

Antimicrobial Prophylaxis for Urinary Tract Infection in Children

Alejandro Hoberman, M.D., and Ron Keren, M.D., M.P.H.

Approximately one third of children who have a urinary tract infection — the most frequent serious bacterial infection in young febrile children — have vesicoureteral reflux, a congenital condition in which the urine flow is retrograde from the bladder toward the kidneys during micturition. Data from observational studies and animal models support the hypothesis that children with vesicoureteral reflux who have urinary tract infection are at increased risk for renal scarring.

Vesicoureteral reflux is graded from I (lowest grade, with reflux into the ureter only) to V (highest grade, with marked ureteral tortuosity, calyceal blunting, and severely dilated renal pelvis). In children with reflux of grades III through V, the risk of renal damage is 4 to 6 times greater than the risk in those with grade I or II reflux and 8 to 10 times greater than the risk in those without reflux.¹ For these reasons, routine evaluation of young children with urinary tract infection includes performance of renal imaging and voiding cystourethrography to determine the presence and degree of reflux.² Although the severity of reflux directly correlates with the incidence of renal scarring, recent studies have shown that reflux is neither necessary nor sufficient for renal scarring. Such damage occurs in some children who do not have reflux and does not occur in many children with high-grade reflux.³

Given the observed association between urinary tract infection in children with reflux and renal scarring, treatment strategies have included surgical or endoscopic correction of reflux and the prophylactic use of antimicrobial agents. The International Reflux Study and other randomized, controlled trials that have compared the combination of surgery plus antimicrobial prophylaxis with prophylaxis alone have shown no differences in rates of recurrent urinary tract infection and renal scarring, findings that led to the adoption of antimicrobial prophylaxis as standard first-line therapy.^{4,5} However, the absence of a placebo or “observation only” group in such studies raised the question of whether either surgery or antimicrobial prophylaxis is actually effective. Four recent clinical trials evaluating the efficacy of continuous antimicrobial prophylaxis showed no reduction in the incidence of recurrent urinary

tract infection,⁶⁻⁹ which led some clinicians to become skeptical about the role of prophylaxis or the need to evaluate children with recurrent urinary tract infection for vesicoureteral reflux.

In this issue of the *Journal*, Craig et al.¹⁰ describe a multicenter, randomized, placebo-controlled trial showing the association between antimicrobial prophylaxis and a modest but significant reduction in the number of recurrent urinary tract infections. Why did this study find a positive effect, whereas previous ones did not?

Several limitations may have affected the results of the previous trials, including insufficient statistical power to detect clinically important differences, a lack of blinding, a misclassification of outcome owing to nonstringent definitions of urinary tract infection, and the use of inclusion criteria that were not representative of all affected children. Table 1 compares the five recent trials on the subject.

In evaluating the sample sizes of these trials, it is useful to note that to detect a reduction in the absolute risk of recurrent urinary tract infection of 10 percentage points (assuming a baseline recurrence rate of 20% in the placebo group), a study would need to enroll approximately 600 children. Thus, the lack of an observed reduction in the risk of recurrent urinary tract infection in some of the studies may have resulted from insufficient statistical power rather than from a lack of efficacy of antimicrobial prophylaxis. In addition, the lack of blinding in some studies may have caused ascertainment bias, which could underestimate the number of urinary tract infections in the prophylaxis group. For instance, parents, clinicians, and investigators caring for children who were known to be receiving antimicrobial prophylaxis might have been falsely reassured at the time of febrile illnesses, which might have resulted in a decreased likelihood that parents would seek care and that clinicians would evaluate children for urinary tract infection. A nonstringent definition of urinary tract infection might have biased results toward the null. In some studies, urinary tract infection was diagnosed from specimens collected from bagged samples, a method known to have a high rate of contamination. Also, in some of the studies, investigators performed routine

Table 1. Recent Studies Evaluating the Efficacy of Antimicrobial Prophylaxis in the Prevention of Recurrent Urinary Tract Infection, According to Grade of Vesicoureteral Reflux.*

Study Reference and Subjects' Grade of Vesicoureteral Reflux	Number of Subjects	Blinded Study	Age of Subjects	Method of Diagnosis	Duration of Follow-up	Receipt of Antimicrobial Agent		Relative Risk	Difference in Absolute Risk
						Yes	No		
						no. of infections/total no. (%)			% (95% CI)
Garin et al. ⁶	218	No	1 mo–18 yr	Bladder catheterization or clean voided collection	12 mo				
None						4/45 (9)	14/60 (23)	0.4 (0.1 to 1.1)	-14 (-28 to -1)
Grades I through III						13/55 (24)	13/58 (22)	1.1 (0.5 to 2.1)	1 (-14 to 17)
Roussey-Kesler et al. ⁷	225	No	1–36 mo	Bag collection	18 mo	18/103 (17)	32/122 (26)	0.7 (0.4 to 1.1)	-9 (-19 to 2)
Grades I through III									
Pennesi et al. ⁸	100	No	0–30 mo	Bag collection	24 mo	18/50 (36)	15/50 (30)	1.2 (0.7 to 2.1)	6 (-12 to 24)
Grades II through IV									
Montini et al. ⁹	338	No	2–84 mo	Bag collection	12 mo	5/129 (4)	3/81 (4)	1.1 (0.3 to 4.6)	0 (-5 to 6)
None						10/82 (12)	9/46 (20)	0.6 (0.3 to 1.4)	-7 (-21 to 6)
Grades I through III									
Craig et al. ¹⁰	576	Yes	0–18 yr	Suprapubic aspiration, bladder catheterization, or clean voided collection	12 mo	15/119 (13)	17/115 (15)	0.9 (0.4 to 1.6)	-2 (-11 to 7)
None						14/122 (11)	21/121 (17)	0.7 (0.4 to 1.2)	-6 (-14 to 3)
Grades I through V						7/47 (15)	17/52 (33)	0.5 (0.2 to 1.0)	-18 (-34 to -1)
Unknown									

* A relative risk of less than 1.0 and a negative difference in absolute risk indicate a decreased risk of urinary tract infection among subjects who received an antimicrobial agent. Values for the difference in absolute risk may not equal the numerical between-group difference because of rounding. Risk values and 95% confidence intervals were calculated with the use of Fisher's exact test (Intercooled Stata software, version 8.0).

urinalysis and surveillance urine cultures every 1 to 3 months, which raises the possibility that some infections were actually episodes of asymptomatic bacteriuria or contamination. Such misclassification of infections may have diluted any actual benefit of antimicrobial prophylaxis, raising the question of whether the apparent lack of effect was a result of ineffective treatment or improper collection methods. Finally, the inclusion criteria of several studies also limit their generalizability. Prophylaxis may be more efficacious for children with reflux of grades III through V than for those with grades I or II, but this hypothesis could not be assessed in studies that limited enrollment only to children with grades I through III of reflux. Furthermore, all five studies enrolled children outside the United States and thus included many uncircumcised boys, which limited the generalizability for circumcised boys.

The study by Craig et al. suggests that antimicrobial prophylaxis for urinary tract infection is modestly effective. With an enrollment of 576 children, the study was adequately powered to detect small but significant differences in outcomes. In addition, the trial included a placebo group and used a stringent definition of urinary tract infection. The trial showed an overall reduction of about 6 percentage points in the absolute risk of symptomatic and febrile urinary tract infections. However, the time-to-event analysis showed that the effect was not sustained, and the number of children (14) who would need to have been treated to prevent one infection was relatively large.

Should the results of this study influence clinical decisions concerning the evaluation and treatment of children with urinary tract infection? Given the modest overall effect size, a one-size-fits-all approach may not be appropriate. The need to detect vesicoureteral reflux is probably the most important issue facing parents and clinicians. The treatment effect of prophylaxis did not differ significantly between children with reflux and those without reflux, although not all participating children underwent voiding cystourethrography. Furthermore, the trial was not powered to detect clinically meaningful effects in subgroups of children, and the reduction in the absolute risk of symptomatic urinary tract infection was greatest for children with grade III through V reflux (6.8 percentage points), as compared with that for children with grade I or II reflux (5.4 percentage

points) or those with no reflux (1.8 percentage points), although this trend was not significant.¹⁰ Early diagnosis and treatment of urinary tract infection and treatment of dysfunctional voiding, which predisposes many children to urinary tract infection, is likely to go a long way toward preventing long-term renal damage. Ongoing randomized, controlled trials in Sweden and the United States¹¹ in children with a wide range of grades of vesicoureteral reflux may tell us whether the diagnosis and treatment of such reflux provide any incremental benefit.

No potential conflict of interest relevant to this article was reported.

From the Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh (A.H.); and the Department of Pediatrics and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia (R.K.).

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