The Role of Antimicrobial Prophylaxis in the Management of Children With Vesicoureteral Reflux—The RIVUR Study Outcomes

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The role of antimicrobial prophylaxis for the prevention of recurrent urinary tract infections in children with vesicoureteral reflux that was identified following a urinary tract infection has been the source of considerable debate. Prior studies had failed to show a benefit in the prevention of recurrent infection. The National Institutes of Health funded the Randomized Intervention for Vesicoureteral Reflux (RIVUR) study to determine if there was a benefit to the use of prophylaxis.

Results of the RIVUR study indicated that there was a 50% reduction in the risk of recurrent urinary tract infection in those children on the prophylaxis arm. Adverse events with the use of prophylaxis were noted to be few. Renal scarring was noted in only a small number of children at study entry and no reduction in scarring was noted between the placebo and the treated groups. The impact of the RIVUR study on the current evaluation and management of children with urinary tract infections and vesicoureteral reflux is detailed.

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INTRODUCTION

The role of antimicrobial prophylaxis in the management of children with vesicoureteral reflux (VUR) has been controversial. Recent studies have questioned the benefit of prophylaxis in the prevention of urinary tract infections (UTI) and renal scarring. Concerns have also been raised regarding the potential risks of long-term prophylaxis including bacterial resistance, anaphylaxis, and lack of compliance. Additionally, many specialty societies have put forth guidelines for the evaluation and management of children with UTI and VUR based on the results of these published studies. In an effort to definitively address the debate regarding the benefits of prophylaxis in children diagnosed with VUR, the National Institutes of Health initiated a large multi-institutional study—Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR). The results of the study have been recently published. It included 607 children who were randomized to placebo or prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMZ) to determine the benefit of prophylaxis in the prevention of UTI and renal scarring in young children with VUR.

BACKGROUND

UTI occurs in 1.6% of boys and 7.8% of girls. There is some variability based on age, with higher incidence in infant male children and in older children presenting with bladder and bowel dysfunction (BBD). Febrile UTI in children, with or without VUR, has been noted to lead to renal scarring with the long-term potential for secondary effects of hypertension or compromised kidney function.

Recognition of an increased risk of UTI and scarring of the kidney with pyelonephritis in children with VUR[1] had initially led to the recommendation for long-term utilization of prophylaxis. The knowledge that VUR in children has the potential to resolve spontaneously discouraged early surgical intervention in such patients[2] in deference to management strategies that use long-term prophylactic regimens to reduce the risk of infection, until VUR resolved spontaneously.

There has also been increasing recognition that not all children with VUR have permanent kidney injury despite repeated UTIs. On the other hand, multivariate risk analysis indicates that scarring of the kidney is commonly noted in infant boys with high-grade VUR, suggesting possible congenital dysplasia rather than pyelonephritis-induced scarring of the kidney.[3] Distinguishing the subset of children who are at risk for ongoing scarring of the kidney with VUR has, however, been difficult, leading to the earlier recommendation that all children be placed on prophylaxis to prevent the potentially devastating impact of kidney injury.

RECENT STUDIES

A list of recent studies on the role of antimicrobial prophylaxis in children with VUR is listed in Table 1. Garin and colleagues[4] published a randomized controlled trial comparing prophylaxis with no treatment in children with UTI and were not able to demonstrate any benefit in the prevention of recurrent infection in those children on the prophylaxis. Montini and others,[5] in a 12-month multi-institutional study on the benefit of prophylaxis, also did not demonstrate any difference in the incidence of recurrence of UTI in children with or without reflux. There was an increase in the risk of recurrent UTI in children with grade III VUR. Additionally, there was no

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difference in scarring of the kidney based on the use of prophylaxis. Pennesi and coworkers[6] studied 100 children <30 months of age identified with VUR after an initial episode of pyelonephritis. Patients were randomized to either prophylaxis or just routine follow-up for 4 years and evaluated for recurrence of UTI or development of scarring of the kidney. No difference was noted between the 2 groups for either infection or scarring of the kidney. Roussey-Kesler and coworkers[7] also reported on the results of a prospective study of children with VUR (grades I to III), ages 1 to 30 months randomized to prophylaxis or observation for 18 months. There was no overall difference between the 2 groups in the development of recurrent UTI; however, there was a reduction in UTI in boys, particularly in those with grade III reflux, which was the highest grade of VUR included in the study.

The Swedish Reflux Study[8,9] that randomized children with grades III and IV VUR to 3 arms—prophylaxis, endoscopic injection with dextranomer hyaluronidase (Deflux, Q-Med AB, Uppsala, Sweden), or surveillance published its results in 2010. Two hundred three children (125 girls and 78 boys), aged 1 to 2 years, were randomized. There was a marked reduction in the incidence of recurrent UTI in girls (19% on prophylaxis vs 57% on surveillance); however, they were not able to show a similar reduction in boys. They were also able to demonstrate a reduction in scarring of the kidney noted on follow-up. Craig and colleagues[10] evaluated a large cohort of children presenting after the first UTI (42% with VUR) randomized to prophylaxis or placebo and found a reduction in the incidence of recurrent UTI with the utilization of prophylaxis (13% prophylaxis vs 19% placebo). In the children with VUR, this reduction was noted across all groups, irrespective of grade of VUR.

CLINICAL SUMMARY

- Renal ultrasound is a poor indicator for diagnosing the presence of vesicoureteral reflux.
- Antibiotic prophylaxis reduces the risk of UTI recurrence in young children with VUR.
- Role of antibiotic prophylaxis in the prevention of renal scarring in children with VUR remains disputed/doubtful.

The recently published RIVUR study included 607 children (558 girls) with grades I to IV VUR identified after an initial or second febrile or symptomatic UTI.[11] Children were 2 to 72 months of age and were recruited within 112 days of their UTI. They were randomized to prophylaxis with TMP/SMZ or placebo.[12] Strict guidelines were used to ensure that all patients recruited met the inclusion criteria. Children were recruited from 19 clinical sites, and data was managed through an independent data co-ordinating center. On entry into the study, patients had evaluation with dimercaptosuccinate (DMSA) kidney scan to evaluate for scarring of the kidney. Patients were followed for 2 years with periodic clinic and telephone follow-up.

Voiding cystourethrogram and DMSA kidney scans were done at study entry and exit, and an additional DMSA kidney scan was done at 1 year. Primary study end point was development of recurrent UTI. Important secondary end points included development of scarring of the kidney, antimicrobial resistance, and treatment failure.[11] All radiographic studies were reviewed by 2 blinded reference radiologists, and differences in opinion were adjudicated to obtain a consensus reading. Before activation of a site, completion of a radiology pilot was required to guarantee veracity of the radiology data that were transmitted to the reference radiologists.

Across 19 clinical sites, from June 2007 to May 2011, 10,756 children were screened, of whom 12% (1311 children) met eligibility criteria. A total of 607 children were enrolled, 554 (91%) after their first UTI and the rest after a second UTI. The median age of enrolled children was 12 months and 558 (92%) were girls; 509 children completed the first-year visit and 520 completed the second-year visit. Of enrolled children, 290 children had bilateral VUR (48%) and 80% had grades II or III VUR. At baseline, 92 children had evidence of kidney involvement on DMSA renal scanning (21, decreased uptake and loss of contour; 71, decreased uptake without loss of contour). All radiographic studies were reviewed by independent, blinded, study radiologists.

Recurrence of febrile/symptomatic (F/S) UTI occurred in 39 of 302 children on prophylaxis compared with 72 of 305 children on placebo, a 50% reduction in the incidence of recurrent UTI. Additionally, 10% of children had F/S UTI within 336 days of enrollment in the prophylaxis group compared with 106 days in the placebo group. The benefit of prophylaxis noted earlier did not change when controlled for age, VUR grade, previous UTI, or scarring of the kidney at baseline. As noted earlier, 91 children had evidence of kidney injury at baseline. There was no significant difference in the incidence of new kidney scars, any single scars, or severity of scars between the 2 groups. There was no increase noted in stool colonization with resistant *Escherichia coli* in the children on prophylaxis. Among those children who had recurrence of UTI, 63% were resistant to TMP/SMZ in the prophylaxis group compared with 19% in the placebo group.

There was a higher incidence of recurrent F/S UTI in children with grades III to IV VUR compared with those with grades I to II VUR. Prophylaxis was more protective in children who presented with a febrile index UTI compared with those who presented with just a symptomatic UTI.

At baseline, 126 children were toilet trained and 71 (56%) of them had BBD. At study end, 318 children were toilet trained and 154 (48%) demonstrated evidence of BBD. Recurrent UTI was more significantly reduced using prophylaxis in children with BBD compared with those who did not have BBD.

IMPACT OF THE RIVUR STUDY RESULTS

RIVUR Cohort and Comparison With Previous Studies

The RIVUR study was limited to the management of children who were diagnosed with VUR, and evaluated

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