Why Does Prevention of Recurrent Urinary Tract Infection not Result in Less Renal Scarring? A Deeper Dive into the RIVUR Trial

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Abbreviations and Acronyms

AP = antibiotic prophylaxis

BBD = bowel bladder dysfunction

DMSA = dimercaptosuccinic acid

NRS = new renal scarring

RIVUR = Randomized Intervention for Children with Vesicoureteral Reflux

rUTI = recurrent urinary tract infection

UTI = urinary tract infection

VUR = vesicoureteral reflux

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Purpose: The RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) trial reported that antibiotic prophylaxis reduced recurrent urinary tract infection but antibiotic prophylaxis was not associated with decreased new renal scarring. However, the original reports did not assess the relationship among recurrent urinary tract infection, new renal scarring and antibiotic prophylaxis in detail. Therefore, we investigated the relationship among these issues.

Materials and Methods: We included subjects with dimercaptosuccinic acid scan within 6 months of enrollment and at least 1 followup dimercaptosuccinic acid scan from the RIVUR trial. The primary outcome was recurrent urinary tract infection associated new renal scarring, defined as recurrent urinary tract infection and new changes on dimercaptosuccinic acid scan. Due to a low number of events, propensity score was used to adjust for confounders. Multivariate logistic regression was fitted to investigate the associations between the covariates and the outcome.

Results: A total of 489 patients (91% female, mean age 20.3 months) were included in the study. Any new renal scarring was more common among those with recurrent urinary tract infection (OR 4.1, 95% CI 2.0–8.5, $p < 0.01$) after adjusting for age, sex, index urinary tract infection, duplication, bowel bladder dysfunction and antibiotic prophylaxis. Recurrent urinary tract infection associated new renal scarring occurred in 5 of 244 (2%) patients on antibiotic prophylaxis and 13 of 245 (5%) on placebo. Compared to antibiotic prophylaxis, placebo was associated with a higher risk of recurrent urinary tract infection associated new renal scarring (OR 3.1, 95% CI 1.0–8.8, $p = 0.04$) after adjusting for age, sex, race, index urinary tract infection, bowel bladder dysfunction, duplication, hydronephrosis, vesicoureteral reflux grade and baseline renal scarring. There were no differences in scar severity at final dimercaptosuccinic acid scan ($p = 0.88$) or change from baseline ($p = 0.53$) between antibiotic prophylaxis and placebo.

Conclusions: Recurrent urinary tract infection was associated with new renal scarring in the RIVUR trial. When limited to recurrent urinary tract infection associated new renal scarring, antibiotic prophylaxis was associated with a decreased risk of this outcome. It remains unclear why new renal scarring developed in a proportion of subjects without recurrent urinary tract infection. The results should be carefully interpreted due to the inherent limitations.

Key Words: kidney, vesico-ureteral reflux, urinary tract infections, antibiotic prophylaxis

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SIGNIFICANT controversy and variability exist regarding the management of vesicoureteral reflux.[1] In particular, the effectiveness of antibiotic prophylaxis in children with VUR has been highly debated.[2] In 2014 the multi-institutional RIVUR trial was published, demonstrating that AP had a strong protective effect on recurrent urinary tract infection in VUR.[3] However, the incidence of new renal scarring was not significantly different between those on AP vs placebo. While the lack of impact on NRS prompted many to conclude that AP is not an effective intervention in primary VUR, this result is puzzling if our underlying understanding of reflux nephropathy is correct. If VUR associated pyelonephritis leads to renal injury through an inflammatory cascade, why did a 50% reduction in rUTI not result in less new scarring? Possible explanations include the relatively low baseline prevalence of scarring, the short study duration (2 years) and the early treatment of rUTI (and, thus, prevention of scar development) among AP and placebo subjects in the clinical trial setting. Others argue that other factors such as innate immunity[4] or BBD[5] are more significant contributors.

However, none of these explanations addresses the fundamental paradox of the RIVUR results. rUTI was significantly more common among those in the placebo group and NRS was significantly more common among subjects with rUTI, yet NRS was not more common in the placebo group. This apparent discrepancy prompted us to dig deeper as we sought to better understand the relationship among prophylaxis, recurrent infection and renal scarring. Specifically, we sought to determine the relationship of AP to the incidence of NRS specifically occurring after rUTI, and we hypothesized that rUTI associated NRS would be more common in patients on placebo than in those on AP.

MATERIALS AND METHODS

Data Source and Cohort Selection

The RIVUR trial was a multicenter, randomized, double-blinded, placebo controlled trial designed to determine whether daily antimicrobial prophylaxis is superior to placebo in preventing rUTI in children with VUR. The trial cohort and rationale were published previously.[3] Study eligibility included 1) age at randomization between 2 months and 6 years, 2) a diagnosed first/second febrile or symptomatic index UTI within 16 weeks before randomization and 3) presence of VUR (on voiding cystourethrogram). Patients were followed for 2 years with a primary outcome of recurrence of febrile and/or symptomatic UTI.

Per trial protocol the study participants were scheduled for 3 DMSA renal scans. The baseline scan was obtained within 2 weeks of randomization and within 16 weeks of the index UTI. A second DMSA scan was obtained within 21 days of the 12-month followup visit. The third DMSA scan was targeted within 10 days of the study exit visit at 24 months after randomization. For all children in whom treatment failed the outcome DMSA scan was obtained approximately 4 months after meeting the criteria for treatment failure. The DMSA scan review protocol by central readers was previously described.[6] Each kidney was divided into 12 zones. The severity (grade) of the renal scarring was categorized as mild (1 to 2 segments affected), moderate (3 to 4 segments affected), severe (more than 4 segments affected) and global atrophy.

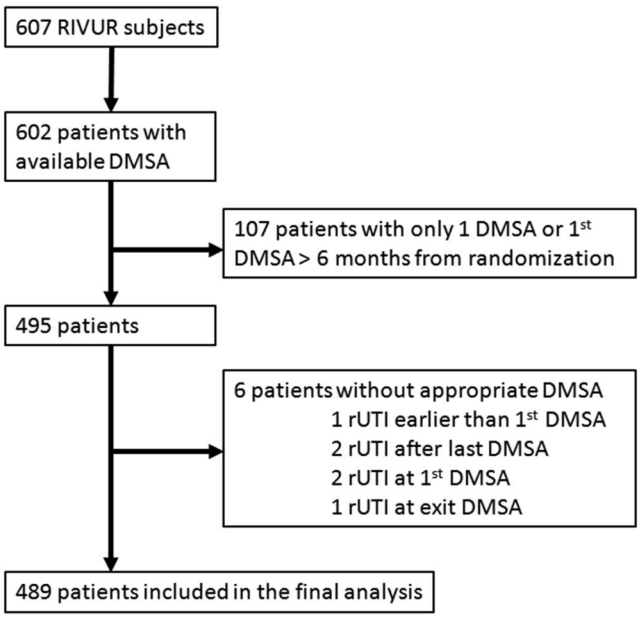
We reviewed the RIVUR data from the National Institute of Diabetes and Digestive and Kidney Diseases data repository. We included subjects with a baseline DMSA study within 6 months of enrollment (to reduce possible bias toward more baseline scarring) and at least 1 followup DMSA scan. Those whose first DMSA scan was more than 6 months after the index UTI, those with rUTI before the first DMSA scan (meaning no baseline DMSA scan available) and those with rUTI occurring after the last DMSA scan (ie no DMSA scan to reflect the rUTI impact) were excluded from the study (see figure).

Covariates and Outcome Definition

The primary outcome was rUTI associated NRS, defined as rUTI and NRS detected after a rUTI event. NRS was defined in the RIVUR protocol as a change in number of renal segments with scarring between initial DMSA and last DMSA. Subjects with NRS but no rUTI, with rUTI but no NRS, and those with neither were defined as negative for the primary outcome.

Covariates included demographic factors (age, gender, race), bowel bladder dysfunction (among toilet-trained children, defined by dysfunctional voiding scale per protocol), index UTI presentation (number of episodes, fever, symptoms), ultrasound results (hydronephrosis, hydroureter, bladder wall thickening) and VUR grade/laterality.

The RIVUR trial used stringent criteria for UTI.[7] For index or recurrent UTI the event must have met all of the criteria of pyuria on urinalysis, culture proven infection



Flow chart of cohort selection

with single organism (50,000 CFU/mm^3 or greater for catheterized or suprapubic aspirated specimen, 100,000 CFU/mm^3 or greater for clean voided specimen), fever (38C or greater) or UTI symptoms within 24 hours of urine collection (suprapubic, abdominal or flank pain/tenderness; urinary urgency, frequency or hesitancy; dysuria; foul smelling urine; or failure to thrive, dehydration or hypothermia in infants age 4 months or younger).

Statistical Analysis and Model Development

Bivariate analyses were performed to compare potential predictors between those with rUTI associated NRS and those without. We used the chi-square test and Fisher's exact test as appropriate based on data characteristics and distribution.

Due to the low number of NRS events and to account for patient characteristics associated with targeted exposure such as treatment arm (AP vs placebo), a propensity score was built to account for possible confounding effects in the final multivariate model. For treatment arms the patient characteristics were relatively even between the AP and placebo groups (supplementary table 1, https://www.jurology.com). However, to ensure minimal residual confounding effect we built the propensity score for treatment arms with variables including age, sex, race, prior UTI counts/type, BBD, duplication, hydronephrosis, VUR grade and baseline renal scarring. Similarly, a propensity score was developed for rUTI with age, sex, index UTI count, duplication, BBD and antibiotic prophylaxis. Two multivariate logistic regression models were then fitted, one with treatment arm and propensity scores as independent variables and rUTI associated NRS (new scar that occurred in the setting of rUTI) as outcome, and the other with rUTI and propensity scores as independent variables and all NRS (any new scar regardless of whether rUTI occurred) as outcome. Additionally, to investigate possible discrepancy in the severity of scarring, we looked at the breakdown of scarring severity by rUTI as well as NRS grade by treatment arm. An alpha of 0.05 and 95% CIs were used as criteria for statistical significance. All analyses were performed using SAS® 9.4.

RESULTS

Demographics and Cohort Selection

We identified 489 participants (244 on AP, 245 on placebo) with initial DMSA scan performed within 6 months of enrollment as baseline as well as a followup DMSA scan. The overall RIVUR outcomes for this cohort were similar to those reported in the primary RIVUR data, with the findings again showing a significant association of AP with rUTI, and of rUTI with any NRS, but not of AP with any NRS (table 1). This similarity suggests that the subset is representative of the broader RIVUR cohort.

The general characteristics of the cohort are presented in supplementary table 2 (and detailed in supplementary tables 3-5, https://www.jurology.com). Mean age was 20.3 months. Female patients constituted 91% of the overall cohort. Most (92%) patients had a history of a single index UTI. A minority (23%) of patients were toilet-trained at enrollment and of these patients 51% had BBD. Approximately half (48%) of the patients presented with grade 3-4 VUR. Baseline renal scarring was relatively rare (3.6%). Recurrent UTI was found in 18% (89) of patients. Any NRS occurred in 7.5% (37) and rUTI associated NRS was found in 3.7% (18) of patients.

Any New Renal Scarring and rUTI

The univariate associations of these patient characteristics with outcomes are shown in supplementary table 2 (https://www.jurology.com). Compared to children without rUTI, those with rUTI were older (23.6 vs 19.6 months, p=0.01), more likely to have had 2 (vs 1) index UTIs (14.6% vs 6.8%, p=0.03) and more likely to have had more baseline scarring (8.9% vs 2.5%, p=0.01). Children with any NRS were also more likely to be older (median 26 vs 11 months, p <0.01), have hydronephrosis (14% vs 4%, p=0.02) or have grade 4 VUR (32% vs 7%, p <0.01).

On multivariate analysis incorporating propensity score, recurrent UTI (OR 4.1, 95% CI 2.0–8.5, p <0.01) remained independently and significantly associated with any NRS after adjusting for age, sex, index UTI count, duplication, bowel bladder dysfunction and antibiotic prophylaxis.

Table 1. *Associations of major RIVUR outcomes including rUTI and any NRS with AP, and with each other*

		No. Treatment Arm (%)		No. rUTI (%)	
	No. Pts	AP	Placebo	Yes	No
rUTI	89	28 (11.5)	61 (24.9)		
No rUTI	400	216 (88.5)	184 (75.1)		
p Value		<0.01			
Any NRS	37	17 (7.0)	20 (8.2)	18 (20.2)	19 (4.7)
No NRS	452	227 (93.0)	225 (91.8)	71 (79.8)	381 (95.3)
p Value		0.73		<0.01	
rUTI associated NRS	18	5 (2.0)	13 (5.3)		
No rUTI associated NRS	471	239 (98.0)	232 (94.7)		
p Value		0.06			

P values generated by Fisher's exact tests for all categorical comparisons.

Recurrent UTI Associated New Renal Scarring

Factors related to rUTI associated NRS are shown in supplementary table 2 (https://www.jurology.com). As with any new renal scarring, rUTI associated NRS was significantly linked to older age group (median 26 vs 12 months, p=0.04) and grade 4 VUR (28% vs 8%, p=0.04). On the other hand, rUTI associated NRS was not significantly associated with sex, race, index UTI symptoms/presentations, BBD, ultrasound results (hydronephrosis, duplication) and baseline DMSA findings.

In contrast to the effect of AP when looking at any NRS, rUTI associated NRS was more common in the placebo (5.3%) than in the AP arm (2%) (OR 2.7, 95% CI 0.9–7.6, p=0.06). After adjusting for age, sex, race, prior UTI counts/type, BBD, duplication, hydronephrosis, VUR grade and baseline renal scarring, placebo remained associated with a higher risk of rUTI associated NRS (OR 3.0, 95% CI 1.0–8.8, p=0.04) compared to AP.

There were roughly equal numbers of patients with rUTI associated NRS (18 [3.7%], of whom 13 had VUR grade 3-4) compared to those who had NRS despite no documented rUTI (19 [3.9%], of whom 12 had VUR grade 3-4). The distributions of VUR grades for these 2 groups were similar (p=0.6). Final NRS grades were similar between rUTI associated vs nonrUTI associated NRS (table 2). Further breakdown by treatment showed that more severe (moderate/severe) NRS was distributed similarly between AP and placebo. On the other hand, the placebo group had milder NRS, especially those with rUTI (10 of 14 vs 2 of 9 on AP, p=0.04).

DISCUSSION

This study was prompted by the seeming paradox in the RIVUR findings that rUTI was more common among subjects who were on placebo, and NRS was more common among those with rUTI, yet there was no difference in NRS observed between AP and placebo. Why did the strong effect of AP on rUTI not extend to NRS prevention?

One of the most prominent findings in our study was that when we defined the outcome of interest as NRS specifically associated with rUTI, subjects on AP were significantly less likely than those on placebo to have this outcome. This apparent protective effect of AP on NRS associated with rUTI is consistent with the classic proposed mechanism of reflux nephropathy.[8,9] However, these findings alone do not fully explain the RIVUR trial results and many questions remain. Why did NRS develop in so many subjects (mostly in the AP arm) despite the absence of rUTI during the study period? Is there another mechanism, apart from UTI, that contributes to scar formation? Why was the AP protective effect not observed in overall NRS formation despite a very strong association between rUTI and higher NRS rate (with 4.1 times the odds of NRS developing if the patient had rUTI, and AP known to reduce rUTI by half by the RIVUR report)?[3]

A possibility is that the subjects with NRS without rUTI actually did have rUTI that was undiagnosed. Given the stringent RIVUR protocol and close followup this scenario seems unlikely but must be considered. It is also possible that at least some of the NRS outcomes represent the consequences of insults suffered before study entry, but which continued to evolve during the study period. In such cases the DMSA scan appearance may worsen as progressive inflammation and resultant scarring manifests, despite the absence of any new clinical UTI episodes. While this may explain why some patients without rUTI had NRS, one would expect that such patients would be equally distributed between the AP and placebo arms. Above and beyond these "sterile NRS" cases, one would still expect some NRS to be due to actual rUTI events occurring during the study period. As these events were significantly more common in the placebo arm, we would expect that the NRS associated with these events (rUTI associated NRS) would result in a higher overall incidence of NRS in the placebo arm. Instead, the sterile NRS events occurred slightly more frequently in the AP arm, balancing out the increase in rUTI associated NRS in the placebo arm, resulting in a similar incidence of overall NRS. Why these sterile NRS events occurred disproportionately in the AP group, and their significance, remain difficult to explain.

Table 2. *Breakdown of patients with NRS by renal scarring grades on final DMSA*

	No. Mild	No. Moderate	No. Severe	Total	p Value*
Final scarring grade:					
NRS with rUTI	12	2	4	18	
NRS without documented rUTI	11	6	2	19	
NRS with rUTI (+) study end renal scarring grade:					
AP	2	1	2	5	0.3
Placebo	10	1	2	13	
NRS with rUTI (−) study end renal scarring grade:					
AP	7	3	2	12	0.67
Placebo	4	3	0	7	

* Generated by Fisher's exact tests for all categorical comparisons.

Further complicating the picture is the role of congenital renal dysplasia, which can be difficult to distinguish from acquired renal scarring on DMSA scan. We typically think of congenital dysplasia as being associated with high grade VUR. However, it is also more common in patients diagnosed prenatally with urinary tract dilation (excluded from the RIVUR trial) and it is also associated with diffuse renal scarring.[10–13] We did not observe more cases of global renal scarring in patients with sterile NRS compared to rUTI associated NRS. Furthermore, congenital dysplasia at study entry would have been noted on the baseline DMSA scan, and NRS was based on a change from baseline, diminishing the confounding effect of dysplasia. The overall distribution of NRS severity was similar whether the NRS was rUTI associated or sterile.

Our study findings should be viewed in the context of its limitations. Although the RIVUR trial represented the most comprehensive, best described cohort of such children available, specific cohort characteristics warrant consideration. The RIVUR trial enrolled children 2 months to 6 years old with a heavy female predominance and most with mild to moderate VUR. Children with congenital anatomical abnormalities were excluded from analysis, which may impact the generalizability, especially for patients out of the range of the cohort.[3]

Additionally, the power of our study is limited by the cohort sample size and the overall low rate of NRS. The RIVUR trial was not powered to study NRS as a primary end point and, thus, it was not surprising that NRS was not found to be significantly associated with AP in the initial report. A fair portion (19%, 118 of 607) of the original RIVUR cohort had DMSA studies with inappropriate timing and/or low quality, which led to even lower statistical power to differentiate the AP effect on renal scarring.

Moreover, the relatively short study period may preclude detection of new renal scar formation as some such cases may take more than 2 years to manifest. The "healthy volunteer" phenomenon may also have a role. Patients enrolled in a randomized controlled trial may be less likely to experience renal scarring due to parental/provider vigilance and care at the first signs of UTI. Lastly, RIVUR subjects were recruited after their first or second UTI. Given that the risk of renal scarring after only 1 to 2 UTIs is reported to be quite low, it is not surprising that renal scarring events were uncommon.[14]

CONCLUSIONS

Recurrent UTI was associated with new renal scarring in the RIVUR trial. When limited specifically to new renal scarring associated with rUTI, AP was associated with a decrease in the risk of this outcome. It remains unclear why new renal scarring developed in a proportion of RIVUR subjects without rUTI. The results of this analysis should be carefully interpreted due to the inherent limitations of being a secondary analysis of the RIVUR trial.

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EDITORIAL COMMENTS

With the 2014 publication of the RIVUR trial,[1] pediatric urologists anticipated that questions about the utility of antibiotic prophylaxis in patients with VUR and UTI would be settled. Although the RIVUR trial (and a followup renal scarring analysis) demonstrated fewer recurrent UTIs in patients assigned to AP (reference 6 in article), no difference in NRS was observed among children in the AP vs placebo groups. Thus, practitioner bias about AP largely guides clinical application of RIVUR findings, as those who believe in AP tout the rUTI reduction and those who do not believe in AP emphasize equivalent NRS rates.

To explain why AP reduced rUTI but not NRS, Wang et al conducted a statistically sophisticated secondary analysis of RIVUR data, focusing on patients with NRS and rUTI. Recurrent UTI associated NRS rates were low in the AP and placebo groups (2% vs 5%) and the difference in NRS rates between the groups was statistically significant. There also remains an unexplained subset of patients without rUTI in whom NRS developed. The net result is still no overall difference in NRS when comparing patients receiving AP vs placebo. Ultimately, prior biases will likely continue to guide clinical recommendations about antibiotic prophylaxis among patients with UTI and VUR.

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Although the RIVUR trial findings regarding its primary outcome, namely a 50% reduction in UTI, are unquestionably significant,[1] much controversy has surrounded its secondary outcomes, particularly the lack of renal scar prevention (reference 6 in article).

Why does antibiotic prophylaxis work to prevent UTIs but not renal scarring? Competing theories have been advanced to explain this phenomenon, including that the RIVUR trial's lower than expected renal scarring rate was a "healthy volunteer" effect (8% vs 42% in a previous meta-analysis)[2] or a Hawthorne effect of sorts, with providers and parents treating UTIs more rapidly than in patients not enrolled in a trial.

Against this backdrop, the authors are to be congratulated for this novel analysis of RIVUR data, which provides important insights into the RIVUR trial's most significant quirk. Among patients with baseline and end of study DMSA scans, prophylaxis was associated with a reduction in renal scarring after UTI.

This analysis should be taken with a grain of salt, as secondary analyses are notoriously error prone when focused on selected populations with stringent exclusion criteria. Nonetheless, this work helps to explain (at least in part) one of the more vexing findings of the RIVUR study. Further study is required to understand other key aspects, including why some children without recurrent UTI nonetheless had new renal scars. Clearly, we still have much to learn about vesicoureteral reflux and reflux nephropathy.

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