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 reflex with a voiding cystourethrogram (VCUG). The etiological association between reflex and infection was assumed since up to 40% of children with infection are found to have reflex. Evidence from the 1960s appeared to demonstrate that the diagnosis and treatment of reflex 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 alleg that the radiographic detection of reflex is not necessary in all children after an infection. Furthermore, when reflex is detected the recommendations for treatment are controversial and contradictory. Depending on the consultant a child with reflex may be placed on long-term antibi 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. 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. Cooper and Thompson et al prospectively observed children with reflex 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. Rates of renal disease secondary to reflex remained unchanged for 3 decades in children found to have reflux after an initial urinary tract infection. 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...
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). Quality of life and resource use data will 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


