Vesicoureteral Reflux: the RIVUR Study and the Way Forward

Common clinical practice has been that all children who present with a urinary tract infection (UTI) must be evaluated for vesicoureteral reflux with a voiding cystourethrogram (VCUG). The etiological association between reflux and infection was assumed since up to 40% of children with infection are found to have reflux. Evidence from the 1960s appeared to demonstrate that the diagnosis and treatment of reflux were necessary to prevent further infection and renal scarring from pyelonephritis. This literature is now being questioned, and conventional diagnostic and therapeutic recommendations are being challenged. Some specialists now allege that the radiographic detection of reflux is not necessary in all children after an infection. Furthermore, when reflux is detected the recommendations for treatment are controversial and contradictory. Depending on the consultant a child with reflux may be placed on long-term antibiotic prophylaxis, observed off prophylaxis, or undergo surgical procedures such as cystoscopic Deflux® injection, or open intravesical, extravesical or laparoscopic ureteral reimplantation.

Pediatric urologists have been basing recommendations on 3 decades of poorly controlled studies. These studies suggest that episodic treatment of infections in patients with known reflux results in unacceptably high rates of new renal damage.[1,2] These older studies were not blinded or well controlled, they relied on excretory urograms to detect scarring instead of radionuclide imaging, and did not use the International Classification System. The few prospective studies that were controlled compared surgery to continuous prophylaxis such as the International Reflux Study or the Birmingham Cooperative Study, but did not have an observation arm.[3,4] Cooper[5] and Thompson[6] et al prospectively observed children with reflux on and off prophylaxis, and found similar rates of infection. However, in these 2 studies scarring was often assessed by renal ultrasound rather than dimercapto-succinic acid (DMSA) renal scans, and voiding function was not routinely or prospectively measured. Recently Garin et al reported on a small group of children with reflux off prophylaxis, and after 1 year the infection rate was similar to that of children on medication.[7] Rates of renal disease secondary to reflux remained unchanged for 3 decades in an Australian study, suggesting that the identification and treatment of reflux have not reduced the incidence of clinically significant reflux nephropathy.[8] In a recent meta-analysis only 8 randomized, controlled trials of children with reflux could be found, 1 of which compared prophylaxis to placebo.[9] This small trial did not find an increased risk of renal scarring in children observed off prophylaxis.[10] The authors of the meta-analysis concluded that properly designed placebo controlled trials were needed to determine the efficacy of long-term antimicrobial prophylaxis.

In this issue of The Journal Roussey-Kesler et al (page 674) entered the debate with a study purporting that antibiotic prophylaxis in infant boys and girls with low grade (I, II and III) reflux offers little therapeutic advantage. The average age at study entrance was approximately 1 year, and 2 groups equally matched for gender and reflux grade were observed on trimethoprim/sulfamethoxazole (TMP/SMZ) or nothing for 18 months. The study end point was urinary tract infection. Cultures were obtained for fever or urinary symptoms in the presence of abnormal urinary dipstick findings. Urine specimens were obtained by collection bag in children who were not toilet trained. None of the boys was circumcised. DMSA renal scans were not routinely done at study entry or exit. Slightly more children in the nonprophylaxis group (26%) had UTIs than in the medicated group (17%) but this difference was not statistically significant. A quarter of the children with UTIs in the prophylaxis group had organisms sensitive to medication, suggesting noncompliance. However, boys with grade III reflux appeared to fare much better on prophylaxis. The authors conclude that antibiotic prophylaxis confers little benefit for most children with low grade reflux, and suggest that VCUG might not be necessary or appropriate after an episode of pyelonephritis. This study, along with the majority of those published beforehand, does not definitively answer 2 major questions: "is reflux significant enough in the etiology of urinary tract infection and renal scarring to warrant detection and treatment?" and "can we better define the minority of children in whom reflux is significant to avoid over treating the rest?"

The RIVUR study (*R*andomized *I*ntervention for children with *V*esico*U*reteral *R*eflux) is a multicenter, double-blind, randomized, placebo controlled trial designed to evaluate the effectiveness of antimicrobial prophylaxis in children found to have reflux after an initial urinary tract infection. The RIVUR study represents a collaboration of 15 clinical trial centers throughout North America, a central Data Coordinating Center (DCC) at the University of North Carolina at Chapel Hill, and the National Institute of Diabetes and Digestive and Kidney Diseases. The RIVUR trial was designed to be generalizable to most children with reflux, and to yield scientifically and statistically valid results. The primary outcome is the development of recurrent febrile or symptomatic UTI. Secondary outcomes include the development of renal scarring and antimicrobial resistance. A total of 600 children, boys and girls, 2 to 72 months old, with grades I to IV reflux discovered after a first UTI, will be enrolled. Children

0022-5347/08/1792-0405/0
THE JOURNAL OF UROLOGY®

Vol. 179, 405-407, February 2008
Printed in U.S.A.
DOI:10.1016/j.juro.2007.10.100

with a history of multiple prior infections will not be included to reduce the likelihood of preexisting UTI associated renal scarring. Renal ultrasound is being used to exclude other congenital urological conditions from analysis. VCUG and DMSA renal scan must be performed within 10 weeks of the presenting UTI. All clinical trial centers are following standardized procedures for DMSA scanning, as well as for radiographic and clinical data collection. All radiographic studies are being read by 2 reference radiologists who confer to agree on a single interpretation. Radiographic and clinical data are entered online and transmitted to the DCC.

Children are being randomized to prophylaxis with TMP/SMZ or placebo. A placebo has been developed that is indistinguishable from the antibiotic and packaged in identical bottles. The medication and placebo bottles are coded uniquely, and the linkage between the code and bottle contents is known only to members of the DCC. Each subject will be observed for 2 years. There will be in person study visits every 6 months and telephone interviews every 2 months. DMSA renal scan will be performed at 12 and 24 months. Additional scans will be performed after febrile UTIs in children whose baseline DMSA renal scan shows severe scarring. Treatment failure is defined as 2 febrile UTIs, or a total of 4 nonfebrile and febrile UTIs within the study period, or new renal scarring seen on followup DMSA scan. All cases categorized as treatment failures will be discontinued from study medication or placebo and referred to local pediatric urologists for further treatment, but will continue to be followed for the full 2-year enrollment period. The protocol has been approved by an independent Data Safety Monitoring Board, who will periodically review the safety and efficacy data during the study.

Rectal swab cultures are being obtained to assess for alterations in microbial flora, in particular, stool Escherichia coli resistance to TMP/SMZ. Complete blood counts will be obtained to monitor for TMP/SMZ related leukopenia. Renal function is assessed using serum creatinine and cystatin C, as well as urinary microalbumin levels. Urine and blood samples are sent to a central repository for future chemical and genetic studies. In children 3 years old or older voiding function and constipation will be assessed by questionnaire (Dysfunctional Voiding Scoring System, Paris Consensus on Childhood Constipation Terminology).[11,12] Quality of life and resource use data will also be collected during in-person and telephone interactions. Data concerning study visits, visits to the primary care physician or emergency department, days of missed work or school, alternate day care arrangements due to UTI, and hospitalizations will be collected. Compliance will be measured by weighing the medicine bottles at each study visit. Parents are also being asked about the frequency of medication administration during the every 2-month telephone calls.

It is hoped that the RIVUR study will provide answers to practical clinical questions. In addition, future chemical and genetic studies on repository material may better define the mechanism of recurrent infection and renal injury in children, and identify those who may be at highest risk. It is time that we recognize the need to base our decisions on data that is obtained from studies relatively free of bias. However, until these data are available, under diagnosis and under treatment should be approached with caution.

Saul P. Greenfield
Department of Pediatric Urology, Women & Children's Hospital of Buffalo
Buffalo, New York

Russell W. Chesney
Le Bonheur Children's Medical Center
Memphis, Tennessee

Myra Carpenter
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Marva Moxey-Mims, Leroy Nyberg and members of the RIVUR Steering Committee
National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, Maryland

Alejandro Hoberman
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Ron Keren
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Ranjiv Matthews
Johns Hopkins School of Medicine
Baltimore, Maryland

Tej Mattoo
Wayne State University School of Medicine
Detroit, Michigan

REFERENCES

1. Lenaghan D, Whitaker JG, Jensen F and Stephens FD: The natural history of reflux and long-term effects of reflux on the kidney. J Urol 1976; **115:** 728.
2. O'Donnell B, Moloney MA and Lynch V: Vesico-ureteric reflux in infants and children: results of "supervision", chemotherapy and surgery. Br J Urol 1969; **41:** 6.
3. Birmingham Reflux Study Group: Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Br Med J 1987; **295:** 237.
4. International Reflux Study Committee: Medical versus surgical treatment of primary vesicoureteral reflux: a prospective international reflux study in children. J Urol 1981; **125:** 277.
5. Cooper CS, Chung BI, Kirsch AJ, Canning DA and Snyder HM 3rd: The outcome of stopping prophylactic antibiotics in older children with vesicoureteral reflux. J Urol 2000; **163:** 269.
6. Thompson RH, Chen JJ, Pugach J, Naseeer S and Steinhardt GF: Cessation of prophylactic antibiotics for managing persistent vesicoureteral reflux. J Urol 2001; **166:** 1465.

7. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A and Young L: Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006; **117:** 626.
8. Craig JC, Irwig LM, Knight JF and Roy JP: Does treatment of vesicoureteric reflux in childhood prevent end-stage renal disease attributable to reflux nephropathy? Pediatrics 2000; **105:** 1236.
9. Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G and Craig JC: Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials. Arch Dis Child 2003; **88:** 688.
10. Reddy PP, Evans MT, Hughes PA, Dangman B, Cooper J, Lepow ML et al: Antimicrobial prophylaxis in children with vesico-ureteral reflux: a randomized prospective study of continuous therapy vs intermittent therapy vs surveillance. Pediatrics, suppl., 1997; **100:** 555.
11. Farhat W, McLorie GA, O'Reilly S, Khoury A and Bagli DJ: Reliability of the pediatric dysfunctional voiding symptom score in monitoring response to behavioral modification. Can J Urol 2001; **8:** 1401.
12. Benninga M, Candy DC, Catto-Smith AG, Clayden G, Loening-Baucke V, Di Lorenzo C et al: The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. J Pediatr Gastroenterol Nutr 2005; **40:** 273.