Corticosteroids to prevent kidney scarring in children with a febrile urinary tract infection: a randomized trial

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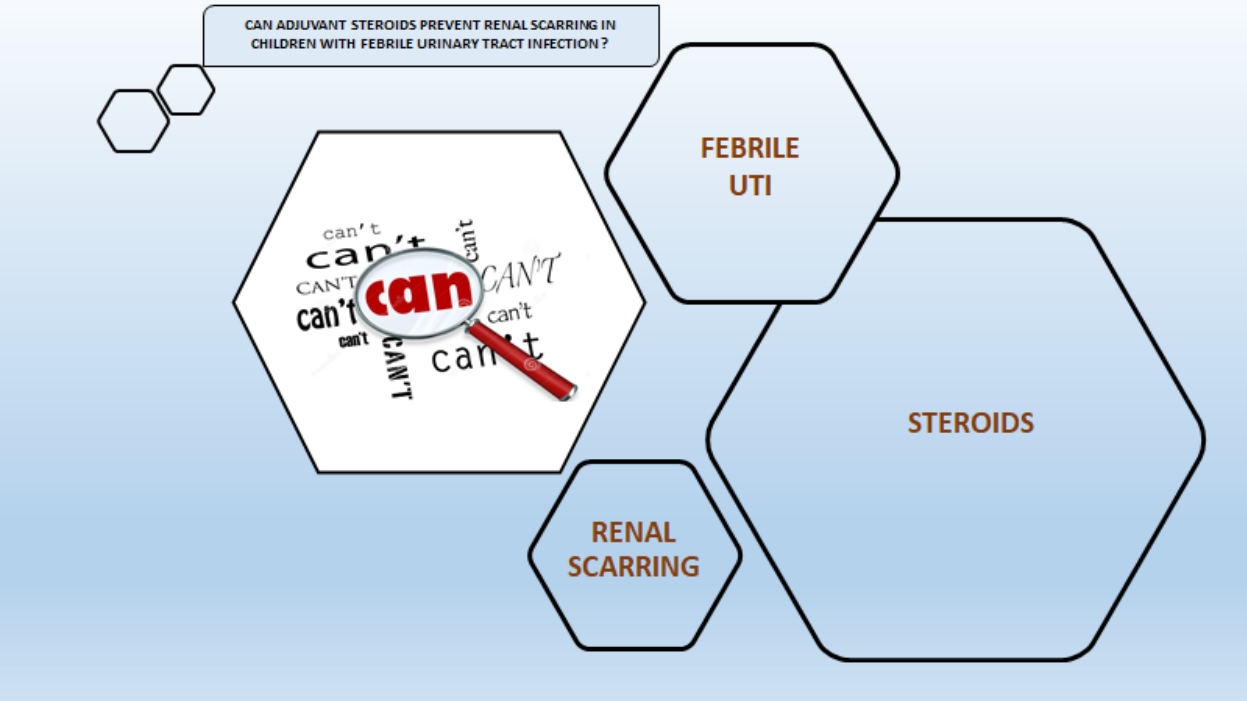
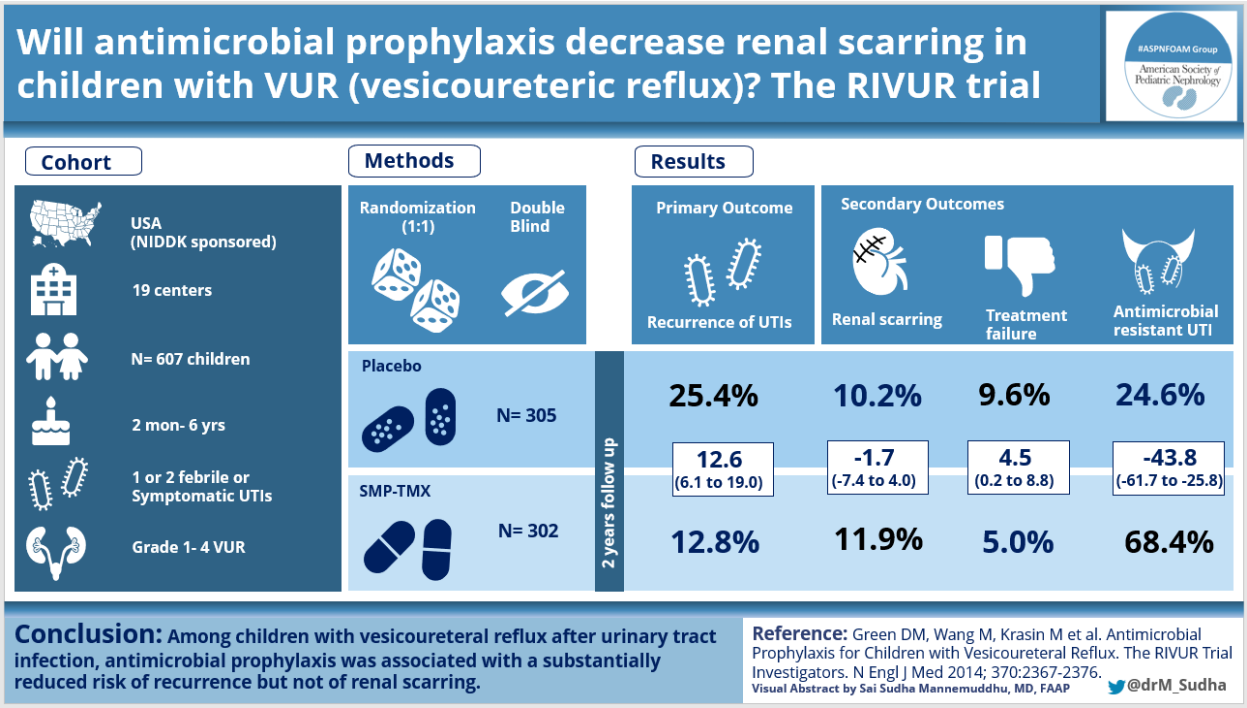


INTRODUCTION

Urinary tract infection (UTI) is the most common and frequently encountered clinical problem in children accounting for approximately 5 to 15% of emergency room visits. Children with febrile UTIs may be at increased risk of kidney damage through scarring in the kidneys that was postulated to occur as a result of acute inflammatory response during the processes of clearing the infection.This can potentially lead to serious morbidity and mortality due to complications like hypertension and end-stage kidney disease (ESKD) at a very young age.

The exact mechanism behind UTIs leading to scarring in the kidneys is unclear and poorly understood and is likely multifactorial. It was hypothesized that scarring in the kidneys occurs as a result of localized infection causing release of inflammatory mediators like cytokinins, chemokines, bacterial toxins/peptides and complement proteins . The infection can be treated but the inflammation caused by these mediators can promote renal scarring.
Current treatment guidelines for febrile UTIs in children primarily focus on correcting the underlying causes and treating the urinary tract infection with antimicrobial agents. But this approach alone is not sufficient in preventing renal scarring of kidneys as demonstrated by the RIVUR study.

Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial was conducted to see if long-term antibiotic prophylaxis prevented recurrence of UTIs, occurrence of renal scars or contributed to antimicrobial resistance. This study concluded that treatment with antibiotics alone did not decrease scarring.

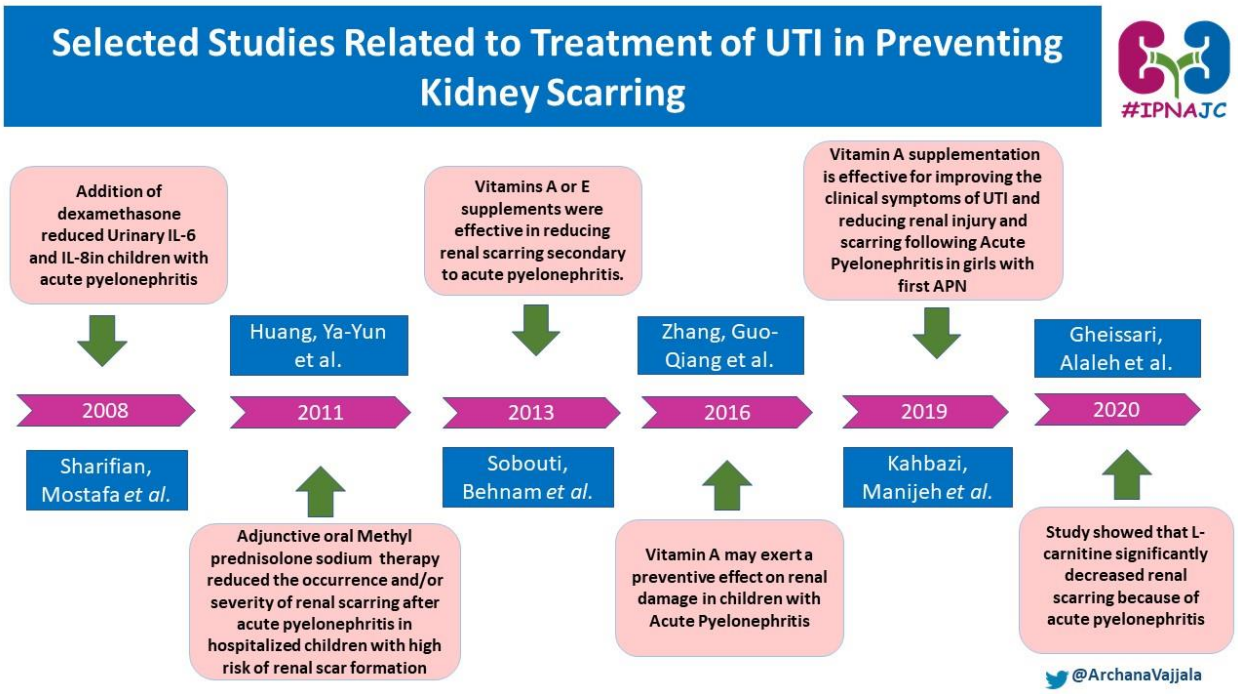


This entertained the idea that preventing the release of inflammatory mediators by the use of anti inflammatory drugs may prevent permanent renal scarring, and was tested by many, with limited success.

Here are some clinical trials in children with UTIs

- Some studies showed that Vitamins A or E supplements reduce scarring in kidneys
- L-carnitine significantly decreases renal scarring due to acute pyelonephritis.
- Vitamin A, an antioxidant, has shown to reduce kidney scarring in four trials (three from Iran and one from China) but all of these trials were limited by a low number of participants (N=248), very few male subjects (% range), and a possible selection and performance bias.
- More recently, a group in Taiwan evaluated the effectiveness of oral methylprednisolone treatment (1.6 mg/kg once a day for 3 days) in patients with acute pyelonephritis and found a significant reduction in scarring in the treatment group but this study was limited by small numbers (N=84)

A study (N=54)on the role of dexamethasone on decreasing urinary cytokines in children with acute pyelonephritis concluded that dexamethasone combined with antibiotics significantly decreases urinary interleukins (UIL) UIL-6 and UIL-8 levels in patients with acute pyelonephritis suggesting that the clinical use of corticosteroids may prevent scar formation following febrile UTI.



Nonetheless, these promising findings set the stage for the current study by Shaikh et al., who performed a large-scale double-blind placebo-controlled randomized clinical trial to assess the use of dexamethasone to prevent kidney scarring in children with febrile UTIs.

This study aimed to determine whether adjuvant corticosteroids will reduce kidney scarring in children diagnosed with febrile UTI treated with antibiotics.

THE STUDY

Question:
Can adjuvant corticosteroids reduce kidney scarring in children with first febrile UTI?

Study design: Double-blind, Placebo-controlled, randomized trial

Funding Source:

Research reported in this publication was supported by the NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) (NIDDK; R01DK087870)

Study centers: Multicenter Study involving 6 hospitals in USA

- Children's Hospital of Pittsburgh, PA
- Nationwide Children's Hospital, in Columbus, OH
- American Family Children's Hospital in Madison, WI
- Children's National Health System, in Washington, DC
- Hasbro Children's Hospital in Providence, RI
- Primary Children's Hospital in Salt Lake City, UT

Allocation: Randomization

Study period: Oct 2011- Aug 2017

Intervention: Stratified according to duration of fever prior to diagnosis (< 48 h vs. ≥ 48 h) and site of enrollment. At each study site, within each stratum, they randomly assigned children in blocks of four in a 1:1 ratio. Children receive a 3-day course of either oral corticosteroid (dexamethasone 0.15 mg/kg/r dose) or placebo, each twice daily.

All children received 10 days of antibiotics (chosen by the treating physician) for UTI

INCLUSION CRITERIA	EXCLUSION CRITERIA
Children aged 2 months to 6 years	Previous history of UTI
First febrile UTI based on urinalysis exhibiting pyuria (≥ 10 WBC/mm3 in an uncentrifuged specimen, ≥ 5 WBC/hpf in a centrifuged specimen, or ≥ 1+leukocyte esterase on dipstick)	Antibiotics use with in the last 7 days of enrollment (except last 48 hours)
Temperature ≥ 38.3 °C	Chronic diseases
	Genitourinary anomaly
	Bagged urine
	Kawasaki disease
	Allergy to dexamethasone
	Steroids use with in the last 14 days of enrollment
	Immune deficiency

Outcomes:

The two main primary outcomes of interest were:

- Kidney scarring
- Severe kidney scarring

- Kidney scarring was determined by the majority of DMSA. Three reference radiologists/nuclear medicine physicians blinded to treatment assignment read the DMSA scans.
- Scarring was defined as photopenic cortical defect(s) with or without loss of contour or volume.
- Severe kidney scarring was defined as having greater than 4 affected renal segments or global atrophy (i.e., diffuse scarring or shrunken kidney)
- All outcome DMSA scans were obtained at least 4 months after febrile UTI

Statistics / Sample Size:

Our planned sample size of 160 evaluable children (i.e., children with a completed late DMSA kidney scan) in each treatment group assumed an $\alpha = 0.05$ and afforded the ability to detect a 10% absolute reduction (from 15 to 5%) in the proportion of children with kidney scarring with a statistical power of 80%
Aim was to detect a difference of 10% because this would translate to a number needed to treat 10. We felt that detecting smaller differences was not a priority in this initial study. All analyses were based on the intention-to treat principle and used two-sided tests.

FOLLOW UP:

To monitor the child's well-being and to ensure compliance (defined as taking at least 80% of scheduled doses) with the study product, parents were contacted by telephone (up to two attempts daily) for 3 days after enrollment or until fever resolved. Children with a positive culture (defined as a catheterized specimen with growth of one or more uropathogens at ≥ 50,000 CFU/mL or clean catch urine specimen with growth of one or more uropathogens at ≥ 100,000 CFU/mL) remained in the study. Children with a negative urine culture were withdrawn from the study, parents were instructed to stop the study product and no outcome assessments were performed. As per standard of care, voiding cystourethrograms were not performed routinely.

ANALYSIS:

Over the period of the study, from 20011–2017 of 3702 children aged 2 months-6 years were screened, 1483 were eligible; of these, we enrolled and randomized 546 children(Fig. 1). After withdrawal of children with negative urine cultures, 197 children randomized to adjuvant corticosteroid and 188 children randomized to placebo were followed prospectively (Fig. 1)

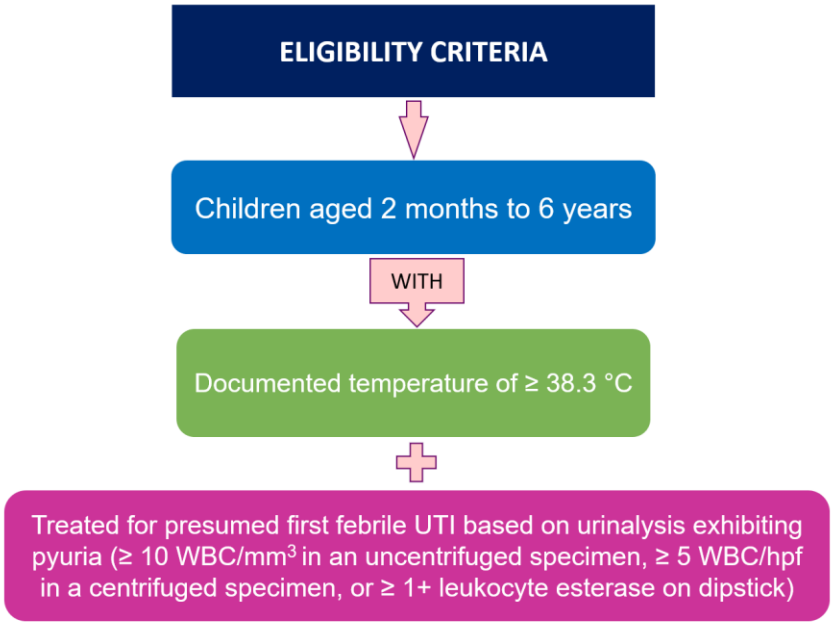


Figure 1 showing enrollment, randomization and followup of children in the study

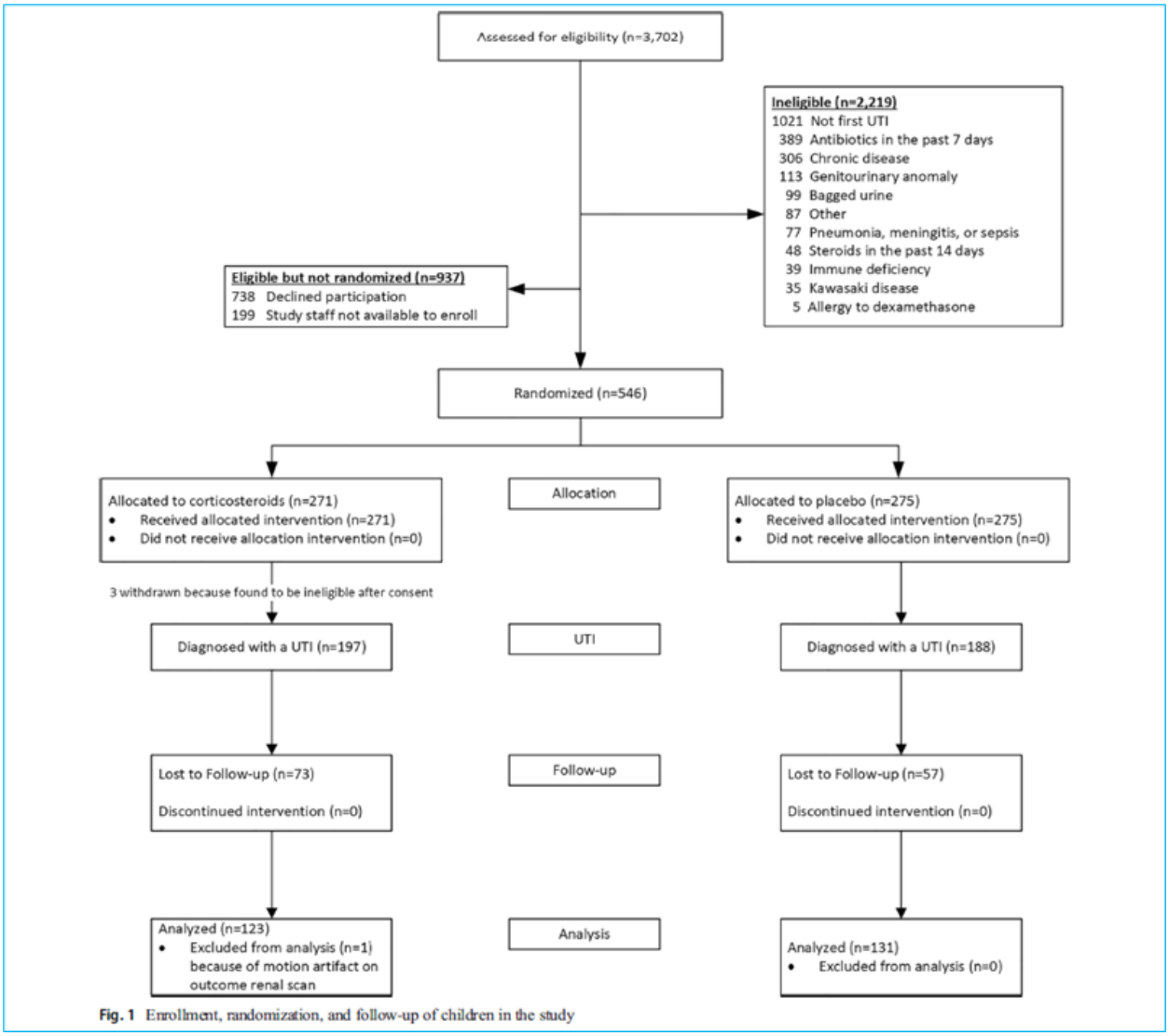


Fig. 1 Enrollment, randomization, and follow-up of children in the study

Characteristic differences

The table 1 below shows the demographic and clinical characteristics of randomized children with a urinary tract infection according to the treatment group.

Table 1 Selected demographic and clinical characteristics of randomized children with a urinary tract infection according to the treatment group[a]

Characteristic	Corticosteroid group ($N = 197$)	Placebo group ($N = 188$)
No. of children (percent)		
Age at entry, months		
2–23	145 (73.6)	132 (70.2)
24–71	52 (26.4)	56 (29.8)
Sex		
Male[b]	14 (7.1)	17 (9.0)
Female	183 (92.9)	171 (91.0)
Race		
Caucasian	128 (65.0)	126 (67.0)
African American	41 (20.8)	28 (14.9)
Other/multiracial	28 (14.2)	34 (18.1)
Health insurance status		
Private	81 (41.1)	97 (51.6)
Medicaid	108 (54.8)	86 (45.7)
None	6 (3.0)	3 (1.6)
Unknown	2 (1.0)	2 (1.1)
Fever duration before diagnosis		
<48 h	110 (55.8)	96 (51.1)
≥ 48 h	87 (44.2)	92 (48.9)

[a] No significant differences noted between the two treatment groups except for mean age (17.2 months vs. 20.8 months in the corticosteroid and placebo groups, respectively, $p = 0.046$)

[b] 13 of 31 (42.0%) of included males were circumcised

No significant differences between treatment groups were apparent except that children in the corticosteroid group were significantly younger. Authors state that, the analysis of the primary outcome for kidney scarring was adjusted for age in
addition to the study stratification variables (duration of fever prior to diagnosis)

RESULTS:

Overall, 34 children (39 kidneys) exhibited the evidence of scarring of kidneys.
Kidney scarring was present in 16.8% (22/131) of children randomized to placebo and in 9.8% (12/123) of children randomized to adjuvant corticosteroids (p = 0.16 adjusting for duration of fever and age; absolute risk reduction of 5.9% [95% CI − 2.2, 14.1]). When the analysis was repeated using the kidney as the experimental unit, the percentage of scarred kidneys in the placebo and adjuvant corticosteroids groups was 9.9% and 5.3%, respectively (p = 0.11). Three children, all in the placebo group, had severe kidney scarring (p = 0.25; absolute risk reduction of 2.3% [95% CI, − 0.3, 4.9])
Agreement between radiologists on the presence of scarring on the outcome DMSA kidney scan was reported as moderate (Fleiss Kappa = 0.52).

Table 2 describes the renal scarring according to treatment group

Table 2 Renal scarring according to the treatment group

Renal scarring	Corticosteroid treatment group	Placebo treatment group	Absolute difference in risk in % (95% CI)	*P* value
	No. of children with renal scarring/total (%)		Percentage points	
Overall	12/123(9.8%)	22/131 (16.8%)	5.9% (− 2.2, 14.1)	0.16[a]
Severe	0/123 (0%)	3/131 (2.3%)	2.3% (− 0.3, 4.9)	0.25

[a] Adjusted for duration of fever before presentation (our stratification variable) and age. Unadjusted *p* value was 0.10

The only predictor of kidney scarring was age (Table 3); older children were more likely to exhibit kidney scarring (the odds [CI] of kidney scarring was 2.8 [1.3–5.8] fold higher in children ≥ 24 months compared with younger children).
Based on these findings, it is evident that age was the only predictor for kidney scarring with older children (>24m) were more likely to exhibit kidney scarring compared to younger children

Table 3 describes the predictors of renal scarring in children with an outcome renal scan

Table 3 Predictors of renal scarring in children with an outcome renal scan

Characteristic at entry*	Corticosteroid ($N = 123$)	Placebo ($N = 131$)	Odds ratio (95% CI)	***P* value**[a]
No. of children with renal scarring/total (%)				
Age				.008
< 24 months	8/95 (8.4)	10/91 (11.0)	Reference	
≥ 24 months	4/28 (14.3)	12/40 (30.0)	2.75 (1.30–5.80)	
Gender				.39
Female	10/114 (8.8)	20/120 (16.7)	Reference	
Male	2/9 (22.2)	2/11 (18.2)	1.67 (0.52–5.38)	
Race				.48
White	6/74 (8.1)	18/89 (20.2)	1.33 (0.60–2.95)	
Other race	6/49 (12.2)	4/42 (9.5)	Reference	
Fever duration before presentation				.48
< 48 h	6/68 (8.8)	10/67 (14.9)	Reference	
≥ 48 h	6/55 (10.9)	12/64 (18.8)	1.30 (0.63–2.68)	
Fever duration before study product dispensed				.70
< 48 h	6/63 (9.5)	9/59 (15.3)	Reference	
≥ 48 h	6/60 (10.0)	13/72 (18.1)	1.16 (0.56–2.41)	
Ibuprofen use within 24 h of enrollment				.56
Yes	4/66 (6.1)	14/78 (17.9)	Reference	
No	8/57 (14.0)	8/53 (15.1)	1.24 (0.60–2.57)	
Ibuprofen use during treatment				.70
Yes	2/31 (6.5)	5/29 (17.2)	Reference	
No	10/92 (10.9)	17/102 (16.7)	1.20 (0.49–2.92)	
Leukocyte esterase				.21
1+ or less	3/18 (16.7)	3/16 (18.8)	Reference	
2+	2/15 (13.3)	7/28 (25.0)	1.12 (0.35–3.57)	
3+	7/90 (7.8)	12/87 (13.8)	0.55 (0.20–1.51)	
Infecting organism				.20
E. coli	11/117 (9.4)	19/121 (15.7)	Reference	
Other organism	1/6 (16.7)	3/10 (30.0)	2.18 (0.65–7.27)	

[a] *P* values listed correspond to prediction of renal scarring; for this, treatment groups were combined and adjusted for. *p* values for interaction (not listed) were all non-significant for the above variables

Children randomized to adjuvant corticosteroids were more likely to exhibit fussiness, otherwise There were no significant differences in selected Adverse events

Table 4 describes the distribution of selected adverse events within the first 2 weeks of taking a study product in the randomized children who received allocated intervention.

Table 4 Distribution of selected adverse events within 2 weeks of taking study product in randomized children who received allocated intervention

Adverse event	Treatment group		*P* value
	Corticosteroid ($n = 271$)	Placebo ($n = 275$)	
Number (percent) of children			
Non-serious adverse events			
Diarrhea	19 (7.0)	16 (5.8)	0.69
Fussiness	25 (9.2)	8 (2.9)	0.004
Vomiting	2 (0.7)	7 (2.5)	0.18
Sleepier than usual	4 (1.5)	1 (0.4)	0.21
Apparent abdominal pain	1 (0.4)	0	0.50
Serious adverse events			
Hospitalization (any cause)[a]	6 (2.2)	7 (2.5)	> 0.99
Bacteremia	1 (0.4)	1 (0.4)	> 0.99
Renal abscess	0	0	N/A

[a] In children initially managed as outpatients

COMPLIANCE:

Of the children with data on compliance, 93.4% (171/183) of children randomized to corticosteroid and 95.1% (176/185) of children randomized to placebo reportedly received at least 80% of scheduled study product doses (p = 0.63)
The proportion of evaluable children (i.e., children who returned for a DMSA kidney scan) in each group was 62.9% (124/197) and 69.7% (131/188) for the corticosteroid and placebo groups, respectively.

DISCUSSION:

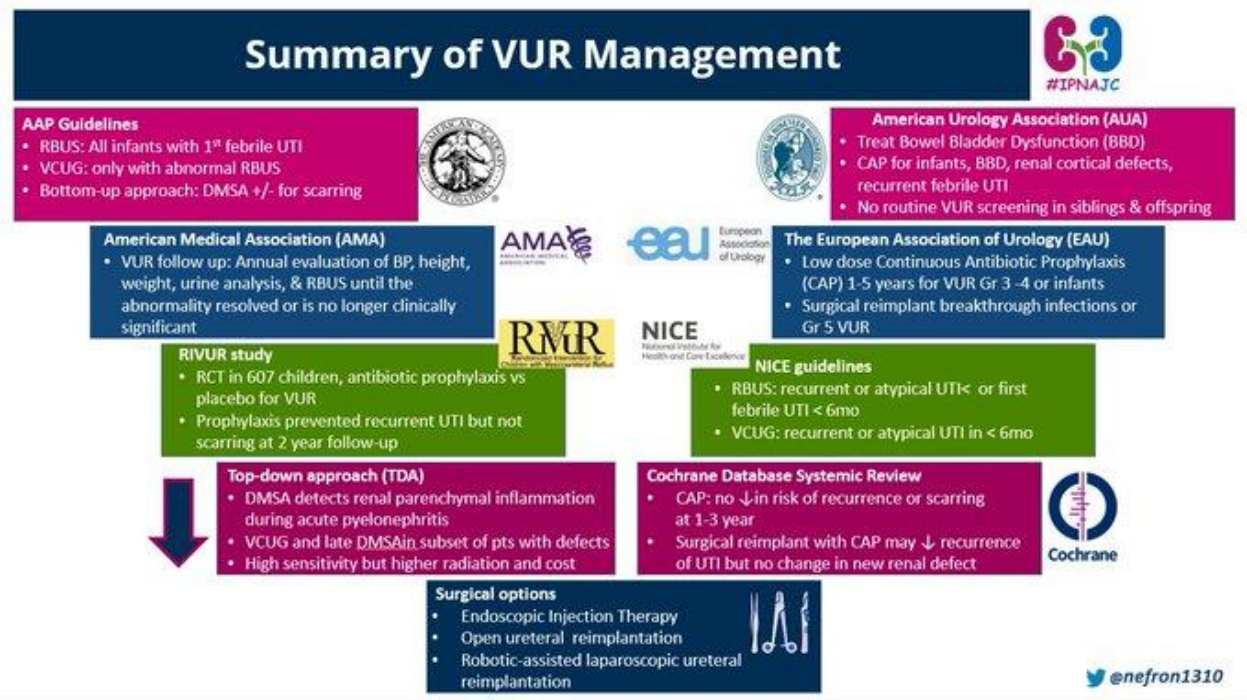
- According to the findings of the study, children treated with adjuvant steroids along with antibiotics for first febrile UTI had developed fewer kidney scars compared to children who received antibiotics alone.

- Regarding predictors of kidney scarring, children aged 2 years and older have significantly greater odds of kidney scarring which is consistent with previous studies.

- This study adds to the existing literature the effectiveness of adjuvant steroids with antibiotics in reducing kidney scarring in children with first febrile UTI.

- Children with high grade VUR are known to be at higher risk of kidney scarring, and these patients are more likely to benefit from use of corticosteroids.

Here is a VA summarizing the various management guidelines from various societies by [shweta shah]



Here is an excellent table summarizing the diagnostic recommendations for UTI/ VUR by **Swasti Chaturvedi**

Summary of UTI/VUR Diagnostic recommendations

#IPNAJC

SOCIETY	AGE	US	VCUG	DMSA
NICE 2007	<6 mo	All children	Atypical/Recurrent UTI	Atypical/Recurrent UTI
	6mo-3 yrs	Atypical/Recurrent UTI	Atypical/Recurrent UTI AND specific features	Atypical/Recurrent UTI
	>3 yrs	Atypical/Recurrent UTI	Not indicated	Recurrent UTI
AAP 2011	≤24 mo	All children	Abnormal US or other specific circumstances	
CPS 2014	< 2yrs	All children	Abnormal US/Recurrent UTI	Only if UTI diagnosis in doubt
EAU/ESPU2016		All children	Either VCUG or DMSA is indicated in bottom-up or top-down approach	
Italian 2011	<36 mo	All children	Abnormal US or risk factors	Abnormal US or VUR

NICE: National Institute for Health and Care Excellence; AAP: American Academy of Pediatrics; CPS: Canadian Paediatric Society; EAU: European Association of Urology; ESPU: European Society for Pediatric Urology

@SwastiThinks

STRENGTHS:

- largest study focusing on the efficacy of steroids in preventing renal scarring following a febrile UTI.
- This study included all children with febrile UTI, unlike the previous studies that mainly concentrated on the efficacy of steroids in children with pyelonephritis
- This study avoided specimens collected from perineal bags
- Interpretation of the DMSA scans by 3 independent radiologists/ nuclear medicine physicians has added strength to the study.

LIMITATIONS:

- Inadequate sample size because of high false positive results on urine analysis highlighting the need to address the inadequacies of the available screening test for UTI

- A high attrition rate was observed owing to lack of engagement of some parents in the study and a long follow up period for DMSA scan following their child's fUTI

- For some parents the time required to travel to the tertiary regional hospital, the need for intravenous access, and exposure to radiation were concerns

- There was a lack of baseline DMSA scan, to determine the existence of kidney dysplasia/hypoplasia (considered to be a phenocopy of a severely scarred kidney on

DMSA scan) and to rule out the presence of preexisting kidney scars. The authors anticipated a low rate of kidney scarring and that likely equal numbers would have been assigned to each treatment arm. Baseline DMSA scan detering recruitment was also a concern. The radiation exposure of the DMSA scan (approx equivalent to 28 chest X-rays/yr) may have resulted in some failures in recruitment and presenting for the follow-up DMSA scan post-infection

Interestingly, in one study that assessed patient and family satisfaction with a number of genitourinary imaging modalities, the voiding cystourethrogram and the DMSA scan were deemed equivalent in the pain inflicted on the child, the length of the procedure, and the anxiety that was induced in the child

- There was an underrepresentation of boys with UTIs who often have an abnormal DMSA scan, often due to congenital hypoplasia/dysplasia. Only 8% of the children studied were boys. Children of Hispanic descent known to have higher risk of scarring, were also underrepresented in the study, encompassing only 16% of the cohort. Furthermore, the Hispanic children who were enrolled in the study were significantly less likely to return for the follow-up DMSA scan

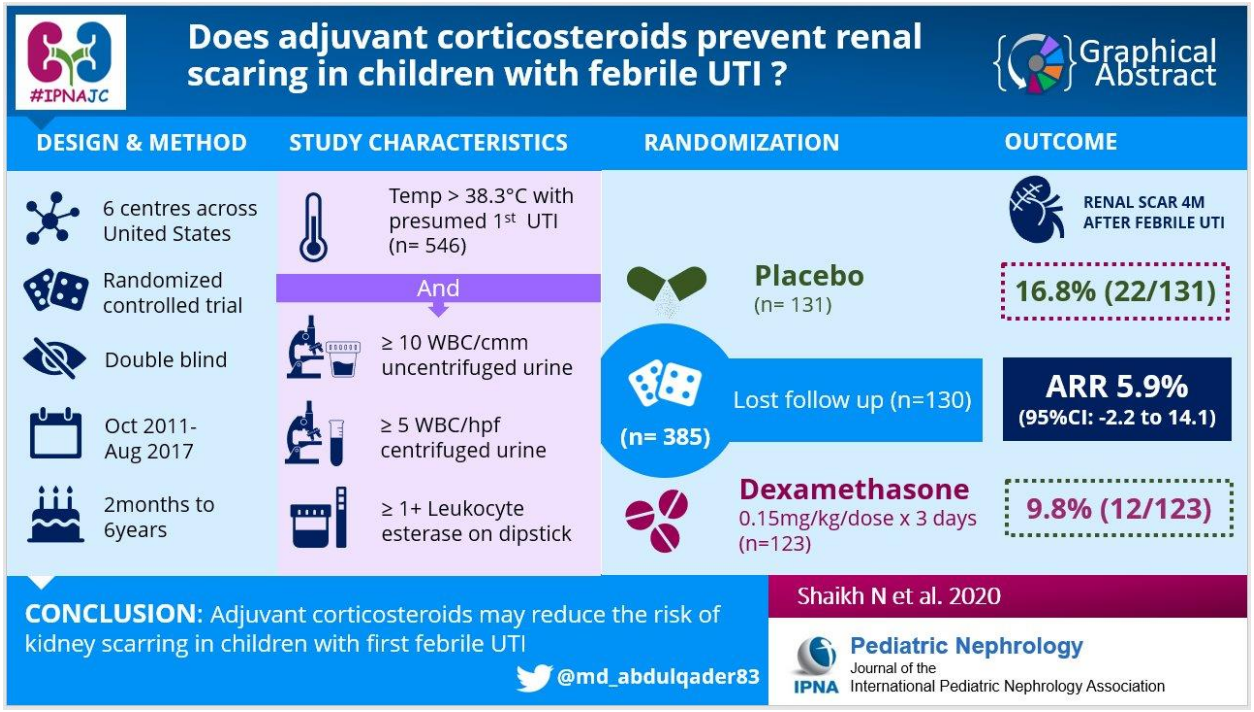
FUTURE STUDY SUGGESTIONS:

There are very few studies looking at biomarkers of children at high risk of kidney scarring from UTIs. It would have been extremely valuable to include some assessment of urine and blood biomarkers in this study to better understand the pathogenesis of inflammation and scar formation.
One study from Japan of 49 infants examined a number of potential urinary biomarkers and identified angiotensin to be highly correlated with kidney scarring . Future studies need to incorporate urinary biomarkers to understand the groups that are at high risk of kidney scarring. This could then be used to identify specific groups of children who would be most likely to benefit from treatments to prevent scarring.

CONCLUSION:

According to this study, children randomized to adjuvant corticosteroids tended to develop fewer kidney scars compared to those who were randomized to receive placebo but a statistically significant difference was not achieved. This study was also limited by not reaching its intended sample size making it challenging to interpret the results. Hence, future studies, focusing on development of renal scarring in children with fUTI treated with steroids may be warranted

Here is an excellent VA summarizing the study by Abdul Qader



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