EDITORIAL

Antibiotic Prophylaxis for Vesicoureteral Reflux — Answers, Yet Questions

Julie R. Ingelfinger, M.D., and F. Bruder Stapleton, M.D.

Vesicoureteral reflux, the retrograde flow of bladder urine into the ureter, is common in young children with urinary tract infections and is associated with renal scarring. Reflux is generally discovered when a voiding cystourethrogram is obtained after a urinary tract infection and is categorized as grade I (retrograde flow of urine into the ureter alone) to grade V (massive reflux into a distorted ureter and calyceal system). After an observational study by Edwards et al.[1] showed that vesicoureteral reflux improved or resolved with long-term, low-dose antibiotic treatment to prevent infection, such treatment gained popularity. Nearly four decades later, we still are puzzling over whether antibiotic prophylaxis has value in reducing renal injury and altering the natural history of vesicoureteral reflux and urinary tract infection.

Some progress occurred when the well-controlled International Reflux Study in Children[2] noted that vesicoureteral reflux often improved as children matured and that antibiotic prophylaxis alone was as effective as antibiotic prophylaxis plus surgical correction, although surgical treatment was often performed for severe reflux. After that study, antibiotic prophylaxis became standard clinical practice. Although less invasive endoscopic correction of reflux is now common, all but the most severe grades of reflux are currently more often managed with antibiotic prophylaxis. In recent years, concomitant with concerns about antibiotic resistance, many children who have had a urinary tract infection and have reflux are treated with watchful waiting and reculture of urine samples if another infection is suspected. Early studies comparing surgical intervention with antibiotic therapy did not include placebo groups. Thus, the safety of observation alone has been unclear.

Previous studies[3-6] addressing whether watchful waiting is safe have often been underpowered. A well-powered, placebo-controlled, randomized study by Craig et al.[6] that involved children from birth to 18 years of age showed a modest decrease in new infections in the prophylaxis group. However, it was unknown whether vesicoureteral reflux was present in 17% of participants. More recently, Brandström et al.[7,8] reported an open-label, randomized study in which Swedish children 1 to younger than 2 years of age (63% girls) with grade III or IV vesicoureteral reflux were assigned to antibiotic prophylaxis (with trimethoprim, nitrofurantoin, or cefadroxil), endoscopic treatment, or surveillance only. There were no significant between-group differences in outcomes among boys, but girls assigned to surveillance had more recurrent infections. Girls assigned to prophylaxis had fewer scars at the 2-year follow-up.[8] Thus, the value of antibiotic prophylaxis as the standard of care has remained controversial.

The RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) trial investigators now report in the *Journal* the results of a multisite study in which 607 children (2 to 71 months of age), with vesicoureteral reflux (grade I to IV) after a first or second urinary tract infection, received either trimethoprim–sulfamethoxazole or placebo and were followed for 2 years.[9,10] Fewer recurrent urinary tract infections occurred in the prophylaxis group (39 of 302 children) than in the placebo group (72 of

305 children), with a relative risk of 0.55 (95% confidence interval, 0.38 to 0.78). However, more children in the prophylaxis group had resistant isolates (63%, vs. 19% in the placebo group). Antibiotic prophylaxis was particularly effective in children whose index infection was febrile and in those with bladder and bowel dysfunction. Although the number of renal scars was limited, no significant between-group difference in renal scarring was observed at 2 years.

The present study has some important features: the participants were young children (younger than 6 years of age), rather than children from infancy through late adolescence; the criteria for diagnosis of urinary tract infection were stringent; and renal scarring was centrally scored by two radiologists on the basis of radionuclide scanning performed at baseline and after 1 and 2 years. Adherence to study medication reflected real life — 77% of parents reported having administered the study medication at least 75% of the time, and 85% reported having administered it at least 50% of the time. There were no significant between-group differences in adverse clinical events. In a subgroup analysis, recurrent infection was more common among those children with grade III or IV reflux at baseline than among those with grade I or II reflux (22.9% vs. 14.3%).

Of course, as in most studies of complex conditions, unresolved questions remain. Only one form of antibiotic prophylaxis was used; therefore, the effectiveness of other prophylactic antibiotic strategies remains untested. The evaluation of scarring was determined after only 2 years, leaving the long-term degree of renal injury unknown.

Sadly, the decision to use antibiotic prophylaxis in children with reflux remains a clinical dilemma, despite this well-done study. In the face of the emergence of antibiotic resistance, the lack of a significant between-group difference in renal parenchymal scarring, and questions about generalizability, the RIVUR study results would imply that the general recommendation of prophylactic antibiotics for vesicoureteral reflux in young children awaits more evidence before universal adoption.

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From the Department of Pediatrics, University of Washington School of Medicine, Seattle (F.B.S.).

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