

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

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SUMMARY

This is a multi-centric randomized controlled trial [1] comparing cotrimoxazole prophylaxis *versus* no prophylaxis in children (<6 years old) with vesicoureteral reflux (VUR) detected after a first or second episode of urinary tract infection (UTI). The trial was designed to determine efficacy in preventing recurrence of UTI and renal scarring, as well as antibiotic resistance patterns. It was conducted across 19 sites in the United States, recruiting subjects over nearly five years, with follow-up for at least two years. Among 86% children who completed the study, the investigators observed lower recurrence of UTI in the intervention group (14.8%) in comparison to controls (27.4%). Intention-to-treat analysis showed similar results but lesser magnitude of difference (25.5% *vs* 37.4%). However, there was no difference in the incidence of renal scarring (new scarring or worsening of pre-existing scarring); 11.9% and 10.2% in the intervention and control groups, respectively. The prevalence of antibiotic resistance increased significantly with prophylaxis. The investigators concluded that antibiotic prophylaxis is useful to prevent repeat episodes of UTI in children with VUR.

COMMENTARIES

Pediatric Nephrologist's Viewpoint

The RIVUR trial conducted in North America randomized 607 children aged below 6 years, with VUR grades I-IV, after a UTI, to receive either trimethoprim-sulfamethoxazole or placebo for 2 years [1]. Thirty-nine of 302 children on prophylaxis had UTI as compared to 72 of 305 children on placebo [relative risk 0.55 (95% CI, 0.38 to 0.78)]. Benefits were more in children with febrile index UTI and in those with bladder-bowel dysfunction (BBD). There was no difference in renal scarring between the two groups. More children on prophylaxis (63%) than on placebo (19%) had resistant isolates.

A very small number of boys (9%) were enrolled, limiting applicability of its results to boys. While primary VUR is commonly reported in girls, such huge gender disparity has not been shown outside US [2-4]. This is

important as boys did not benefit from prophylaxis in the Swedish study [4]. Results of subgroup analyses (with reasonable number of subjects and event rates) show that effect of prophylaxis was not significant in grade III-IV VUR and in absence of BBD. Thus it seems that prophylaxis is beneficial to a distinct patient population comprising of girls with low grade reflux and BBD. Increasingly, VUR is recognized as a heterogeneous condition with regional and genetic differences [5]. It appears from this trial that prophylaxis would reduce morbidity related to UTI but not long-term consequences of renal scarring (hypertension, renal failure) at the cost of increased antimicrobial resistance. A prudent way forward will be that the use of prophylaxis is based on risk-stratification rather than mere presence of reflux.

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Pediatric Surgeon's Viewpoint

The present study proves the supremacy of antimicrobial prophylaxis over watchful waiting approach for patients with grade I to grade IV VUR. Of the grades of VUR studied, the pediatric surgeons and pediatric urologists are usually involved in the management of children with grade IV VUR. For lower grades of VUR, we are consulted only when there are repeated episodes of breakthrough infections, or when there are issues about non-compliance. One of the shortfalls of this study is to study grades I to IV VUR together. The authors should have studied patients with grades I and II, and those with grades III and IV reflux, separately. Second, there is no mention whether those patients with bladder and bowel dysfunction had any urodynamic studies, or had concomitant bladder and bowel dysfunction management. For the patients with grade III and IV reflux, surgical correction and endoscopic management of VUR should also have been added. An earlier study [6] – also referred by the authors of this paper – documented that the incidence of pyelonephritis was significantly higher in the medical group than the surgical group [6]. Endoscopic management is known has equivocal results in comparison to surgical correction in grades III and IV

VUR [7]. So, the management of VUR should entail as follows: Grade I and II – antimicrobial prophylaxis or watchful waiting, Grade III and IV – endoscopic management, and Grade V – surgical correction. RIVUR trial data is relevant mainly for group I and II VUR.

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Evidence-based-medicine Viewpoint

Relevance: It is reported that UTI occurs in 8-10% girls and 2-3% boys during infancy and childhood [8,9], with 5% risk of recurrent infections and renal scarring [10] that may be associated with long-term complications, including hypertension and chronic renal disease [11]. Children with VUR are at increased risk of recurrent infections and more serious consequences [12]. Therefore, recent national [13] and international [14] guidelines recommend screening for VUR and antibiotic prophylaxis after the first confirmed episode of UTI. However, a previous exploration of evidence [15], did not demonstrate reduction of recurrence of UTI with antibiotic prophylaxis, in children with or without VUR. Two systematic reviews [16,17] also did not find strong evidence of benefit in either group of children. Against this backdrop, this RCT [1] is both relevant and timely.

Critical appraisal: This study is an example of a well-designed and well-conducted randomized trial. There was appropriate allocation sequence generation and blinding. Multiple outcomes were determined, with stringently defined UTI being the primary outcome. No urine bags were used for specimen collection. Follow-up nuclear scans for renal scarring were also read by pediatric nuclear medicine experts. The sample size was calculated *a priori*, and almost 86% children could be followed up for the primary outcome. Follow-up duration

was sufficiently long to record development of the relevant outcomes. Data were analyzed as per protocol as well as by intention-to-treat analysis. Although compliance to prophylaxis was less than perfect, it probably matches the pattern in real-life. Overall, the study is a methodologically high-quality trial, with low risk of bias.

Based on these characteristics, it should be relatively easy to accept the reported findings, especially as it is in line with other recent well-designed studies [18,19]. The difficulty arises on two fronts: (i) the overall significance of the new data in this trial, and (ii) its implications for practice.

The two Cochrane reviews [16,17] did not demonstrate statistically significant reduction in risk of recurrence of UTI in children with VUR, but these excluded a couple of large relevant trials [4,19]. This necessitates a fresh meta-analysis pooling data from the missed trial and the current RCT [1], which shows (**Fig. 1**) that the relative risk of recurrence of UTI with prophylaxis is 0.70 (95% CI 0.48, 1.04; 7 trials, 1473 participants) when the *per-protocol* data of new RCT are included. Re-analysis using ITT data (**Fig. 2**) shows almost similar results [RR 0.73 (95% CI 0.52, 1.03; 1553 participants)]. These data suggest that despite this large well-designed study, the evidence is still equivocal and does not demonstrate a statistically significant benefit of prophylaxis, although there is a trend in this direction.

Further, both Cochrane reviews and the current RCT clearly showed that antibiotic prophylaxis did not prevent development of renal scarring. Fresh meta-analysis (**Fig. 3**) including the new data also confirms this (RR 0.62, 95% CI 0.27, 1.40; 6 trials, 1244 participants). This appears surprising because reduction in UTI would be expected to reduce long-term scarring and its complications. Absence of this benefit calls for search of other

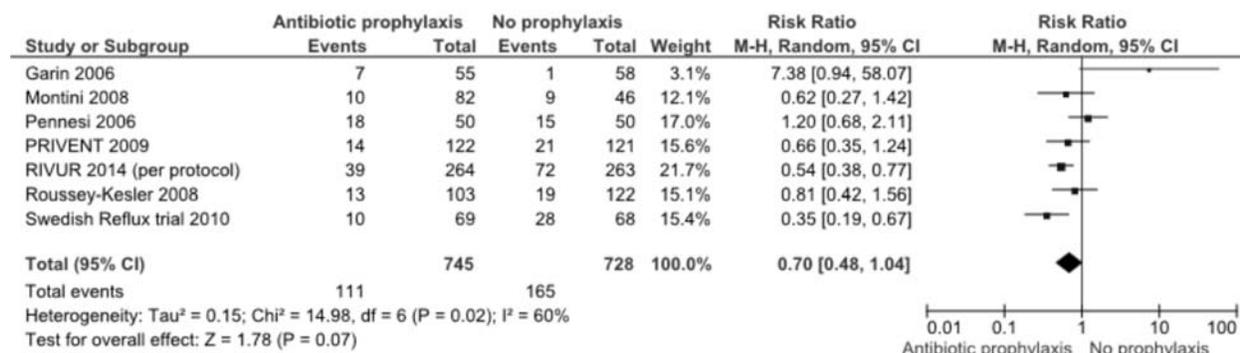


FIG. 1 Meta-analysis of antibiotic prophylaxis versus no prophylaxis for prevention of UTI recurrence (including RIVUR 2014 per protocol data).

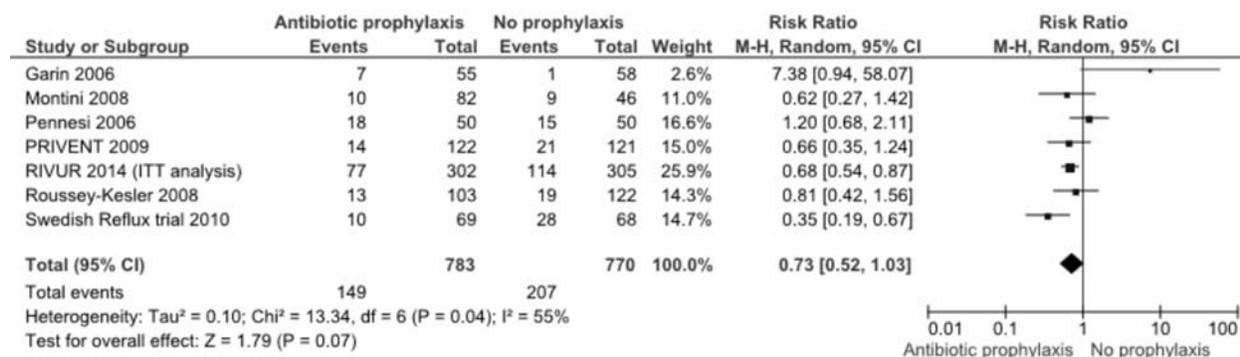


FIG 2: Meta-analysis of antibiotic prophylaxis versus no prophylaxis for prevention of recurrence of UTI (including RIVUR 2014 intention-to-treat analysis of data).

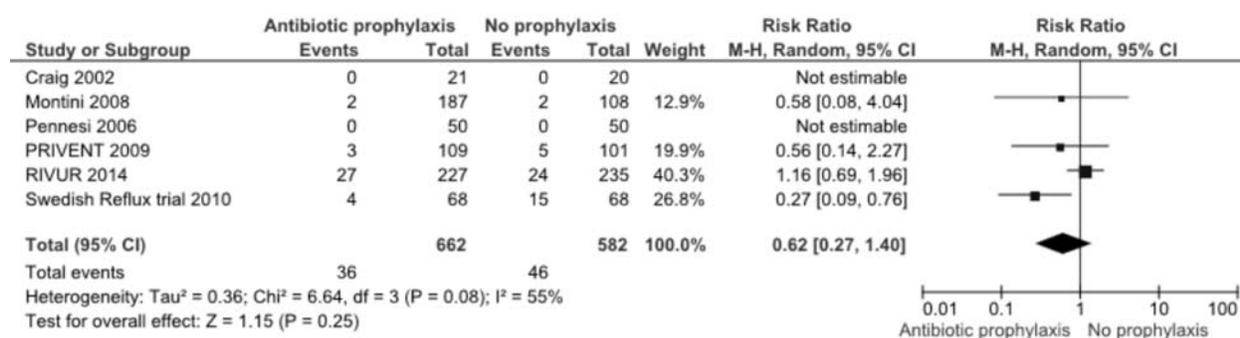


FIG. 3 Meta-analysis of antibiotic prophylaxis versus no prophylaxis for prevention of new or worsening renal scarring

more effective approaches to manage VUR. In this context, recent experience with dextranomer/hyaluronic acid polymer to treat VUR (20) is promising. In a series with 54 children (81 VUR units), treatment resolved VUR in 72 (89%). Renal scarring remained status quo or regressed in 75%. If this modality becomes routine, the management paradigm may shift from watchful waiting with prophylaxis. Another important reason to lean away from prophylaxis is the associated increase in prevalence of antibiotic-resistant bacteria over time (>25% in this RCT), and episodes of UTI caused by resistant bacteria (>65%). This suggests that cotrimoxazole prophylaxis cannot be continued indefinitely. Fresh research is required to study the pattern with antibiotic rotation regimens.

Extendibility: There are several reasons that the data from this study can be extended to the Indian setting. UTI is fairly common, although appropriate diagnosis using stringent criteria and appropriate urine collection methods, need improvement. *E. coli* is the most commonly isolated organism in children [21], and Cotrimoxazole the most commonly chosen agent for prophylaxis. On the other hand, not all centers have access to modalities for detecting VUR and/or renal

scarring. In such settings, should physicians continue prescribing prophylaxis (hoping for reduced recurrence of UTI but being aware that it increases risk of episodes with resistant organisms, and has no benefit on scarring) or abandon the practice altogether. Unfortunately, current high quality evidence does not resolve the issue, and may necessitate a well-designed RCT in Indian children.

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