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The RIVUR Study: A factual interpretation of our data

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Abstract

Vesicoureteral reflux (VUR) increases the risk of urinary tract infection (UTI) and renal scarring. Many prospective studies have evaluated the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children with VUR. Of these, the RIVUR trial was the largest, randomized, placebo-controlled, double blind, multicenter study in 607 children aged 2–72 months with grade I–IV VUR, and a first or second symptomatic UTI. The median age of children in the RIVUR trial was 12 months, 92% were female, 91% were randomized after a first UTI, 86% had a febrile index UTI, and 71 (56%) of 126 toilet-trained children had bladder bowel dysfunction. Trimethoprim/sulfamethoxazole reduced the risk of UTI recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74) as compared to placebo. No significant difference was seen in renal scarring between the two groups. However, this does not invalidate the role of prophylaxis in preventing renal scars because RIVUR and other recent prospective studies were not designed to address renal scarring as a primary study endpoint. In view of the RIVUR and other studies that showed similar results, albeit in selected groups of patients, the debate about antimicrobial prophylaxis should shift from “no prophylaxis” to “selective prophylaxis” in children with VUR.

Introduction

Vesicoureteral reflux (VUR) increases the risk of urinary tract infection (UTI) and renal scarring [1, 2]. In the last decade many prospective studies have been done to evaluate the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children with VUR. This includes the RIVUR study, which was the largest, randomized, placebo-controlled, double blind, multicenter study in young children 2–72 months old with grade I–IV VUR and first or second symptomatic UTI. The primary outcome of the study was UTI recurrence and the secondary outcomes included renal scarring, antibiotic

resistance and treatment failure. Pilot studies were done for consistency in methodology and imaging quality for dimercaptosuccinic acid (DMSA) renal scans and voiding cystourethrograms (VCUG). Digital images for DMSA scans were read independently by two central radiologists, as were the images for VCUG/renal ultrasound by another two radiologists. Any difference of opinion was adjudicated between the two in the team. Altogether 607 children were randomized from 19 centers with very diverse clinical settings; 302 received trimethoprim/sulfamethoxazole (TMP.SMZ) prophylaxis and 305 received exactly matching placebo [3].

Study results

The median age of the children in the RIVUR study was 12 months, 92% were females, 91% were randomized after a first UTI, 86% had a febrile index UTI, and 71 of 126 toilet-trained children had bladder bowel dysfunction (BBD). Recurrent UTI occurred in 39/302 children on prophylaxis compared with 72/305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of UTI recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74). Only 37 children (8.3%) had new renal scars during the study period; 8.2% on prophylaxis versus 8.4% on placebo (absolute risk difference 95% CI 0.19 (−4.9 to 5.3). No significant difference was seen in stool *Escherichia coli* resistance, but the first symptomatic UTI recurrence with resistant *E. coli* was significantly more likely to occur among those on prophylaxis (63%) compared with those on placebo (19%), (absolute risk difference (95% CI) −44.0 (−64.1 to −24.0 (p = <0.001) [4].

Discussion

The most recent prospective studies that have evaluated the efficacy of antimicrobial prophylaxis in children with VUR are summarized in Table 1. Some of these studies, including the one by Garin et al, showed no significant difference in recurrence of UTI with antimicrobial prophylaxis [5–7], whereas others, including the RIVUR study showed that prophylaxis significantly lowered risk of UTI in some children with VUR [8–10]. Roussey et al reported a significant decrease in UTI recurrence in boys, particularly those with grade III VUR, which was the highest grade included in the study. The PRIVENT study reported a 52% decreased risk of UTI (relative risk of active to placebo of 0.66; 95% CI, 0.35–1.23) with prophylaxis in patients with VUR. The Swedish reflux trial reported a significantly lower risk of febrile UTI recurrence in girls with grade III–IV VUR as compared to those on surveillance (p= 0.0002). In the RIVUR study, the hazard ratios for UTI recurrences consistently favored prophylaxis, irrespective of sex, age at entry, degree of VUR, first versus second UTIs before enrolment, TMP/SMZ resistant pathogen causing index UTI, and status of VUR during the study period. Children with baseline BBD, as well as those with a febrile index infection, derived particular benefit with reductions in recurrence of 80% and 60%, respectively [4].

Renal scarring was a secondary end-point for the RIVUR study and no significant difference was noted with antimicrobial prophylaxis. Similar observations have been reported by other studies. However, this does not invalidate the role of prophylaxis in preventing renal scars

because none of these studies, including the RIVUR study, were sufficiently powered to evaluate differences in renal scarring. Furthermore, the scarring outcome in the RIVUR study could have been affected by multiple factors, including a prompt diagnosis and treatment of UTI recurrence in study children, exclusion of those with more than two infections, and the duration of follow-up. Appropriately designed studies with longer follow-up are needed to evaluate the role of antimicrobial prophylaxis in the prevention of renal scarring.

Demonstration of a high rate of uropathogen resistance to the antimicrobial being used for prophylaxis has been previously reported; however, such a resistance pattern was not noted in stool specimens of children in the RIVUR study. Also, index UTI caused by TMP/SMZ-resistant uropathogen did affect the benefit of antimicrobial prophylaxis in the RIVUR study.

RIVUR and other recent studies

Comparison of the RIVUR study with other recent studies can be misleading because of significant qualitative differences. The RIVUR trial had the largest sample size with 2–6 times more patients as compared to other studies in children with VUR. Only PRIVENT and RIVUR were placebo-controlled, double-blind trials and had the most rigorous patient inclusion and exclusion criteria. Older children, including teenagers, as well as children with asymptomatic UTI were excluded, as were children with no pyuria. Urine in non toilet-trained children was collected by urethral catheterization only. Pilot studies were done to have consistency in methodology and interpretation of VCUG and DMSA scans.

Limitations with other prospective studies cited by Cara-Fuentes et al in their editorial commentary have been highlighted in many publications. These include a 2011 Cochrane analysis, which reported considerable heterogeneity (design or reporting limitations) in the analysis of these studies, with only one study adequately blinded [11]. A recently published systematic review on the role of antimicrobial prophylaxis in children with VUR evaluated 1547 studies, 8 of which were included in the meta-analysis [12]. Of the 8 studies, only PRIVENT and RIVUR studies were graded as having low risk of bias; all other 6 were deemed to be at a high risk of performance and detection bias [5, 9, 10, 13–15]. The meta-analysis revealed that prophylaxis is effective in preventing recurrence of UTI, and that the effect is more pronounced in the two studies with low-risk of bias.

RIVUR and the American Academy of Pediatrics (AAP) guidelines

In 2011, the AAP Subcommittee on Urinary Tract Infection published its clinical practice guidelines for the management of first febrile UTI in children 2–24 months old. Its recommendation against routine antimicrobial prophylaxis in young children after first febrile UTI was based on data collected mainly from studies with a high risk of bias [5–7, 10]. The bias and other flaws in these studies are not mitigated by the AAP subcommittee's analysis of data limited to infants up to 24 months of age in their respective patient populations.

Authors of the guidelines acknowledged the importance of the RIVUR study and a possible need to review guidelines once the study results are published. Soon after publication of the

RIVUR study, the AAP Subcommittee reaffirmed the applicability of its guidelines (www.aapnews.org; July 2014, page 5). The reaffirmation is based on the assertions that VUR does not “appear” to be a major cause of renal damage, active treatment of VUR “seems” not to reduce the occurrence of chronic kidney disease, prophylaxis for infants and young children does not “appear” to reduce renal scarring, and the benefit of prophylaxis “appears” to be a quite “modest” in delaying/preventing recurrence of UTI. However, it is difficult for any clinician to translate these passive assertions into a blanket advice against prophylaxis while counseling a parent of an infant with VUR, particularly since RIVUR and other studies have shown significant decrease in UTI recurrence with prophylaxis in children with VUR.

Furthermore, the RIVUR study was not designed to validate the role of VCUG after first UTI because all children in the study had VUR, which was a study inclusion criterion. However, in view of the RIVUR study and other study results, it seems prudent to diagnose VUR after first UTI in selected children so that the risk of UTI recurrence can be reduced with prophylaxis. A need for VCUG in a selected group of patients with first febrile UTI is also supported by the American Urological Association [2, 16] and the European Association of Urology (<http://www.uroweb.org/guidelines/online-guidelines>). The Executive Committee, Section on Urology (AAP) has expressed significant reservations about the AAP recommendation against routine VCUG after a first febrile UTI. It stated that the guidelines are based on studies that collected urine in non toilet-trained children by bag specimens in spite of the guidelines emphasizing the importance of urine collection method, did not include circumcision status or evaluation of BBD, lacked statistical power, DMSA scans were not done in all studies, and compliance with medication not evaluated. The committee concluded that “the recommendation is based on a flawed interpretation of limited data” and “these conclusions are premature and represent a misinterpretation of the data presented” adding further that the VCUG should remain an accepted option after a febrile in selected children [16]. The potential risks of not doing VCUG after UTI were highlighted in a study that evaluated the National Institute for Health and Clinical Excellence (NICE) imaging guidelines to a historic cohort of 934 patients with UTI. Of these, 105 patients had abnormal renal imaging findings and only 44 (42%) would have been diagnosed by using NICE criteria. Of the remaining 61 (58.1%) patients, 32 (52.5%) had significant urological anomalies including at least Grade III VUR and or renal scarring that would have been missed [17].

RIVUR and statistical issues in the editorial commentary

The Cara-Fuentes et al editorial commentary includes a *post hoc* redefining of outcomes and misrepresentations of the statistical concepts and results reported in the RIVUR trial. The RIVUR trial was designed with *first* post-randomization UTI as the primary outcome. Participants were followed to ascertain additional UTIs to determine those meeting a secondary outcome of treatment failure.

Analysis of our primary outcome by considering exactly 1 post-randomization recurrent UTI, ignoring those with more than 1 recurrent UTI and thereby combining those with 2 or more UTIs together with those children who had no recurrent UTI, as suggested in the

commentary is an illogical and uninterpretable statistical comparison. The authors go on to separately consider those children who had 3 or 4 post-randomization UTIs (N=5 in the prophylaxis group and N=8 in the placebo group, difference of 3 patients). While this may be a clinically relevant outcome, it is not the outcome that RIVUR and most studies of recurrent UTI have used. Indeed, we know of no published trial with 3 or more recurrent UTIs as a pre-specified outcome. Therefore, to assert that the RIVUR Investigators recommend “starting routine long term urinary antibiotic prophylaxis in 302 patients to benefit only three patients” is inaccurate and misleading.

While Cara-Fuentes et al are entitled to believe that a 50% reduction of the risk of recurrent UTI with prophylaxis (or doubling of the risk of recurrent UTI with placebo) is a “slight benefit”, it is not correct to assume this occurred when “almost half of the children did not have VUR”. While it is correct that VUR had resolved in half of the 428 children who had a VCUG performed at 2 years post-randomization, it is not known when the VUR resolved and whether it resolved before or after any recurrent UTI occurred.

In their discussion of ‘time to first recurrent UTI’, Cara-Fuentes et al focus on “the 10% difference between the two groups as expected” and “10% threshold of significance” in a statistically naïve transference of assumptions that were made in the original RIVUR power assumptions to evaluate the level of statistical significance of the trial results. As described in the RIVUR protocol (available online through the *New England Journal of Medicine* materials accompanying the full article [4], *a priori* power analyses were performed using varied assumptions for the expected event rates in the placebo and prophylaxis groups, as well as rates for non-compliance and attrition. The purpose for these power analyses was to identify an appropriate sample size to address the primary hypothesis. In our report, we always acknowledged that subgroup analyses such as those discussed by Cara-Fuentes et al, would be under-powered except for marked differences; that is, the sample size in the RIVUR study might be insufficient to detect important treatment group differences in subgroup analyses. In particular, insufficient power would be expected for the subgroups depicted in Figure S2 in the online supplementary appendix to the RIVUR results paper [4] (restricted to children younger than 2 years of age and sub-grouped by VUR grade such that each subgroup was comprised of <95 children). Interpretation of RIVUR subgroup analyses must acknowledge the sample size limitations. Therefore, it is incorrect to conclude that “no benefit was observed in what has been considered a high risk group, such as young children with VUR grade III and IV”. Non-statisticians must be reminded frequently that “absence of evidence is not evidence of absence”.

Lastly, we did not include a comparator group of children without VUR to investigate whether VUR increases the risk of UTI because it would be unethical to randomize children without VUR to antimicrobial prophylaxis. Absence of VUR was a study exclusion criterion. However, a RIVUR ancillary study “Careful Urinary Tract Infection Evaluation (CUTIE)” has been completed and does provide a comparator group of children without VUR who followed identical UTI definitions and study procedures of the RIVUR study. Results of the CUTIE study and analyses of joint RIVUR and CUTIE data will be published in the near future.

Conclusion

The RIVUR study was not designed to evaluate the AAP guidelines. The study was initiated 5 years before and completed 2 years after the guidelines were published. It showed a 50% reduction in recurrences of UTI for children receiving antibiotic prophylaxis. The results of RIVUR and other studies that showed similar results, albeit in selected groups of patients, cannot be ignored. We cannot overlook the significant limitations with most of the studies included in the AAP meta-analysis for its guidelines on antimicrobial prophylaxis and VCUG after first UTI in young children. We also must not pass the onus for preventing morbidity of UTI recurrence and potential renal injury to parents, because of the challenges associated with clinical presentation and diagnosis of UTI in infants and young children. As clinicians, we bear the responsibility to share evidence-based results with parents who have the right to make a choice about what's best for their children. We also need to keep in mind the limitations of renal imaging, including renal ultrasound, VCUG and DMSA renal scan. In view of the RIVUR study results, the debate about antimicrobial prophylaxis should shift from “no prophylaxis” to “selective prophylaxis” in children with VUR.

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References

1. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010; 126:1084–1091. [PubMed: 21059720]
2. Peters CA, Skoog SJ, Arant BS Jr, Copp HL, Elder JS, Hudson RG, Khoury AE, Lorenzo AJ, Pohl HG, Shapiro E, Snodgrass WT, Diaz M. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. *J Urol*. 2010; 184:1134–1144. [PubMed: 20650499]
3. Carpenter MA, Hoberman A, Mattoo TK, Mathews R, Keren R, Chesney RW, Moxey-Mims M, Greenfield SP. RIVUR Trial Investigators. The RIVUR Trial: Profile and Baseline Clinical Associations of Children With Vesicoureteral Reflux. *Pediatrics*. 2013; 132:e34–e45. [PubMed: 23753091]
4. Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, Kropp BP, Skoog SJ, Nelson CP, Moxey-Mims M, Chesney RW, Carpenter MA. RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014; 370:2367–2376. [PubMed: 24795142]
5. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006; 117:626–632. [PubMed: 16510640]
6. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, Cecchin D, Pavanello L, Molinari PP, Maschio F, Zanchetta S, Cassar W, Casadio L, Crivellaro C, Fortunati P, Corsini A, Calderan A, Comacchio S, Tommasi L, Hewitt IK, Da Dalt L, Zacchello G, Dall'Amico R. IRIS Group. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics*. 2008; 122:1064–1071. [PubMed: 18977988]
7. Pennesi MTL, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, Minisini S, Ventura A. North East Italy Prophylaxis in VUR study group. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics*. 2008; 121:e1489–e1494. [PubMed: 18490378]
8. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, Hodson EM, Carapetis JR, Cranswick NE, Smith G, Irwig LM, Caldwell PH, Hamilton S, Roy LP. Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts

- (PRIVENT) Investigators. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*. 2009; 361:1748–1759. [PubMed: 19864673]
9. Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol*. 2010; 184:286–291. [PubMed: 20488494]
10. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, Raymond F, Grellier A, Hazart I, de Parscau L, Salomon R, Champion G, Leroy V, Guignon V, Siret D, Palcoux JB, Taque S, Lemoigne A, Nguyen JM, Guyot C. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol*. 2008; 179:674–679. discussion 679. [PubMed: 18082208]
11. Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev*. 2011; 6:CD001532. [PubMed: 21678334]
12. Wang HH, Gbadegesin RA, Foreman JW, Nagaraj SK, Wigfall DR, Wiener JS, Routh JC. Efficacy of Antibiotic Prophylaxis in Children with Vesicoureteral Reflux: Systematic Review and Meta-Analysis. *J Urol*. 2014
13. Montini G, Hewitt I. Urinary tract infections: to prophylaxis or not to prophylaxis? *Pediatr Nephrol*. 2009; 24:1605–1609. [PubMed: 19444477]
14. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, Minisini S, Ventura A. North East Italy Prophylaxis in VUR study group. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics*. 2008; 121:e1489–e1494. [PubMed: 18490378]
15. Craig JC, Roy LP, Sureshkumar P, Burke J, Powell H, Hodson EM. Long-term antibiotics to prevent urinary tract infection in children with isolated vesicoureteric reflux (a placebo-controlled randomized trial). *J Am Soc Nephrol*. 2002; 13:3A.
16. Wan J, Skoog SJ, Hulbert WC, Casale AJ, Greenfield SP, Cheng EY, Peters CA. Executive Committee, Section on Urology, American Academy of Pediatrics. Section on Urology response to new Guidelines for the diagnosis and management of UTI. *Pediatrics*. 2012; 129:e1051–e1053. [PubMed: 22412033]
17. McDonald K, Kenney I. Paediatric urinary tract infections: a retrospective application of the National Institute of Clinical Excellence guidelines to a large general practitioner referred historical cohort. *Pediatr Radiol*. 2014; 44:1085–1092. [PubMed: 24789768]

Recent prospective studies on antimicrobial prophylaxis in the prevention of UTI recurrence in children with vesicoureteral reflux

Table

Authors (Year)	Patient age range (Mean or Median Age at Randomization) M: Months Y: Years	Number of Patients with VUR (Total Number of Patients in the Study)	VUR grade	Girls	Placebo Used	Duration of Follow-up in Years	Rate of Recurrence of UTI (in those with VUR)		Relative Risk% (95% CI)	Study Conclusion (Prophylaxis decreases risk of UTI recurrence)
							With Prophylaxis	Placebo or Surveillance Only		
Garin et al. (2006)	3M- 12Y (24M [*])	113 (218)	I–III	81%	No	1	13/55 (24%)	13/58 (22%)	1.05 (0.53–2.07)	No
Roussey et al. (2008)	1–36(11.2M)	225 (225)	I–III	69%	No	1.5	18/103 (17%)	32/122 (26%)	0.66 (0.39–1.11)	Yes; selectively in boys
Pennesi et al. (2008)	0–30M (8.6M)	100 (100)	II–IV	52%	No	2	18/50 (36%)	15/50 (30%)	1.20 (0.68–2.10)	No
Montini et al. (2008)	2–84 (14.7M)	128 (338)	I–III	69%	No	1	10/82 (12%)	9/46 (20%)	0.62 (0.27–1.42)	No
PRIVENT (2009)	0–18Y (14M [*])	243 (576)	I–V	64%	Yes	1	14/122 (11%)	21/121 (17%)	0.66 (0.35–1.23)	Yes
Swedish Reflux Trial (2010)	12–24 (21.3 M)	137/203 ^{**}	III–IV	63%	No	2	10/69 (14%)	25/68 (37%)	0.39 (0.20–0.75)	Yes; selectively in girls
RIVUR Study (2014)	2–72 (12M [*])	607 (607)	I–IV	92%	Yes	2	39/302 (13%)	72/305 (24%)	0.55 (0.38–0.78)	Yes

* Median age

** 99 patients were randomized to endoscopic treatment

NA: Not available