Management of Primary Vesicoureteral Reflux in Children

Editorial Commentary

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KEYWORDS

• Vesicoureteral reflux • Febrile urinary tract infection • Recurrent UTI • Renal injury

KEY POINTS

- Decisions must be made about the clinical management of children with vesicoureteral reflux (VUR) and a standardized risk-specific treatment approach is needed that can provide clinicians with an opportunity to standardize care and measure and continuously improve outcomes for these children.
- Clinicians and researchers must begin to think outside of the proverbial VUR box. Clinicians are beginning to understand that there are a variety of abnormalities in host defenses that might predispose some children to recurrent urinary tract infection.
- Knowledge of these deficiencies in specific host defenses may lead to therapies designed to compensate for them.
- There is also much to be learned about host inflammatory response to kidney infection, to explain why some children suffer extensive kidney injury with pyelonephritis, whereas others with the same amount of acute inflammation avoid scarring altogether.

The current paradigm for the management of children diagnosed with vesicoureteral reflux (VUR) after a febrile urinary tract infection (UTI) rests on the assumption that long-term renal insufficiency can be avoided by preventing recurrent UTIs with continuous antimicrobial prophylaxis (CAP) or surgically correcting VUR.[1] The International Reflux Study found that surgical correction of VUR offered no additional benefit compared with CAP alone,[2] although it did not test whether CAP was better than

This editorial commentary was written in response to the article written by Drs Fernando F. Fonseca, Fabio Y. Tanno, and Hiep T. Nguyen, entitled, "Current Options in the Management of Primary Vesicoureteral Reflux in Children" in *Pediatric Clinics of North America* (59:4), August 2012.

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Pediatr Clin N Am 59 (2012) 835–838
doi:10.1016/j.pcl.2012.05.004 **pediatric.theclinics.com**
0031-3955/12/$ – see front matter

no intervention at all. The best evidence regarding the effectiveness of CAP is from the meta-analysis of randomized controlled trials conducted for the 2011 American Academy of Pediatrics[5] (AAP) "Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months," which did not detect a statistically significant benefit of prophylaxis in preventing recurrence of febrile UTI/pyelonephritis in infants without reflux or those with grades I, II, III, or IV VUR. Among the studies included in that meta-analysis, the trial by Craig and colleagues[3] had the strongest design (placebo controlled, adequate power, and stringent UTI definition), and it showed only a modest protective effect of CAP for children with VUR (6% 1-year absolute risk reduction in recurrent UTIs, from 17% down to 11%) that lasted for only the first 6 months of therapy. In 2013, the results of the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial will be published.[4] If this multicenter placebo-controlled trial of prophylactic trimethoprim/sulfamethoxazole for children aged 2 months to 6 years with grades I to IV VUR shows the same marginal benefit of CAP, pediatricians, urologists, and nephrologists will need to reconsider the assumptions that informed the dominant paradigm for managing VUR in the last few decades.

More specifically, they will have to acknowledge that children who develop a UTI can be divided into 2 groups. The first, which comprises most children and the subjects of recent clinical trials, are those with low-grade VUR (grades I–III) and no or minimal kidney scarring at the time of UTI diagnosis. The evidence suggests that only 5% to 30% of these children go on to develop a second UTI,[5] a vanishingly small percentage of them develop renal scarring of any clinical significance,[6,7] and CAP has little, if any, effect on their clinical outcomes. For this reason, the recently revised AAP guideline recommended that (1) the initial work-up of children with first febrile UTI should consist of a renal ultrasound only, which should detect most high-grade VUR and significant renal scarring or anatomic abnormalities of the genitourinary tract; and (2) CAP can be deferred in children with normal renal ultrasound. With this change in recommendations around imaging of young children with first febrile UTI, the large proportion of children who are likely to have a benign clinical course will be spared an invasive voiding cystourethrogram (VCUG), years of CAP, and possibly surgery to correct VUR.

The second group of children, which represents the minority with first UTI, consists of those with high-grade VUR (grades IV–V), more extensive kidney scarring at baseline, and a predisposition to multiple breakthrough UTIs. These children are at the highest risk of suffering clinically significant renal injury, but, because there are so few of them, they are not well represented in recent clinical trials and thus there is considerable uncertainty about what, if any, therapy can effectively protect them from long-term renal insufficiency. They are also the ones most likely to find their way to the offices of pediatric urologists, and so they feature prominently in the pediatric urologic literature, including the review article by Fonseca and colleagues elsewhere in this issue. Given the problem of small numbers, and the reluctance of most physicians and parents to agree to randomization of these high-risk children, it will be difficult to conduct clinical trials to define best practices for them. Some of these children have genetically determined developmental abnormalities of the kidneys and urinary tract, which manifest after birth as VUR and renal dysplasia/hypoplasia.[8] In these children, the UTIs are an epiphenomenon rather than the cause of the renal abnormalities,[9] and there may be little that can be done to prevent the development of renal insufficiency. For others, surgical correction of VUR may remove an important risk factor for recurrent UTI and prevent subsequent kidney injury.

The greatest contribution of the review by Fonseca and colleagues is that it articulates the idea that the risk of recurrent UTI and subsequent renal insufficiency varies