nor that respiratory arousals potentially affected the outcome, the findings nonetheless support the mounting evidence that snoring is implicated in specific neuropsychological deficits in children. In this study, snoring was not related to reduced memory capacity. This is contrary to the findings of 2 groups that have previously reported both reduced verbal and nonverbal memory (Wide Range Assessment of Memory and Learning) in children with objectively measured SDB. However, we found that BSP were significantly associated with and predictive of reduced nonverbal memory performance (numbers subtest). These findings remain unexplained. In larger studies in adults and children, sleep disruption, sleep deprivation, or both have been linked to daytime dysfunction in general and memory impairment in particular. Further studies using a broader range of memory tasks and objective measurement of sleep disruption in a larger sample are needed to assess whether sleep disruption is a primary contributor to memory dysfunction in children, as is suggested in this self-report study.

The second main finding from this study was that children with BSP had significantly more impaired psycho-social functioning than all other groups. Although it is possible that children with problematic behavior simply have poorer sleep, we believe it is likely that sleep disruption per se is important in behavioral regulation. Other potential hypotheses include the possibility that the strong relationship

### Table III. Correlation coefficients for SDSC scores and neuropsychological and psychosocial measures

<table>
<thead>
<tr>
<th>Performance Parameter</th>
<th>Sleep measures (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intelligence (WASI)</strong></td>
<td></td>
</tr>
<tr>
<td>Global IQ</td>
<td>-0.21*</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>-0.23*</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-0.23*</td>
</tr>
<tr>
<td>Similarities</td>
<td>-0.18</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>-0.09</td>
</tr>
<tr>
<td>Block design</td>
<td>-0.03</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>-0.19</td>
</tr>
<tr>
<td><strong>Attention (ACPT)</strong></td>
<td></td>
</tr>
<tr>
<td>Selective attention</td>
<td>0.22</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>-0.01</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Attention (TEA-Ch)</strong></td>
<td></td>
</tr>
<tr>
<td>Sustained (Code transmission)</td>
<td>-0.30*</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
</tr>
<tr>
<td>Short term/working non verbal memory (Numbers total)</td>
<td>-0.35*</td>
</tr>
<tr>
<td>Numbers forward</td>
<td>-0.20</td>
</tr>
<tr>
<td>Numbers backward</td>
<td>-0.32*</td>
</tr>
<tr>
<td>Short/long term verbal memory and learning (Words total)</td>
<td>-0.21</td>
</tr>
<tr>
<td>Words learning</td>
<td>-0.19</td>
</tr>
<tr>
<td>Words short term recall</td>
<td>-0.15</td>
</tr>
<tr>
<td>Words long term recall</td>
<td>-0.14</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>Competent behavior</td>
<td>-0.39*</td>
</tr>
<tr>
<td>Social activities</td>
<td>-0.14</td>
</tr>
<tr>
<td>School progress</td>
<td>-0.29*</td>
</tr>
<tr>
<td>Social competency</td>
<td>-0.42*</td>
</tr>
<tr>
<td>Total problem</td>
<td>0.60*</td>
</tr>
<tr>
<td>Internal behaviour</td>
<td>0.57*</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>0.43*</td>
</tr>
<tr>
<td>Somatic</td>
<td>0.45*</td>
</tr>
<tr>
<td>Anxious</td>
<td>0.54*</td>
</tr>
<tr>
<td>External behaviour</td>
<td>0.56*</td>
</tr>
<tr>
<td>Delinquency</td>
<td>0.47*</td>
</tr>
<tr>
<td>Aggression</td>
<td>0.57*</td>
</tr>
<tr>
<td>Social problems</td>
<td>0.45*</td>
</tr>
<tr>
<td>Thought problems</td>
<td>0.46*</td>
</tr>
<tr>
<td>Attention</td>
<td>0.31*</td>
</tr>
</tbody>
</table>

*P < .05.  †P < .01.  ‡P < .005.  §P < .001.  ||P < .0001.
between behavioral sleep problems and behavior may be caused by parental generalization of nighttime and daytime behavioral problems in their children, particularly in problematic children, or that a high percentage of these behavioral problems may be caused by parenting styles that reflect poor behavior management both at night and during the day. However, daytime behavioral problems have been observed in children with non-behavioral sleep disorders that disrupt sleep, such as periodic limb movement disorder\(^{34,35}\) and parasomnias.\(^{36}\) It therefore would seem improbable that the findings in this study would be entirely explained by parental generalization or parenting style. As such, this study suggests that poor sleep consolidation, disrupted sleep, or both are associated with problematic daytime behavior and further suggests that despite the subjective nature of parental reporting, behavior in children with these sleep problems may be more problematic than in children who snore.

The third main finding in this study was that a combination of snoring and BSP showed a greater impact on neuropsychological functioning than BSP or snoring alone. In this study, it is not possible to assess whether these increased decrements are caused by increased severity of either SDB or BSP in this group or even whether daytime sleepiness may have played a mediating role in daytime function. However, the findings suggest that cognitive and behavioral dysfunction may be related to the severity of co-existing and co-morbid sleep problems in a dose-dependent manner and points to the need for children who snore to be screened for additional sleep disorders in future studies. Failing to do so may obstruct a more complicated relationship between sleep and daytime function and, thereby, our understanding of behavior in children who snore or who have other chronic sleep problems. To date, only Owens et al.\(^{15}\) have evaluated the role of co-morbid behavioral sleep problems on behavior in children with SDB. They found significantly more problematic behaviors in children with SDB and behavioral sleep disorders similar to those found in this study (reluctance going to bed and difficulty with sleep onset; \(n = 22\)) compared with children with SDB alone (\(n = 78\)). This study supports these findings, and together they suggest that disruption of sleep architecture may overlap between SDB and BSP, thus becoming an important effect modifier of the association between SDB and daytime function.

Limitations of this study include the voluntary nature of participation and a potential self-selection bias for parents wanting a free psychological assessment. However, it would be difficult to explain why this might apply more to children who snore or have BSP than to control subjects. Also, the data were collected through self-report, with no objective evaluation of sleep disturbance or hypoxia. Subjects were chosen from a clinical population, with group entry based on parental responses; the testing psychologist was aware of the child’s group status at testing, and efforts to control testing times to account for the effect of circadian variations on performance may not have been sufficient. Another issue is that the arbitrary separation of sleep problems on the basis of a questionnaire did not take into account the potential co-morbidity of other sleep problems. A final limitation of this study is the small sample size, despite an initial pool of 166.

This study assessed neuropsychological function in children with non-respiratory BSP. It therefore augments previous studies, in which sleep disruption from non-hypoxic

| Table IV. Results of stepwise regression for predicted contributions to neuropsychological and psychosocial test scores with predictive \(R^2\) |
|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Parameter       | Predictor     | Coefficient     | Standard error  | Standard coefficient | \(R^2\) | F-value |
| Intelligence    |               |                 |                 |                 |                 |                 |
| Global IQ       | Snoring       | -2.86           | 0.83            | -0.35           | 0.13            | 11.8\(^{1}\) |
| Attention       |               |                 |                 |                 |                 |                 |
| Selective attention (ACPT) | Snoring | 3.09           | 0.86            | 0.37            | 0.14            | 12.8\(^{1}\) |
| Impulsivity (ACPT) | Snoring | 1.28           | 0.34            | 0.38            | 0.14            | 14.0\(^{1}\) |
| Sustained attention (TEA-Ch) | Snoring | -0.25         | -0.55           | 0.23            | 0.08            | 8.0\(^{1}\) |
| Memory          |               |                 |                 |                 |                 |                 |
| Memory numbers total (CMS) | BSP | -0.16         | 0.04            | -0.35           | 0.12            | 11.2\(^{4}\) |
| Behavior        |               |                 |                 |                 |                 |                 |
| Competent behavior | BSP  | -0.66         | 0.19            | -0.34           | 0.15            | 14.7\(^{1}\) |
| Total problematic behavior | BSP | 1.40         | 0.22            | 0.56            | 0.36            | 42.1\(^{8}\) |
| Internalized problematic behavior | BSP | 1.13         | 0.18            | 0.57            | 0.32            | 39.9\(^{9}\) |
| Externalized problematic behavior | BSP | 1.22         | 0.19            | 0.56            | 0.32            | 37.8\(^{8}\) |

Only regression results that were significant are reported.

\(^{1}\)\(P < .01\).
\(^{4}\)\(P < .005\).
\(^{8}\)\(P < .001\), and
\(^{9}\)\(P < .0001\).
sleep disorders resulted in increased behavioral problems, and allows a better evaluation of the relationship among snoring, sleep disruption, and daytime function. The findings suggest snoring and BSP are associated with neuropsychological and psychosocial function in different ways. It is unclear why snoring could be associated with some deficits and BSP with others. It is possible that mechanisms specific to snoring and not present in BSP, such as hypoxia, may account for the differences observed in neuropsychological deficits in this sample. Further studies with objective measurements are needed to clarify this issue. However, if disruption of sleep architecture is associated with the neuropsychological and psychosocial development of children, it would be of considerable clinical importance, because behaviorally based sleep problems, which disrupt sleep, are among the most common problems in pre-school and school-aged children and have considerable secondary effects on families and the community. This is particularly significant because of the results of a recent study in which 80% of significant sleep problems in children were left undetected and untreated by primary health care practitioners.

REFERENCES

DIAGNOSIS OF HIRSCHSPRUNG’S DISEASE: A PROSPECTIVE, COMPARATIVE ACCURACY STUDY OF COMMON TESTS

Fleur de Lorijn, PhD, Johannes B. Reitsma, PhD, Weger P. Voskuil, PhD, Daniel C. Aronson, PhD, Febo J. ten Kate, PhD, Anne M. J. B. Smeets, PhD, Jan A. J. M. Taylor, PhD, and Marc A. Benninga, PhD

Objective  To compare the diagnostic accuracy of contrast enema (CE), anorectal manometry (ARM), and rectal suction biopsy (RSB) for the detection of Hirschsprung’s disease (HD).

Study design  Following a prospective protocol, infants suspected of HD underwent all 3 index tests. Children with positive results on 2 or more index tests or who continued to have severe bowel problems underwent a full thickness biopsy as reference standard. Clinical follow-up was the reference standard in all other children.

Results  Between 2000 and 2003, 111 consecutive patients (67 boys; median age, 5.3 months) in whom HD was suspected were enrolled. HD was found in 28 patients. RSB had the highest sensitivity (93%) and specificity (100%) rates, but values were not significantly different from CE (sensitivity, 76%; specificity, 97%) or from ARM (sensitivity, 83%; specificity, 93%). Inconclusive test results occurred in 8 infants with CE, in 15 infants with ARM because of agitation, and in 2 infants with RSB.

Conclusion  RSB is the most accurate test for diagnosing HD, and it has the lowest rate of inconclusive test results. (J Pediatr 2005;146:787-92)

In most infants and children with constipation, no obvious cause can be identified. A rare cause of constipation is Hirschsprung’s disease (HD), which is characterized by the absence of ganglion cells from the anal rectum to a variable length as high as the duodenum. The extent of the aganglionic segment varies, but in most patients the lesion does not extend beyond the rectum and sigmoid colon. In a few cases, however, the aganglionosis may involve the colon. The clinical symptoms of HD may become manifest in the neonatal period, and they include lack of passage or delayed passage of meconium beyond 24 hours and signs and symptoms of large bowel obstruction such as biliary vomiting, a distended abdomen, severe defecation problems and/or enterocolitis.

Several tests are used in the examination of patients in whom HD is suspected. The presence of a caliber change, with a dilated normal colon to a narrowed aganglionic bowel, may be demonstrated by using contrast enema (CE). Anorectal manometry (ARM) assesses the rectoanl inhibitory reflex (RAIR), which is absent in children with HD. The third option consists of a rectal suction biopsy (RSB), which shows an elevated cholinesterase activity and may even show aganglionosis in case of HD. Because RSB is a superficial biopsy, it is not always possible to detect with certainty the presence or absence of ganglion cells. Therefore, all positive RSB test results were confirmed with a full-thickness biopsy (FTB), which contains rectal mucosa and underlying muscle. This test provides the most definitive answer, but is invasive and requires general anesthesia.

There has been considerable debate about the most appropriate diagnostic approach for HD, because CE, ARM, and RSB all produce false-negative and false-positive test results. Each of these tests has both advantages and disadvantages in availability, technical difficulty, radiation exposure, and invasiveness. The diagnostic accuracy of each investigation has never been compared directly in a prospective study. Therefore, the aim of our study was to compare the diagnostic accuracy of CE, ARM, and RSB in infants in whom HD was suspected.

<table>
<thead>
<tr>
<th>HD</th>
<th>Hirschsprung’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM</td>
<td>Anorectal manometry</td>
</tr>
<tr>
<td>RSB</td>
<td>Rectal suction biopsy</td>
</tr>
<tr>
<td>CE</td>
<td>Contrast enema</td>
</tr>
<tr>
<td>FTB</td>
<td>Full thickness biopsy</td>
</tr>
<tr>
<td>RAI</td>
<td>Rectoanal inhibition reflex</td>
</tr>
</tbody>
</table>

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METHODS

Between 2000 and 2003, we enrolled 122 consecutive patients in whom HD was suspected in our prospective study. All patients had severe defecation problems from birth and abdominal distension and/or could not be weaned off laxative treatment. Data on gestational age and first passage of meconium after birth were collected. All patients were referred to our outpatient pediatric motility clinic in a tertiary medical hospital by pediatricians or pediatric surgeons to exclude or confirm HD. ARM was performed in our outpatient pediatric motility unit. CEs were performed at the pediatric radiology suite, and a pediatric surgeon, mostly on an outpatient basis, performed all RSBs. CE, ARM, and RSB were performed in arbitrary order, on the basis of the availability and planning situation in the hospital. Eleven of the 122 infants did not undergo all investigations and were therefore excluded from the study. Reasons all 3 tests weren’t performed included lack of permission given by the parents to perform all 3 tests in 4 infants and parents who did not show up for 1 or more investigations in 4 infants. RSB was considered to be too invasive because of prematurity in 2 children and because of autoimmune hepatitis in 1 child. In all other 111 children, the 3 tests were performed within 3 weeks. The investigators were informed about the clinical status of the patients, but did not know the outcome of the other tests. All data were prospectively collected on pre-designed case record forms.

Contrast Enema

Pediatric radiologists or residents performed the radiological examination of the colon in a routine manner using standard CE techniques. Children did not undergo bowel preparation before CE. A diluted (1:3) hyperosmolar water-soluble contrast medium (amidotrizoic acid) was administered rectally. A small rectal catheter was used and placed in the rectum as distally as possible. No balloon catheters were used. All CE images were read by the same pediatric radiologist (A.M.S.). The classical finding in patients with HD is that of a caliber change between a small or normal-sized distal aganglionic segment and a dilated proximal ganglionic bowel. The presence or absence of this caliber change was considered to be a positive or negative test result, respectively.

Anorectal Manometry

In all children, ARM, using a purpose-built silicone rubber micromanometric anorectal catheter (od 2.0 mm), was performed after bowel preparation with an enema. The catheter incorporated a 1.5-cm-long sleeve sensor and an array of 3 side-holes spaced 0.5 cm apart for measurement of anal sphincter pressures and 1 side-hole located 0.5 cm proximal of the sleeve for measurement of basal pressure within the rectum. All side-holes were perfused with sterile degassed water at a rate of 0.2 mL/min. An air channel was present on the tip of the catheter. Rectal distension was produced with a highly compliant 4-cm-long distending rectal balloon, tied at the end of the catheter.

The catheter was positioned with the sleeve straddling the anal sphincter high-pressure zone and the balloon in the rectum. To elicit a RAIR, 2 to 60 mL of air was insufflated in the balloon for rectal distension. The reflex was defined as normal when rectal distension produced a relaxation of the anal sphincter pressure of at least 5 mm Hg for 2 to 5 seconds. When the RAIR was observed 3 times, it was concluded that ARM could not support the diagnosis of HD. Recording sessions lasted 30 minutes on average.

Rectal Suction Biopsy

In all patients, 4 RSBs were taken at 4 different sites: 2 and 4 cm from the dentate line anteriorly and 2 and 4 cm from the dentate line posteriorly. The suction biopsy specimens were examined for routine histology and for acetylcholinesterase (AchE) histochemistry. Bowel specimens were fixed in 4% formaldehyde buffered with phosphate-buffered saline, dehydrated, and embedded in paraffin. Tissue sections were made at 5 μm, stretched, and dried at 57°C overnight. The sections were rehydrated in an alcohol series, and endogenous peroxidase activity was blocked by 1% H2O2 in methanol for 1 hour.

Acetylcholinesterase activity was determined as previously described by Karnovsky and Roots. Non-specific acetylcholinesterase was inhibited by 2.5 × 106 mol/L tetraisopropylpyrophosphoramide (ISO-OPMA). Ganglion cells were determined with a hematoxylin–eosin staining. An RSB was considered to be positive when the acetylcholinesterase activity was elevated in combination with an absence of ganglion cells. When ganglion cells were present, HD was excluded. The biopsies were evaluated by an experienced histopathologist with specific interest and expertise for HD (F.J.t.K.).

Final Diagnosis

The final diagnosis of HD was made by the absence of ganglion cells in a full thickness biopsy or from the operative specimen, or was rejected by thorough clinical follow-up, including a hospital visit to confirm the disappearance of complaints. Children with positive results on 2 or more index tests or children who continued to have severe complaints despite intensive laxative treatment during follow-up were verified through a full thickness biopsy (n = 32). In all other children, clinical follow-up was used to demonstrate the disappearance of complaints. The minimum length of follow-up was 6 months.

Full thickness biopsy specimens were obtained with the patient under general anesthesia by a pediatric surgeon at 2 cm above the dental line, posteriorly. These specimens were handled in a routine manner in the pathology laboratory of our tertiary center. Full thickness specimens were examined for the presence or absence of ganglion cells in Auerbach’s plexus, located between the longitudinal and circular muscle layers of the bowel wall. The same histopathologist examined all sections.

Statistical Analysis

Sensitivity and specificity rates for all 3 index tests and 95% CIs with the method of Wilson were calculated. We
tested for differences in sensitivity rates, specificity rates, and inconclusive results between tests by using the McNemar test for paired observations. The diagnostic odds ratio was used to test whether the overall accuracy of an index test differed between subgroups of patients (young versus old). Patients with inconclusive test results were excluded in the calculation and the comparison of sensitivity rate, specificity rate, and diagnostic odds ratio. In all analyses, 2-sided \( P \) values <.05 were considered to be statistically significant.

## RESULTS

Of the 111 children included in the study, 67 (60%) were boys (Table I). The median age of the total group was 5.3 months (range, 4 days–12 years). A final diagnosis of HD was made in 28 children (25.2%). The other 83 children were classified as having functional constipation. The median age at intake was significantly lower in children with HD than in children with functional constipation. As expected, significantly more children with HD had a delay in meconium passage than children with functional constipation.

A total of 28 patients had positive results on 2 or more index test. In all 28 children, HD was confirmed with FTB. In 4 patients, however, the results of fewer than 2 index tests were positive for HD. Because these patients had such severe and acute defecation problems, laparotomy was necessary to relieve colonic distension. During the surgical procedure, a FTB was performed, which definitely excluded HD in these 4 infants. In 21 of the 28 infants with HD (75%), the length of the aganglionic segment was limited to the rectosigmoid. In 5 patients (18%), the aganglionic segment extended to the splenic flexure, and in 1 patient, it extended to the ascending colon. Only 1 patient had a total aganglionosis coli. The children who did not undergo a FTB were observed for at least 6 months. After 6 months, a normal defecation pattern developed in 68% of these children without the use of laxatives, 9% had a normal defecation pattern with the use of laxatives, and mild defecation problems needing oral laxatives persisted in 23% of the children. In these latter 32% of children, RSB results had been normal.

### Contrast Enema

Table II shows the sensitivity and specificity rates for each index test. A caliber change was seen in 19 of 28 patients with HD (68%). No caliber change was observed in 6 patients with histologically proven HD. Five of them were <1 year old. In the other 3 patients, CE was inconclusive for technical reasons: the catheter was not removed from the rectum during the recording period, too fast injection of contrast that sometimes leads to overdistension of the bowel, or both. Furthermore, a caliber change was present in 2 patients, both <1 year old, with functional constipation. In 8 infants, CE results were non-conclusive, mostly because of technical failures as aforementioned. No adverse effects occurred during or after the CE procedures. The sensitivity and specificity rates of a CE was 76% and 97%, respectively. The overall accuracy of a CE is both not significantly different in infants <1 month old compared with infants ≥1 month (100% versus 90%, \( P = .27 \)) or in children >1 year old compared with younger children (94% versus 89%, respectively; \( P = .21 \)).

### Anorectal Manometry

Positive test results (absence of the RAIR) were found in 19 of the 28 children with HD. Four children with histologically proven HD showed a relaxation of the IAS with balloon distension. Three of them were <1 month old. This resulted in a sensitivity rate of 83%. In 15 infants, the results of ARM could not reliably be analyzed because of agitation during the procedure; 5 of these patients had HD. Even after inflation of as much as 60 mL of air in the rectal balloon, 5 children with functional constipation showed no reflex relaxation of the sphincter complex, leading to a specificity rate of 93% (95% CI, 0.85–0.97). No adverse effects occurred during or after the ARM procedures. The accuracy of ARM was not significantly different in infants <1 month old compared with infants ≥1 month old (84% versus 90%, \( P = .70 \)) or in children >1 year old compared with younger children (94% versus 89%, respectively; \( P = .47 \)).
Table II. Raw data of test results per index test and comparison of sensitivity and specificity rates for contrast enema, anorectal manometry, and rectal suction biopsy in patients suspected of Hirschsprung's disease

<table>
<thead>
<tr>
<th></th>
<th>Contrast enema</th>
<th>Anorectal manometry</th>
<th>Rectal suction biopsy</th>
<th>CE vs ARM P value</th>
<th>CE vs RSB P value</th>
<th>ARM vs RSB P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>76% (57%-89%)</td>
<td>83% (63%-93%)</td>
<td>93% (77%-98%)</td>
<td>1.00</td>
<td>.29</td>
<td>.69</td>
</tr>
<tr>
<td>TP/(TP + FN)</td>
<td>19/(19 + 6)</td>
<td>19/(19 + 4)</td>
<td>25/(25 + 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>97% (91%-99%)</td>
<td>93% (85%-97%)</td>
<td>100% (96%-100%)</td>
<td>.22</td>
<td>.50</td>
<td>.06</td>
</tr>
<tr>
<td>TN/(TN + FP)</td>
<td>73/(73 + 2)</td>
<td>68/(68 + 5)</td>
<td>82/(82 + 0)</td>
<td>.17</td>
<td>.11</td>
<td>.002</td>
</tr>
<tr>
<td>Inconclusive (%)</td>
<td>11 (9.9%)</td>
<td>15 (13.5%)</td>
<td>2 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity and specificity rates are given between brackets. TP = True positive test result; FN = false negative test result; TN = true negative test result; FP = false positive test result; CI = confidence interval, CE = contrast enema, ARM = anorectal manometry, RSB = rectal suction biopsy.

Rectal Suction Biopsy

Positive biopsy results were found in 25 of 28 children with HD. Two children, both <1 month old, had a false-negative test result for RSB. Although the RSB in these infants showed a normal acetylcholinesterase activity, no ganglion cells could be identified. In 1 child, the RSB results were not conclusive, and 1 more inconclusive RSB result occurred in a patient without HD. In both inconclusive cases, the biopsy was too superficial and did not contain muscularis mucosa. RSB produced no false-positive test results. One patient had rectal blood loss after the RSB procedure, but no surgical re-examination was needed to stop it. This meant that the sensitivity and specificity rates of RSB were 93% (95% CI, 0.77-0.98) and 100% (95% CI, 0.96-1.00), respectively, excluding the 2 patients with inconclusive test results. The accuracy rate of RSB was 90% in infants <1 month old and 100% in infants ≥1 month old (P = .11), whereas the accuracy rate was 100% in children >1 year old and 97% in children ≤1 year old (P = .32).

Direct Comparison of Accuracy

Table II shows a raw overview of test results per index test. The pairwise comparison of sensitivity and specificity rates between different tests showed that RSB had the highest sensitivity rate (93%), but it was not significantly different from CE (76%, P = .29) and from ARM (83%, P = .69). The specificity rate of the RSB was higher (100%) compared with that of CE (97%, P = .50) and ARM (93%, P = .06).

DISCUSSION

The results of this prospective study demonstrate that RSB is the most accurate test for diagnosing HD, with a sensitivity rate and specificity rate of 93% and 100%, respectively. This was however, not significantly different from the rates of CE (76% and 97%, respectively) and ARM (83% and 93%, respectively). RSB also had the lowest rate of inconclusive test results and provides a histological diagnosis. As many as 80% to 90% of infants with HD fail to pass meconium in the first 24 hours of life.1 Delayed passage of meconium by itself is not a good discriminative clinical symptom to differentiate between HD and functional constipation, because 30% to 40% of children with functional constipation and 30% to 35% of healthy pre-term infants have delayed meconium production.9,10 In patients with delayed passage of meconium and other important clinical signs of HD such as vomiting and abdominal distension, however, rapid diagnostic tests are necessary. Severe intestinal obstruction leading to enterocolitis remains the most common cause of morbidity and mortality in HD.1

The hallmark feature of HD with a CE is the presence of a caliber change.10 In accordance with earlier studies,10-12 no caliber change was found in 6 patients with HD (30%), 5 of whom were <1 year old, and in 1 patient with total aganglionosis coli. Taxman et al suggested that in young infants the caliber change is more difficult to demonstrate.20 False-negative test results are also reported in 75% of children with total aganglionosis.12-14 Furthermore, rectal wash-outs and even digital rectal examinations may decompress the distended proximal bowel, with distortion of the caliber change leading to false-negative test results.4 We have no explanation as to why false-positive test results were found in 2 patients with functional constipation, both of whom were <1 year old. Long-term follow-up of these patients revealed no defecation problems, thereby excluding HD. Although the CE is a simple test to perform, the radiation exposure is high, and an experienced pediatric radiologist is essential to evaluate and score the radiography results.

The literature contains conflicting data about the accuracy of ARM in neonates. Some studies reported that the RAIR does not occur in premature or term infants until the 12th day after birth because of physiologic immaturity of anorectal function.15,16 We demonstrated that premature infants older than 26 weeks' postmenstrual age have a well-developed RAIR on rectal distension.17,18 In this study, 5 infants, 3 of whom were <1 year old, without HD showed an absence of the RAIR on ARM (false-positive test results). False-positive test results might be caused by insufficient inflation of the balloon. We used a maximum volume of 60 mL, which might not have been enough to distend the rectum in some children because of a congenital megarectum or a megarectum caused by severe constipation. Furthermore, technical factors such as an air leak in the circuit might cause false-positive test results. False-negative test results were
found in 4 infants, 3 of whom were <1 month old. In a study by Aaronson and Nixon,19 26% of the patients with a final diagnosis of HD showed a normal RAIR. The authors attributed these false-negative results to displacement of the transducer probe with side-hole sensors. With the use of a sleeve sensor that allows for sphincter movement and pressure measurement over the length of the sleeve, the displacement can be avoided.17 Therefore it seems unlikely that our false results are caused by displacement of the probe. Furthermore, they proposed that some of the false-negative results might be a consequence of relaxation of the external anal sphincter, rather than the internal anal sphincter. We have no other explanation as to why the RAIR was present in the 4 children with HD.

Because of agitation during the procedure, we were not able to analyze the manometry tracings reliably in a substantial number of patients. To improve cooperation, it might have been helpful to perform ARM with mild sedation or anesthesia in these young infants. The RAIR can be elicited even when ARM is performed using general anesthesia.20 ARM is a non-invasive diagnostic test and is easy to perform in children >1 year old. It therefore has often been suggested as an ideal screening tool. However, the equipment is expensive, and extensive experience is necessary to perform this procedure to evaluate the test-results in infants <1 year old.

In our study, RSB produced no false-positive test results. Two false-negative test results were found, both in patients <1 month old. Hamoudi et al.21 described as many as 29% of false-negative test results in children with HD, whereas other authors22,23 reported that nearly 100% diagnostic accuracy was achieved with acetyl cholinesterase histochemistry. Possible causes for false-negative test results include: variability in the biopsy site, too superficially taken biopsy material that lacks muscularis mucosa, immaturity of the enzyme system, and technical variations in performance of the stain, and the muscularis mucosa, immaturity of the enzyme system, biopsy site, too superficially taken biopsy material that lacks muscularis mucosa. We have no other explanation as to why the RAIR was present in the 4 children with HD.

In conclusion, RSB is a reliable, quick, and simple test that provides a tissue diagnosis and was the most accurate test for diagnosing HD. A negative test result virtually rules out the disease when the tissue is obtained from the correct site and when the specimen contains at least a small amount of muscularis mucosa. When symptoms still strongly suggest the diagnosis of HD, we prefer to perform ARM before repeating the RSB. If there is no ARM experience in the hospital, RSB should be repeated. In our opinion, the value of a CE in the work up of HD is limited because of its fairly low sensitivity rate and high radiation exposure. Only when the diagnosis HD has been established, CE might be helpful for the surgeon in assessing the localization of the caliber change and thus the length of the aganglionic segment.

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50 Years Ago in The Journal of Pediatrics

LIBERAL VISITING POLICIES FOR CHILDREN IN HOSPITALS

Citizens’ Committee on Children of New York City, Inc. J Pediatr 1955;46:710-6

The constant presence of parents and other family members on inpatient units of pediatric hospitals is so commonplace now that it is easy to forget the era when hospitalization for a child meant forced separation from parents for extended periods. This article is an eye-opening reminder of the controversies from previous decades about visiting hour policies and the medical determination of “what is best” for the hospitalized child. A public interest group offered this article to The Journal, presenting the results of its survey of visiting hour practices in 75 New York City area hospitals, along with some of the rationale behind the varied practices, and gentle, but clear, recommendations for liberalization.

At the time of the survey, more than half of the hospitals restricted visits to less than 4 days per week, often for no more than 1 hour each day. Restriction was justified on the basis of space limitations, fear of infection, personnel shortages, and the potential disruptions caused by the presence of worried parents. On a positive note, some hospitals were experimenting with more liberal policies, and good outcomes were reported by previously skeptical physicians and nurses. A trend toward daily visiting appeared likely in the near future.

Optimistically, the committee concluded, “The old barriers between those who serve children and the parents of the children whom they serve are being whittled down,” and “there is reason to believe that ultimately all hospitals will adopt procedures which reflect their acceptance of the parent as a key figure in his child’s physical and emotional well-being.” It is frightening to consider that we could have practiced in any way inconsistent with these statements.

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10.1016/j.jpeds.2005.01.056
SATISFACTION IN DIFFERENT LIFE DOMAINS IN CHILDREN RECEIVING HOME PARENTERAL NUTRITION AND THEIR FAMILIES

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Objective To assess the quality-of-life (QOL) of children receiving home parenteral nutrition (HPN).

Study design A national multicenter study of 72 patients (median age 4 years) presenting with a digestive disease requiring HPN, and 90 siblings, 67 fathers, and 69 mothers of these children. Median duration of HPN was 2 years (3 months-18 years). QOL was measured using validated, nondisease-specific questionnaires appropriate to the children’s ages.

Results The QOL scores were high in patients of all ages and were not significantly different from scores in a reference population of healthy children and adolescents. Lower QOL scores were recorded in the domains related to hospital, health, doctors, medications, and obligations. The QOL was not affected in siblings but was significantly impaired in parents, especially in mothers, who showed a lower level of satisfaction than did fathers for items related to work, inner life, and freedom. Presence of an ileostomy was the only factor that influenced QOL, especially of adolescents.

Conclusions QOL of HPN-dependent children and siblings is not different from that of healthy children, suggesting that these children actively use effective coping strategies. In contrast, the QOL of parents of HPN-dependent children is low. (J Pediatr 2005;146:793-7)

Parenteral nutrition (PN) is a life-saving procedure in children who have intestinal failure.1 A child expecting to need prolonged PN support can be discharged for home parenteral nutrition (HPN) once the parents, and the child whenever possible, are taught to administer this procedure.2 In addition to the underlying disease, this complex technology for nutritional support may have an impact on quality-of-life (QOL).3 HPN is a time-consuming, intrusive procedure, and HPN patients are often troubled by the inconvenience of a high intestinal output, presence of a stoma, altered body image, and fear of complications. HPN also may affect the family’s ability to function well, as shown in other chronic pediatric diseases. We hypothesized that an invasive procedure such as HPN could have deleterious consequences on all family members.

There is no single definition of QOL.4 It is usually considered as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. It is the subjective perception of satisfaction or happiness with life domain of importance to the individual. QOL is a rich multidimensional concept that includes three broad domains of functioning: physical, psychological (cognitive and emotional), and social. QOL is considered an important determinant of the effectiveness of health technologies.4 However, QOL has been assessed rarely in adult patients receiving HPN.5-10

To determine whether HPN, and underlying digestive disease, adversely influences QOL of children and their families, we conducted a national multicenter study involving all the pediatric HPN-authorized centers in France. We also aimed to assess factors influencing QOL of the children treated by HPN.

METHODS

We conducted a cross-sectional, national, multicenter study involving the five pediatric HPN-authorized centers in France. Patients were eligible for the study if they

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HPN Home parenteral nutrition
PN Parenteral nutrition
QOL Quality-of-life

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were 19 years of age or younger and being treated by HPN for a digestive disease. All associated nondigestive diseases known to directly influence QOL, such as malignancy, cystic fibrosis, neurodevelopmental retardation, diabetes, and transplantation, were excluded. Demographic (family dynamics, number of siblings) and medical information (type of digestive disease, existence of a stoma, duration and characteristics of PN) were recorded for each child.

QOL was measured using validated, self-reported, nondisease-specific questionnaires according to the children’s ages, which rated the perceived satisfaction toward a wide range of life domains.11-13 The questionnaires are organized into four domains: health, relationships, inner life, and material conditions. Patients rate their level of disturbance on a 5-point scale or, for younger children, by indicating a face expressing different emotional states; a lower rating denotes greater disturbance. The questionnaires are made of a structured format scale composed of about 30 items. For patients <3 years of age, the Qualin questionnaire was completed by both of the child’s parents and doctors.11 For children between 3 and 11 years of age, we used the Auquei questionnaire, which consists of a 26-item, structured format scale assessing the child’s satisfaction and self-rating of QOL.12 Patients ≥12 years of age completed the OK.ado questionnaire for adolescents.13 Validation and reliability of these questionnaires were assessed using different samples of sick and healthy children, confirming acceptability, internal consistency, criterion validity, construct validity, and sensitivity.13-14

The questionnaires were mailed to the total cohort of 104 patients fulfilling the inclusion criteria at the five pediatric HPN-authorized centers in France. Seventy-two patients (70%) agreed to participate in the study; 34 patients were from the Necker Hospital in Paris, 17 from the Edouard Herriot Hospital in Lyon, 12 from the Jeanne de Flandre Hospital in Lille, 7 from the Robert Debré Hospital in Paris, and 2 from the Purpan Hospital in Toulouse. Informed consent was obtained for all families and children included in the study. The median age of the children was 4 years, ranging from 1 to 19 years; 50% were ≤2 years of age, 36% were 3 to 9 years, and 14% were ≥10 years; 59% were males. Fifty-six of the 72 children studied came from nuclear two-parent families, whereas 12 children were from single-parent families (information lacking for 4 children). Forty-three of our patients (60%) started PN before 1 year of age; 18 (25%) between 1 and 5 years of age, and 10 (15%) after 5 years of age. The patients received PN at home 5.5 times a week, and 38% of them had a stoma. The median duration of HPN was 4.8 years, ranging from 3 months to 18 years. More than 40% of patients had HPN for >3 years. Patients had various conditions associated with the disease, including short bowel syndrome (N = 31), intestinal pseudo-obstruction (N = 15), refractory diarrhea (N = 9), Hirschsprung disease (N = 7), gastrochisis (N = 4), and other miscellaneous conditions (N = 5). The 33 patients who declined to participate in the study did not differ from the studied population in age, proportion of males and females, digestive system disease, age at beginning of PN, duration of HPN, presence of a stoma, or family dynamics. The rate of refusal was similar among the five centers participating in the study.

Seventy-eight of 90 siblings (median age 11 years, 1.5 to 26 years), 62 of 67 fathers (median age 40 years, 24 to 56 years), and 68 of 69 mothers (median age 37 years, 23 to 58 years) also agreed to participate. Siblings who were children completed the same QOL questionnaire as the patients, according to their ages; 7 siblings completed the Qualin questionnaire, 41 the Auquei questionnaire, and 18 the OK.ado questionnaire.11-13 Parents completed the Subjective Quality of Life Profile questionnaire validated for adults, which incorporates two approaches—satisfaction/dissatisfaction and degree of expected changes—to explore various life domains such as somatic and psychic functioning, social insertion, and relational life.15

Data from the patients were compared with a database obtained from a reference pediatric population (Script Inserm database) of 491 healthy children assessed in primary school, 268 healthy adolescents assessed in secondary school, and 90 mothers of healthy children.16

Statistical Analysis

Responses to each question were coded as numbers (from −2 to +2 for the Qualin, Ok.ado, and Subjective Quality of Life Profile questionnaires and from 0 to 3 for the Auquei questionnaire). The Student’s t test was used to compare patients with healthy controls, the paired Wilcoxon’s signed rank test was used to compare QOL of infant assessed by the parents and the doctors, and the Pearson’s correlation coefficient was used to correlate QOL with other variables (age, duration of HPN, etc.). A P value <.05 was considered significant.

RESULTS

Of the 104 eligible patients, 72 (70%) agreed to participate. We collected a questionnaire from every included patient. The response rate for each item of the questionnaires ranged from 75% to 100%; the average response rate for each item was 95%. Response rates did not differ significantly between centers (54%-100%) or by patient age (60%-77%) (Figure 1).

The QOL scores were high across all age groups and did not differ significantly from scores in a reference population of healthy children and adolescents.

For infants, lower scores were recorded by parents of infants than in healthy infants of the same age for health, eating, and speaking. When the doctors were asked to rate their patients’ QOL, the doctors’ scores were significantly lower than the parents’ scores. QOL was rated high (score >1) by parents in 22 of 34 items, whereas doctors rated QOL high for only 12 of 34 items (P <.05) (Figure 2; available online at www.us.elsevierhealth.com/jpeds).

The QOL scores for children 3 to 11 years of age assessed using the Auquei questionnaire did not differ significantly from those of healthy children of the same age.
The QOL mean score was 2.09 in both patients and healthy children, and QOL was rated highly in 21 of 33 items of this questionnaire. Patients had significantly lower scores than controls on items related to hospital, health, doctors, medication, and obligations. Thinking about being a grown-up also was scored significantly lower by patients compared with controls. (Figure 3; available online at www.us.elsevierhealth.com/jpeds).

The QOL scores for adolescents also were high and differ significantly from those of the reference population of healthy adolescents; the mean QOL score was 0.75 for patients and 0.54 for healthy adolescents (P < .025). Adolescent patients had negative scores only for items related to world events, doctors, and medications. There were significant differences between boys and girls in this age group; girls had higher scores on items related to schoolwork, music, and school results (P < .05). The adolescents’ scores were lower in patients than in healthy adolescents for health (0.11 ± 1.23 SD for patients and 0.89 ± 0.99 SD for healthy adolescents, P = .002) and sport (0.67 ± 1.03 SD for patients and 1.4 ± 0.98 SD for healthy adolescents, P = .02) (Figure 4; available online at www.us.elsevierhealth.com/jpeds). At the opposite, scores on items related to school and relations with adults were higher in patients than in healthy adolescents (P < .01) (Figure 4).

The QOL scores of siblings did not differ significantly from those of patients; mean scores were 2.14 for child siblings and 2.09 for child patients, and 0.82 for adolescent siblings and 0.75 for adolescent patients. The QOL scores of siblings differed significantly from those of patients only on two items of the Auquei questionnaire; siblings had higher satisfaction scores related to eating and health than did patients.

Parents’ satisfaction was on average with a mean score of 0.41 ± 0.40 SD on a scale ranging from -2 for total dissatisfaction to +2 for complete satisfaction. Mothers of children treated with HPN had lower QOL scores than the reference mother population (0.40 in mothers of treated children and 0.82 in mothers of healthy children, P < .001). Mothers’ satisfaction scores were lower than the fathers’ scores for items related to work (P = .01), inner life (P = .05), and freedom (P = .04). The mothers’ QOL scores were not significantly correlated with their children’s scores.

The patients’ QOL scores were not significantly different between nuclear, two-parent and single-parent families. The patients’ QOL scores were not significantly correlated with the characteristics of HPN such as duration, start of PN in early childhood, number of perfusions per week, and number of hospitalizations. The only parameter significantly associated with QOL was the presence of a digestive stoma and this association varied with the patient’s age. Infants and young children (Qualin questionnaire) with a stoma were significantly more autonomous than those without a stoma, and their parents recorded that the children slept better, cried less when alone, and had less need for attention and care. For children 3 to 11 years of age (Auquei), the presence of a stoma did not influence QOL. In contrast, adolescents with a stoma had a lower QOL for items related to social life and the future (contact with your family, autonomy, thinking about health, thinking to the future or life in general).

**DISCUSSION**

Our study addressed QOL of children receiving HPN, including patients, siblings, and parents. Indirect approaches have been used previously to assess QOL of children receiving HPN. In a pilot study of 10 HPN children, we showed that mothers’ anxiety, assessed by the Max Hamilton anxiety scale, was maximal at the time of initial diagnosis when the most frequent manifestations of anxiety were anxious humor, insomnia, and depression. Anxiety decreased when the family was trained in the delivery of HPN and was minimal at follow-up, when the child returned home on HPN and the mother was more confident with the technique of HPN. We also found that maternal anxiety occurred more frequently at follow-up in the children with a worse prognosis and that anxiety was associated with fear of being judged, culpability,
and septicemia. Negative factors affecting anxiety in mothers were job renunciation and an unsettled future. Continued care and close follow-up of these patients had a positive influence on the confidence and anxiety levels of the mothers, who expected the medical team to give reassurance and information.17 Another study using a semi-directive questionnaire showed that HPN improved several aspects of QOL of children and parents, mainly social indices, when compared with the preceding period of hospitalization.18 We recently used triaxial accelerometry to compare total energy expenditure in 11 children treated by HPN in free-living conditions with that of healthy children paired for age, sex, and body composition.19 We found that physical activity did not differ between the two groups, suggesting that HPN does not interfere with the usual daily activities of children. Using a Child Behavior Checklist filled out by parents, Engstrom and coworkers recently found that children and adolescents with HPN are quite distressed psychologically.20

Studies on QOL of adults have produced contradictory results.5-10 One study showed that patients on HPN have lower satisfaction in several life activities such as marriage, sex, friendship, and standard of living than controls.9 Adult patients on HPN reported depression, financial instability, marital disintegration, inability to return to an appropriate work or social setting, and fear of becoming a burden.5,7,10 However, other studies of younger adult HPN-dependent patients and their caregivers have reported that QOL, self-esteem, life satisfaction, family cohesion, and quality of patient–caregiver relationships were similar to the published norms for healthy populations.5,6

Children differ from adults in QOL issues related to HPN. Depression, financial concerns, sexual dysfunction, and unemployment are obviously much less important problems for children. Although we could not separate the consequences of HPN itself from the effects of the underlying digestive disease, our results clearly show that QOL of HPN-dependent children does not differ from that of healthy children, suggesting that HPN-dependent children and adolescents use effective coping strategies. A good QOL in children on HPN also could be explained by the fact that children grew accustomed to differences in life relative to their peers because most of them started PN very early in life. These children on HPN have not had a healthy life with which to compare and this may differ from adults who may have had a healthy life with which to compare.

Our study, because of its design, carries two main limitations. First of all, it was impossible to differentiate between the effects of HPN and the effects of the underlying medical condition20; this is confirmed in our study by showing that adolescents on HPN had worse QOL scores when having a stoma than those without stoma. Studying a control group with the same digestive disease but without HPN,8 or performing longitudinal studies comparing patients with the same digestive disease, during and off HPN,7 should answer this question. However, on a practical point of view, such studies would be impossible to perform or should be biased by the fact that children without PN (or weaned from PN) have better health conditions than when treated by HPN. The second shortcoming is that we used nondisease-specific questionnaires made of a structured format scale. A generic questionnaire may not detect changes relevant to children with a particular illness because of its focus on issues common to all children.21 Use of open-ended questions would probably allow the patients and their families to express some dissatisfaction in relation to items not addressed by the questionnaire. Indeed, several patients and parents spontaneously expressed frustration about several items specific to HPN that they did not find on our generic questionnaire. Interview should reveal more in-depth issues such as psychological distress as recently demonstrated by Engstrom.20 QOL can be considered only as the result of adaptive mechanisms to chronic disease and such complex and time consuming technique as HPN. Anthropologic and psychological approaches are needed to better and more deeply characterize consequences of HPN on patients.

We also evaluated QOL of the siblings and parents.22 Having a child with a chronic disease may induce profound alteration of family functioning. Parents (especially mothers) are burdened with their child on HPN who requires special attention. Despite the lack of information in the literature, one could expect that siblings may suffer from these situations, and that there may be consequences that affect their own QOL. Our data suggest, however, that having a sister or a brother with a chronic disease requiring HPN does not influence the QOL of siblings. With the same limitation as for patients, our study using questionnaires made of a structured format scale might have missed some issues. A psychological approach with open interview should definitively answer this question.

The QOL of parents was impaired, especially that of the mothers, who are usually more involved in the daily care of children and more likely to stop working outside the home. It has been shown previously that having a child on HPN has a major impact on the QOL of parents. Wong et al gave a general health questionnaire and a questionnaire developed for the British Artificial Nutrition Survey to 11 parents of children with chronic intestinal failure requiring HPN and to a control group of 11 parents of aged-matched healthy children.23 The general health questionnaire showed that 7 of the 11 parents with children on HPN exceeded the threshold for psychiatric morbidity. There was a significant deterioration from before to after the child’s diagnosis for social life, family life, sexual life, and work for these parents. Parents caring for children on HPN also were more likely to be physically tired and to have difficulties in taking holidays, going shopping, and spending time with their partners. A recent study on children and adolescents after kidney or liver transplantation found that one-third of the mothers expressed the need for psychological support.22 Deterioration of family life with poor social life activities and overall QOL after the child started HPN was reported in 31 families of children receiving HPN.24 However, it was shown that the overall social situation of the parents seems to be satisfactory even if attachment, which deals with deeper, emotional relations, is affected.20

We found that except for presence of a stoma, no factor related to HPN influenced QOL. This was surprising because
we had expected that children with more severe disease requiring frequent hospitalizations and daily PN infusion would have poor QOL. It is possible that the small sample size in each age group limited the study’s statistical power. However, we found that the presence of an ileostomy negatively influenced QOL of adolescents, which is consistent with data from adult studies. However, in our study, an ileostomy had no negative influence on QOL of the younger children, and QOL was better in infants with an ileostomy.

Considering the invasive nature and burden of HPN, our data showing good QOL of both patients and siblings might be considered surprising. These results draw attention to the importance of remaining alert to the possibility that there are difference in the perceptions of clinicians and children or parents when describing childhood QOL, as we observed in our study when infants’ QOL was evaluated by parents and doctors. QOL reflects the coping strategies developed by patients and their families when faced with an invasive technique such as HPN. It was very recently demonstrated that several coping strategies have a significant and independent relationship with several domains that constitute the health-related QOL of children with juvenile idiopathic arthritis. In adults treated by HPN, it also has been shown that low QOL was associated with fewer family coping skills, whereas higher QOL was associated with higher self-esteem and quality of the relationship. We showed in our study that several domains such as relation to adults and school activities were much higher scored in HPN adolescents compared with controls. Our study shows that patients receiving HPN and their parents can develop and use strategies to achieve a good QOL. Good QOL does not mean that patients, siblings, and parents do not experience distress and constraints because previous studies have demonstrated that these do occur in families enduring daily HPN. Healthcare professionals should be aware of these problems and offer the necessary support to families providing this demanding type of care for their children.

REFERENCES

EXTREMELY LOW BIRTHWEIGHT NEONATES WITH PROTRACTED VENTILATION: MORTALITY AND 18-MONTH NEURODEVELOPMENTAL OUTCOMES

Michele C. Walsh, MD, MS, Brenda H. Morris, MD, Lisa A. Wraige, MPH, Betty R. Vohr, MD, W. Kenneth Poole, PhD, Jon E. Tyson, MD, MPH, Linda L. Wright, MD, Richard A. Ehrenkranz, MD, Barbara J. Stoll, MD, and Avroy A. Fanaroff, MB, BCH, for the National Institutes of Child Health and Human Development Neonatal Research Network

Objective To compare duration of ventilation to mortality and adverse neurodevelopmental outcomes among extremely low birth weight (ELBW; 501-1000 g) infants.

Study design Retrospective analysis of prospectively collected data from 5364 infants with a birthweight of 501 to 1000 g born at National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers from 1995 to 1998. The main outcome measures were: survival, duration of mechanical ventilation, and neurodevelopmental outcome.

Results Overall survival was 71%. The median duration of ventilation for survivors was 23 days; 75% were free of mechanical ventilation by 39 days, and 7% were ventilated for ≥60 days. Of those ventilated for ≥60 days, 24% survived without impairment. Of those ventilated for ≥90 days, only 7% survived without impairment. Of those ventilated ≥120 days, all survivors were impaired.

Conclusions The prognosis for ELBW with protracted ventilation remains grim. The cohort who remain intubated have diminished survival and high rates of impairment. Parents of these infants should be informed of changes in prognosis as the time of ventilation increases. (J Pediatr 2005;146:798-804)
mechanical ventilation, and to compare these infants with infants who were ventilated for shorter periods of time.

METHODS

This study was a retrospective analysis of data prospectively collected at the 15 participating centers of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Collected data described the characteristics of the pregnancy and deliveries of 5364 live born ELBW neonates between January 1995 and December 1998. Detailed data on treatments, including duration of mechanical ventilation, were collected using standardized protocols and pre-coded forms from birth until death, discharge, or 120 days of age. Data on respiratory support were collected on days 1, 7, 14, 21, 28, 60, 90, and 120. A day was assigned as a ventilated day if the infant was treated with a mechanical ventilator, but not continuous positive airway pressure (CPAP), during any portion of the day. If an infant was subsequently intubated for any reason, those days of ventilation were included in the total days. The overall outcome of survival with impairment was defined as survival to 18 to 22 months of age with one or more of the following: Mental Developmental Index <70, Physical Developmental Index <70, moderate or severe cerebral palsy, blindness in both eyes, or deafness. Outcome data were collected for the entire hospitalization including any time before transfer to the Network center. All data were abstracted from clinical records by trained study coordinators using an extensive manual with standardized variable definitions. Data were entered in preformatted entry software at each location and electronically transmitted to a central data center (Research Triangle Institute, Research Triangle Park, NC). The Institutional Review Board at each participating institution approved the study.

Follow-Up Assessment Methods

The follow-up assessment methods at 18 to 22 months postmenstrual age have been previously described. Verbal or written consent was obtained at all sites based on Institutional Review Board requirements. The assessment consisted of a medical and social history, physical examination, neurologic assessment, developmental testing, and a parent interview.

The Bayley Scales of Infant Development–II, (BSID–II) including the Mental Scale, Psychomotor Scale, and the Behavior Rating Scale, were administered by developmental specialists trained to reliability by gold standard examiners. BSID–II scores of 100 ± 15 represent the mean ± 1 standard deviation expected for a normal population. Two hundred and eighty-six infants had no Mental Development Index assigned, and 321 infants had no Psychomotor Development Index assigned. Severely delayed infants too impaired to be tested were assigned a Bayley score of 49. Extensive attempts were made to test all children in the 18 to 22 month window; however, because of issues with illness or tracking, 90 infants were evaluated at >22 months of age. These data are included because the BSID–II scores are adjusted for age.

The neurologic examination is based on the Amiel-Tison neurologic assessment. Infants were scored as normal if no abnormalities were observed in the examination. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity with abnormal control of movement and posture. Infants with exclusive or persistent toe walking but without other limitations of function were categorized as “mild” cerebral palsy. All definitions were reviewed and approved by a central review committee.

Socioeconomic information, including maternal and paternal education and occupation, marital status, insurance status, income level, and a detailed medical interview, including hearing and vision status, were obtained. Hearing information was obtained from parental report supplemented with the results of audiologic evaluations when available. Deafness was defined as hearing impairment requiring amplification. A standard eye examination was performed to evaluate tracking, nystagmus, and roving eye movements. Vision status and information from any postdischarge ophthalmologic examinations were obtained and supplemented by information from the parent. Blindness was defined as no functional vision in both eyes. In this report, the overall outcome of survival with impairment was defined as survival to 18 to 22 months of age with one or more of the following: Mental Developmental Index <70, Physical Developmental Index <70, moderate or severe cerebral palsy, blindness in both eyes, or deafness.

Statistical Analyses

All outcomes were analyzed for the total cohort, and in 250-g birthweight intervals from 501 to 750 g and 751 to 1000 g. To obtain information useful in defining prognosis and counseling parents, analyses were performed to assess the likelihood of survival and survival without impairment for ELBW infants who have ongoing respiratory support after a specific duration of mechanical ventilation (eg, 7 total days of mechanical ventilation). Groups were analyzed on specific days of treatment to provide data that are useful in counseling families. For example, on day 14 of ventilation, it is not known whether the patient will be ventilated for 15 days or 60 days, thus the outcomes of all ventilated for 14 or more days were assessed. Infants were assessed weekly for the first month of life, and then at monthly intervals. Duration of ventilation was analyzed with mean, median, and inter-quartile range. Separate descriptive analyses were performed for each interval assessed (7, 14, 21, 28, 60, 90, and 120 days). Survivors were compared with nonsurvivors by univariate analyses with Student’s t test for continuous variables, and χ² analysis for categorical variables. Associations between impairment and days on a ventilator, maternal and neonatal variables, and in-hospital morbidities were explored using a logistic regression model. For these analyses, days on a ventilator were treated as a continuous variable and impairment as a binary variable. Based on a priori considerations, candidate factors examined included birth outside the treating center, antenatal steroid use, maternal education, race, cesarean section, birth weight, small for gestational
age (SGA; <10% for postmenstrual age), gender, early-onset sepsis (positive blood culture at <72 hours of age), late-onset sepsis (positive blood culture at $\geq$72 hours of age), grade III or IV intraventricular hemorrhage (IVH), periventricular leukomalacia (defined as cystic lesions), postnatal steroid exposure, and necrotizing enterocolitis (modified Bells criteria, stage 2 or 3). This model also was run with a second order term for days on a ventilator to test for a nonlinear relationship between days on a ventilator and impairment. This second order term was nonsignificant. Logistic regression models also were completed for the binary outcome “death or impairment” using the subset of infants ventilated for 60 days. Results were expressed as odds ratios and 95% confidence intervals. All data were analyzed at the Research Triangle Institute, Research Triangle Park, NC, using Statistical Analysis Systems software (SAS Institute Inc., version 8.2, Cary, NC).

RESULTS

Population

Of 5364 live born infants, 3782 survived to hospital discharge; 82 neonates died after initial hospital discharge but before 18 months of age, and 659 were lost to follow-up. Thus, 3041(80%) of the 3782 infants who survived to discharge were evaluated for outcomes (Figure 1). Neonates were born at a weight of 766 ± 140 g (mean ± standard deviation), 25.8 ± 2.2 weeks postmenstrual age, were 50.1% male, and 43.8% African American. The mother’s age at delivery was 26.6 ± 6.9 years (mean ± standard deviation), and 52.7% of mothers were unmarried; 89% of infants were delivered at the participating tertiary centers and 69% had received one or more doses of antenatal corticosteroids. Fifteen percent of the infants were small for gestational age.

Comparison of the infants who were followed and lost to follow-up is shown in Table 1. Infants who were followed were slightly smaller and modestly more ill than those infants who were not followed. Although these differences were statistically significant in this large cohort, it is unlikely that the small differences are clinically meaningful.

Ventilation Experience and Mortality

Most infants (89%) were treated with endotracheal intubation and mechanical ventilation on the first day of life (Figure 1). Five hundred and seventy-four (11%) infants were cared for without mechanical ventilation, of whom 249 (43%) survived. Of the 325 infants who died without ever being ventilated, 322 died within 12 hours of birth. This early age of death suggests that these infants were clinically judged to be too immature or compromised to be offered mechanical ventilation. Seventy-four percent of those with mechanical ventilation were administered surfactant for respiratory distress syndrome. The duration of ventilation for ventilated survivors and nonsurvivors are compared in Table II. Of the neonates treated with ventilation, most were weaned from mechanical ventilation early in their hospital course. For survivors and nonsurvivors together, the median duration of ventilation was 18 days (23 days in survivors and 6 days in nonsurvivors). Seventy-five percent of the cohort of tiny infants did not require mechanical ventilation by 36 days (39 days in survivors). Three hundred and seventy-two infants (7%) were ventilated for $\geq$60 days, 72 (1.3%) infants were ventilated $\geq$90 days, and 10 infants were ventilated for $\geq$120 days.

Table 1. Comparison of those followed and those lost to follow-up

<table>
<thead>
<tr>
<th>Lost n = 659</th>
<th>Followed n = 3041</th>
<th>P value</th>
</tr>
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<tr>
<td>Birth weight (g - mean (SD))</td>
<td>812 ± 124</td>
<td>799 ± 128</td>
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<tr>
<td>Gestational age (wk - mean (SD))</td>
<td>26.6 ± 2.1</td>
<td>26.3 ± 2.0</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>304 (46%)</td>
<td>1431 (47%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>246 (38%)</td>
<td>1361 (44.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>86 (13.2%)</td>
<td>372 (12.3%)</td>
</tr>
<tr>
<td>White/other</td>
<td>317 (48.8%)</td>
<td>1304 (42.9%)</td>
</tr>
<tr>
<td>CLD, n (%)</td>
<td>221 (34.4%)</td>
<td>1179 (39.5%)</td>
</tr>
<tr>
<td>Late-onset sepsis, n (%)</td>
<td>209 (31.7%)</td>
<td>1107 (36.4%)</td>
</tr>
<tr>
<td>IVH 3 or 4, n (%)</td>
<td>95 (14.5%)</td>
<td>551 (18.2%)</td>
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<tr>
<td>NEC, n (%)</td>
<td>49 (7.4%)</td>
<td>256 (8.4%)</td>
</tr>
<tr>
<td>ROP, n (%)</td>
<td>400 (67.8%)</td>
<td>2075 (72.1%)</td>
</tr>
</tbody>
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CLD, Chronic lung disease; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

Figure 1. Flow chart of population studied: 5364 ELBW neonates were followed, of whom 4752 (89%) were treated with mechanical ventilation. The outcomes of the cohort are shown.
Survival was evaluated by the total cumulative days of ventilation (Figure 2). For durations of ventilation <28 days, survival remained steady at approximately 85%. Of the 372 ventilated for $\geq 60$ days, 282 (75.8%) survived. Infants who were ventilated for $\geq 60$ days compared with those ventilated for <60 days were smaller (mean birthweight 698 ± 113 vs 771 ± 140 g; $P<.001$), more immature (mean gestational age 24.8 ± 1.6 vs 25.9 ± 2.2 weeks; $P<.001$), less often classified as SGA (8.9% vs 15.7%; $P<.001$), and less often born in the treating center (85.2% vs 89.0%; $P= .025$). Of the 72 infants ventilated for >90 days, 39 (54.2%) survived. Of the 10 infants who were ventilated for $\geq 120$ days, 5 (50%) survived.

Neurodevelopmental Outcomes in Survivors

Overall, 844 of 2755 tested (31%) had a Mental Developmental Index <70, 608 of 2112 (22%) had a Psychomotor Index <70, and 9% had moderate/severe cerebral palsy. Table III compares the neurodevelopmental outcomes by duration of ventilation. Impairment increased when infants remain ventilated past 28 days, with an increase in the proportion of infants having Bayley developmental indices <70 and with cerebral palsy, blindness, or deafness. All of the five survivors who were ventilated for $\geq 120$ days were classified as abnormal on their follow-up assessment. Figure 2 demonstrates the increasing probability of impairment as duration of ventilation increases.

Predictors of Neurodevelopmental Impairment

To obtain information useful in defining prognosis and in counseling parents, logistic regression models estimated the strength of the relationship between duration of mechanical ventilation and neurodevelopmental impairment. Duration of ventilation was a significant risk factor for impairment (OR 1.18 per week of ventilation; 95% CI 1.14–1.22). The value of 1.18 is the extent to which the odds of impairment increase per week of ventilation. Thus, the odds of impairment increase by a factor of 1.94 per 4 weeks of ventilation, and by a factor of 3.76 per 8 weeks of ventilation. Furthermore, the risk of impairment associated with protracted mechanical ventilation is similar to that associated with periventricular leukomalacia (OR 3.72; CI 2.52–5.50). Additional factors significantly

Table II. Ventilation experience of survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Duration of ventilation, d</th>
<th>All ventilated infants (n = 4752)</th>
<th>Survivors* (n = 3533)</th>
<th>Nonsurvivors (n = 1219)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>23.8 ± 22.4</td>
<td>26.7 ± 21.7</td>
<td>15.6 ± 22.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median</td>
<td>18</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>25th percentile</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>75th percentile</td>
<td>36</td>
<td>39</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Postnatal corticosteroid treatment at $\geq 12$ h of age† (%)</td>
<td>47</td>
<td>52</td>
<td>28</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Classified at discharge. Statistical comparisons are between survivors and nonsurvivors in each class.
†4794 infants survived $>12$ h of age, of whom 4542 were ventilated.
groups of patients to an individual, to assist those who wish to individualize counseling for families of infants receiving protracted ventilation, regression equations limited to those ventilated for $\geq 60$ days were generated. For those infants ventilated for $\geq 60$ days, the odds ratio for the risk of death or impairment can be calculated with the equation:

$$OR = e^{(\Sigma \beta)}$$

where $\Sigma \beta = (0.24 \text{ (Male)} + 0.58 \text{ (Severe IVH)}$

$+ 0.74 \text{ (Non-white)} + 1.57 \text{ (SGA)}$

We attempted to construct similar models for the patients ventilated for $\geq 90$ days. However, the numbers were too small to allow meaningful modeling.

**Table III. Neurodevelopmental outcomes at 18 months corrected age compared by total days of ventilation**

<table>
<thead>
<tr>
<th>Days of ventilation</th>
<th>Normal neurologic exam (%)</th>
<th>Cerebral palsy (%)</th>
<th>Blind (%)</th>
<th>Deaf (%)</th>
<th>BSID-II MDI Mean (SD)</th>
<th>BSID-II (PDI) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(n = 182)</td>
<td>90</td>
<td>2.3</td>
<td>1.2</td>
<td>89 ± 16</td>
<td>94 ± 15</td>
</tr>
<tr>
<td>≥1</td>
<td>(n = 2859)</td>
<td>77</td>
<td>9</td>
<td>1.8</td>
<td>79 ± 18</td>
<td>82 ± 19</td>
</tr>
<tr>
<td>≥7</td>
<td>(n = 2240)</td>
<td>74</td>
<td>11</td>
<td>2.2</td>
<td>77 ± 18</td>
<td>80 ± 19</td>
</tr>
<tr>
<td>≥14</td>
<td>(n = 1949)</td>
<td>72</td>
<td>12</td>
<td>2.4</td>
<td>76 ± 18</td>
<td>79 ± 19</td>
</tr>
<tr>
<td>≥21</td>
<td>(n = 1580)</td>
<td>70</td>
<td>13</td>
<td>2.8</td>
<td>75 ± 18</td>
<td>78 ± 19</td>
</tr>
<tr>
<td>≥28</td>
<td>(n = 1234)</td>
<td>67</td>
<td>14</td>
<td>2.8</td>
<td>73 ± 18</td>
<td>76 ± 19</td>
</tr>
<tr>
<td>≥60</td>
<td>(n = 245)</td>
<td>63</td>
<td>14</td>
<td>2.8</td>
<td>66 ± 18</td>
<td>67 ± 19</td>
</tr>
<tr>
<td>≥90</td>
<td>(n = 38)</td>
<td>53</td>
<td>23</td>
<td>3.7</td>
<td>59 ± 14</td>
<td>60 ± 20</td>
</tr>
<tr>
<td>≥120</td>
<td>(n = 5)</td>
<td>46</td>
<td>27</td>
<td>8.1</td>
<td>52 ± 6</td>
<td>49 ± 20</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study summarizes the findings for a large heterogeneous and contemporary group of ELBW infants cared for at 15 centers and relates their survival and neurodevelopmental outcomes at 18 to 22 months of age to their respiratory course in the neonatal period. These tiny infants have been the focus of the frontier of neonatal care. Seventy-five percent of ELBW infants in this cohort who survived were ventilated for a cumulative total of $\geq 39$ days. The 25% of ELBW infants who remain ventilated for $>39$ days represent a high-risk subgroup for both mortality and impaired neurodevelopmental outcomes. Only 7% of this ELBW cohort were ventilated for $\geq 60$ days. These infants have diminished survival and little chance of survival free of neurodevelopmental impairment. Recognizing that ventilator dependence beyond 39 days identifies an ELBW neonate as an outlier may prompt earlier evaluation and interventions that may modify the patient’s course.

**Table IV. Comparison of risk of death or neurodevelopmental impairment associated with additional risk factors when ventilated at 60 days of age**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Odds Ratio, (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, not SGA, no severe IVH</td>
<td>Reference</td>
</tr>
<tr>
<td>White, not SGA, severe IVH</td>
<td>1.79 (0.97 – 3.30)</td>
</tr>
<tr>
<td>Non-white, not SGA, no severe IVH</td>
<td>2.09 (1.23 – 3.56)</td>
</tr>
<tr>
<td>Non-white, not SGA, severe IVH</td>
<td>3.74 (1.66 – 8.42)</td>
</tr>
<tr>
<td>White, SGA, no severe IVH</td>
<td>4.80 (1.11 – 20.87)</td>
</tr>
<tr>
<td>White, SGA, severe IVH</td>
<td>8.60 (1.74 – 42.56)</td>
</tr>
<tr>
<td>Non-white, SGA, no severe IVH</td>
<td>10.03 (2.07 – 48.68)</td>
</tr>
<tr>
<td>Non-white, SGA, severe IVH</td>
<td>17.97 (3.28 – 98.47)</td>
</tr>
</tbody>
</table>

$MDI$, Mental Developmental Index; $PDI$, Psychomotor Developmental Index.

**Figure 3.** Adjusted odds ratio and 95% confidence levels for impairment. Duration of ventilation (risk per week of ventilation) and other factors that may be associated with neurodevelopmental impairment are shown.
There have been few recent studies relating duration of mechanical ventilation to outcome at 18 months or later, particularly studies addressing ELBW infants treated since surfactant therapy and antenatal corticosteroids became widely used. Gaillard and colleagues reported the outcomes of neonates with protracted ventilator dependence who were treated with both surfactant and antenatal steroids. Of those ventilated ≥49 days, mortality was 50%, with 64% of the survivors demonstrating some degree of neurodevelopmental disability. Their small study included infants as large as 34 weeks gestation, and thus might be expected to have more favorable outcomes than the present study’s smaller infants. Thomas and coworkers reported the outcomes of a single center cohort of 41 infants that included only neonates born at 24 to 29 weeks between 1995 and 1999. They analyzed the impact of discontinuous episodes of ventilation and found that discontinuous episodes of ventilation were associated with a somewhat improved outcome. Unfortunately, the dataset used in the current study does not permit an analysis of continuous versus discontinuous ventilation.

Protracted ventilation alone may not cause a poor outcome but instead may serve as a marker for severity of illness. High rates of neuro-behavioral impairment have been noted in all ELBW survivors. Periventricular leukomalacia, emphasizes the severity of their neurologic injury because the brain is at a critical stage of development, and it sustains repeated injuries from multiple clinical illnesses associated with prematurity combined with the environmental impacts of an intensive extra-uterine environment. Infants with protracted ventilator dependence represent the most severely ill of the cohort of all ELBW. The strong association between protracted ventilator dependence and neurologic injury, represented by severe IVH and periventricular leukomalacia, emphasizes the severity of their illness. The current data do not allow determination of the causal relationship between the two factors.

Recent meta-analyses of the use of postnatal steroids have documented an increased risk of neurodevelopmental impairment. In this study, postnatal steroids were not significantly associated with neurodevelopmental impairment (OR 1.13; CI 0.91-1.40). It is likely that postnatal steroid exposure is another marker for significant lung disease that competes in any model with days of ventilatory support, and thus minimizes the impact of postnatal steroids.

The strengths of this study include the assessment of a large multi-center cohort of ELBW infants, a high follow-up rate of survivors, and a standardized assessment method to ensure reliable evaluations across all centers. Some potential limitations deserve discussion. First, this is not a population-based cohort, and this may limit the generalizability of the findings to other populations. It does reflect care at large academic centers in the United States, and as such the population is biased toward socially disadvantaged women and their infants. Second, 20% of the survivors were lost to follow-up, although those lost were clinically similar to those followed. Thus, it is unlikely that those lost biased the overall results. Third, intubation and mechanical ventilation was the initial strategy used in 89% of these infants. Newer respiratory care approaches are emphasizing CPAP as a primary ventilatory modality. Future studies should evaluate whether such a strategy would improve overall outcomes. However, even in a strategy that emphasizes CPAP, those ventilated for weeks or months are at the highest risk for adverse outcomes. Finally, we have previously reported marked differences in care between centers that contribute to differences in outcomes. Thus, individual centers may have outcomes that diverge from these aggregate results.

Data presented in this study may be valuable to neonatologists and to the parents of these infants in anticipating long-term care needs. Most parents are told at the time of delivery about the chances of survival and morbidity in their infant. However, as demonstrated in this study, the risk of mortality and neurodevelopmental disability increases dramatically if that infant requires protracted mechanical ventilation. Although data describing the outcomes for groups will not accurately predict the outcome for any one individual, such outcome data often are requested by parents. These data may assist parents and physicians by realistically framing the probability of survival and neurodevelopmental abnormality, assisting in evidence-based decision making.

APPENDIX


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REFERENCES


ENDOTHELIN-1 IN HUMAN INTESTINE RESECTED FOR NECROTIZING ENTEROCOLITIS

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Objectives We asked if the tissue concentration of the potent vasoconstrictor endothelin-1 (ET-1) is greater in areas of human preterm intestine that demonstrate histologic evidence of necrotizing enterocolitis (NEC) when compared with relatively healthy areas within the same resection specimen. We then evaluated if ET-1 participates in hemodynamic regulation within intestinal subserosal arterioles harvested from portions of human preterm intestine that demonstrate NEC.

Study design Human preterm intestine resected for NEC was divided into three zones based on proximity to the perforation (zone 1 most proximal, zone 3 most distal). Histologic evidence of NEC was determined in each zone (normal = 0, advanced necrosis = 6). The tissue concentration of ET-1 was determined by enzyme-linked immunosorbent assay within intestinal homogenates prepared from each zone. Arteriolar hemodynamics were determined in vitro on subserosal arterioles harvested from different zones. Arteriolar flow rate, diameter, and resistance were determined at pressure gradients (ΔP) of 20 and 40 mmHg under control conditions and again after blockade of endothelin ETₐ receptors with BQ610 (10⁻⁹ mol/L).

Results The tissue concentration of ET-1 (pg/mg protein) and histologic score in the three zones were: zone 1: 84 ± 14, 5.5 ± 0.3; zone 2: 99 ± 12, 4.7 ± 0.4, and zone 3: 33 ± 9, 0.8 ± 0.6, respectively (M ± SD, n = 10 resection specimens, P < .05, zone 3 vs zones 1 and 2). Zone 2 arterioles demonstrated significantly lower flow rate and diameter and increased resistance under control conditions than zone 3 arterioles when ΔP was either 20 or 40 mmHg (n = 7, P < .05). Treatment with BQ610 had no effect on zone 3 arterioles but significantly vasodilated zone 2 arterioles, increasing flow rate and vessel diameter, and decreasing vascular resistance (n = 7, P < .05).

Conclusions The tissue concentration of ET-1 is greater in human preterm intestine that demonstrates histologic evidence of NEC. Arterioles harvested from intestine exhibiting histologic evidence of NEC demonstrate vasoconstriction when compared with arterioles from relatively healthy intestine in the same resection specimen. This vasoconstriction was reversed by blockade of endothelin ETₐ receptors. (J Pediatr 2005;146:805-10)

The histopathology of intestine resected for necrotizing enterocolitis (NEC) often demonstrates coagulation necrosis, particularly in the muscularis layers of the intestinal wall. Coagulation necrosis is the footprint of preceding ischemia; hence, its presence within intestine resected for NEC provides a compelling argument that intestinal ischemia occurs at some point during the evolution of this disease. Several agents with the potential to alter intestinal hemodynamics have been considered as mechanisms responsible for NEC-related ischemia, including platelet activating factor (PAF), inducible nitric oxide synthase, leukotrienes, prostaglandins, and cytokines.

The complexity of NEC pathogenesis suggests that an additional vasoactive agent, or agents, may be involved in disease pathogenesis. Clues regarding the identity of this agent might be deduced from existing data regarding the epidemiology and etiology of NEC. First, NEC often progresses rapidly to tissue necrosis; hence, the agent should elicit profound and sustained ischemia capable of generating cellular hypoxia and death. Second, NEC-related ischemia appears to begin in the gut microvasculature; hence, the agent should be locally produced, ie, within the microvasculature or gut parenchyma. Finally, vasoactive factors relevant to NEC pathogenesis have already been identified; hence, any

<table>
<thead>
<tr>
<th>ANOVA</th>
<th>Analysis of variance</th>
<th>PAF</th>
<th>Platelet activating factor</th>
<th>ΔP</th>
<th>Pressure gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1</td>
<td>Endothelin-1</td>
<td>NEC</td>
<td>Necrotizing enterocolitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ET-1, a potent vasoconstrictor agent, generates a profound degree of ischemia that is sustained for hours because of a unique interaction between ET-1 and its receptor.\(^8\) If not balanced by concomitant vasodilatory stimuli, ET-1-induced ischemia can generate hypoxia and tissue death.\(^10\) ET-1 is produced at several sites within the intestine, including vascular endothelial cells, submucosal stroma, and circularis muscularis layers of the gut wall.\(^11\) ET-1 induces vasoconstriction by binding to \(\text{ET}_A\) receptors present on vascular smooth muscle,\(^12\) receptors that are present within the newborn intestine\(^13\) and whose activation can generate intestinal tissue damage when excessive amounts of ET-1 are present.\(^14\)

The present work tested two hypotheses: first, the concentration of ET-1 within human intestine that demonstrates histopathologic features of NEC is increased when compared with areas within the same resection specimen that appear relatively healthy. Second, the role of ET-1 in hemodynamic regulation of arterioles harvested from human intestine that demonstrate histopathologic features of NEC is increased when compared with arterioles harvested from relatively healthy areas within the same resection specimen.

**METHODS**

**Study Population**

The project was approved by the Institutional Review Board of Columbus Children's Hospital and parental consent was obtained before recovery of tissue. Two groups were studied. Group 1 consisted of all infants who underwent intestinal resection for NEC during the study period. None of these infants demonstrated isolated gut perforations. Group 2 consisted of all infants <1 month of postnatal age who underwent intestinal resection for indications other than NEC (eg, congenital bowel malformation). Enrollment began in September 2002 and continued until February 2004. At this time, 10 resection specimens had been collected in group 1, and 5 specimens had been collected in group 2. Statistical analysis of relevant study variables generated from these specimens proved significant; thus, further enrollment was terminated.

**Tissue Acquisition and Processing**

The pathologist examined the resection specimen and retained those portions that were necessary to make a tissue diagnosis. The remainder of the tissue was placed into iced Krebs buffer. The NEC specimens were divided into zones: zone 1 was tissue at the site of perforation; zone 2 was tissue \(0.5\) cm, but \(<1.0\) cm from the site of perforation; and zone 3 was the resection margin. None of the zone 2 tissue demonstrated visible necrosis, whereas all the tissue in zone 1 was clearly necrotic based on gross examination alone (ie, black-green in color, thinning of gut wall, friable). Suberosal arterioles (<150 \(\mu\)m) were harvested from zones 2 and 3, and were placed into iced Krebs buffer. Zone 1 tissue was in an advanced state of necrosis that precluded vessel harvest. Then, tissue from each zone was divided into two full-thickness portions: one was placed into 10% neutral buffered formalin for subsequent histologic examination, whereas the other was snap frozen in liquid \(\text{N}_2\) and used to measure tissue ET-1 concentration. Specimens in group 2 were processed in the same manner except that division of the specimens into zones was not carried out.

**Histologic Analysis**

The study design was based on comparison among areas within the same resection specimen that demonstrated different histologic levels of disease, ie, each resection specimen served as its own control. To this end, histologic examination was carried out on a portion of each zone from each resection specimen to confirm the extent of disease by means of simple scoring system that capitalized on the histology characteristic of NEC.\(^1,2\) The scoring system included the following descriptors: (1) loss of villi; (2) loss of mucosal crypt architecture; (3) hemorrhagic necrosis; (4) coagulation necrosis; (5) submucosal edema; and (6) thinning of the intestinal wall. Each descriptor was assigned a weight of 1, so that potential scores could range from 0 (no disease) to 6 (advanced necrosis). Scoring was carried out in a blinded fashion; thus, the scorer did not know the zone from which the sample was taken and was unaware of biochemical or physiologic end points derived from that sample.

**Measurement of ET-1**

Frozen intestinal samples were pulverized under liquid \(\text{N}_2\) using a mortar and pestle. The resultant powder was added to buffer (75 mL absolute ethanol, 2.5 mL glacial acetic acid, 22.5 mL double distilled \(\text{H}_2\text{O}\)) and homogenized on ice. Homogenates were centrifuged twice and protein concentration of the final supernatant was determined by the bicinchoninic acid method (Pierce, Rockford, Ill). Peptide extraction was carried out on supernatant added to 1 mL of buffer A (1% trifluoroacetic acid) applied to C-18 columns pre-equilibrated with 100% acetonitrile. After three washes with buffer A, peptides were eluted from the column with buffer B (60% acetonitrile in 1% trifluoroacetic acid). Elutants were dried on a centrifugal concentrator without heat and stored at \(-80^\circ\text{C}\) until final assay. ET-1 concentration was determined by enzyme-linked immunosorbent assay using antibody purchased from Bachem (Peninsula Labs, San Carlos, Calif) and expressed as pg ET-1/mg protein within the supernatant.

**Arteriolar Hemodynamics: Harvest**

Arterioles were harvested from the subserosa with the aid of a dissecting microscope. Arterioles were easily differentiated from venules because arteriolar diameter was <50% of venules and because the thickness of the arteriolar wall was greater than that of the venule. Arteriolar harvest was
carried out 1 to 2 hours after the initial intestinal resection. The tissue was kept in 4°C Krebs buffer before and during vessel harvest; thereafter, arterioles were kept in this buffer until being mounted for study. A pilot study was carried out to determine if storage of arterioles in this manner altered subsequent reactivity; thus, arterioles were studied after 2 to 12 hour storage in iced Krebs buffer. These studies (n = 3) demonstrated that storage of arterioles for up to 12 hours had no effect on the vascular response to the perturbations applied as part of the experimental protocol (ie, KCl and isoproterenol challenge to confirm vessel viability; endothelin receptor blockade). Data presented herein were obtained from arterioles stored for <3 hours before study, ie, arteriolar harvest and subsequent mounting for study occurred in <5 hours from the time of initial gut resection.

**Arteriolar Hemodynamics: Apparatus**

Arterioles were studied using an in vitro microvascular apparatus (Living Systems, Burlington, Vt) as previously described. Arterioles were mounted in the proper proximal-distal orientation on two glass micropipettes situated in a plexiglass chamber. Krebs buffer aerated with 95% O₂ and 5% CO₂ and warmed to 38°C was used to perfuse the arteriole. Pressure across the arteriole was measured by micro-pressure transducers placed immediately proximal (Pₚ) and distal (Pₜ) to the glass cannulae, whereas flow rate was measured with a micro-flowmeter placed within the proximal perfusion circuit. Arteriolar pressure was generated by means of two pumps, one each at the proximal and distal sides of the perfusion circuit. The Pₚ and Pₜ pumps were independently controlled by servo mechanisms driven by the Pₚ and Pₜ pressure transducers, respectively; hence, the desired Pₚ and Pₜ were set into the servo devices and pumps were servo-activated to establish, and thereafter maintain, these pressures. It is important to note that flow across the arteriole was established by setting Pₚ > Pₜ, thus creating a pressure gradient, or ΔP, across the arteriole. The pumps served only to pressurize the perfusion circuit; hence, flow rate was a dependent variable, ie, dependent on ΔP and vascular resistance across the arteriole. The chamber, and hence the external surface of the arteriole, was continuously suffused with Krebs buffer (38°C) recirculated at a rate of 50 mL/minute (total suffusate buffer volume 200 mL). The chamber was placed on the stage of an inverted microscope set in line with a video camera from which vessel diameter was measured. The laboratory is equipped with two separate microvascular platforms.

**Arteriolar Hemodynamics: Experimental Protocol**

Arterioles harvested from zones 2 and 3 were studied simultaneously. Arterioles were preconditioned by setting both Pₚ and Pₜ at 20 mmHg (ie, ΔP = 0), thus pressurizing the vessel in the absence of flow, for a period of 1 hour. Arteriolar viability was confirmed by noting ≧25% diameter reduction in response to KCl (100 mmol/L), followed by ≧15% diameter increase in response to 10⁻⁹ mmol/L isoproterenol. To begin the study protocol, Pₚ was increased to 25 mmHg and Pₜ reduced to 5 mmHg, establishing a ΔP of 20 mmHg and hence flow across the arteriole. Hemodynamic measurements (flow rate, arteriolar diameter) were recorded when new steady-state conditions were established. Pₚ was then increased to 45 mmHg while Pₜ was kept at 5 mmHg, thus increasing ΔP to 40 mmHg, and a second set of measurements were made when a new steady-state prevailed. These ΔP levels were selected because they represent pressures normally present within the intestinal microcirculation. Pₚ and Pₜ were then both reset to 20 mmHg, reducing ΔP to 0 mmHg and thus eliminating flow. After 30 minutes, the endothelin ETₐ receptor antagonist BQ610 (10⁻⁹ mol/L) was added. Thirty minutes thereafter the study protocol was repeated.

**Statistical Evaluation**

Differences in the tissue concentration of ET-1 and in the histologic score among the three zones were determined by separate one-way analyses of variance (ANOVA). Differences in hemodynamic data were determined by a three-way ANOVA that incorporated zone of arteriolar harvest (zone 2 vs zone 3), ΔP (20 vs 40 mmHg), and treatment (control vs BQ610) as main effects. In all ANOVAs, post-hoc t tests were carried out to determine significance. A level of P <.05 was accepted as evidence of statistical significance. These three-way ANOVAs were carried out on measured variables (flow rate, vessel diameter) and on arteriolar resistance, calculated as the ratio of ΔP to flow rate. All data are given as mean and standard deviation (M ± SD).

**RESULTS**

**Patient Demographics**

Infants in group 1 (n = 10) had a gestational age of 28 ± 3 weeks and birth weight of 1025 ± 280 g. None of the group 1 infants were small for gestational age. The age of onset of NEC was on postnatal day 11 ± 6. The indication for laparotomy was peritoneal free air and in each case necrotic bowel with perforation(s) was observed and resected. None of these NEC cases were clustered, and none represented focal perforation, variants of NEC that may have unique pathogenetic mechanisms. All 10 case patients in group 1 underwent resection of the distal small intestine, whereas only 3 of 10 had concomitant resection of the cecum or colon; in all of the latter cases, the pathologist did not provide sufficient cecal or colonic tissue to the study. Consequently, this study presents data derived solely from distal small intestine. Infants in group 2 (n = 5) had a gestational age of 39 ± 3 weeks and a birth weight of 3600 ± 345 g (P <.05 compared with group 1). The indication for laparotomy in group 2 infants was congenital gastrointestinal stenosis or atresia. All group 2 infants had intestinal resection on postnatal day 1.

**Histologic Findings**

In group 1, a progressive increase in the NEC histology score was noted in comparison of zones 3, 2, and 1 (Table 1).
Histology of tissue samples in zone 3, the relatively healthy resection margin, was ≤1 in all 10 specimens; no evidence of hemorrhagic or coagulation necrosis was present in any zone 3 specimen. In contrast, all tissue designated as zone 2 (diseased tissue) demonstrated loss of villi, as well as hemorrhagic and coagulation necrosis. Zone 1 tissue consistently demonstrated overwhelming necrosis, as evidenced by profound thinning of the intestinal wall. Therefore, tissue in zones 1 and 2 demonstrated clear evidence of NEC, whereas tissue in zone 3 was relatively healthy in appearance. The histologic score of intestine resected from group 2 infants was 0.4 ± 0.2 (M ± SD), ie, the tissue demonstrated normal intestinal histology.

Intestinal ET-1

The tissue concentration of ET-1, expressed as pg ET-1/mg protein, was significantly greater in zones 1 and 2 (diseased tissue) when compared with zone 3 (relatively healthy tissue) (Table I). The ET-1 concentration in group 2 infants was similar to that noted in group 1, zone 3.

Hemodynamic Data

Arterioles were successfully harvested from 7 of 10 group 1 infants. Hemodynamics were significantly different between zone 2 and 3 arterioles under control conditions (Table II). Arteriolar resistance was significantly greater and diameter less in zone 2 than in zone 3 arterioles when ΔP = 20 mmHg. Increase of ΔP from 20 to 40 mmHg caused a significant increases in vessel flow and diameter, and a concomitant decrease in resistance in zone 3 arterioles; by contrast, zone 2 arterioles failed to demonstrate changes in flow and diameter, whereas resistance actually increased. Application of BQ610 changed hemodynamics differently in zone 2 and 3 arterioles. When compared with control, flow rate and diameter were greater, whereas resistance was less at ΔP = 20 mmHg in zone 2 arterioles; in contrast, BQ610 had no effect on arteriolar hemodynamics in zone 3 arterioles at ΔP = 20 mmHg. The subsequent increase in ΔP from 20 to 40 mmHg significantly increased arteriolar flow rate and diameter, and reduced resistance to similar degrees in both zone 2 and 3 arterioles; hence, BQ610 significantly changed the response of zone 2 arterioles to the increase in ΔP from 20 to 40 mmHg when compared with the response noted under control conditions, but it had no effect on the response of zone 3 arterioles. These findings suggest that blockade of ETA receptors caused zone 2 arterioles to function in manner similar to zone 3 arterioles.

Arterioles were successfully harvested from 4 of 5 group 2 infants. The hemodynamic responses of arterioles harvested from group 2 subjects was similar to that noted in group 1, zone 3 arterioles. Differences between group 2 arterioles and those in group 1, zone 2 were present and were similar to those noted between zone 3 and zone 2 arterioles (Table II).
DISCUSSION

Our results support the experimental hypotheses. The tissue concentration of ET-1 was greater in zone 2 than zone 3, i.e., greater in the area of resected intestine that demonstrated histologic evidence of NEC. As well, arterioles harvested from zone 2 demonstrated a significantly greater response to blockade of the endothelin ETA receptors which mediate endothelin-induced vasoconstriction, suggesting that the role of ET-1 in hemodynamic regulation was greater in these arterioles when compared with those harvested from zone 3.

Previous studies have implicated ET-1 in intestinal vascular dysfunction and tissue injury. Whittle and Esplugues demonstrated generation of hemorrhagic necrosis of the gastric mucosa following direct application of ET-1. Mirua and colleagues reported a profound reduction of NEC. These agents can enhance the rate of ET-1 production but also be recovered from human preterm intestine resected for NEC. Boros reported that ET-1 participated in the generation of sustained intestinal ischemia and subsequent tissue damage following intra-arterial infusion ET-1; furthermore, this group demonstrated that endotoxin-induced intestinal microvascular dysfunction was mediated, in part, by ET-1. Boros reported that ET-1 participated in the generation of sustained intestinal ischemia and subsequent tissue damage following a single episode of ischemia-reperfusion. King-VanVlack et al noted that ET-1 induced submucosal microvascular dysfunction when applied topically to the overlying mucosa; furthermore, they noted that ET-1 exerted a proinflammatory action, as evidenced by an increase in microvascular permeability. These observations clearly support the possibility that ET-1 participates in the generation of intestinal ischemia and tissue damage.

Other agents have been identified as potentially relevant in the induction of NEC-related ischemia and most of these have the potential to interact with ET-1 to generate vascular dysfunction. PAF, a proinflammatory lipid mediator, is increased in the plasma of infants with NEC. PAF can interact with ET-1 at two levels: first, ET-1 can activate PAF, i.e., PAF can act downstream of ET-1. Second, the capacity of PAF to generate an inflammatory response generates a microvascular environment that favors increased transcription of ET-1. Cytokines and inducible nitric oxide synthase have been recovered from human preterm intestine resected for NEC. These agents can enhance the rate of ET-1 transcription, thus increasing the presence of ET-1 within the intestine. Luminal infusion of acidified casein and calcium gluconate, agents present within the lumen of intestine resected for NEC, causes release of prostaglandin E2, 6-ketoprostaglandin F1α, and leukotriene B4, agents capable of causing vascular dysfunction, primarily by induction of vasoconstriction. The co-existence of another vasoconstrictor, ET-1, would have the potential to enhance eicosanoid-induced ischemia. Within this context of the myriad vasoactive factors present in NEC, it is not feasible to speculate on the relative role of ET-1 in NEC pathogenesis, nor is it presently possible to assign ET-1 a position in the temporal cascade of events that besiege the intestinal microvasculature during this process.

ET-1 concentrations were for homogenates from whole intestine for each of three zones; hence, there is no information about the site(s) within the gut wall where increased ET-1 production occurred. In human intestine, ET-1 is produced within the vascular endothelium in both conduit vessels and the microvasculature, and also in the submucosal stroma and circularus muscularis layers. It might thus be argued that if the increased tissue ET-1 concentration noted in zones 1 and 2 occurred within a nonvascular space (eg, submucosal stroma), then it might not be geographically positioned to interact with ETA receptors present on vascular smooth muscle. However, the tissue half-life of ET-1 is substantial, and its translocation from an extravascular site of production to adjacent vascular smooth muscle has been reported. It is thus feasible that ET-1 produced by outside of an intestinal microvessel might still exert vasoconstriction capable of altering intestinal microvascular hemodynamics.

The basal vessel diameter, flow rate, and resistance of subserosal arterioles harvested from zone 2 reflected a state of relative vasoconstriction when compared with zone 3. This vasoconstriction was significantly attenuated by blockade of ETA receptors with BQ123. ET-1 exerts its vasoconstrictor effect by binding to the ETA receptor, a member of the seven transmembrane spanning, G protein linked family of receptors that is principally located on vascular smooth muscle. BQ123 is a highly selective, nonpeptide ETA antagonist, hence, the relative vasodilation noted in zone 2 arterioles following this agent permits the conclusion that ET-1 was a participant in the basal vasoconstriction noted in these vessels. In this context, the degree of ET-1-induced vasoconstriction noted in zone 2 arterioles was not only statistically significant, but physiologically relevant; thus, the flow rate in zone 2 arterioles at ΔP = 40 mmHg, a perfusion pressure present within the intestinal microcirculation, was approximately 30% of that present in zone 3 arterioles. If this difference were extrapolated to the in vivo circumstance, the compromise in the rate of blood flow, and hence oxygen delivery by this degree of vasoconstriction, would be sufficient to cause intestinal tissue hypoxia.

Subserosal arterioles represent the first portion of the intestinal intramural microvasculature. These arterioles, derived from the terminal mesenteric arcade, pierce the intestinal wall to form an arteriolar plexus within the submucosa. Smaller arterioles are then derived from this submucosal plexus to form independent mucosal and muscularis microcirculations. All portions of this microvascular network, from subserosal arterioles to precapillary arterioles, function as resistance vessels; hence, all play a role in flow regulation. Selection of subserosal arterioles for study herein was based on their availability for in vitro study; smaller downstream arterioles must be studied in vivo because of their small size. Although the behavior of subserosal arterioles might not precisely predict that of the downstream microvascular elements, they are a portion of the gut microvasculature that participate in flow regulation. These results can be interpreted as evidence that ET-1 participates in hemodynamic regulation within portions of intestine that demonstrate histologic evidence of NEC.
The present data do not demonstrate a cause-and-effect relationship for ET-1 within zone 2, the microvascular dysfunction in arterioles from zone 2, and the tissue damage. The descriptive nature of the results reflect experimental design limitations inherent in using freshly resected human intestine. However, this approach provides important and novel insight into the pathophysiology of NEC as it occurs in human preterm infants.

REFERENCES

Objective  To determine clinical outcomes and the prevalence of prothrombotic conditions in patients who had neonatal renal venous thrombosis (RVT).

Study design  A retrospective cohort of neonates with RVT who were admitted to 4 pediatric centers from 1980 to 2001 was identified. Information on clinical presentation, laboratory and radiological investigation, and treatment were abstracted. Survivors were evaluated for renal status and prothrombotic conditions.

Results  Forty-three patients with neonatal RVT were identified. RVT was unilateral in 24 patients (56%) and associated with thrombi at other sites in 32 patients (74%). Clinical presentations included renal failure in 24 patients (56%), thrombocytopenia, anemia, or both in 22 patients (51%), and renal mass in 21 patients (49%). Neonatal interventions included anticoagulants in 28 patients (65%), antihypertensive medications in 9 patients (21%), peritoneal dialysis in 2 patients (5%), and nephrectomy in 2 patients (5%). The median age at follow-up was 3.7 years (range, 0.5-20.2 years). Thirteen patients (34%) had hypertension, and 11 patients (29%) had renal failure. End-stage renal disease developed in 3 patients, and they underwent live-related renal transplants. Twelve of the 28 patients (43%) examined had prothrombotic abnormalities.

Conclusion  Neonatal RVT is associated with significant renal morbidity and a high prevalence of prothrombotic abnormalities. (J Pediatr 2005;146:811-6)

Renal venous thrombosis (RVT) is the second most common venous thromboembolic event in neonates.1-4 RVT has variable clinical features, which can include hematuria, oliguria-anuria, renal mass, hypertension, thrombocytopenia, decreased renal function, and abnormal Doppler ultrasound scanning results. Minimum diagnostic criteria include the presence of microscopic or macroscopic hematuria with ultrasound scanning evidence of an enlarged, echogenic kidney with loss of corticomedullary differentiation.5 Findings on Doppler ultrasound scanning include a decrease in the amplitude or absence of venous signal, abnormal flow patterns in a number of renal venous branches, or evidence of venous collateral development.6

Risk factors for the development of RVT include maternal diabetes mellitus (either type 1 or gestational),7,8 pathologic states associated with thrombosis (eg, shock, dehydration,9 perinatal asphyxia,10 polycythemia, cyanotic heart disease), sepsis,11 umbilical venous catheterization, and conjoined twins.12 Inherited prothrombotic abnormalities13-20 have been described in case reports of RVT. However, the prevalence of these disorders has not been studied in a cohort of patients with neonatal RVT.

Management of RVT is generally supportive, but may also include anticoagulation therapy, fibrinolytic therapy, or both. The sequelae of RVT reported in the literature include glomerular disease (3%-100%), tubular dysfunction (9%-47%), hypertension (9%-100%), and evidence of renal scarring or atrophy (27%-100%).6,21-35 The reported variation in the degree of morbidity suggests an underlying heterogeneity in the etiology of RVT that may

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### Table

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Activated protein C</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RVT</td>
<td>Renal venous thrombosis</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolic event</td>
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</table>
**Table I. Neonatal characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (n = 43)</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>24-42 weeks</td>
</tr>
<tr>
<td>Birthweight (n = 43)</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>0.76-5.7 kg</td>
</tr>
<tr>
<td>Apgar score at 1 minute (n = 38)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>0-9</td>
</tr>
<tr>
<td>Apgar score at 5 minutes (n = 38)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>2-10</td>
</tr>
<tr>
<td>Male sex (n = 43)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>65%</td>
</tr>
<tr>
<td>Mode of delivery (n = 43)</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>23</td>
</tr>
<tr>
<td>Cæsarean Section</td>
<td>16</td>
</tr>
<tr>
<td>Instrumentation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>9%</td>
</tr>
</tbody>
</table>

*Values are median (range) or number (%).

lend itself to individualized management strategies to prevent long-term renal complications.

The objective of this study was to determine the clinical outcomes and prevalence of prothrombotic conditions in neonates with RVT.

**METHODS**

**Study Design and Patient Population**

Children who had RVT diagnosed during the neonatal period were identified retrospectively from the Divisions of Neonatology and Nephrology and Health Record Department databases of 4 pediatric centers (Toronto, Hamilton, Ottawa, and London) in the province of Ontario, Canada, using the terms “neonates,” “renal venous thrombosis,” “hypertension,” and “renal failure.” Patients were included when a review of clinical data indicated that they satisfied the minimum diagnostic criteria for neonatal RVT, namely the presence of macroscopic or microscopic hematuria with ultrasound scanning evidence of an enlarged, echogenic kidney with loss of corticomedullary differentiation.5,6,36

**Data Collection**

**NEONATAL DATA.** A retrospective chart review was performed to determine maternal medical and obstetrical history, and the infant’s condition at birth including resuscitation, neonatal diagnoses, and outcomes. Collected diagnostic information included urinary abnormalities, results of haematological and biochemical tests, coagulation profile, thromboembolic work-up, and radiology investigations.

**POST-NEONATAL FOLLOW-UP INFORMATION.** Follow-up on the clinical course and outcomes, results of diagnostic tests, and medications were retrieved with a standardized data collection form from the records of the nephrology clinics.

Patients not being observed by a nephrologist at the time this study was initiated were recalled for an evaluation of their renal status. On recall visits, when possible, each patient underwent a physical examination (including anthropometric measurements and blood pressure), Doppler renal ultrasound scanning, urine and blood tests, and work-up for prothrombotic abnormalities. Alternatively, results of previously performed clinical tests were collected. Patients were examined with nuclear renal scanning when clinically indicated. Hypertension was defined as blood pressure higher than the 95th centile for age, sex, and height centiles37 or the requirement for antihypertensive medication.

**Investigations**

The diagnosis of renal atrophy was made when serial measurements (≥2 or more ultrasound scans) of renal length showed declining values less than the third percentile.38 Glomerular filtration rate (GFR) was estimated with the Schwartz formula.39 Patients were classified as normal (GFR >80 mL/min/1.73m²), early renal failure (GFR 40–70 mL/min/1.73m²), chronic renal insufficiency (GFR 20–40 mL/min/1.73m²), chronic renal failure (GFR 10–20 mL/min/1.73m²), and end-stage renal disease (GFR <10 mL/min/1.73m²).40

**Testing for Prothrombotic Abnormalities**

Screening for inherited prothrombotic abnormalities included functional and protein assays of antithrombin, protein C and S levels, and genetic testing for factor V Leiden, prothrombin gene 20210A, and methylenetetrahydrofolate reductase (MTHFR). Other tests included lupus anticoagulant, activated prothrombin time, clotting time, thrombin time, activated protein C (APC) resistance, reptilase time, antiphospholipid antibodies, and factor assays.

Plasma anti-thrombin III activity was measured with a chromogenic assay.41 Plasma levels of protein C and protein S were determined with commercially available reagents (Protein C, Dade Behring, Newark, Del; Protein S, Diagnostica Stago). PCR of genomic DNA was used to identify factor V Leiden and prothrombin G20210A.43 The MTHFR C677T polymorphism was identified with polymerase chain reaction (PCR) using the primers sense 5’ TGAAGGAGAGGTG-TCTGCGGGA 3’ and antisense 5’ AGGACGGTGCCG-TGAGAGT 3’ and PCR conditions 94°C—2 minutes, 60°C—2 minutes, 72°C—3 minutes for 30 cycles.

Lupus anticoagulant was identified by measuring clotting in the presence of Russell Viper Venom,44 activated prothrombin time in the presence of platelet lysate,45 and clotting time in the presence of tissue thromboplastin. Thrombin time was measured as the clotting time after the addition of thrombin to citrated plasma46 by using the reptilase-Batroxobin test (Dade Behring, Mississauga, Ontario, Canada). Plasma factors VIII, IX, XI, and XIII and thrombin activity were measured with established methods.44,47

**Data Analysis**

The data were analyzed with SPSS software (SPSS for Windows, version 9.0, 1999, Chicago, Ill) and presented as median (range) or percentages when appropriate.

**Ethics Approval**

The study was approved by the research ethics boards at all 4 institutions. Informed consent was obtained from the
parents or guardians of the patients in the study and from the subjects themselves when appropriate.

RESULTS

Neonatal Presentation of RVT and Renal Morbidity

Forty-eight neonates with a possible diagnosis of renal venous thrombosis were identified from the databases. Of these, 43 met the eligibility criteria; all patients exhibited Doppler ultrasound scanning evidence of RVT. Five neonates were excluded because they did not fulfill the inclusion criteria.

Information on the neonatal demographic characteristics and risk factors for RVT is presented in Table I. Predisposing factors were identified in 21 neonates (49%) and included the presence of an umbilical venous catheter (n = 7), perinatal asphyxia (n = 5), congenital heart disease (n = 3), maternal diabetes mellitus (n = 3), hypernatremic dehydration (n = 2), and twin pregnancy (n = 1).

Data on the mode of presentation, extent of the thrombus, and neonatal management are presented in Table II. The most common presenting features were renal failure, thrombocytopenia, and/or anemia and palpable renal mass. Ten of the 24 neonates (42%) who had renal failure had bilateral RVT. RVT was associated with thrombi at other sites in three quarters of our cases, with thrombi noted in the inferior vena cava (n = 25), inferior vena cava and adrenal vein (n = 5), inferior vena cava and portal vein (n = 1), and the adrenal vein (n = 1). Six of the 7 neonates who had an umbilical venous catheter had associated thrombi in the inferior vena cava. In the 23 of the 28 neonates with RVT who received anticoagulation/anti-thrombolytic therapy, there was presence of thrombi at other sites.

Post-neonatal Clinical Outcomes Follow-up Data

Of the 43 neonates with RVT, 3 infants died between the ages of 1 and 3 months. Mortality was attributed to causes unrelated to RVT and included respiratory failure caused by chronic lung disease and sepsis in 1 infant, postoperative bilateral chylothorax and hydrocephalus in another infant with transposition of the great arteries, and an endocardial cushion defect and congenital diffuse lymphangiomatosis in a third infant with trisomy 21.

Forty children in the initial cohort (n = 43) were recalled prospectively for follow-up. One subject refused to attend the clinic for assessment, and 1 subject was lost to follow-up. Thus data are available for 38 patients. The median age at follow-up was 3.7 years (range, 0.5-20.2 years). Clinical assessment revealed hypertension in 13 subjects (34%) and renal failure in 11 subjects (29%). Of these subjects, on the basis of the calculated GFR, 3 had end stage renal failure, 2 had chronic renal failure, 4 had chronic renal insufficiency, and 2 had early renal failure. All 3 children who had end-stage renal disease underwent live-related renal transplant. Nephrectomy was performed in 2 children for management of hypertension at the age of 1 year in one and 11 years in the other. Renal atrophy was detected in 25 children (66%).

Thirteen of the 38 children (34%) underwent a technetium-99m diethylenetriamine penta-acetic acid renal scan. Six patients (16%) had non-functioning unilateral kidneys (<10% differential function or indistinguishable from background activity), 7 patients (35%) had unilateral function

Table II. Presentation, extent, treatment, and clinical outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subtype</th>
<th>Number of patients (n = 43)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Renal failure</td>
<td>24</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia/anemia</td>
<td>22</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Abdominal mass</td>
<td>21</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Antenatal</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Extent of thromboses</td>
<td>Unilateral</td>
<td>24</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>19</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>Associated with other thrombi</td>
<td>32</td>
<td>74%</td>
</tr>
<tr>
<td>Specific neonatal treatments</td>
<td>Subcutaneous low-molecular weight heparin</td>
<td>17</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Systemic heparin</td>
<td>7</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Systemic tissue plasminogen activator</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Other neonatal treatments</td>
<td>Anti-hypertensives</td>
<td>9</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Unilateral nephrectomy</td>
<td>2</td>
<td>5%</td>
</tr>
</tbody>
</table>
between 10% and 35%, and no patient had a differential function of the affected kidney >35%.

Prothrombotic Abnormalities

Consent was obtained for 28 of the 43 (65%) patients for evaluation of prothrombotic abnormalities. At the time of follow-up, none of these infants had had a recurrence of a venous thromboembolic event (VTE). One infant without a prothrombotic abnormality died at the age of 2.5 months. In 3 of 28 infants (10%), the family history was positive for thrombotic conditions. Twelve of 28 children tested (43%) had abnormal prothrombotic results, which are listed in Table III. Four children had >1 type of prothrombotic abnormality. One patient with lupus anticoagulant was heterozygous for factor V Leiden and MTHFR.

<table>
<thead>
<tr>
<th>Prothrombotic condition</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(total number of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients tested = 28)</td>
<td></td>
</tr>
<tr>
<td>Protein C or S deficiency</td>
<td>5</td>
<td>18%</td>
</tr>
<tr>
<td>Abnormal factor VIII levels</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Factor V Leiden heterozygote</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td>Factor V Leiden and MTHFR heterozygote</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Factor V Leiden homozygote</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Prothrombin gene 20210A heterozygote</td>
<td>1</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table III. Results of prothrombotic work-up

DISCUSSION

Since the 1970s, 16 studies have reported on the long-term outcome of neonatal RVT. The duration of follow-up ranged from 1 to 192 months. A large variation in the rates of glomerular and tubular defects, systemic hypertension, and abnormalities on renal imaging among studies has been noted, which could possibly be explained by the differences in the number of cases reported in each study and the duration of follow-up. In the largest series to date of 59 neonates with RVT,35 significant renal morbidity was reported despite the use of anticoagulant/antithrombotic treatment.

Significant renal morbidity was also noted in our cohort during the neonatal period and on follow-up. Our study is the second largest series that describes the outcome of patients with neonatal RVT and has the longest duration of follow-up. The cases described were identified from 4 pediatric centers within the province of Ontario. Because these centers have the support of neonatal and nephrology services, they were likely to represent the moderate-to-severe cases. Because they were identified from various databases, neonates with mild disease may have not been referred to these centers, and silent clinical disease may remain undiagnosed. Thus, this should not be viewed as an epidemiological study.

The neonatal clinical presentation and associated risk factors were in accord with the previous published data. Management of neonatal RVT is mainly supportive, with careful attention to fluids and electrolytes, treatment of infection, dialysis when necessary, and the use of thrombolytic agents. Several studies have attempted to evaluate the role of thrombolytic agents in this population. The results are inconclusive, and the benefit of such therapies in preventing long-term morbidity remains unclear.

All patients with neonatal RVT should be followed up to document the normalizing of renal function. Patients with bilateral RVT require lifelong follow-up because of the high likelihood of chronic renal failure. It should be recognized that some neonates who are labeled as having unilateral RVT may have bilateral disease or damage to the contralateral kidney (for example, from acute renal failure caused by acute tubular necrosis developing into cortical necrosis) and may need a longer follow-up period. Patients require a clinical examination for the sequelae of chronic renal failure, including hypertension and proteinuria, both of which may cause progression of renal failure and could be amenable to treatment. Renal function should be monitored by using serial plasma creatinine levels and calculation of GFR. Formal measurement of GFR is recommended at 12 months of age to ascertain cases of chronic renal failure; however, it should be kept in mind that the estimated GFR may be overestimated from plasma creatinine (because of muscle bulk). Serial Doppler ultrasound scanning examination should be performed to delineate the extent of the thrombus that may help in outlining the length of anticoagulant treatment. It will also demonstrate the change from the acute finding of enlarged, echogenic kidney(s) to the chronic changes with renal atrophy. Nuclear medicine imaging with technetium-99m dimercaptosuccinic acid is indicated to assess the functional status of the kidney.

Thrombophilic Disorders as Etiology of Neonatal RVT

A high prevalence of inherited prothrombotic conditions was documented in 43% of our tested population. In our series, the main abnormality identified was protein C or S deficiency in 5 subjects, followed by factor V Leiden heterozygosity in 4 subjects.

The literature on the association of prothrombotic abnormalities and neonatal RVT is limited to several case reports and 2 case control studies. Heller et al evaluated 65 neonates and infants as old as 1 year who had abdominal venous thrombosis and 100 age- and sex-matched healthy control subjects for prothrombotic conditions. Of these 65 subjects, 31 neonates and infants had RVT. Among patients with RVT, factor V Leiden mutation was found in 9, MTHFR genotype was found in 2, protein C deficiency was found in 2, and antithrombin deficiency was found in 1.
In the most recent study by Kosch et al,\textsuperscript{35} the presence of at least 1 established prothrombotic risk factor was noted in 67.8% of the patients with neonatal RVT, compared with 11.9% in the control children. Abnormalities identified were the presence of factor V mutation and elevated lipoprotein a levels, protein C and antithrombin deficiencies, and increased anti-cardiolipin antibodies. With our findings, these results strongly suggest that genetic prothrombotic risk factors play an important role in RVT. Our study systematically estimated the prevalence of prothrombotic abnormalities in patients with neonatal RVT.

Despite the presence of prothrombotic abnormalities, none of our patients have yet experienced a recurrence of VTE after the neonatal period. In the study by Kosch et al,\textsuperscript{35} the risk of recurrent thrombosis was reported to be 4.3% (with 3 of 4 cases of recurrent symptomatic thrombosis occurring during puberty from the original cohort of 94 neonates), although little information was provided about the location of the thrombi and whether they were spontaneous or provoked by other environmental risk factors. In the series by Kosch et al,\textsuperscript{35} 1 patient had homozygous factor V Leiden and another had protein C deficiency. Long-term anticoagulation therapy may be appropriate for abnormalities such as these. However, at this time, there are no data to support this; each case has to be considered with an individual risk-benefit ratio.

It is well known that thrombosis is multifactorial. The interaction of existing or acquired risk factors with the presence of inherited prothrombotic abnormalities predispose individuals to VTE. In such individuals, the risk of occurrence of thrombosis in the presence of acquired risk factors such as surgery, immobilization caused by plaster casts and prolonged travel, and the use of oral contraceptives and pregnancy in women is unknown.\textsuperscript{48} Therefore testing patients with thrombosis for prothrombotic abnormalities may be advantageous. If an abnormality is identified, these patients should be referred to specialists who can advise the patient/family about symptoms and signs of deep vein thrombosis/pulmonary embolism, provide guidelines on the intermittent use of preventive treatment with anticoagulation in high-risk situations such as surgery or prolonged immobilization for a fractured bone, and advise women about potential pregnancy and the use of birth control measures. However, no consensus exists in the literature on the provision of thromboprophylaxis during the aforementioned situations because the clinical decision is clouded by lack of knowledge of the risk/benefit ratio about the use of anticoagulation and the risk of recurrences on VTEs in these patients.

Neonates with RVT should be tested with a full thrombophilia screen to identify antithrombin, protein C and S deficiencies, and factor V Leiden and prothrombin 20210A gene defects. If protein C and S deficiencies are noted in the neonatal period, these values need to be rechecked after the acute event and while the patient is not receiving anticoagulation therapy. The full thrombophilia screen should include anti-cardiolipin antibodies and lupus anticoagulant, although it is more sensible to check the mother for these because there are reports of transplacental anticardiolipin immunoglobulin G causing thrombosis in neonates. There is emerging data on the association of elevated lipoprotein (a) levels\textsuperscript{55} and neonatal RVT, although it is unclear how relevant these levels are and whether special diets or other treatments can normalize them, affect outcome, or both.

The authors acknowledge the collaborative work of the units involved in the data collection, especially Jacqueline Wasson, Tara C. Griffin, and Annett Filler of Hamilton, London, and Ottawa, respectively, without whom this project would not have been possible.

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CONGENITAL CYTOMEGALOVIRUS INFECTION: ASSOCIATION BETWEEN VIRUS BURDEN IN INFANCY AND HEARING LOSS

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Objective To determine the relationship between the virus burden in infancy and hearing loss in congenital CMV infection.

Study design A cohort of 76 infants with congenital cytomegalovirus (CMV) infection identified by means of newborn virologic screening was monitored for outcome. The amount of infectious CMV was analyzed in urine specimens obtained during early infancy. Peripheral blood (PB) samples obtained during early infancy were available from 75 children and CMV DNA was quantitated with a real-time quantitative polymerase chain reaction.

Results Infants with clinical abnormalities at birth (symptomatic congenital CMV infection) had higher amounts of CMV in urine ($P = .005$) and CMV DNA in PB ($P = .001$) than infants with no symptoms. Eight children with and 4 children without symptoms had hearing loss. Among children without symptoms, those with hearing loss had a significantly greater amount of CMV in urine ($P = .03$) and PB virus burden ($P = .02$) during infancy than those with normal hearing. Infants with $< 5 	imes 10^3$ pfu/mL of urine CMV and infants with $< 1 	imes 10^4$ copies/mL of viral DNA in PB were at a lower risk for hearing loss.

Conclusion In children with asymptomatic congenital CMV infection, hearing loss was associated with increased amounts of urine CMV and PB CMV DNA during early infancy. (J Pediatr 2005;146:817-23)

Cytomegalovirus (CMV) is a common cause of congenital infection and a leading cause of hearing loss in children in the United States.1-4 Most children (approximately 85%) with congenital CMV infection develop normally, without any permanent perceptual, cognitive, or motor deficits.2,3,5,6 Sensorineural hearing loss (SNHL) is observed in approximately 10% to 15% of children with congenital CMV infection.4,7-10 The majority of children with CMV-related hearing loss experience delayed onset loss and continued deterioration of hearing function (progressive hearing loss) during childhood.4,7,9

The pathogenesis of congenital CMV infection and the mechanisms of SNHL in children with this intrauterine infection have not been defined. The presence of microcephaly, seizures, abnormal tone, or chorioretinitis in the newborn period has been shown to predict cognitive and motor deficits.11-15 However, evidence of central nervous system involvement at birth in children with clinically apparent or symptomatic congenital CMV infection does not predict SNHL.16,17 The amount of systemic CMV burden has been shown to correlate with the risk of CMV disease in immunocompromised hosts, including patients with acquired immunodeficiency syndrome and allograft recipients.18-20 In addition, a reduction in viral load with antiviral therapy has been used effectively both to prevent and treat CMV disease in immunocompromised individuals.21,22 More new reports have demonstrated that increased amniotic fluid CMV burden was predictive of intrauterine transmission.23,24 Infants with symptomatic congenital CMV infection excrete more CMV in urine in the first few months of life and exhibit higher peripheral blood (PB) viral load than those with asymptomatic infection.25-27 In a recent study of children with symptomatic congenital CMV infection from our laboratory, the group of children with SNHL had increased amounts of infectious CMV in urine during infancy than children with normal hearing; however, this difference was not statistically significant.
The relationship between the virus burden and outcome in children with asymptomatic congenital CMV infection has not been defined. To determine the association between the measures of systemic virus burden in infancy and CMV-related hearing loss, the amount of infectious CMV in urine and the quantity of CMV DNA in PB were determined in a cohort of children with congenital CMV infection who were prospectively monitored.

METHODS

Study Population and Specimens

Between August 1994 and October 1998, 96 children with congenital CMV infection were identified by means of the presence of CMV in saliva specimens obtained during the first week of life at the University of Alabama at Birmingham Hospitals.28,29 Of the 93 children who were congenitally infected and enrolled in follow-up, urine specimens collected during the first month of life were available from 83 children (65 without symptoms, 18 with symptoms). Seventy-six children (58 without symptoms, 18 with symptoms) underwent at least 2 follow-up hearing evaluations, with at least 1 hearing test at 1 year of age or older, and this group constituted the study population. Of the 76 study children, a PB sample was unavailable from 1 infant with asymptomatic infection. The demographic characteristics were not different between the study children and children enrolled in the follow-up from whom urine specimens, hearing outcome data, or both were unavailable. The 10 children with unavailable urine specimens had asymptomatic congenital CMV infection and had normal hearing. The 7 children with asymptomatic CMV infection who underwent only 1 hearing evaluation during infancy had normal hearing. The urine and PB specimens were collected at the time of the initial study visit during the first month of life. Urine samples were analyzed for the amount of CMV excretion immediately after sample collection, and the results were reported as plaque forming units per milliliter of urine (pfu/mL).

Follow-up of Children

Children enrolled in the study were monitored according to a standard protocol described previously.4 Audiologic evaluations consisted of assessment with auditory brainstem evoked response audiometry (ABR), immittance measures of middle ear function, and/or pure-tone and speech audiometry appropriate for the child’s developmental level. The study children were routinely tested with ABR between 3 and 8 weeks of age and re-tested at 6 to 12 months of age. Behavioral audiometric evaluations with visual reinforcement procedures were performed beginning at 9 months of age, with follow-up assessments every 6 months until valid pure tone thresholds could be obtained for each ear, which usually occurred between 2.5 and 3 years of age. Thereafter, children were seen annually unless test results or parental concerns indicated a need for additional testing. A child was considered to have SNHL when air conduction thresholds at 1 or more frequencies were greater than 20 dB in conjunction with normal tympanograms, normal otoscopic findings, and/or normal bone conduction thresholds.47 Progressive hearing loss was defined as sensorineural decrease in hearing ≥10 dB at any 1 frequency or ABR threshold, documented on 2 separate evaluations. Delayed or late-onset hearing loss was defined as 1 or more hearing evaluations with a normal threshold documented for each ear before the onset of SNHL. For the purposes of this study, children with conductive hearing loss in the absence of SNHL were not considered to have hearing loss.

Quantitative Titration of Urine CMV

The amount of CMV in urine was determined by plating serial 5-fold dilutions of the urine specimens in 24-well plates seeded with human fibroblasts, as described previously, and the TCID50 was calculated with the Reed and Muench method.26 The urine samples were assayed immediately after collection, and the results were reported as plaque forming units per milliliter of urine (pfu/mL).

Real-time Polymerase Chain Reaction

The investigators who performed the real-time polymerase chain reaction (PCR) assays were blinded to the results of the audiologic follow-up. The CMV primers were selected from the highly conserved AD-1 region of the major envelope glycoprotein B.31-33 The forward primer was 5’-AGG TCT TCA AGG AAC TCA GCA AGA and the reverse primer was 5’-CGG CAA TCG GTT TGT TGT AAA. The internal probe 5’-ACC CCG TCA GCC ATT CTC TCG GC was labeled at the 5’ end with fluorescent dye 6-carboxyfluorescein as the reporter dye and the 3’ end with the quencher dye 6-carboxytetramethylrhodamine.

Real-time PCR Conditions

The PCR was performed with an ABI Prism 7700 Sequence Detection System (Applied Biosystems, Foster City, Calif). The reaction mixture contained CMV primers at 400 nM concentration and the probe at 150 nM concentration. TaqMan universal master mix (2X), containing AmpliTaq Gold DNA polymerase, deoxynucleoside triphosphates with dUTP, AmpErase UNG, Passive Reference 1, and optimized buffer was obtained from Perkin-Elmer Applied Biosystems. Each 25 μL mixture contained 20 nM of the master mix and 5 μL of the test sample. The PCR cycle parameters were 2 minutes of incubation at 50°C and 10 min at 95°C, followed by 45 cycles of 95°C for 15 seconds and 60°C for 1 minute.
Quantitative PCR

To establish the standard curve, a plasmid (pTZG) containing the target sequence of the CMV glycoprotein B was constructed. The purified plasmid was quantitated spectrophotometrically, and the copy number of molecules was calculated. Quantitation of CMV DNA in test samples was achieved by using serial 10-fold dilutions of the previously quantified plasmid standards. Plasmid standards and test samples were run in triplicate, and the average values were used to determine the CMV viral load. CMV virus burden in whole blood was expressed as CMV genomic equivalents per milliliter of blood (ge/mL). To control for the sample preparation and amplification, primers for amplification of a housekeeping gene, G3PDH, was included in each PCR assay. The PCR conditions were optimized by amplifying the target sequence from the plasmid pTZG, and the sensitivity of the assay has been determined to be approximately 50 genomic equivalents per 1 mL of blood.

Data Analysis

The demographic characteristics, newborn findings, outcome data, and the results of urine CMV titration and the PB real-time PCR were collected on case report forms and entered into SAS V8 data sets (SAS Institute, Cary, NC). Relative risk (RR) and 95% CI were calculated to assess the risk of hearing loss among the study children. The relationship between the virus burden and hearing loss in children with asymptomatic and symptomatic congenital CMV infection was examined with non-parametric methods, and statistical significance was determined with the Wilcoxon rank sum test. The statistical significance of outcome data among the 3 groups of children with differing amounts of viruria and PB viral load was determined with the $\chi^2$ test for trend analysis.

RESULTS

Characteristics of Children

The demographic characteristics of the children enrolled in the study according to their hearing status are shown in Table I. Most of the study children were African American and born to single young mothers (<20 years) who received prenatal care at the public health clinics. A third of the children with SNHL (4/12) were premature (<37 weeks gestation), whereas only 9% of the children with normal hearing (6/64) were preterm (RR = 3.3; 95% CI, 1.2-9.0). However, the number of infants born at <32 weeks gestation was not different between the group of children with SNHL and the group of children with normal hearing (Table I). Ten of the children with symptoms were part of an earlier study of predictors for hearing loss in children with symptomatic

### Table I. Demographic characteristics and clinical findings at birth for the study children with congenital cytomegalovirus infection according to their hearing status

<table>
<thead>
<tr>
<th>Finding</th>
<th>Children with hearing loss (n = 12)</th>
<th>Children with normal hearing (n = 64)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic at birth</td>
<td>8 (67%)</td>
<td>10 (16%)</td>
<td>4.3 (2.1-8.6)</td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks gestation</td>
<td>4 (33%)</td>
<td>6 (9%)</td>
<td>3.3 (1.2-9.0)</td>
</tr>
<tr>
<td>&lt;32 weeks gestation</td>
<td>1 (8%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>3 (25%)</td>
<td>7 (11%)</td>
<td>2.3 (0.7-7.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>11 (92%)</td>
<td>55 (85%)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>White</td>
<td>1 (8%)</td>
<td>9 (15%)</td>
<td>1.0 (0.6-1.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (50%)</td>
<td>31 (48%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (50%)</td>
<td>33 (52%)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>11 (92%)</td>
<td>55 (85%)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>Married</td>
<td>1 (8%)</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>Maternal prenatal care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public health clinics</td>
<td>11 (92%)</td>
<td>62 (96%)</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>Private provider</td>
<td>1 (8%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>10 (83%)</td>
<td>41 (64%)</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>≥20 years</td>
<td>2 (17%)</td>
<td>23 (36%)</td>
<td></td>
</tr>
</tbody>
</table>

*P = .0006.
†P = .046.
‡Referent group includes mothers who received prenatal care given by a private provider and the 1 mother who had no prenatal care.
Table II. Follow-up parameters in children with congenital cytomegalovirus infection according to the presence of clinical findings at birth and the results of hearing assessments on follow-up

<table>
<thead>
<tr>
<th>Finding</th>
<th>Asymptomatic infants (n = 85)</th>
<th>Symptomatic infants (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hearing loss (n = 4)</td>
<td>Hearing loss (n = 8)</td>
</tr>
<tr>
<td>Mean duration of follow-up (months, ± SD)</td>
<td>39.3 ± 23.9</td>
<td>49.1 ± 18.1</td>
</tr>
<tr>
<td>Median number of hearing evaluations (range)</td>
<td>7 (2-14)</td>
<td>9 (3-17)</td>
</tr>
<tr>
<td>Number of hearing evaluations</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>46</td>
</tr>
<tr>
<td>Mean amount of CMV in urine (pfu/mL ± SD)</td>
<td>1.6 × 10^5 ± 2.1 × 10^5</td>
<td>4.9 × 10^5 ± 9.2 × 10^5</td>
</tr>
<tr>
<td>Mean PB blood virus burden (ge/mL ± SD)</td>
<td>8.7 × 10^5 ± 1.6 × 10^6</td>
<td>6.2 × 10^5 ± 1.9 × 10^6</td>
</tr>
</tbody>
</table>

*P = .03.
†P = .02.

congenital CMV infection. There were no significant differences between the groups of children with and without symptoms in various demographic characteristics, including race, sex, marital status of the mother, source of the prenatal care, and maternal age. One infant with symptomatic congenital CMV infection received ganciclovir for 6 weeks during early infancy as part of a phase III clinical trial, and this child had SNHL that was detected during the first month of life.

**Results of Follow-up**

The children enrolled in the study were observed for a mean duration of 34.1 ± 17.9 months, and the median number of hearing evaluations was 6 (range, 2–17). Twelve of the 76 children enrolled in the study (16%) had SNHL (Table I). Significantly more children with symptomatic infection (8/18, 44%) had SNHL, compared with 4 of the 58 children with an asymptomatic infection (7%; RR = 4.3; 95% CI, 2.1–8.6). The children enrolled in the study underwent at least 2 hearing evaluations, at least 1 test when they were 12 months of age or older (Table II). Delayed onset hearing loss, progressive hearing loss, or both was observed in two thirds of the children with hearing deficit (8/12).

**CMV Disease in Newborns and Viral Load**

The mean urine CMV level in the group of infants with symptomatic congenital CMV infection (2.4 × 10^5 ± 9.5 × 10^5 pfu/mL) was greater than that of infants with asymptomatic infection (3.9 × 10^4 ± 9.7 × 10^4 pfu/mL), and this difference was statistically significant (P = .009).

Similarly, infants with symptomatic infection had a significantly higher mean amount of CMV DNA in PB than infants with asymptomatic infection (4.0 × 10^5 ± 3.6 × 10^5 copies/mL and 8.2 × 10^4 ± 4.1 × 10^5 copies/mL, respectively; P = .001).

**Viruria and Outcome**

The group of 12 children with SNHL had a significantly higher mean level of urine CMV during early infancy than the 64 children with normal hearing (mean values, 3.8 × 10^5 ± 7.6 × 10^5 pfu/mL versus 3.0 × 10^4 ± 7.5 × 10^4 pfu/mL; P = .003). As can be seen in Figure 1A, the group of 4 children with asymptomatic infection and SNHL had significantly higher mean CMV urinary excretion than the children with asymptomatic infection and normal hearing (mean values, 1.6 × 10^5 ± 2.1 × 10^5 pfu/mL and 2.9 × 10^4 ± 7.8 × 10^4 pfu/mL, respectively; P = .03). Among children with symptomatic infection, no significant difference was observed in CMV viruria between the group of children with SNHL and the group of children with normal hearing (mean values, 4.9 × 10^5 ± 9.2 × 10^5 pfu/mL and 3.8 × 10^4 ± 5.9 × 10^4 pfu/mL, respectively; P = .24).

The relationship between the amount of CMV in urine and SNHL was further examined with the χ^2 test for linear trend analysis (Figure 2). The study population was arbitrarily divided in 3 groups according to the amount of CMV in urine: children with a concentration <3.5 × 10^3 pfu/mL, children with a concentration between 3.5 × 10^3 and 2.5 × 10^4 pfu/mL, and children with a concentration of >2.5 × 10^4 pfu/mL. The subjects were distributed equally among the 3 groups. As can be seen in Figure 2, only 1 of the 26 children with urine CMV <3.5 × 10^3 pfu/mL (4%) had SNHL, whereas 3 of the 26 children with urine CMV between 3.5 × 10^3 and 2.5 × 10^4 pfu/mL (12%) had SNHL, and 8 of the 24 children with urine CMV >2.5 × 10^4 pfu/mL (33%) had SNHL (P <.01).

**PB Virus Burden and Outcome**

The amount of CMV DNA in PB samples from 5 infants with asymptomatic infection was less than the level of detection for the real-time PCR assay, and none of these
5 children had hearing loss. The group of 12 infants (4 with asymptomatic infection and 8 with symptomatic infection) who had SNHL had significantly higher mean CMV DNA values than the infants with normal hearing (mean values, $3.7 \times 10^5 \pm 9.7 \times 10^5$ ge/mL and $5.1 \times 10^4 \pm 2.4 \times 10^5$ ge/mL, respectively; $P < .0001$). Among children with asymptomatic infection, the 4 children with SNHL had higher mean PB CMV DNA amounts ($8.7 \times 10^5 \pm 1.6 \times 10^6$ ge/mL) than children with normal hearing ($1.1 \times 10^4 \pm 1.5 \times 10^4$ ge/mL; $P = .02$; Figure 1B). In infants with symptomatic infection, the level of PB virus burden during early infancy was not different between the group of children with and the children without hearing loss (Figure 1B).

Similar to the results of urinary virus shedding, an association between the PB virus burden during infancy and SNHL was observed when the children enrolled in the study were divided arbitrarily in 3 groups of an equal number of children: children with a viral load $<3.5 \times 10^3$ ge/mL, children with a viral load between $3.5 \times 10^3$ ge/mL and $2.5 \times 10^4$ ge/mL, and children with a viral load $>2.5 \times 10^4$ ge/mL. The results were analyzed with the $\chi^2$ test for linear trend analysis. As shown in Figure 2, none of the 25 children with a viral load $<3.5 \times 10^3$ ge/mL had SNHL, whereas 2 of the 25 children in the group with virus burden between $3.5 \times 10^3$ ge/mL and $2.5 \times 10^4$ ge/mL (8%) and 10 of the 25 children with viral load $>2.5 \times 10^4$ ge/mL (40%) had SNHL ($P = .0001$).

**DISCUSSION**

In infants with asymptomatic congenital CMV infection, a high virus burden during the first month of life is associated with SNHL. This association was apparent whether virus burden was assessed by using the quantity of infectious CMV in urine or the amount of PB CMV DNA. The results of this prospective study indicate that there is a threshold level of virus burden below which the risk of hearing loss is very low. None of the 41 children with a PB viral load $<1.0 \times 10^4$ ge/mL and only 1 of 26 infants with urine CMV levels $<5.0 \times 10^3$ pfu/mL had SNHL. These
findings imply that it may be possible to identify children with asymptomatic congenital CMV infection at increased risk for SNHL by measuring virus burden during early infancy. If confirmed in future studies of congenital CMV infection with larger sample sizes, early identification of children who are at risk for SNHL will greatly improve the counseling provided to the parents of infected neonates. Because most children with congenital CMV infection develop normally without any sequelae, the ability to identify children at risk for SNHL early in life can lead to a better use of resources by targeting these children for closer monitoring and intervention. Finally, early identification of at-risk children will be crucial for the evaluation of future antiviral therapies to prevent or reduce the incidence of CMV-related hearing loss.

The pathogenic features of congenital CMV infection that result in SNHL have not been defined. Systemic virus burden has been shown to predict the likelihood of CMV disease in individuals who are immunocompromised, such as patients with acquired immunodeficiency syndrome and allograft recipients. In women with primary CMV infection during pregnancy, CMV DNA in amniotic fluid between 21 and 25 weeks gestation was predictive of intratereine transmission. Higher amniotic fluid viral loads were also associated with symptomatic congenital infection. Children with symptomatic congenital CMV infection born to mothers with primary maternal CMV infection had significantly higher viral loads than children with asymptomatic infection. We reported recently that disseminated infection at birth in infants with symptomatic congenital CMV infection as evidenced by the presence of petechiae, hepatitis, and thrombocytopenia was associated with an increased likelihood of SNHL. By using the χ² test for trend analysis, an association between the amount of CMV in urine and SNHL was also observed in that study. Studies of a limited number of temporal bones from infants with congenital CMV infection and experiments in the guinea pig model of congenital CMV infection demonstrated the presence of CMV antigens in the cells of the inner ear. These observations and the results of this study suggest that increased virus burden and continued viral replication in the affected organ systems leading to the loss of non-regenerating inner ear hair cells, spiral ganglion cells, or both could play an important role in the pathogenesis of CMV-related SNHL.

The relationship between a high virus burden in infancy and the likelihood of SNHL suggests a role for antiviral therapy in decreasing the incidence and severity of CMV-related hearing loss. However, a number of unresolved issues remain about the role of antiviral therapy in children with congenital CMV infection; these include the optimal timing and duration of antiviral therapy and the target population that would receive the most benefit from the therapy. In a phase II study of ganciclovir treatment of symptomatic congenital CMV infection, urinary CMV excretion decreased with antiviral therapy; however, viruria returned to near pretreatment levels after the cessation of therapy. A randomized controlled trial has examined the effect of ganciclovir therapy for 6 weeks during early infancy on hearing outcome in children with symptomatic congenital CMV infection involving the central nervous system. Of the 100 children enrolled in the study, the results of baseline and 6-month follow-up hearing evaluations were only available in 42 patients. Twenty-one of 25 infants treated with ganciclovir (84%) had improved hearing or maintained normal hearing between baseline and 6 months, compared with 10 of 17 children randomized to no treatment (59%; P = .06). In addition, none of the 25 children treated with ganciclovir had worsening in hearing between baseline and 6 months, versus 7 of the 17 children who were control subjects (41%; P < .01). When the hearing outcome at 1 year or older was compared between the groups, 68% of the children who were control subjects (13/19) had worsening of hearing, compared with 21% of children in the ganciclovir-treated group (5/24; P < .01). However, significant adverse effects were seen in about two thirds of infants receiving ganciclovir.

Therefore, further studies are needed before a recommendation for the use of antiviral therapy in the clinical treatment of children with congenital CMV infection can be made.

In conclusion, children with asymptomatic congenital CMV infection with higher amounts of infectious CMV in urine and CMV DNA in PB during early infancy are more likely to have SNHL. The demonstration that the risk of hearing loss increases when subjects are grouped according to increasing virus burden breakpoints suggests the role of virus burden and viral replication in the pathogenesis of congenital CMV infection. The exact role of virus burden in the pathogenesis of SNHL (in particular, delayed onset hearing loss, progressive hearing loss, or both) will need to be defined in future prospective studies that include a larger number of children with congenital CMV infection with sufficient follow-up.

REFERENCES

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Congenital Cytomegalovirus Infection: Association Between Virus

FATTY ACID ETHYL ESTERS: QUANTITATIVE BIOMARKERS FOR MATERNAL ALCOHOL CONSUMPTION
CYNTHIA F. BEARER, MD, PhD, LUIS MANUEL SANTIAGO, MPH, MARY ANN O’RJDAN, MS, KEVIN BUCK, BA, SIEMAY C. LEE, MD, AND LYNN T. SINGER, PhD

Objective To develop a laboratory marker to identify newborns exposed to alcohol.

Study design Meconium was collected from 30 infants from Jordan who were unexposed and from 248 Cleveland study infants of varying exposure status. Retrospective maternal alcohol histories were obtained. Fatty acid ethyl esters (FAEEs) were quantified with gas chromatography/flame ionization and compared between abstainers and non-abstainers to identify FAEEs of interest. The area under the receiver operating characteristic curve, sensitivity, specificity, and positive and negative predictive values were calculated by using definitions of drinking obtained from a graphical representation.

Results Six of 7 FAEEs were significantly different between the non-abstainers and at least 1 of 2 of the abstaining groups. FAEEs best predicted drinks per drinking day, and ethyl linoleate had the greatest area under the curve (76%), with a sensitivity rate of 88%, a specificity rate of 64%, a positive predictive value of 9%, and a negative predictive value of 99%. No combination of FAEEs was better than a single ester for identifying drinkers.

Conclusion Ethyl linoleate in meconium is a useful biological marker for identifying infants not exposed in utero to high levels of alcohol in a high-risk, substance-abusing, clinic-based sample. (J Pediatr 2005;146:824-30)

Heavy drinking during pregnancy is the cause of fetal alcohol syndrome (FAS), the leading known cause of mental retardation.1 Conservative estimates place the incidence of FAS at 0.33 of 1000 live births.1 More prevalent are infants with a spectrum of outcomes, including alcohol-related birth defects, alcohol-related neurodevelopmental defects, and subtle effects on a variety of behavioral, educational, and psychological tests, resulting from low to moderate levels of drinking during pregnancy. Together, these effects are estimated to be present in 1% of all newborns2 and to cost from $75 million3 to $9.7 billion per year.4

There is a lack of clinical tools for assessing levels of drinking in pregnant women and identifying newborns who were exposed to alcohol. In one study, the diagnosis of FAS was missed in 100% of newborns in whom FAS was subsequently diagnosed in childhood.5 Identification of affected newborns is desirable to facilitate early intervention, minimize secondary disabilities,6 and identify mothers at high risk for drinking during gestation. Recent research has focused on developing biomarkers to identify maternal drinking during pregnancy. Maternal biomarkers showing promise include a combination of 4 maternal blood measurements: hemoglobin acetaldehyde adducts, gamma glutaryl transferase, mean corpuscular volume, and carbohydrate deficient transferrin.7

For identification of exposed neonates, fatty acid ethyl esters (FAEEs), non-oxidative metabolites of ethanol, in meconium are being investigated. In adults, FAEEs have been tested as a biological marker for alcohol-related fatalities.8 Initially described in the cord blood of an infant born to an alcoholic mother,9 FAEEs were subsequently...
identified in meconium.\textsuperscript{10} In our initial study of a Cleveland population, mothers of infants whose meconium contained ethyl linoleate reported drinking an average of 10 drinks per week in the month before pregnancy.\textsuperscript{11} The amount of reported drinking (3 drinks/week) by mothers whose infants did not have ethyl linoleate in their meconium was significantly different.\textsuperscript{11} Four-fold higher levels of FAEEs were found in the meconium of an infant born to an alcoholic compared with that of a control infant.\textsuperscript{12} FAEEs are also found in the meconium of infants born to mothers from abstaining populations.\textsuperscript{13} Thus, there is a need to quantify FAEEs to determine the level of alcohol exposure. With a highly alcohol exposed mixed race/Cape Colored population from South Africa, the sensitivity and specificity rates of ethyl oleate for detecting women who drank an average of 3 or more drinks per drinking day was 84.2\% and 83.3\%, respectively.\textsuperscript{14} These results prompted a quantitative reanalysis of our previous work in a Cleveland population.\textsuperscript{12} With gas chromatography/flame ionization detection (GC/FID), we quantified the FAEEs from the meconium of the Cleveland population\textsuperscript{11} and a comparison Jordan population to further investigate the relationship between FAEE quantity and maternal self-reported drinking. In addition, we investigated the clinical usefulness of this biomarker.

**METHODS**

**Cleveland Study Subjects**

Postpartum women were recruited from a large urban, teaching hospital in Cleveland, Ohio, to participate in a 2-year longitudinal study on the neurobehavioral effects of prenatal cocaine exposure.\textsuperscript{15-18} Women were predominantly African-American (83\%), of low socioeconomic status (99\%), and identified from a population screened for risk of substance abuse during pregnancy. Informed consent was obtained as approved by the institutional review board of MetroHealth Medical Center.

**Jordan Comparison Subjects**

Postpartum Muslim women and their infants were recruited from a large urban hospital in Amman, Jordan. The meconium from Jordan was expected to have fewer false negative results than abstainers from the Cleveland study group because there is a strong religious, cultural, and societal prohibitive influence against drinking by Jordanian Muslim women.

**Meconium Collection**

A total of 275 samples of meconium were obtained from 248 study infants in Cleveland and 30 samples from 30 comparison infants in Jordan. Meconium stool from each infant was scraped from the diaper, collected into falcon tubes (15 mL, polypropylene, Becton-Dickinson), and frozen at $-80\degree C$ until analysis.

**FAEE Analysis**

The analyses were performed by investigators who were blinded to the questionnaire results. A total of 1 g wet weight of meconium was used for analysis. An a priori exclusion criteria was constructed to ensure the best representation of each meconium sample (Figure 1). For samples <1 g (83 samples), the whole sample was used. Samples <0.5 g (38 samples) were excluded. The analysis of FAEEs has been previously described.\textsuperscript{11,19} In brief, 100 \textmu L of 1 mMol/L ethyl heptadecanoate was added to each meconium sample as an internal standard. Only samples with ethyl heptadecanoate percent recovery $\geq 50\%$ were analyzed (230 samples). FAEEs were extracted with acetone/hexane and isolated with silica column chromatography. The isolated FAEEs were identified and quantified with gas chromatography using a flame ionization detector (HP5890 Series II). Peak areas were obtained by integration with HP Chemstation software and valley to valley baseline. Peaks with an area $\geq 500$ and with retention times $\pm 0.1$ minutes of authentic standards were used in the analysis. FAEEs from 10 samples were confirmed with gas chromatography with mass spectroscopy detection (GC/MS). The limit of detection was 2 pmole of ethyl heptadecanoate on column. For individuals with >1 sample (14 individuals), the sample with greater weight and higher recovery was selected. Of these 216 samples, 22 had no maternal interview data. All the Jordanian samples were 1 g and had recovery $\geq 50\%$. The remaining 194 samples from Cleveland and all 30 samples from Jordan were used for further analyses (Figure 1).

**Maternal Prenatal Substance Abuse Assessment**

The maternal postpartum interview\textsuperscript{20-22} was used to estimate maternal alcohol use during the month before and for each trimester of pregnancy. For each period, mothers were requested to recall both the amount and frequency of alcohol...
use, and 3 drinking measures of alcohol intake were calculated: (1) number of drinks per drinking day (DRDD), (2) number of drinking days per week (DYWK), and (3) number of drinks per week (DRWK). To estimate the amount of alcohol used, the DRDD was computed on the basis of the amount of beer, wine, or hard liquor consumed, with 12 oz of beer, 4 oz of wine, or 1 oz of hard liquor assumed to be equivalent to 1 drink (0.5 ounces of absolute alcohol). DYWK was estimated on a Likert-type scale, ranging from 0 (less than once per month) to 7 (daily use). The DRWK was calculated by multiplying DRDD by DYWK. The postpartum interview was conducted as soon as possible after the birth of the child, generally within 1 month.

### Statistical Analysis

The purpose of the analyses was to develop a clinically useful tool to aid in screening infants for prenatal alcohol exposure. Analyses were carried out first to eliminate any FAEEs that lacked the potential to be predictive of alcohol intake, second to determine by a principal component analysis whether some combination of FAEEs reduced noise and redundancy, third to define subjects as “drinkers” or “non-drinkers” on the basis of each of the 3 measures of alcohol intake, and fourth to use these definitions to estimate area under the receiver operating characteristics curve (AUC), sensitivity rate, specificity rate, and positive (PPV) and negative (NPV) predictive values.

Abstainers were strictly classified as Cleveland mothers who denied using alcohol, cocaine, tobacco or marijuana (n = 25) during the month before and during pregnancy. The remainder were classified as non-abstainers (n = 169). Subjects in the non-abstainer group reported the use of any drug, but not necessarily alcohol. This effectively created an internal comparison group, in addition to the external (Jordan) comparison group (Figure 1). This conservative approach to classification of abstainers and non-abstainers makes it less likely that we will be able to find significant associations, because undoubtedly our non-abstaining group includes some abstainers. There was no significant difference in the

### Table I. Characteristics of drinking of Cleveland non-abstainers (n = 169)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Period</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
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</thead>
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<tr>
<td>DRDD</td>
<td>Month before</td>
<td>2.54 ± 4.64</td>
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<td>2.00 ± 4.31</td>
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<tr>
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<td>1.09 ± 2.72</td>
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<td>0-22.0</td>
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<tr>
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<td>1.02 ± 2.83</td>
<td>0</td>
<td>0-22.0</td>
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<td>DYWK</td>
<td>Month before</td>
<td>2.56 ± 2.03</td>
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<td>0-25.70</td>
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<td>1st trimester</td>
<td>2.75 ± 2.18</td>
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<td>0-25.70</td>
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<tr>
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<td>2.80 ± 2.28</td>
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<td>0-25.70</td>
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<tr>
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<td>2.07 ± 1.94</td>
<td>1.5</td>
<td>0-25.70</td>
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<td>DRWK</td>
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<td>8.19 ± 19.36</td>
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<td>0-138.6</td>
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<td>6.71 ± 17.41</td>
<td>0</td>
<td>0-138.6</td>
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<td>2nd trimester</td>
<td>3.75 ± 23.12</td>
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<td>0-110.0</td>
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<tr>
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<td>3rd trimester</td>
<td>3.41 ± 13.52</td>
<td>0</td>
<td>0-110.0</td>
</tr>
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</table>

### Table II. Comparison between study groups

<table>
<thead>
<tr>
<th>FAEEs</th>
<th>Cleveland non-abstainers (median [range])</th>
<th>Jordan (median [range])</th>
<th>Cleveland abstainers (median [range])</th>
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<tbody>
<tr>
<td>N</td>
<td>169</td>
<td>30</td>
<td>25</td>
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<tr>
<td>Ethyl myristate*</td>
<td>52§ (0-21461)</td>
<td>32 (0-233)</td>
<td>35 (0-2697)</td>
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<tr>
<td>Ethyl palmitate*</td>
<td>166§ (0-27245)</td>
<td>72 (274-336)</td>
<td>65 (0-3524)</td>
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<td>Ethyl palmitoleate*</td>
<td>695 (124-50241)</td>
<td>805 (290.5-2109)</td>
<td>574 (65-2172)</td>
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<tr>
<td>Ethyl oleate</td>
<td>317§ (0-344047)</td>
<td>108 (0-569)</td>
<td>142 (0-55213)</td>
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<tr>
<td>Ethyl linoleate*</td>
<td>282§ (0-627705)</td>
<td>97 (0-1490)</td>
<td>118 (0-77056)</td>
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<tr>
<td>Ethyl linoleate*</td>
<td>143§ (0-173558)</td>
<td>79 (0-421)</td>
<td>80 (0-31389)</td>
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<tr>
<td>Ethyl arachidonate*</td>
<td>208§ (0-23560)</td>
<td>144 (0-2586)</td>
<td>0 (0-2349)</td>
</tr>
<tr>
<td>Score†</td>
<td>1.73§ (1.42-3.55)</td>
<td>1.58 (1.45-1.98)</td>
<td>1.60 (1.42-2.95)</td>
</tr>
</tbody>
</table>

*ng/g wet weight.
†Unitless because it is the result of the principal component analysis.
‡Cleveland non-abstainers mean log (FAEE + 100) of meconium statistically significantly different than Jordan, with P < .0001.
§Cleveland non-abstainers mean log (FAEE + 100) of meconium statistically significantly different than Cleveland abstainers, with P < .05.
The proportion of African American mothers in the 2 groups (79% non-abstainers vs 92% abstainers, \(P = 0.18\) with Fisher exact test). The alcohol use of the non-abstainers is summarized in Table I.

To screen for the most predictive FAEE(s), the means of the \(\log_{10}\) transformed FAEE concentrations were compared with 2 sample \(t\) tests to compare Jordan control subjects, Cleveland abstainers, and Cleveland non-abstainers. The FAEE(s) with significant differences at a level of \(P < 0.05\) between the Cleveland non-abstainers and at least 1 of the comparison groups were selected for further analysis (Table II).

Second, a principal component analysis with only the FAEEs with a significant difference between groups showed that only 1 linear combination of the FAEEs explained 91% of the variance of these highly correlated measures. A score for each subject was calculated by using this linear combination.

Third, each measure of alcohol intake (X-axis) was plotted against \(\log(\text{ng/g}+100)\) FAEE (Y-axis) for each period. On the basis of the graphical representation of the data, subjects were defined as “drinkers” or “non-drinkers” for the respective measure. Figure 2 is an example of such a graphical representation with DRDD as the drinking measure. As can be seen, defining drinking as \(\geq 7\) drinks per drinking day (solid line) allows a cutoff value of ethyl linoleate (dotted line) in which only 1 subject is misclassified. With these definitions, receiver operating characteristics (ROC) curves were generated to select the FAEE concentrations that yielded the best sensitivity and specificity and at which the values would be dichotomized into “positive test” and “negative test”. Figure 3 shows a representative ROC curve for the 2 most useful FAEEs and the score from the principal component analysis.

All analyses were done with \(\log_{10}\) transformations of the FAEE levels. Log transformations are routinely used to convert values that increase exponentially to a scale in which the increase is linear, thus allowing for standard statistical methods to be used. A constant value of 100 was added, which effectively set the value of the samples with values below the limit of detection at 100 to allow for log transformation. The alpha level was set at 0.05. All analyses were done with SAS software version 8.1 (SAS Institute, Carey, NC).

RESULTS

Study Group Differences in FAEE

Table II represents the medians and ranges of each FAEE by study group. Four of the 7 FAEEs being studied (ethyl myristate, ethyl palmitate, ethyl oleate, ethyl linoleate) have statistically significant differences in the mean (\(\log_{10}\)) concentration between the Cleveland non-abstainers and both the Jordan control subjects and the Cleveland abstainers. Ethyl linolenate is significantly different only between meconium samples of Cleveland non-abstainers and the Jordanians, and ethyl arachidonate is different only between the Cleveland non-abstainers and the Cleveland abstainers. Ethyl linoleate is significantly different only between meconium samples of Cleveland non-abstainers and the Jordanians, and ethyl arachidonate is different only between the Cleveland non-abstainers and the Cleveland abstainers. Ethyl palmitoleate is the only FAEE with no significant differences among the study groups and is excluded from subsequent analysis. Although both control groups have limitations (Jordanian group may have different diets, genetic background, and environmental exposures; the Cleveland abstaining group may have more underreporting), the finding that both groups have FAEE levels that are significantly less than those of the Cleveland non-abstainers strengthens this finding.

Principal Component Analysis

Only 1 linear combination of FAEEs is required to explain the variance between the FAEEs. Scores for each subject using the 4 or 5 most heavily weighted FAEEs or all 6 FAEEs were calculated. Further evaluation showed no...
difference in predictive value of these 3 scores. Thus, only scores calculated with the 4 FAEEs are shown. Comparison of these scores between study groups is shown in Table II. The scores are significantly different between the Cleveland non-abstainers and both the Cleveland abstainers and the Jordanian groups for all FAEEs except ethyl palmitoleate.

### Table III. Receiver operating characteristics curve analysis

<table>
<thead>
<tr>
<th>FAEE prenatal period</th>
<th>AUC (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>FAEE cutoff point (ng/g)</th>
<th>FAEE cutoff point Log(ng/g + 100)</th>
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<td><strong>Drinker ≥7 drinks/drinking day</strong></td>
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<tr>
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*Unitless value.

## Definition of “drinking” for Each Measure of Exposure

The graphical analyses of the data indicate that not only are the Cleveland abstainers different from the non-abstainers in overall FAEE concentrations, but that within the non-abstaining group, the concentrations are dependent on the...
level of drinking. An example of a graphical analysis for DRDD versus ethyl linoleate is shown in Figure 2. As can be seen in the figure, defining drinking as \( \geq 7 \) DRDD (solid line), and using a cutoff value of 2.8 (631 ng/g; dashed line) yields only 1 false negative result. This pattern was the same for all periods studied. Therefore, to analyze the predictive values of the FAEE to detect “drinking,” we chose the definition of “drinking” as \( \geq 7 \) DRDD. Using the same approach, we defined “drinking” for each of the other measures. For DRWK, “drinking” was defined as \( \geq 21 \) DRWK, and for DYWK, “drinking” was defined as \( \geq 5 \) DYWK for all prenatal periods.

**ROC Analysis**

The first 2 analyses aforementioned established a relationship between reported drinking and FAEE concentrations in meconium. The ROC analyses were used to determine which of the measures of alcohol exposure was best associated with FAEE concentration, for which period(s) the concentrations were the most predictive, and which of the individual FAEEs or the score from the linear combination of FAEEs was the most useful in the clinical setting. In general, values of AUC, sensitivity rate, specificity rate, PPV, and NPV for each of the 3 drinking measures were consistent across periods. The FAEEs and the score were most predictive of DRDD (Table III). For DRDD, all the FAEEs had AUCs between 63% and 76% during all prenatal periods. The FAEEs with the best performances for DRDD were ethyl oleate, ethyl linoleate, and ethyl arachidonate (Table III).

The ROC analysis for DRWK is reported in Table III. Using \( \geq 21 \) DRWK as the definition of “drinking,” the AUC ranged from 54% to 71% for all periods, FAEEs, and score values. Ethyl arachidonate showed the most consistent result with AUCs of 63% to 70%, sensitivity rates of 72% to 88%, specificity rates of 58% to 63%, PPV of 9% to 18%, and NPV of 96% to 99%.

For DYWK, all the FAEEs had AUCs ranging from 52% to 67% (data not shown). Because of the low values of the AUCs, no further analysis with this measure of drinking was done.

We conclude that FAEE concentrations in general are related to prenatal alcohol exposure, particularly at high levels of DRDD and DRWK. With NPVs \( \geq 98\% \) and \( \geq 94\% \), respectively, FAEE levels in meconium are particularly well suited for identifying those babies who have not been exposed to these high levels of drinking in utero. In addition, the principal component score had no better predictive value than the single most predictive FAEE for each alcohol measure.

**Discussion**

Screening of newborns for prenatal ethanol exposure has been done routinely by history-taking alone. The identification of a biological marker that better represents the amount of prenatal drinking to which an infant has been exposed is a challenging task. This study showed that, in a high-risk, predominately African American Cleveland population using a GC/FID assay, FAEE in meconium was most related to the self-reported DRDD. These findings are consistent with our published findings from a cohort of women in South Africa. In that study, we found that ethyl oleate correlated best to DRDD and that the correlation of ethyl oleate to maternal history increased with stage of pregnancy. However, there are important differences between these 2 studies. First, women in the South African population were heavier drinkers. The DRDD, DYWK, and DRWK medians were 5.2 ± 4.0 (range, 0–15), 1.3 ± 1.5 (range, 0–6.7), and 12.6 ± 21.0 (range, 0–102.8), respectively. In the Cleveland non-abstaining population, these values were 2.54 ± 4.64 (range, 0–39.6), 2.56 ± 2.03 (range, 0.25–7.0), and 8.19 ± 19.36 (range, 0–138.6). Having a higher range of drinking in the South African population would result in better correlation.

Second, the degree of error or noise in the South African reports of drinking may be less than that of the Cleveland population. The South African population was followed prospectively, whereas the Cleveland group had retrospective alcohol histories. Previous studies have shown that antenatal self-reported drinking more accurately predicts outcome than retrospective reports. The South African population is expected to more accurately report drinking because of a greater acceptance of drinking during pregnancy among this population. In addition, there may be cultural differences in the amount of alcohol reported in a drink. One report has shown that women markedly underestimate the amount of alcohol they consume because of the volume of their drinks. This study, although converting type of drink to standard drink, did not try to estimate the size of each reported drink.

Third, the sensitivity and specificity rates of the measurement of the FAEE were better in the South African study. The South African meconium was analyzed with a GC tandem mass spectrometer, an instrument with greater sensitivity and specificity than the GC/FID used to analyze the samples from the Cleveland and Jordan populations. Thus, higher predictive values in the South African study may be caused by lower noise in both the questionnaire data and the meconium data.

Fourth, the meconium analyzed in this study was from 1 meconium stool selected arbitrarily from all the meconium excreted by the infant. Preliminary data from other laboratories suggest that meconium is formed sequentially, with earlier gestational ages represented in the first meconium passed, and subsequent ages represented in subsequent meconium stools. Alternatively, FAEEs could accumulate uniformly throughout meconium and not in concurrently forming meconium at the time of exposure. The samples used in our study, which were unsystematically scraped from the neonate’s diaper, may not represent accurate levels of FAEEs corresponding to a particular gestational age. Future studies will need to serially collect all meconium to determine whether FAEE amounts vary within samples from the same infant.

Fifth, the 2 populations studied were culturally and ethnically distinct. Thus both genetic and dietary differences may account for the different findings in these 2 studies.
Several important questions need to be addressed in future studies. Do FAEEs distribute evenly throughout meconium? Animal studies would permit both control over the timing and quantity of alcohol consumption and the sequential collection of meconium. Do FAEEs identify a high-risk population of children? Studies on FAEE and outcome should be pursued to determine how well the biomarker can predict future adverse events in infants exposed to prenatal alcohol, establish a gold standard test, and implement early intervention programs for exposed children. FAEE in meconium show promise as a useful biological marker for determining alcohol exposure in utero.

REFERENCES

Siblings of children with serious illness are at risk for long-term psychosocial difficulties; their needs are not routinely addressed in current medical practice. The pediatrician, by necessity, focuses on the ill patient, and it is difficult to expand that focus to include the needs of the sibling. Spinetta et al.1 published guidelines that outlined general principles for helping siblings throughout various phases of cancer; yet sibling needs remain unaddressed in medical centers. Physicians face increasing pressure to see more patients in less time while simultaneously being asked to expand the scope of their responsibility to include family centered care, with little or no training to do so. The social worker provides an advocacy role for the patient and the parents but rarely has resources to provide support for the well sibling; the psychologist or psychiatrist is called on only on dire occasions. Family-centered care often translates to responding to parental needs and neglects sibling concerns. To support the emotional needs of siblings of children with various chronic/serious conditions, we recently established the Sibling Center at our medical center. This pilot program pioneers a psycho-educational model for siblings of children with serious medical illness.

RESEARCH BACKGROUND AND SCOPE OF THE PROBLEM

There are immediate and long-term emotional, behavioral, physical, and psychosocial effects of having a sibling with a childhood illness.2-9 Serious long-term effects were noted in a sample of 75 adults who had grown up with a sibling affected by cystic fibrosis, including survival guilt; global anxiety; fear of an early death for themselves; fear of intimacy; excessive concerns for others; heightened sense of vulnerability; somatic expressions, including headaches, ulcers, or “identification illnesses” that mirror symptoms of cystic fibrosis; and sleeping difficulties, including severe nightmares.10,11 Psychosocial issues for siblings include resentment, anger, anxiety, depression, jealousy, and guilt; fear of the patient’s death; fear of their own death; psychologic and physical isolation from parents; and behavioral problems.11-15 Certain subsets of children are at increased risk for adjustment problems.3,16,17

Family Communication

Many families with a chronically ill child tend not to communicate about the disease.11,18-24 The demand of keeping a family secret is a heavy burden for a young sibling and can threaten healthy development. There is often much anger expressed at parents as a consequence of feeling excluded from disclosure. Studies of siblings of children with cancer have shown that children coped better and felt less isolated when they were informed about the illness and the treatment program.25 Families who communicate well before the death of a child tend to communicate well after the death; this communication is indicative of how well a surviving sibling will adjust to the loss.26 Family secrets can lay the groundwork for traumatic responses to the illness and death.27 Siblings may not be able to grieve the loss until the traumatic aspects are resolved.28

Clinicians frequently have little information on how parents actually communicate the news of fatal illness to their children, particularly siblings. An important question in families with a fatally ill child is: Who tells the children? As Davis29 pointed out in his study of families with a child with polio, explanations offered by physicians are frequently confusing and veiled with ambiguity. It is the pediatrician who often suggests to the family that they treat the child and the illness as “normal as possible,” which is in fact good for the patient. The impact on siblings, however, of growing up within a family in which an exceptional situation is treated as if it were normal is of questionable value. It may set a pattern in which dissociation from the illness experience is reinforced in order for the sibling to continue with “normal” developmental tasks.
School Difficulties

The well child may have trouble with concentration while at school because he or she is distracted by worries about life at home. Difficulty may also arise because the sibling may have frequent school absences. This may be due to the sibling’s desire to spend time with the sick brother or sister or the family’s need for the sibling to baby-sit for other children on clinic appointment days.

Impact of Parental Mourning on Siblings

Parental accessibility for the support of the surviving sibling is vital to the adjustment process. Parental preoccupation with their own grief can have consequences for surviving children. Horowitz found survivors unable to cope effectively with the present because they were busy trying to assimilate the past. Found reported the depressed mother to be considerably impaired in her role. Siegel and Gorey discussed parental mourning in detail. Recent data on responses of parents grieving the loss of their child suggest that parents grieve for much longer periods of time than was assumed. Frequent responses include idealization, sublimation, memorialization, and refocusing on the surviving child, with profound consequences for the sibling’s identify and self-esteem.11,22,35

About 18% of children in the United States have a chronic medical condition. Many of these have a condition severe enough to affect daily life. The scope of the problem can be seen in the burgeoning body of support groups for siblings such as Sibshops, children’s books with such informative titles as I Wish I was Sick Too and What about Me? When Brothers and Sisters Get Sick, as well as web sites for sibling support (e.g., “Band-aides and Blackboards” and “The Sibling Connection”). Although web-based Internet and group support can be helpful, it does not provide one-to-one counseling with a professional over time, nor is it readily available within the pediatric setting. The Sibling Center was developed to fill this gap.

Goals of the Program

Since this is a pioneering program, there was no ready model to guide the structure of the program. Significant differences exist from a model of traditional psychotherapy in that this is a program identifying at-risk well siblings. The mission was identified as a form of psycho-education, which included psychosocial support, targeted interventions, resource identification, and consciousness-raising.

DESIGN OF THE SERVICE

The program is viewed conceptually as a developmental model rather than a psychiatric one, and since siblings are at risk rather than clinically distressed, the most appropriate department was identified as Pediatrics, specifically the Child Development Center. In addition, the location should be an integral part of the pediatric clinic, with which families were already familiar and comfortable. This averted the risk of “diagnosing” and potentially pathologizing the sibling. Our hospital’s usual informed consent form was reviewed and found to be appropriate.

Training/Supervision

Therapists are selected from trainees in the Child Development Center who are completing licensure hours. Trainees receive an educational seminar presenting research findings on sibling responses to illness. Group supervision takes place once a week and includes families seen for individual treatment during that week. In those meetings, dual supervision takes place: The therapist presents the family, goals of treatment, progress, and so forth; the clinical supervisor oversees in terms of therapy progress; the director suggests ways in which that specific medical condition would affect the family or might be viewed by the sibling—for example, is the condition life-threatening or not, visible or not, genetic or not, and so forth. The director also serves as a link to medical information related to that disorder.

Structure of the Clinical Service

The sequence is as follows: The pediatrician/social worker/nurse practitioner informs the family about the Sibling Center. When the family phones, the clinical supervisor assigns the family to the appropriate therapist. In keeping with a developmental, preventive model, we take the stance that the siblings are not disturbed but at risk and therefore seek no diagnostic labels. We have a four-session model of intervention. In session 1, the therapist meets with parents and well siblings for evaluation and treatment plan development. The therapist seeks specific details concerning the illness, including parental experience of realizing their child was ill, receiving the diagnosis, and communication within the family about the illness. These assessments, combined with assessments of the children, lay the groundwork for the treatment protocol. In sessions 2 and 3, well siblings meet alone with the counselor to identify communication difficulties in the family, to alleviate emotional distress, and to strengthen coping skills. Children and adolescents are seen in rooms supplied with play therapy equipment, including toys and dolls. Session 4 is divided into two parts. The first half is with the sibling alone and the second is with the parents also present to review and develop future plans and to reconstitute the family before it leaves the therapy session. Approximately 6 months after the last session, the therapist sees the family to review the emotional needs of the well sibling. If significant distress is identified for a sibling or parent, the therapist assists the family in identifying an appropriate therapist, based on insurance constraints and geographic proximity.

EXPERIENCE TO DATE AND CASE EXAMPLES

Referrals

We included pediatric medical conditions that would be expected to cause the family to realign around the sick child to
the neglect of the well sibling. This would include severe asthma, congenital heart disease, cystic fibrosis, cancer, blood diseases, diseases of neonates, and transplantation. Our referral network has been educational in itself. We first targeted pediatric subspecialists, but found referrals slow-going. They concentrate by necessity on the ill patient and it is extremely difficult to expand that focus to include the needs of the sibling. When a pediatrician did refer a family and that family expressed gratitude to the physician for the help received, that physician tended to refer more families. Some families have referred themselves after finding a Sibling Center brochure in the hospital and specialty clinic lobbies.

**Outcome Assessment**

We designed a form to evaluate how well the Sibling Center is meeting the needs of its families. There are seven core questions. Five questions have response options ranging from extremely satisfied (5) to not satisfied (1); two had yes/no responses; we also include an open-ended probe: “What other comments or suggestions would you like to share with us about the Sibling Center?” Preliminary data suggest a very positive response; open-ended comments include reports of less angry acting-out sibling behavior, improved family communication, and gratitude for the help given.

**Impact on Therapists**

At first, the therapists were concerned about their ability to handle such emotionally difficult material that would be elicited by a seriously—perhaps fatally—ill child. However, as they began to work with actual families, their confidence quickly grew, and they reported finding this work extremely rewarding. Trained in longer-term therapy, and in particular with families of children with developmental disabilities or learning differences, they were surprised and heartened at how this focused intervention was able to effect considerable change in family functioning. They found the time-limited model refreshing—it created boundaries, particularly reassuring in such emotionally difficult situations as pediatric cancer. Similar to the one-time in-depth clinical research interview,11,41 or even the one-time session by a highly experienced psychoanalyst,42 the Sibling Center’s short-term model was professionally encouraging, as can be seen in the following two examples.

**Family 1**

This family was self-referred, with the father making the initial phone call. There were two children, 4-year-old Michael, recently diagnosed with a chronic kidney disorder, and 6-year-old Sarah. In the first session, the parents discussed various instances of Sarah’s acting out, arising from her jealousy of the time the parents spent with Michael at his doctors’ appointments and giving him medication. In the following week, major themes introduced by Sarah focused on issues of jealousy—wanting to take his medicine and to have her own doctor’s appointments and time with her mother. The therapist invited Sarah to choose a sticker to take home, and she selected one, stating “I’ll take this one, because I know Michael likes it.” In the following sessions, the therapist focused on ways to limit the impact of Michael’s illness on Sarah. Sarah directly asked her mother if she could have a little time every week alone with her, and Mom readily complied. The therapist noted that Sarah had blossomed in her appointments at the Sibling Center and that one reason she loved coming was that she had her own “appointment.”

**Family 2**

The mother phoned for help with her 13-year-old daughter Jenny. Jenny’s 16-year-old sister Connie was diagnosed with a metabolic disorder 5 years prior. In the first session, the mother explained she believed they were in crisis in terms of how she and her daughter were getting along. She described Jenny as insecure and emotional and Connie as the “brilliant one.” The therapist suggested that their comparing the sisters was threatening Jenny’s self-esteem. Dad thought it was significant that they had come together on Jenny’s behalf for once, rather than for Connie. In the second session, Jenny reported that her relationship with her parents had improved, although she still spent a lot of time alone. Mom stated she had never realized how much they had been comparing their two daughters with each other and that she had made a conscious effort not to do so. The therapist recommended that they initiate more family activities so Jenny would not be spending so much time alone. Although they had come to only two sessions, both parents and Jenny believed that they did not need to be seen any more at this time.

**CONCLUSIONS**

These cases illustrate typical responses on the part of parents to having an ill child and feelings of the well siblings. A common thread for these siblings has been jealousy; whether actively admitted to or not, and attention-seeking behavior. Another thread was the proclivity of the well sibling—even so young as 6 years old—to put the ill sibling’s needs before his or her own. Our major intervention has been to define this situation as challenging, to increase awareness that well siblings are at risk, and that acting-out behavior has a communicative purpose; therefore, the major role has been educational. Second, the sibling’s relationship with the therapist has proven to be crucial, as it signified to siblings that this was their appointment, their time. One of the most useful recommendations—and the most concrete—has been that the parent would spend at least some time alone with the well sibling. For some siblings, this involved a cherished shared activity; for others, it was the sheer time alone with the parent that was so meaningful. At times of acute crisis such as hospitalizations, some families made promises to the well sibling that this would happen the following week, and honored them.

It is likely that private psychotherapy would be effective as well. However, the sibling may be labeled as having “problems” rather than being “at risk.” In addition, many families who would not seek therapy because of a perceived
stigma or prohibitive costs may accept a program such as ours. In fact, the Sibling Center has served as a bridge to ongoing therapy for families who would not have considered therapy had they not had this experience. Our preliminary results as well as outcome data from a residential camp intervention for siblings and parents and a sibling-parent group intervention have showed significant improvement for siblings.

We developed our Sibling Center within the resources, strengths, and limitations of our particular institution. Each institution will have to decide how best to implement such a program, the particular setting, key players, and so forth, but we offer our decisions and experiences thus far as a guide. It was encouraging that even therapists somewhat new to the field have been able to effect considerable change in a relatively short period of time. Ideally, it would be preferable to prevent sibling problems from the beginning of identification of the ill child by the medical team. Perhaps proactively raising parental awareness of the potential for siblings to have problems and/or extending an invitation for someone on the medical team to meet with the siblings to help them understand the disease could be cost-effective in clinics that do not have the capacity to develop a more substantial program. This intervention could be evaluated for its effectiveness. In conclusion, we urge pediatricians to include siblings of ill children in their models of family-centered care and to develop interventions to avert long-term distress.

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REFERENCES


Many cases of acute retinal necrosis caused by HSV-2 have been reported in children, teenagers, and young adults as a result of reactivation of congenital or neonatal infections, which may have been subclinical. Pediatricians should be aware of this entity and alert to recurrences that may be delayed by years. (J Pediatr 2005;146:836-8)

Acute retinal necrosis (ARN) is an uncommon disease characterized by rapidly progressive peripheral retinal necrosis. Early therapy is essential to preserve vision and prevent involvement of the other eye, but in spite of treatment outcome often is poor.1-3

Varicella-zoster virus (VZV) is the most commonly identified cause, accounting for 50% to 80% percent of cases, with herpes simplex virus (HSV) responsible for most other cases.4-6 Rarely, cytomegalovirus has been implicated. ARN caused by HSV most often occurs in association with, or many years after, HSV encephalitis or meningitis, or it may follow neurosurgery, trauma, or administration of systemic corticosteroids.2,7,8 Of note, many cases of HSV-2 ARN have been reported in children, teenagers, and young adults (Table). Thus it has been proposed that most cases of HSV-2 ARN result from reactivation of congenital or neonatal herpes, which may have been subclinical.1-5,9-11 Pediatricians, who are often the first to evaluate these patients, may be unaware of this entity and of the importance of prompt therapy. We report on a child with HSV-2 ARN, initially misdiagnosed as conjunctivitis, presenting 9 years after neonatal encephalitis.

CASE REPORT

A 9-year-old child was taken to her pediatrician because of a "red eye." The child, whose mother had development of genital herpes post-partum, had a history of neonatal HSV meningoencephalitis, resulting in neurologic deficits (inability to speak or control oral secretions). When eye findings did not improve after 5 days of topical antibiotics, the child was referred to an ophthalmologist. Ophthalmologic examination revealed severe anterior uveitis in the left eye with synchiae between the pupil and lens. The fundus could not be visualized. After 10 days of oral and topical corticosteroids and atropine drops, the patient’s visual acuity in the left eye was limited to hand motions only. A dilated retinal examination showed moderate conjunctival congestion, marked anterior chamber inflammation, a dense vitritis, and areas of retinal whitening. The patient was diagnosed with ARN, and intravenous acyclovir was initiated. The following week, intravitreal corticosteroid injection and vitrectomy with scleral buckle were performed. There was pallid edema of the optic disc, and the retinal vessels were attenuated. Laser was applied posterior to the band of confluent retinitis. Vitreous was positive for HSV-2 by polymerase chain reaction (PCR) at Yale New Haven Hospital Virology Laboratory, using published methods.12 Insufficient sample remained for virus isolation. The patient was negative for HIV and HSV-1 antibodies, but positive for HSV-2 antibodies.

The patient was treated with 2 weeks of acyclovir intravenously, followed by 6 weeks of valacyclovir orally. Six weeks after stopping therapy, there was a sudden decrease in vision with vitreal haze. An additional 2 weeks of intravenous acyclovir therapy was followed by valacyclovir orally, and the cells cleared. At 1-year follow-up, the patient remains on suppressive valacyclovir therapy and has a visual acuity of 20/60.

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Confirming the cause of ARN has been facilitated by the increasing availability of PCR. Both vitreous and aqueous fluids have been used, and typically 200 μL of sample are tested. HSV type can be determined by using type-specific primers and probes, as well as restriction enzyme digestion or melting curve analysis of amplified products. HSV PCR is not standardized, and reliability of results varies among laboratories. In addition, accurate type-specific antibody assays are now available commercially and were used in this patient.

HSV-2 is the most common cause of ARN identified in childhood. Cases of HSV-2 ARN have been reported in children with documented or a strongly suggestive clinical history of neonatal herpes infection. It has been postulated that most cases of HSV-2 ARN occurring in children and young adults without a history of neonatal herpes in fact represent reactivation of congenital or neonatal HSV infections. Subclinical congenital or neonatal herpes was suspected in some cases because of the presence of chorioretinal scarring. In 3 cases, presence of HSV-2 antibody was documented in mothers.

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<th>Age</th>
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<th>Neonatal herpes infection</th>
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<th>Craniotomy, immunosuppression or trauma</th>
<th>Prior ARN</th>
<th>Chorioretinal Scars</th>
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<td>9</td>
<td>16 yr</td>
<td>F</td>
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<td>10</td>
<td>30 yr</td>
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<td>11</td>
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<td>Yes</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>PCR, vitreous</td>
</tr>
</tbody>
</table>

N/A, Not available.
*Mother with HSV-2 antibodies.

**DISCUSSION**

Confirming the cause of ARN has been facilitated by the increasing availability of PCR. Both vitreous and aqueous fluids have been used, and typically 200 μL of sample are tested. HSV type can be determined by using type-specific primers and probes, as well as restriction enzyme digestion or melting curve analysis of amplified products. HSV PCR is not standardized, and reliability of results varies among laboratories. In addition, accurate type-specific antibody assays are now available commercially and were used in this patient.

Herpes Simplex Virus Type 2 Acute Retinal Necrosis 9 Years After Neonatal Herpes
the patient’s neonatal history and by determining maternal HSV-2 antibodies.

Early symptoms of ARN overlap with those of common conjunctivitis. ARN usually causes a slowly progressive red eye and blurred vision. Pain may range from mild irritation to intense photophobia. Dilated fundoscopic examination reveals the hallmark of the disease: necrotizing retinitis with early appearance and rapid confluence of white patches in the retina peripherally. The most common cause of vision loss after treatment is retinal detachment with traction of the vitreal membrane. Optic neuropathy, as in our case, is not uncommon and can limit visual recovery. The opposite eye is affected in about one third of patients, but occurrence can lag by months to several years. Early antiviral therapy limits the extent of necrosis and decreases risk of retinal detachment and involvement of the opposite eye.

In our case, HSV-2 ARN presented 9 years after neonatal meningoencephalitis. Diagnosis and antiviral therapy were delayed for 2 weeks until the dilated retinal examination was performed. Pediatricians and pediatric ophthalmologists should be aware of this entity and alert to recurrences involving the same eye or the other eye that may be delayed by years. Parents of children with a history of neonatal HSV disease, neurologic disease, or prior ARN should be advised that any redness, pain, or decreased vision in the eye merits prompt evaluation by an ophthalmologist.

REFERENCES
DETECTION OF AUTOIMMUNE REGULATOR GENE MUTATIONS IN CHILDREN WITH TYPE 2 AUTOIMMUNE HEPATITIS AND EXTRAHEPATIC IMMUNE-MEDIATED DISEASES

TIM O. LANKISCH, M.D., CHRISTIAN P. STRASSBURG, M.D., PH.D., DOMINIQUE DEBRAY, M.D., MICHAEL P. MANNS, M.D., PH.D., AND EMMANUEL JACQUEMIN, M.D., PH.D.

Autoimmune regulator gene mutations were identified in 3 children with type 2 autoimmune hepatitis and extrahepatic immune diseases, including 1 child with immune hepatitis recurrence after liver transplantation. These findings suggest that autoimmune regulator gene variants might predispose children to systemic autoimmune disease, a recurrence of immune disease, or both. (J Pediatr 2005;146:839-42)

Autoimmune hepatitis (AIH) is an immune-mediated chronic inflammatory disease of the liver of unknown etiology that leads to hepatic parenchyma destruction when left untreated. AIH may be associated with extraphepatic immune-mediated manifestations, which can include endocrine diseases. This association suggests that AIH may be associated with a general predisposition for organ autoimmunity and that autoimmune disease of other organs and AIH may share etiological mechanisms.

Autoimmune regulator gene (AIRE) mutation is responsible for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). AIRE is expressed in cells involved in induction and maintenance of immune tolerance, but not in those cells representing the target of autoimmune destruction. AIRE consists of 14 exons, and its mutations are inherited in a Mendelian fashion. The main clinical symptoms of the autosomal recessively inherited APECED are candidiasis, hypoparathyroidism, and adrenocortical failure. The diagnosis is established when 2 of these 3 symptoms are present. Only one third to 50% of patients with APECED display all 3 components simultaneously. APECED can be further accompanied by alopecia, hypogonadism, vitiligo, and intestinal dysfunction among other conditions. Hepatitis occurs in as many as 20% of patients with APECED, ranging from a mild to fulminant course. However, AIRE variants do not appear to be associated with an overall cohort of adults with AIH, and another study has suggested that an AIRE gene abnormality does not contribute to the development of isolated AIH in children.

Treatment of acute liver failure in AIH includes immunosuppression or, as a final therapeutic option, orthotopic liver transplantation (OLT). The clinical course of patients who have undergone a transplant for AIH can vary from the achievement of sustained remission to the recurrence of AIH with the possibility of a fatal course. Because of the role of AIRE, a candidate gene for general predisposition to autoimmunity, we hypothesize that it may be involved in complex pictures of autoimmune diseases and their recurrence after liver transplantation in children with AIH. Therefore, the aim of this study was to search for AIRE mutations and APECED-related autoantibodies (anti-CYP450 1A2, -SCC, and -C17) in children who have AIH with or without extraphepatic immune-mediated symptoms, recurrence of immune-mediated process after liver transplantation, or both.

PATIENT CASE REPORTS

In the series of patients examined for AIH in Bicêtre hospital, only DNA and serum samples of 5 patients with type 2 AIH were available. Patients 1, 2, and 3 had complex...
extrahepatic immune diseases, whereas patient 4 had no extrahepatic immune disease, and patient 5 had celiac disease.

Patient 1

This patient was born to North African consanguineous parents and had a brother affected with adrenocortical failure. At the age of 3 years, she had acute hepatitis and severe coagulopathy (prothrombin time <50%) associated with anti-liver–kidney microsomal type 1 (LKM-1) CYP2D6 antibodies and a liver histology compatible with AIH. She had antithyroid and anti-Langerhans islet cell antibodies. Response to immunosuppression was positive. The course was further characterized by the appearance of hypoparathyroidism, adrenocortical failure, and gastric atrophy. The now 20-year-old patient is in remission with steroids and azathioprine.

Patient 2

This patient was born to Caucasian consanguineous parents. The father had hypoparathyroidism and dental enamel dysplasia; the mother had thyroiditis, and the maternal grandmother had diabetes mellitus. At the age of 6 months, the patient had acute fulminant hepatitis in the presence of anti-liver cytosolic (LC-1) antibodies against FTCD and a liver histology compatible with AIH. The disease did not respond to immunosuppression. OLT was performed. In the further course of disease, autoimmune enteropathy with villous atrophy developed, requiring total parenteral nutrition. Liver histology was compatible with autoimmune hepatitis, and anti-LC-1 antibodies recurred. Despite treatment with azathioprine, steroids, tacrolimus, ursodeoxycholic acid, and parenteral nutrition the patient died when he was 3.5 years old.

Patient 3

This patient was born to Caucasian non-consanguineous parents. The family history was inconspicuous. Autoimmune enteropathy with villous atrophy and anti-gut antibodies (anti-brush border) was diagnosed when the patient was 10 months old, and autoimmune nephropathy with extramembranous glomerulopathy and anti-kidney antibodies (anti-tubular basal membrane) was diagnosed when he was 15 months old. At 2 years, he had acute hepatitis and severe coagulopathy. Anti-LKM-1 CYP2D6 antibodies were detectable and histology was compatible with AIH. The patient responded to steroids, azathioprine, and transient cyclosporin A therapy.8 The patient is 13 years old, and the liver disease is still well controlled.

Patient 4

This Caucasian patient had no family history of autoimmune disease. At age 8 months old, she had acute fulminant hepatitis, anti-LKM-1 antibodies, and liver histology compatible with AIH. Immunosuppressive therapy failed, and OLT was performed. There were no signs of extrahepatic manifestations. At the age of 2 years, her liver histology showed severe signs of chronic rejection. There was no therapeutic benefit from the administration of tacrolimus, ursodeoxycholic acid, and steroids. After her second OLT, hepatic artery thrombosis developed, and she received a third graft, but eventually died when she was 3.5 years old.

Patient 5

This Caucasian patient had an aunt with thyroiditis. When she was 9 months old, celiac disease with villous atrophy and celiac antibodies developed, and she was put on a gluten-free diet. At the age of 1 year, she had acute hepatitis and severe coagulopathy. Liver histology showed signs of autoimmune hepatitis, and anti-LC-1 antibodies were positive. She responded well to immunosuppression, including cyclosporin A, azathioprine, and steroids. Except for celiac disease, she did not have any extrahepatic symptoms.

When applying the international scoring system for diagnosis of autoimmune hepatitis,12 all 5 children had a score >15, which corresponds to a definite diagnosis of AIH.

AIRE Gene Analysis

Blood samples were used to prepare genomic DNA. All 14 exons of the AIRE gene were amplified by using polymerase chain reaction (PCR) with 14 pairs of specific primers, as previously published.6 The nucleotide sequences were determined both on the coding and reverse strands with an ABI 310 automated sequencer (Applied Biosystems). In case of identification of a missense mutation, a total of 100 control chromosomes were screened. Informed consent was obtained from each family included in the study.

Determination of APECED-related Autoantibodies

Serum autoantibody testing for liver membrane antibodies (LM, directed against CYP1A2) and autoantibodies against CYP450 SCC and CYP450 C17 was performed by Western blotting, as described previously.11,13

RESULTS

The results of serum autoantibody testing and AIRE genotyping experiments are summarized in the Table. Patient 1 had a homozygous deletion in exon 10, leading to a frame shift and a stop codon at amino acid 448 (P398fsX448). Autoantibody testing revealed the presence of anti-CYP450 SCC and anti–CYP450 C17, but the absence of anti-CYP1A2. Patient 2 harbored a homozygous nonsense mutation in exon 6 (R257X). Autoantibody testing was negative for anti-CYP450 SCC, anti-CYP450 C17, and anti-CYP1A2. Patient 3 carried a heterozygous missense mutation in Exon 12 (R441C), which was also found heterozygous in 3 of 50 healthy blood donors, that was analyzed to establish the presence of a single nucleotide polymorphism. Autoantibody testing revealed the presence of anti-CYP450 SCC and anti-CYP 450 C17, but the absence of anti-CYP1A2. In patients 4 and 5, no AIRE mutations and no APECED-related autoantibodies were identified.
AIRE gene analysis P398fsX448 Anti-CYP450 C17 12 1 2 2 Anti-CYP450 SCC 12 1 2 2

Autoimmune Hepatitis And Extrahepatic Immune-Mediated Diseases Detection Of Autoimmune Regulator Gene Mutations In Children With Type 2 Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM (anti-CYP450 IA2)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Anti-CYP450 SCC</td>
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<td>—</td>
<td>+</td>
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<td>Anti-CYP450 C17</td>
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<td>—</td>
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<td>AIRE gene analysis</td>
<td>P398fsX448 homozygous exon 10</td>
<td>R257X homozygous exon 6</td>
<td>R441C Heterozygous exon 12</td>
<td>No mutation</td>
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</table>

The heterozygous missense mutation in patient 3 was also found in 3 of 50 healthy blood donors who underwent analysis to establish the presence of a single nucleotide polymorphism. LM = Liver membrane.

DISCUSSION

All 5 children had acute type 2 AIH, and AIRE mutations were identified in 3 patients with extrahepatic immune diseases, including 1 patient with recurrence of immune hepatitis after OLT.

Patient 1 was initially treated for acute AIH, and the main APECED symptoms developed later during the course of the disease. APECED in small children frequently begins with candidiasis and not with the presentation of AIH. This suggests that in children acute AIH with severe coagulopathy may represent the onset of APECED. In patient 2, a homozygous deletion in exon 6 leading to a frame shift was detected, which is well known as a major mutation in Finnish patients with APECED. Extrapancreatic manifestations included autoimmune enteropathy. After OLT, AIH recurred, followed by a severe and fatal clinical course. Because the AIRE gene is relevant for the maintenance of tolerance and does not only indicate autoimmunity targeting endocrine glands, the presence of unknown AIRE mutations in type 2 AIH represents a risk factor for APECED and therefore for the development of extrapancreatic manifestations. In this context, the detection of AIRE mutations may identify a general predisposition to autoimmunity and may indicate a possible recurrence of the autoimmune liver disease after liver transplantation. This may account for a more severe or even fatal clinical course, as shown in this study. Mutation analysis of the AIRE gene could therefore be performed as a prognostic marker in patients with an acute presentation of type 2 AIH.

Patient 3 harbored a heterozygous mutation in exon 12 (R441C), which was also found heterozygous in 6% of healthy blood donors. We therefore believe that this mutation may represent a single nucleotide polymorphism (SNP) in an exon rarely affected by mutations and not analyzed so far in larger study cohorts. Although this mutation is heterozygous and likely represents a SNP, it may be a marker for the development of extrapancreatic manifestations, such as autoimmune enteropathy or nephropathy, which needs clarification in larger cohorts of APECED and patients with AIH.

In patients 4 and 5, no AIRE mutations were identified. It is likely that other genes may be involved in autoimmunity process and may favor extrahepatic autoimmune disease. In a recent series reporting on AIH, AIRE abnormality was not found in adults and children with type 1 or type 2 AIH and without extrahepatic autoimmune manifestations.

Our analysis of serum autoantibodies failed to detect anti-CYP1A2 autoantibodies in any of the 5 patients, which is a specific but insensitive marker for APECED hepatitis. This suggests that in these children, acute AIH with AIRE mutations does not appear to be characterized by the early development of this previously described APECED autoantibody marker. However, the adrenal autoantigens anti-CYP450 SCC and anti-CYP450 C17, which are found in Sardinian patients with APECED who have adrenocortical failure, were detected in patients 2 and 3, pointing to the presentation of APECED syndrome with acute AIH as a disease component.

In summary, although the link between AIRE gene mutations and AIH is not known, AIH may be a first manifestation of APECED, followed by the subsequent development of extrahepatic disease manifestations. In addition, it is suggested that AIRE defects might represent a predisposition to recurrence of immune hepatitis after OLT. AIRE genotyping in children with type 2 AIH and acute presentation may therefore contribute to the identification of patients who are at risk for the development of extrahepatic immune diseases or the recurrence of immune liver disease after OLT. This might improve the management and the outcome of this liver disease in similar pediatric and possibly adult patients. These data incite the search for AIRE mutations in a larger cohort of children with type 1 and 2 AIH.

REFERENCES


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FRASIER SYNDROME COMES FULL CIRCLE: GENETIC STUDIES PERFORMED IN AN ORIGINAL PATIENT

NICHOLAS J. WANG, BS, HAE-RI SONG, MD, N. CAROLYN SCHANEN, MD, PhD, NEIL L. LITMAN, MD, AND S. DOUGLAS FRASIER, MD

Frasier syndrome is a relatively rare disorder associated with XY gonadal dysgenesis, gonadoblastoma, and kidney failure. In this report, we identify a classic mutation in the Wilms’ tumor 1 gene in one of the original cases of Frasier syndrome reported in this Journal in 1964. (J Pediatr 2005;146:843-4)

In 1964, this Journal published a report describing phenotypic female identical twins with XY gonadal dysgenesis with streak gonads, gonadoblastoma, and chronic kidney failure.1 Similar patients were subsequently described, and in 1987 Moorthy et al2 collected 6 patients and suggested that this condition be called Frasier syndrome (FS, OMIM 136680).

FS is caused by mutation in the Wilms’ tumor gene (WT1) located on chromosome 11p13,3 which encodes a Zinc-finger protein that has been implicated as causing a number of disorders in urogenital development. The mutations that cause FS occur within intron 9, affecting a donor splice site3,4 that is critical for expression of an alternatively spliced isoform of the WT1 protein, which differs in the presence or absence of a 3-amino acid sequence of lysine, threonine, and serine (KTS). The mutations lead to a shift in the ratio of the KTS and +KTS isoforms that are produced, from 2:1 +KTS/KTS to 1:2 +KTS/-KTS.3,4 A related disorder, Denys-Drash syndrome (DDS, OMIM 194080), which is defined by Wilms’ tumor in association with pseudohermaphroditism and diffuse mesangial5,6 and isolated sclerosis7 are also caused by mutations in WT1, typically involving the coding sequence. Microdeletions within chromosome 11p13 that include the WT1 gene and the PAX6 gene lead to WAGR syndrome (OMIM 194072), a complex phenotype associated with Wilms’ tumor, aniridia, genitourinary abnormalities, hemihypertrophy and mental retardation.6 Curiously, in spite of the occurrence of Wilm’s tumor in DDS and WAGR, mutations in WT1 are not common in patients with sporadic or familial Wilm’s tumor,8 and Wilm’s tumor is not typically seen in patients with FS.9

In this study, we located the surviving twin (Patient 2) described in the original report that defined the FS phenotype. She had received a kidney from her father in 1967 at age 13 years and has subsequently remained in excellent health, with no recurrence of and no new malignancies. We show that this original patient carries a classic FS mutation in WT1.

METHODS

After informed consent was obtained using an Institutional Review Board–approved protocol, a blood sample was obtained from the patient (Patient 2 from the original report). Genomic DNA was extracted from peripheral white blood cells using a PureGene DNA purification kit (Gentra) according to the manufacturer’s protocol. Polymerase chain reaction amplification of exon 9 of the WT1 gene was performed using genomic DNA (100 ng) with primers WT9a sense (5’-TAGGGCCGAGGCTAGACCTCCTCTGT-3’) and WT9b antisense (3’-ATCCCTCTCATCAACCAATTTCATTTC-3’) as previously described.3 The resulting amplimer was gel purified and sequenced in both directions using the WT9a and WT9b primers with an ABI Prism Dye Terminator sequencing kit (Perkin-Elmer).

RESULTS

We targeted our mutation analysis to the region of the WT1 gene where mutations have been identified in other patients with FS and found that the patient is heterozygous for a guanine>adenine point mutation in the +5 position of the splice donor site within intron 9 (IVS9 +5G>A).4 The mutant allele was detected as a dual peak in the

DDS Denys-Drash syndrome FS Frasier syndrome
The phenotypic overlap between the disorders is demonstrated by the variable expressivity of the mutation and the complexity of DNA amplification from that sample.

We have found an FS mutation in one of the original patients described with this syndrome. This particular mutation has been found in 26% of the patients collected by Melo et al. Because previous studies demonstrated that the children were identical twins, it is highly likely that the patient’s sister had the same mutation, although we were not able to prove this experimentally. Our findings close the diagnostic circle in this patient originally described 40 years ago.

We are indebted to the patient for participating in the study and to Eric Vilain and Naghmeh Dorrani for their assistance.

REFERENCES


Figure. Chromatogram shows heterozygous G>A mutation (sense, left panel) or C>T mutation (antisense, right panel) in donor splice site in intron 9 of WT1.
A boy with sickle cell disease was admitted after presenting with painful crisis and *Salmonella* nontyphi sepsis. He was transfused, rehydrated, and treatment with analgesia, intravenous Ceftriaxone, and Amikacin was commenced. Three days later, he was noted to have a warm, tender, fluctuant mass in the region of the sterno-manubrial junction. Attempted needle aspiration failed to locate any purulent material. Repeat chest radiographs revealed a dislocation of the sternomanubrial joint, with the first sternebra hinging forward on the first intersternebral growth plate in the manner of a trap door (Figures 1 and 2; Figure 2 available online at www.us.elsevierhealth.com/jpeds). The sternebra was banded flat against the chest with tape, resulting in complete clinical resolution of the abnormality. When reviewed 4 years later, there was no residual cosmetic or functional abnormality (Figure 3 available online at www.us.elsevierhealth.com/jpeds).

The dislocation of a sternal ossification center described above, “trap door sternum,” may have resulted from sternal avascular necrosis, infarction in the region of the first intersternebral joint, disruption of the joint, and hinging forward of the sternebra on the superior joint. Sternebral avascular necrosis has been described, sometimes associated with resorption of bone leading to sternal cupping, but sternal joint involvement has not been described.

No previous reports of sternebral dislocation associated with sickle cell disease were found. In other clinical scenarios, such as trauma, where sternebral dislocation has occurred, both surgical correction and conservative management have been used.

A presternal mass in a patient with sickle cell disease in the absence of suppuration may be “trap-door sternum,” which can and should be managed conservatively.

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REFERENCES

**Isolation and bronchiolitis**

*To the Editor:*

The recent article by Muething and colleagues addressing the guideline for the management of bronchiolitis\(^1\) was helpful in that the authors were able to standardize treatment protocols very nicely, thereby decreasing unnecessary imaging and procedures. I do have one concern about the practicality of this guideline, related to the issue of isolation once admitted. In the hospital where I did my training, all children who were Respiratory Syncytial Virus-positive (RSV+) were placed in contact isolation, and we would cohort the children who were RSV+ together. The admission of children with suspected RSV was often delayed by hours because of the difficulty of assigning a bed to a child in the emergency department before the result of the nasopharyngeal wash was received or without one being done. Is there a similar policy in the authors’ hospital, and if so, how did they get around it without doing a nasopharyngeal wash? This question might seem trivial in that it doesn’t clinically make a difference, but in the real world of a busy hospital, it can make all the difference in patient and family satisfaction and comfort.

Jacob Rosenberg, MD, FAAP
Island Pediatric Associates
Long Beach, NY 11561

**REFERENCE**


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**Reply**

*To the Editor:*

We wish to thank Dr Rosenberg for his interest and insightful comments. The issue of isolation and prevention of spread is an important one with bronchiolitis and is addressed in our guideline. The guideline and references are available at [www.cincinnatichildrens.org](http://www.cincinnatichildrens.org). Several studies have shown multiple viruses are responsible for bronchiolitis by incorporating evidence at the point of care. J Pediatr 2004;144:703-10.

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**Inadequacy of IV vitamin A supplementation of extremely preterm infants?**

*To the Editor:*

Ambalavanan et al\(^1\) note that most neonatologists in the United States do not supplement extremely-low-birth-weight infants with vitamin A because they consider the benefit to be either small or unproven. Neither is routine intramuscular supplementation established in the United Kingdom. Supplementation is given intravenously (IV), or not at all, pending the establishment of enteral feeding. There are few data about this practice, although it is recognized that administration is more efficient in lipid emulsion than in amino acid-dextrose solution.\(^2\) Prompted by the recent introduction of IV vitamin A (Vitlipid N Infant, Fesenius Kabi, Cheshire, UK) in our unit, we measured plasma vitamin A concentrations in 19 very-low-birth-weight infants at birth, on days 7 and 28, and at 36 postmenstrual weeks. Gestational ages ranged from 24 to 34 weeks (mean ± SD, 28.3 ± 2.8 weeks), and birth weights ranged from 590 to 1460 g (mean ± SD, 1090 ± 260 g). The manufacturer’s recommended dose of 920 IU/kg/day was given from day 2 to infants receiving <75% of expected volume of enteral feeds. Oral vitamin A (2000 IU/day) was given from day 10 when enteral feeds were tolerated. The study was approved by the hospital’s research ethics committee.

More than half of infants had deficient plasma retinol values (<0.35 μmol/L; 10/19, 53%), and 79% of the infants (15/19) had marginal or deficient plasma retinol values (<0.7 μmol/L) at day 7. Mean plasma retinol values on day 7 in infants who had received IV vitamin A did not differ from those of infants who did not receive supplementation. By 36 postmenstrual weeks, plasma retinol values were deficient in 60% of infants (6/10) and marginal or deficient in 80% of infants (8/10).

The results of this small study emphasize the need highlighted by Ambalavanan et al\(^1\) to develop safe, effective, and acceptable methods of parenteral administration of vitamin A to extremely preterm infants.

**REFERENCE**

To the Editor:

In their paper, Ambalavanan et al conclude that current clinical practices for vitamin A supplementation in extremely-low-birth-weight (ELBW) infants are inconsistent with available evidence. We disagree.

The authors’ support for the use of intramuscular vitamin A in ELBW infants is the metaanalysis by Darlow and Graham, which is largely weighted toward the authors’ own study and includes studies in larger infants and alternate dosages and routes. Of all outcomes analyzed, only 2 showed marginal risk reduction: death or oxygen supplementation at 1 month (0.93; CI, 0.88-0.99) and oxygen need at 36 weeks postmenstrual age (0.87; CI, 0.77-0.99). The conclusion that the number needed to treat (NNT) is “14 to 20 to prevent adverse pulmonary outcomes” is a distortion of the statistics. In reality, these numbers represent mean estimates from 2 different outcomes, not the actual range for a given outcome. Those ranges are: death or oxygen need at 1 month (20;10,100); oxygen need at 36 weeks postmenstrual age (14;7,100). Thus, the NNT may be as high as 100.

In their metaanalysis, Darlow and Graham conclude that universal vitamin A supplementation for ELBW infants is not supported by that data, but rather individualized decisions on the basis of local bronchopulmonary dysplasia risk with the “benefits of a modest reduction in this outcome balanced against lack of other proven benefits and the acceptability of treatment.” It appears the survey respondents agree.

Finally, more study into the pharmacology of vitamin A is necessary before widespread use is considered. A therapeutic window has yet to be defined in the ELBW population. Current supplementation practices result in unpredictable serum levels. For a vitamin with known toxicity, supplementation can have significant risks. Unfortunately, neonatology

REFERENCES


Reply

To the Editor:

We appreciate the comments by West and Cummings on our survey of vitamin A use in extremely-low-birth-weight infants. We agree with Mactier that more research is required on the pharmacology of vitamin A to optimize the dose and route of administration in extremely premature infants and appreciate the caution of West and Cummings in the introduction of new therapies in neonates.

We welcome the investigative work of Mactier et al on the intravenous vitamin A formulation. Their results indicate that the manufacturer’s recommended dose of 920 IU/kg/day was not sufficient to maintain adequate plasma retinol levels in most infants. In the National Institute of Child Health and Human Development (NICHD) vitamin A trial, the control group received about 1000 IU/kg/day (enteral plus parenteral) versus 4000 IU/kg/day in the vitamin A group. However, even the higher intake in the supplemented group was associated with low vitamin A levels (serum retinol <20 mcg/dL) in 25% of the infants. Our subsequent study comparing even higher intakes (10,000 IU 3 times a week) to the standard regimen of 5000 IU given intramuscularly 3 times a week showed that the higher doses did not increase vitamin A concentrations or reduce the incidence of vitamin A deficiency. One possible explanation for why these high intakes of vitamin A do not improve serum levels may be that serum levels of the vitamin A transport proteins retinol-binding protein and transthyretin are decreased by inflammation (ie, they are negative acute-phase reactants), and inflammation is common in these extremely premature infants. Better methods may need to be developed to optimize transport and delivery of administered vitamin A to tissues. It also needs to be determined whether improving delivery to the tissues further improves clinical outcomes without introducing toxicity.

We consider the evidence for the safety of vitamin A administration to be stronger than the evidence for the
safety of many commonly used neonatal therapies, such as methylxanthines, inotropic agents, diuretics, bronchodilators, and postnatal corticosteroids. In the NICHD trial of vitamin A supplementation, masked weekly examinations were performed on 405 infants who received vitamin A supplementation and 402 control infants, and there were no differences in the clinical manifestations of vitamin A toxicity. Follow-up of the infants from this trial at 18 to 22 months showed that the incidence of neurodevelopmental impairment/death in the infants who received vitamin A supplementation was 55%, as compared with 60% in the control infants (RR, 0.94; 95% CI, 0.80-1.07; \( P = .3 \)), and the relative risks of low Mental Developmental Index (MDI) (RR, 0.83; 95% CI, 0.64-1.05; \( P = .1 \)), low Psychomotor Developmental Index (PDI) (RR, 0.84; 95% CI, 0.62-1.12; \( P = .3 \)), and cerebral palsy (RR, 0.86; 95% CI, 0.58-1.24; \( P = .4 \)) were also <1, which is reassuring evidence of safety.

West and Cummings are correct in pointing out that the number needed to treat for death/oxygen need at 1 month may be as high as 100; however, it is just as likely to be as low as 10. We agree with them that the benefits of vitamin A are modest, but in a complex disorder such as bronchopulmonary dysplasia, progress may be possible only in small increments.

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Tumor necrosis factor receptor–associated periodic syndrome in a young adult who had features of periodic fever, aphthous stomatitis, pharyngitis, and adenitis as a child (Saulsbury and Wispelwey). 2005;146:283-5 (CLO)

**Twin, dizygotic**
Dizygotic twin pregnancy conceived with assisted reproductive technology associated with chromosomal anomaly, imprinting disorder, and monochorionic placentation (Yoon et al). 2005;146:565-7 (CLO)
Pediatricians beware: the age of ARTS is upon us (Hall). 2005;146:450-2 (Editorial)
Type 2 diabetes; see Diabetes mellitus, non-insulin-dependent

Tyrosine
High protein diet mimics hypertyrosinemia in newborn infants (Techakittiroj et al.). 2005;146:281-2 (CLO)

U

Ultrasoundography
The changing approach to multicystic dysplastic kidney in children (Welch and Wacksman). 2005;146:223-5 (Editorial)
Proximal focal femoral deficiency—a rare entity in the sonographic differential diagnosis of developmental dysplasia of the hip (Kayser et al.). 2005;146:141 (Insights)
Quantitative bone analysis in children: current methods and recommendations (Specker and Schoenau). 2005;146:726-31
Routine voiding cystourethrography is of no value in neonates with unilateral multicystic dysplastic kidney (Ismaili et al.). 2005;146:759-63

Ultrasoundography, prenatal
Defining significant hydronephrosis (Garel and Grignon). 2005;146:437 (Letter)

Units of measurements; see Weights and measures

Upregulation
Pubertal upregulation of erythropoiesis in boys is determined primarily by androgen (Hero et al.). 2005;146:245-52

Urban population
Use of asthma guidelines by primary care providers to reduce hospitalizations and emergency department visits in poor, minority, urban children (Cloutier et al.). 2005;146:591-7

Urea
Comparison of non-invasive tests to detect Helicobacter pylori infection in children and adolescents: results of a multicenter European study (Megraud and European). 2005;146:198-203
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Urination
The changing approach to multicystic dysplastic kidney in children (Welch and Wacksman). 2005;146:723-5 (Editorial)
Routine voiding cystourethrography is of no value in neonates with unilateral multicystic dysplastic kidney (Ismaili et al.). 2005;146:759-63
The time of passage of the first stool and first urine by the newborn infant (Green). 2005;146:211 (50 years ago)

Uveitis
Uveitis associated with chickenpox (Long). 2005;146:381 (50 years ago)

Varicella; see Chickenpox

Varicose veins
Orbital varices diagnosed as episcleritis in a child with juvenile idiopathic arthritis (Misra and Edelsten). 2005;146:574 (Insights)

Ventilation
Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes (Walsh et al.). 2005;146:798-804

Vertebrae, lumbar; see Lumbar vertebrae

Vertebrae, thoracic; see Thoracic vertebrae

Vertigo

Violence
Post-traumatic stress and its effect on health outcomes in children (Grupp-Phelan and Zatzick). 2005;146:309-10 (Editorial)
Violence exposure and traumatic stress symptoms as additional predictors of health problems in high-risk children (Graham-Bermann and Seng). 2005;146:349-54

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Voiding; see Urination

W

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Weights and measures
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Wheezing; see Respiratory sounds

Wilms’ tumor
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Workforce; see Manpower

Y

Youth; see Adolescence

Z

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