Evidence for and against urinary prophylaxis in vesicoureteral reflux

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Abstract The role of antimicrobial prophylaxis in vesicoureteral reflux (VUR) has come under increasing scrutiny because of better analytical methods in the published literature, knowledge gained from VUR and renal scars diagnosed without preceding urinary tract infection (UTI), and better renal imaging modalities for diagnosing renal scars. A meta-analysis of the five recent randomized studies with a total of 809 patients with VUR diagnosed after UTI reveals a relative risk of UTI recurrence of 0.82 [95% confidence interval (CI) 0.62–1.08; $p=0.16$] with prophylaxis. A meta-analysis of the four studies with a total of 662 patients with UTI with and without VUR evaluated for renal scarring reveals a relative risk of 1.04 (95% CI: 0.84–1.30; $p=0.69$) with prophylaxis. However, these observations need to be interpreted with caution because of the limitations with these studies and their heterogeneity for meta-analysis, particularly for renal scarring. More research is needed to validate the role of prophylaxis in VUR diagnosed after UTI, and even more research is warranted to answer the questions regarding antimicrobial prophylaxis across the spectrum of VUR in different clinical settings.

Keywords Vesicoureteral reflux · Prophylaxis · Reflux nephropathy · Renal scarring

Introduction

About 45 years ago, antimicrobial prophylaxis was introduced as a measure for preventing recurrent urinary tract infection (UTI) in children. The concept of prophylaxis in vesicoureteral reflux (VUR) was reinforced by subsequent observations that associated VUR with recurrent UTI and renal scarring and in some patients, end-stage renal failure (ESRF). Opinion-based recommendations and conclusions derived from poorly designed, nonrandomized studies supported the use of antimicrobial prophylaxis in VUR. This approach was endorsed by many professional societies, such as the American Academy of Pediatrics, the Swedish Medical Research Council, and the American Urological Association. However, recently, the role of antimicrobial prophylaxis in VUR has become a highly contentious issue. The fact that in 2009 this journal had three editorial commentaries [1–3] on the subject is a testimony to the level of interest VUR has generated among clinicians and researchers. The use of prophylaxis in VUR, which seemed very rational for so many decades, has come under increasing scrutiny, partly because of better analytical methods in the published literature, knowledge gained from VUR and renal scars diagnosed without preceding UTI, and better renal imaging modalities for diagnosing renal scars. A lack of convincing evidence for the role of antimicrobial prophylaxis, risk of resistance and other potential side effects of the antimicrobial agent, the hassle of daily medication administration, and the prophylaxis-driven need for repeated renal imaging have prompted new research efforts regarding the role of long-term antimicrobial prophylaxis in VUR.

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Recent randomized studies on antimicrobial prophylaxis in UTI and VUR

In the last 5 years, five randomized studies (Table 1) compared antimicrobial prophylaxis with surveillance only [4–7] or placebo [8] in children with primary VUR. Garin et al. [4] evaluated 218 children with acute pyelonephritis; the study included 113 children with grades I–III VUR. Patients were randomly assigned to prophylactic antibiotic [sulfamethoxazole (SMZ)/trimethoprim (TMP)] or nitrofurantoin or no prophylaxis. Dimercaptosuccinic acid (DMSA) renal scans were done to document renal scarring. At the end of 1 year, no difference was noted in the incidence of UTI, pyelonephritis, or renal scarring between the prophylaxis and no-prophylaxis groups. Roussey-Kesler et al. [5] randomized 225 children with grades I–III VUR to daily SMZ/TMP or no prophylaxis. After a follow-up period of 18 months, there was no significant difference in the occurrence of UTI (17% in treatment group and 26% in untreated control group; $p=0.15$) between the two groups. However, significantly fewer UTIs occurred in boys ($p=0.013$) compared with girls ($p=0.8$) on prophylaxis, and the difference was restricted to boys with grade III VUR ($p=0.04$) and not grade I or II VUR. Pennesi et al. [6] recruited 100 children with grades II–IV VUR diagnosed after a first episode of acute pyelonephritis. Children were randomly assigned to receive SMZ/TMP or no prophylaxis. At the end of 2 years, prophylaxis was discontinued, and patients were followed for another 2-year period, for a total follow-up period of 4 years. DMSA renal scans were done to diagnose renal scars. There was no difference in recurrence of acute pyelonephritis at the 2-year follow-up (36% vs 30% for prophylaxis and no prophylaxis, respectively; $p=0.50$). In the subsequent 2 years during which neither group was on prophylaxis, only three patients had recurrence of UTI, which included one from the intervention group. DMSA renal scans were abnormal in 0%, 30%, and 67% of children with grades II, III, and IV VUR, respectively. No significant difference in renal scarring was noted at 2 years (40% in prophylaxis vs 36% in no-prophylaxis groups; $p=0.4$), and no patients were noted to have new renal scars during the 4-year period. Montini et al. [7] randomized 338 children, including 128 with grades I–III VUR, to antibiotic prophylaxis (SMZ/TMP or co-amoxiclav) or no prophylaxis. At the end of 1-year follow-up, the recurrence rate of UTI and the risk of renal scarring in all patients in the study, including those with VUR, was no different between groups. In the most recent randomized, and the only placebo-controlled study, Craig et al. [8] studied 576 children with a history of at least one UTI. The study included 243 children with VUR. Patients were randomized to SMZ/TMP or placebo, and during a follow-up period of 1 year, 13% patients in prophylaxis group and

Table 1 Randomized studies on antimicrobial prophylaxis for urinary tract infection (UTI)

Authors & year of study	Randomized/ placebo-controlled	Patient age	Total number of patients studied	Patients included	Number of patients with VUR	VUR grade	Urine collection method in non-toilet trained children	Definition of UTI	Duration of follow-up (months)
Garin et al. 2005	Yes/No	1 month– 18 years	218	UTI±VUR	113	I–III	Bladder catheterization in patients unable to void on command	Pyuria and significant bacteriuria	12
Roussey et al. 2008	Yes/No	1 month– 3 years	225	UTI+VUR	225	I–III	Bags	Significant bacteriuria	18
Pennesi et al. 2008	Yes/No	0 month– 2 1/2 years	100	UTI+VUR	100	II–IV	Clean catch, bladder catheterization in septic patients	Pyuria and significant bacteriuria	24–48
Montini et al. 2009	Yes/No	2 months– 7 years	338	UTI±VUR	128	I–III	Bag	Pyuria and significant bacteriuria	12
Craig et al. 2009	Yes/Yes	0–18 years	576	UTI±VUR	243	I–V	Clean catch, bladder catheterization, or suprapubic aspiration	Significant bacteriuria	12

VUR vesicoureteral reflux, UTI urinary tract infection

19% patients in the placebo group had recurrence of UTI [hazard ratio (HR) in the antibiotic group, 0.61; 95% confidence interval (CI) 0.40–0.93; $p=0.02$]. The results favored the use of prophylaxis in all children, except those with index UTI caused by SMZ/TMP-resistant organism.

Meta-analysis of the randomized studies

As shown in Table 2, a meta-analysis of the five published studies with a total of 809 patients with VUR reveals a relative risk (RR) of UTI recurrence of 0.82 (95 CI 0.62–1.08; $p=0.16$) with prophylaxis. A meta-analysis of the four studies with a total of 662 patients evaluated for renal scarring reveals an RR of 1.04 (95% CI: 0.84–1.30; $p=0.69$) with prophylaxis. The analysis for renal scarring is limited by the fact that two studies [7, 8] did not evaluate separately renal scars in patients with VUR, and data presented are for patients with UTI and renal scarring with or without VUR.

Discussion

The above-mentioned randomized studies revealed no [4, 6, 7] or some benefit [5, 8] with prophylaxis in the prevention of UTI recurrence. One study [5] showed significantly fewer UTIs in boys with grade III VUR, which was the highest grade evaluated for the study. The meta-analysis of these studies revealed no benefit of prophylaxis in preventing UTI or renal scarring. However, results from these studies should be interpreted with caution because of a combination of limitations that include lack of blindness in all but one study; number of children with VUR included in all but one study, thus affecting statistical significance; inclusion of grade V VUR patients in one study, which is likely to include a disproportionately higher percentage of patients with renal dysplasia; methods used for urine collection in non-toilet-trained children; relatively short duration of follow-up; and wide age group—up to 18 years in two studies. Extremely low incidence of renal scarring in one study (Table 2) is intriguing. Inconsistencies in methods used for DMSA renal scans and the interobserver variability in their interpretation cannot be ruled out.

It is also important to bear in mind that most of the published literature regarding the role of antimicrobial prophylaxis in VUR relates to children diagnosed with VUR after a UTI. Many current research efforts and this editorial commentary are primarily focused on the use of prophylaxis in such patients. However, VUR can be diagnosed in the absence of a preceding UTI. These include prenatal VUR diagnosed during postnatal evaluation of antenatally diagnosed hydronephrosis; sibling VUR diag-

Table 2 Meta-analysis of the randomized studies on vesicoureteral reflux/urinary tract infection (VUR/UTI)

Authors & year of study	Recurrent UTI		Renal scarring				Relative risk % (95% CI)		
	Number of patients with VUR	Rate of recurrent UTI		Relative risk % (95% CI)	Number of patients with DMSA renal scan	Patients included			
		With prophylaxis	Without prophylaxis						
Garin et al. 2005	113	13/55 (24%)	13/58 (22%)	1.05 (0.53–2.07)	113	UTI+VUR	5/55 (9.0%)	2/58 (3.4%)	2.6 (0.53–13.02)
Roussey et al. 2008	225	18/103 (17%)	32/122 (26%)	0.66 (0.39–1.11)	N/A		N/A	N/A	N/A
Pennesi et al. 2008	100	18/50 (36%)	15/50 (30%)	1.20 (0.68–2.10)	100	UTI+VUR	22/50 (44%)	18/50 (36%)	1.22 (0.75–1.9)
Montini et al. 2009	128	10/82 (12%)	9/46 (20%)	0.62 (0.27–1.42)	295	UTI±VUR	50/187 (26.8%)	33/108 (30.5%)	0.87 (0.60–1.26)
Craig et al. 2009	243	14/122 (11%)	21/121 (17%)	0.66 (0.35–1.23)	154	UTI±VUR	35/71 (49%)	38/83 (46%)	1.07 (0.77–1.50)
Total	809	73/412 (18%)	90/397 (23%)	0.82 (0.62–1.08); $p=0.16$	662		112/363 (31%)	91/299 (30%)	1.045 (0.84–1.30); $p=0.69$

nosed in about one third of siblings of children known to have VUR; VUR associated with congenital renal anomalies such as ectopia, duplication, hypoplasia/dysplasia; VUR associated with some syndromes; and secondary VUR that results from bladder abnormality. Many such VURs have a different clinical course in comparison with those diagnosed after UTI, and yet it is not uncommon to see some of them evaluated and presented together in the literature as a single entity.

A VUR diagnosed after UTI, particularly low-grade VUR, is supposed to get better with time, and as a result, such a VUR in an older child or adolescent cannot be interpreted exactly the same way as VUR in an infant. Coexisting constipation and/or voiding dysfunction and the severity of renal scarring, if present, have an important bearing on the management of VUR in such patients. We also need to keep in mind the limitations of the DMSA renal scan, which is the gold standard for diagnosing renal scars. Some of the mistakes made previously with intravenous pyelography as the diagnostic tool for renal scarring must not be repeated. The differences in methodology used at different medical centers and the interobserver variability in interpretation became very obvious during the pilot study that was done for the ongoing Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study [9]. Finally, DMSA renal scan does not help differentiate between congenital (dysplasia) vs acquired renal scars.

Conclusion

A decision regarding the use of prophylaxis in a particular patient with VUR depends on multiple factors that include the type of VUR, its severity, age at diagnosis, history of preceding UTI, coexisting voiding dysfunction and/or constipation, and severity of renal scarring. In view of the limitations with the above-mentioned studies, more research is needed to validate the role of prophylaxis in VUR diagnosed after UTI, and even more research is warranted to answer the questions regarding antimicrobial prophylaxis across the spectrum of VUR in different clinical settings. Prevention of renal scarring remains the main long-term objective of any intervention. In the studies discussed above, 30% of all patients who had DMSA renal scans had renal scarring, though very few new scars were reported during the follow-up period. Whereas it is likely that some of these scars were congenital in origin, the possibility of scars due to previous subclinical or undiagnosed UTI

cannot be ruled out, particularly since about two thirds of the patients in the studies were females, who have a lower incidence of congenital scars (dysplasia). It is essential that while debating the role of prophylaxis in preventing renal scarring in children with VUR we do not overlook the importance of appropriate management of children whose kidneys are already scarred.

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