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Concise Communication

Outcomes in children with vesicoureteral reflux receiving antibiotic prophylaxis

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Abstract

Antibiotic prophylaxis in children with vesicoureteral reflux (VUR) remains controversial. We reviewed patients diagnosed with VUR after an index urinary tract infection (UTI) who subsequently received antibiotic prophylaxis. Recurrent UTIs in patients with and without urologic anomalies occurred in 57% and 33%, respectively. Multidrug-resistant organisms accounted for 25% of first UTI recurrences.

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Introduction

Vesicoureteral reflux (VUR) is prevalent among children diagnosed with febrile urinary tract infections (UTIs), occurring in up to 35% of children with a first UTI, with underlying urologic anomalies being a common risk factor.[1] Daily antibiotic prophylaxis has been utilized in children with VUR, in an effort to reduce UTI recurrence, but remains variable by institution and among providers. The American Academy of Pediatrics (AAP) has reemphasized with recent guideline iterations, the growing body of evidence suggesting a lack of benefit from daily antibiotic prophylaxis and global concerns with antibiotic resistance.[2] Our study aimed to provide additional data for this practice by determining incidence of UTI recurrence in children receiving antibiotic prophylaxis for VUR, including those with urologic anomalies.

Methods

Study design

We conducted a retrospective evaluation of children receiving care at Riley Hospital for Children [Indianapolis, IN] for an inpatient admission or outpatient urology clinic visit from January 1, 2018 to June 30, 2019. Patients aged 0–71 months were eligible for inclusion if they were diagnosed with VUR via a voiding cystourethrogram (VCUG) after a first or second UTI (index infection). Children with all grades of VUR were eligible for inclusion. UTI was defined as pyuria [≥ 10 white blood cells (WBCs) per μL, or ≥ 5 WBC per high-power field, or positive leukocyte esterase on dipstick] and presence of ≥ 50,000 CFUs per mL of one uropathogen by urine culture. Children were excluded if antibiotic prophylaxis was initiated greater than four months after the index UTI, multiple prophylactic antibiotics were prescribed concurrently, or they underwent a urologic intervention and received less than six months of antibiotic prophylaxis prior. Ethical review and approval were given by the Indiana University Institutional Review Board (IRB).

The primary outcome was the incidence of a recurrent UTI within 24 months after initiation of antibiotic prophylaxis. Children with urologic anomalies were excluded from the primary outcome as a confounder, given the known association with recurrent UTIs but remain an essential population to describe given the paucity of data for this topic. Secondary outcomes included incidence of a recurrent UTI in patients with urologic anomalies, along with incidence of antibiotic resistance, and difference in time to UTI recurrence between patients with and without urologic anomalies. Recurrent UTI was defined as a UTI occurring greater than two weeks from the last day of appropriate treatment for the preceding UTI, or following a negative urine culture, or a UTI with a new organism regardless of the previous treatment course.

Data collection

Baseline characteristics including age, sex, circumcision status, number of prior UTIs, bowel/bladder dysfunction, presence of additional urologic anomalies (ie, hydronephrosis, ectopic ureters,

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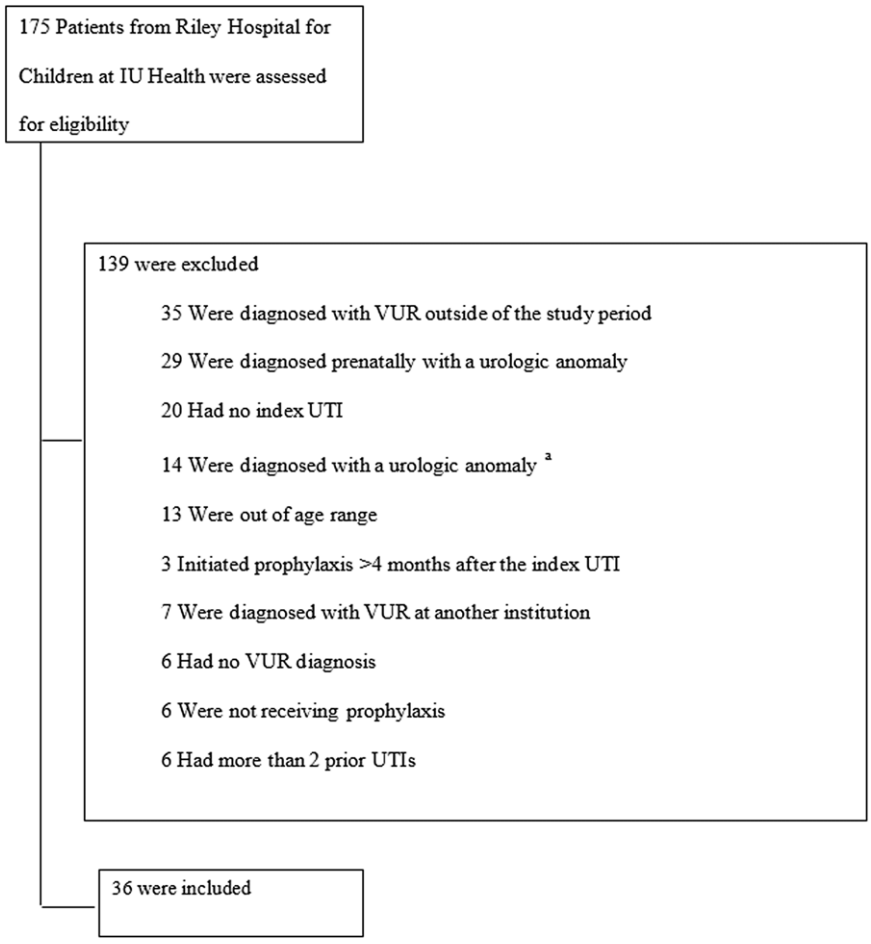

Figure 1. Eligibility flow diagram.

complete ureteral duplication, ureterocele, posterior urethral valve, solitary kidney, multi-cystic dysplastic kidney, neurogenic bladder, pelvic kidney or fused kidney, ureterovesical junction obstruction), and VUR status were determined from chart review.

Data analysis

Descriptive statistics were generated to describe patient characteristics. Frequency and percentage values were given for categorical measures, while continuous variables were measured using median, interquartile range, and range values. Kaplan–Meier and Log Rank procedures compared the time to UTI recurrence between patients with and without urologic anomalies. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) with a 5% significance level.

Results

Thirty-six of 175 patients were eligible for inclusion for the primary analysis (Figure 1). Baseline characteristics are presented in Table 1. The median age was 0.8 years, with a female sex predominance. No patients were diagnosed with grade V VUR. Recurrent UTIs occurred in 12 of 36 patients (33%) within 24 months. The median time to the first recurrent UTI was 3.4 months (interquartile range: 1.7–8.6 months) with patients experiencing up to 3 recurrences. Patients with urologic anomalies had the highest rate of recurrence with 8 of 14 patients (57%). The median time to the first recurrence was 8.7 months (interquartile range: 3.6–12.3 months) with patients experiencing up to 4 recurrences. There was no significant difference in time to UTI recurrence between patients with and without urologic anomalies (Supplementary Figure 1).

33% of organisms cultured at the time of the first UTI recurrence were resistant to the initial prophylactic antibiotic and 25% of organisms met the Infectious Diseases Society of America criteria for multidrug-resistant organism (MDRO) in those without urologic anomalies. 63% of organisms cultured at the time of first UTI recurrence were resistant to the initial prophylactic antibiotic and 25% of organisms met MDRO criteria in those with urologic anomalies (Supplementary Table 1).

Discussion

The major findings of this study are that 33% of patients without urologic anomalies receiving antibiotic prophylaxis had recurrence of UTIs and 33% of organisms cultured at the time of first recurrence were resistant to the initial prophylactic antibiotic. Patients with urologic anomalies had the highest rate of recurrence at 57% within 24 months.

Table 1. Baseline characteristics

Characteristic	Prophylaxis (N = 36)[a]
Age (years)	0.80 (0.40–1.75)[b]
Male sex	6 (17)
Circumcised	1 (17)
Race	
White	31 (86)
African American	0 (0)
Asian	3 (8)
Not specified/other	2 (6)
Ethnicity	
Non-Hispanic	29 (81)
Hispanic	4 (11)
Not specified	3 (8)
History of UTI	
Index infection only	32 (89)
2 infections	4 (11)
Bowel and/or bladder dysfunction	2 (6)
Bilateral VUR	21 (58)
Highest grade of VUR	
None or Unknown Grade	0 (0)
Grade I-II	13 (36)
Grade III-V	23 (64)
Organisms from index UTI	
Escherichia coli	26 (72)
Other	10 (28)
Time to prophylaxis initiation (days)[c]	30 (19–50)[b]
Prophylactic antibiotic	
Trimethoprim-sulfamethoxazole	22 (61)
Amoxicillin	6 (17)
Other	8 (22)

[a]Presented as number (%); unless otherwise specified
[b]Presented as median (interquartile range)
[c]Time to prophylaxis initiation was defined as the time from the date of the index UTI to the date of antibiotic prophylaxis initiation

Data from randomized, controlled trials and systematic reviews evaluating antibiotic prophylaxis in children with VUR diagnosed after a UTI have also found no difference in the incidence of recurrent UTI.[3–6] Notably, a recent randomized, open-label trial evaluated the efficacy of antibiotic prophylaxis in preventing UTI in infants with grade III-IV VUR, which showed a small, but significant benefit in preventing a first UTI, despite an increase in antibiotic resistance in UTI isolates. Interestingly, new kidney scars and estimated glomerular filtration rate (GFR) at 24 months did not significantly differ between groups.[7]

Given the conflicting evidence available, some investigators have attempted to identify risk factors for UTI recurrence, in which benefits may outweigh the risks of antibiotic prophylaxis.[8–10] The RIVUR trial secondary analyses, for example, identified bladder and bowel dysfunction as a possible risk factor.[8] Our description of a subset of patients with urologic anomalies receiving antibiotic prophylaxis also showed a high rate of UTI recurrence, highlighting the risk of antibiotic prophylaxis in a group of patients who may benefit from a procedural intervention for secondary VUR.

Antimicrobial resistance continues to be one of the greatest threats to global public health. Judicious use of all antimicrobials is imperative to combating rising antimicrobial resistance rates. Overall resistance trends found in this study, including 25% of children infected with a multidrug-resistant organism, brings to question opportunities to modify risk factors for antimicrobial resistance and identify risk factors which necessitate continued antimicrobial use, especially given the RIVUR trial found even higher rates of resistance to the prophylactic antibiotic.[8] Many guidelines have revised their antibiotic prophylaxis recommendations to include further restrictions, noting the increasing evidence suggesting no benefit and the propensity to increase antimicrobial resistance.[2]

This study has several limitations and highlights the difficulty of assessing real-world outcomes of widespread antibiotic prophylaxis for children with VUR after an index UTI. Although study design was optimized as permitted, the single center, retrospective design and inclusion of a small sample size due to stringent inclusion criteria may limit its generalizability. We were also only able to evaluate patients who had received antibiotic prophylaxis and daily compliance was assumed. Incidence of renal scarring and reflux nephropathy were not evaluated due to limited availability of nuclear medicine studies among our patients.

These data, however, fill a significant gap in available literature by expounding upon recurrent UTI resistance patterns after exposure to prophylaxis, including patients with urologic anomalies. This study provided a thorough evaluation of collateral resistance to other antibiotic classes and the incidence of multidrug resistance, which can have lifelong, negative impacts on these young patients. Our study adds to the expanding evidence suggesting a lack of benefit from antibiotic prophylaxis and risk of harm with the growing threat of antibiotic resistance. We implore providers to use antimicrobials judiciously, consider non-pharmacologic interventions as appropriate, and cautiously evaluate the risk factors for UTI recurrence, which may benefit from prophylaxis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ash.2024.497

Data availability statement. The data sets generated during and/or analyzed for this study are available from the corresponding author on reasonable request.

Author contributions. M.T and M.K jointly conceived the study. M.T. and K.T. performed the chart reviews. M.T. and L.B. performed the data analysis. M.T, K.T., M.K., J.C., R.H., and J.S wrote the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages.

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References

1. Finnell SM, Carroll AE, Downs SM. Technical report—diagnosis and management of an initial UTI in febrile infants and young children. *Pediatrics* 2011;128:e749–70.
2. Mattoo TK, Shaikh N, Nelson CP. Contemporary management of urinary tract infection in children. *Pediatrics* 2021;147.

3. Hari P, Hari S, Sinha A, Kumar R, Kapil A, Pandey RM, *et al.* Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. *Pediatr Nephrol* 2015;30:479–486.
4. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, *et al.* Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics* 2008;121:e1489–94.
5. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev* 2019;4: Cd001534.
6. Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev* 2019;2:Cd001532.
7. Morello W, Baskin E, Jankauskiene A, Yalcinkaya F, Zurowska A, Puccio G, *et al.* Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. *N Engl J Med* 2023;389:987–997.
8. Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, *et al.* Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014;370:2367–2376.
9. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *Jama* 2007;298:179–186.
10. Zhao B, Ivanova A, Shaikh N. Antimicrobial prophylaxis for vesicoureteral reflux: which subgroups of children benefit the most? *Pediatr Nephrol* 2024;39:1859–1863.