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Uropathogen Resistance and Antibiotic Prophylaxis: A Meta-analysis

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abstract

CONTEXT: Limited data exist regarding uropathogen resistance in randomized controlled trials of urinary tract infection (UTI) prevention and antibiotic prophylaxis.

OBJECTIVE: To assess the effect of prophylaxis on developing a multidrug-resistant first recurrent UTI among children with vesicoureteral reflux.

DATA SOURCES: Cochrane Kidney and Transplant Specialized Register through May 25, 2017.

STUDY SELECTION: Randomized controlled trials of patients ≤18 years of age with a history of vesicoureteral reflux being treated with continuous antibiotic prophylaxis compared with no treatment or placebo with available antibiotic sensitivity profiles.

DATA EXTRACTION: Two independent observers abstracted data and assessed quality and validity per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Adjusted meta-analyses were performed by using a mixed-effects logistic regression model.

RESULTS: One thousand two hundred and ninety-nine patients contributed 224 UTIs. Patients treated with prophylaxis were more likely to have a multidrug-resistant infection (33% vs 6%, $P < .001$) and were more likely to receive broad-spectrum antibiotics (68% vs 49%, $P = .004$). Those receiving prophylaxis had 6.4 times the odds (95% confidence interval: 2.7–15.6) of developing a multidrug-resistant infection. One multidrug-resistant infection would develop for every 21 reflux patients treated with prophylaxis.

LIMITATIONS: Variables that may contribute to resistance such as medication adherence and antibiotic exposure for other illnesses could not be evaluated.

CONCLUSIONS: Prophylaxis increases the risk of multidrug resistance among recurrent infections. This has important implications in the risk-benefit assessment of prophylaxis as a management strategy and in the selection of empirical treatment of breakthrough infections in prophylaxis patients.

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Children with vesicoureteral reflux (VUR) may be managed with continuous antibiotic prophylaxis with the aim of preventing recurrent urinary tract infections (UTIs).[1–3] Although several meta-analyses have been performed to better understand the effectiveness of antibiotic prophylaxis, there has been limited evaluation of potential disadvantages.

Children being treated with prolonged administration of antibiotics have been found to have an increased risk of resistance.[4,5] In most randomized controlled trials (RCTs), authors have published data on uropathogen resistance rates for the prophylactic agent employed. However, in addition to causing uropathogen resistance to the prophylactic agent used for UTI prevention, the development of antibiotic multidrug resistance may also occur. In this study, we evaluated the impact of continuous antibiotic prophylaxis on the development of recurrent UTI with acquired multidrug resistance, hypothesizing that continuous antibiotic prophylaxis would increase multidrug-resistant UTI.

METHODS

Inclusion Criteria and Search Strategy

This individual patient data meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered on The Open Science Framework (accessible at osf.io/d7k2b).[6] RCTs were considered for inclusion if they met the following criteria: (1) age ≤18 years with a history of VUR, (2) treatment with continuous antibiotic prophylaxis for ≥3 months compared with no treatment or placebo, and (3) antibiotic sensitivity profiles for recurrent UTI.

The Cochrane Kidney and Transplant Specialized Register was searched by the information specialist through May 25, 2017, by using search terms based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, including "vesicoureteral reflux," "vesicoureteric reflux," "vesico-ureteral reflux," and "vesico-ureteric reflux."[6,7] The register contains studies from the following: (1) monthly searches of the Cochrane Central Register of Controlled Trials, (2) weekly searches of Medline OvidSP, (3) handsearching of journals and conference proceedings, (4) searching of the current year of Embase OvidSP, (5) weekly current awareness alerts for selected journals, and (6) searches of the International Clinical Trials Register Search Portal and clinicaltrials.gov.[8]

Data Abstraction

All abstracts were independently assessed by 2 reviewers (R.E.S., H.L.C.). For those meeting selection criteria, full-text articles were examined and study-level data were abstracted, including study country, year the study was published, conflict of interest disclosure, and the study fundings.[7,9] Corresponding study authors were contacted to obtain individual patient data. If authors were unable to provide individual patient data or uropathogenic data, the study was excluded from analyses. Additionally, data from patients without VUR were excluded from all analyses.

The primary outcome was multidrug-resistant first recurrent UTI. Acquired multidrug resistance was defined by standardized terminology published by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.[10] Multidrug-resistant UTIs were defined by uropathogens with resistance to any antibiotic in ≥3 antibiotic classes (excluding those to which they are intrinsically resistant).

Risk of Bias Assessment

Working independently, 2 reviewers (R.E.S., H.L.C.) used the Cochrane risk of bias tool and assessed risk of bias in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[11] As per Cochrane guidelines, each domain was assigned high risk, low risk, or unclear risk if there was not sufficient information to make a clear judgement. Overall risk of bias was judged as "low risk," "some concerns," and "high risk." Analysis was stratified by low risk versus higher risk of bias ("some concerns" and "high risk of bias").[12] Publication bias was evaluated by funnel-plot analysis.

Statistical Methods

Comparisons of patient characteristics between the treatment groups (continuous antibiotic prophylaxis versus placebo and/or control) were performed by using Fisher's exact test or χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables. We conducted both unadjusted and adjusted meta-analyses of the association between treatment group and the primary outcome of multidrug-resistant first recurrent UTI among all first recurrent UTIs corresponding to the "one-stage" approach as outlined by Stewart et al.[13] In the unadjusted analyses, we performed DerSimonian and Laird[14] random effects meta-analyses of the odds ratio using fixed continuity correction. Adjusted analyses were performed to control for potential confounders by using mixed-effects logistic regression models. These models included random effects for the treatment group by study and fixed effects for

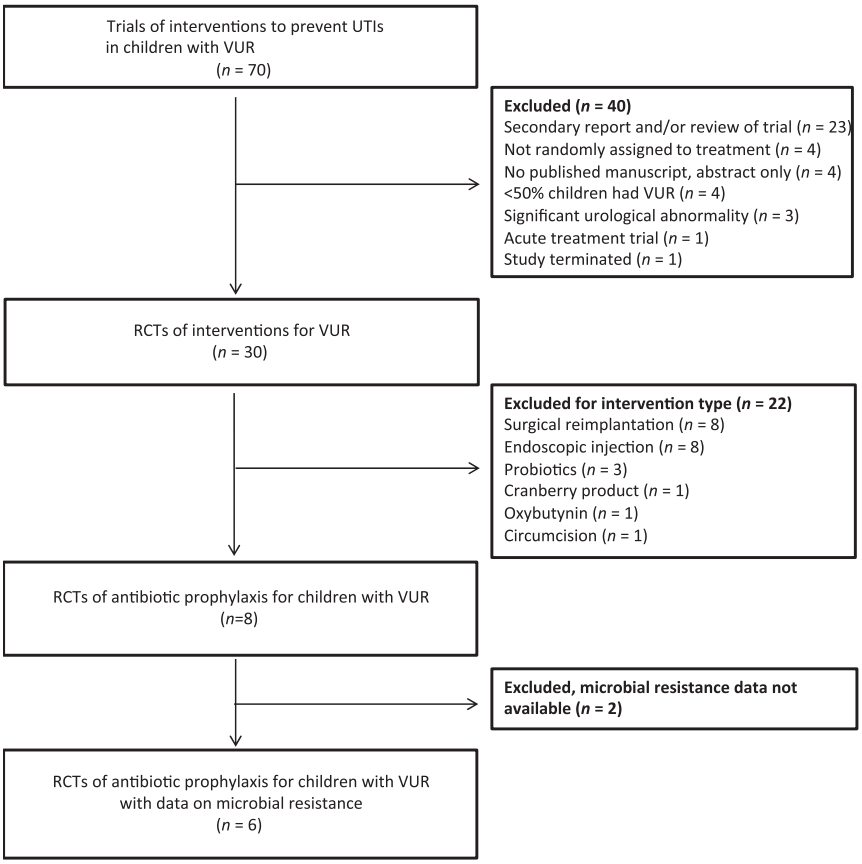

FIGURE 1
Flowchart summarizing literature search results.

age at study enrollment, sex, VUR grade, and history of previous UTI. Study heterogeneity was assessed by using the Higgins and Thompson[15] I^2 method. Risk ratio, risk difference, and number needed to treat were calculated by pooling all patients with VUR across studies within each treatment arm. In additional analyses on patients treated with prophylaxis, we used mixed-effects logistic regression to examine the association of prophylaxis duration and outcomes. All statistical analyses were performed by using Stata 15 (Stata Corp, College Station, TX).

RESULTS

Search Results

Seventy publications were identified by using our search criteria. Thirty studies were RCTs of children with VUR with 8 investigating continuous antibiotic prophylaxis. Two studies were excluded because individual patient-level uropathogenic data could not be provided,[16,17] leaving 6 studies that fulfilled the inclusion criteria (Fig 1).[18–23]

Risk of Bias in Included Studies

Three studies were at high risk for bias because of inadequate blinding.[18,19,21] One of these studies was also at unclear risk for additional bias because randomization was not clearly described.[19] Outcome reporting may be biased in 3 studies due to the method of urine collection.[19,24] Two studies included bagged urine samples,[19,21] and authors of 1 study failed to describe how urine was collected in non–toilet-trained children (Supplemental Fig 3).[22] Funnel plots did not reveal visual evidence of publication bias (Supplemental Fig 4).

First Recurrent UTI

One thousand two hundred and ninety-nine patients with VUR were included in the final analysis, contributing 224 first recurrent UTIs (Table 1). The median patient age at enrollment was 1.3 years (range 0.1–11 years), and female patients made up 83% (186 out of 224) of the cohort. Of all patients with a first recurrent UTI, 27% had nondilating VUR (grades 1 and 2), and 73% had dilating VUR (grades 3–5), which was not statistically different between the control and prophylaxis groups ($P = .62$). Of first recurrent UTIs, 86% were *Escherichia coli*, which was not statistically significant between control (86%) and prophylaxis (85%) groups ($P = .74$). Of first recurrent UTIs by study, none of those in Brandström et al[21] had multidrug resistance, whereas 62% of those in Hari et al[22] had multidrug resistance. The remaining studies had 9% to 25% with multidrug resistance (Table 2). Patients being treated with prophylaxis were more likely to have a multidrug-resistant (33% vs 6%, $P < .001$) first recurrent UTI, and they were subsequently more likely to receive a broad-spectrum antibiotic (68% vs 49%, $P = .004$) for treatment of the recurrent UTI.

Among first recurrent UTIs, patients receiving continuous antibiotic prophylaxis were more likely to develop a multidrug-resistant infection compared with those in the control group (unadjusted odds ratio 5.7; 95% confidence interval [CI]: 2.4–13.5). Studies in which there was a low risk of bias had an odds ratio of 6.6 (95% CI: 2.4–18.3), and those with a higher risk of bias had an odds ratio of 4.1 (95% CI: 0.9–20.0) (Fig 2). After adjusting for age at study enrollment, sex, VUR grade, and history of previous UTI, individuals receiving prophylaxis who developed a recurrent UTI had 6.4 times the odds (95% CI: 2.7–15.6) of a multidrug-resistant first infection compared with those in the control

TABLE 1 Characteristics of Patients With First Recurrent UTI Among Children With VUR

Patient and UTI Characteristics	All UTI			
	Control Group, *n* = 125 (56%)	Prophylaxis Group, *n* = 99 (44%)	Total First Recurrent UTI, *n* = 224	*P*
Study, *n* (%)				.003
Pennesi et al[18] (Italy)	15 (12)	18 (18)	33 (15)	
Roussey-Kesler et al[19] (France)	10 (8)	14 (14)	24 (11)	
Craig et al[20] (Australia)	13 (10)	11 (11)	24 (11)	
Brandström et al[21] (Sweden)	26 (21)	10 (10)	36 (16)	
Hari et al[22] (India)	2 (2)	11 (11)	13 (6)	
Hoberman et al[23] (United States)	59 (47)	35 (35)	94 (42)	
Median age at enrollment, y	1.4	1.2	1.3	.88
Female sex, *n* (%)	104 (83)	82 (83)	186 (83)	.94
VUR grade, *n* (%)				.62
Nondilating (grades 1, 2)	35 (28)	25 (25)	60 (27)	
Dilating (grades 3, 4, 5)	89 (71)	74 (75)	163 (73)	
Unspecified grade	1 (1)	0 (0)	1 (<1)	
UTI before study, *n* (%)	10 (8)	26 (26)	36 (16)	<.001
Enrollment UTI characteristics, *n* (%)				
Infection with *E coli*[a]	104 (85)	74 (84)	178 (84)	.93
Multidrug-resistant infection[b]	19 (16)	10 (12)	29 (14)	.42
Prophylaxis drug, *n* (%)				N/A
TMP and/or SMX	N/A	88 (89)	N/A	
TMP	N/A	9 (9)	N/A	
TMP and/or SMX + amoxicillin	N/A	1 (1)	N/A	
Nitrofurantoin	N/A	1 (1)	N/A	
Fever[c], *n* (%)	98 (79)	79 (82)	177 (80)	.55
New or worsening scar on DMSA[d], *n* (%)	25 (22)	24 (28)	49 (25)	.37
First recurrent UTI organism, *n* (%)				
E coli	108 (86)	84 (85)	192 (86)	.74

P values for categorical variables are from χ^2 tests. *P* values for continuous variables are from a Wilcoxon rank-sum test. *P* value for study is from a Fisher's exact test. Some percentages do not total to 100% because of rounding. DMSA, dimercaptosuccinic acid scan; N/A, not applicable; SMX, sulfamethoxazole; TMP, trimethoprim.

[a] Data not available for 2 patients in control groups and 11 patients in the prophylaxis group. A total of 211 patients included in this analysis.

[b] Data not available for 4 patients in control groups and 14 patients in the prophylaxis group. A total of 206 patients included in this analysis.

[c] Data not available for 1 patient in control groups and 3 patients in the prophylaxis group. A total of 220 patients included in this analysis.

[d] Data not available for 13 patients in control groups and 13 patients in the prophylaxis group. A total of 198 patients included in this analysis.

group. For every 21 patients with VUR treated with prophylaxis, 1 additional multidrug-resistant recurrent UTI would develop (Table 3).

Patients who had a multidrug-resistant enrollment UTI had 4.1 times the odds (95% CI: 1.4–12.0) of developing a multidrug-resistant first recurrent UTI compared with those whose enrollment UTI was not multidrug resistant. After adjusting for multidrug-resistant UTIs in addition to age at study enrollment, sex, VUR grade, and history of previous UTI, those receiving prophylaxis who developed a recurrent UTI had 8.3 times the odds (95% CI: 3.1–22.6) of a multidrug-resistant first infection compared with those in the control group. In these analyses, we excluded patients contributed by Hari et al[22] because sensitivity data for the enrollment UTI were not available for these patients.

A subgroup analysis was performed among patients on prophylaxis in which we evaluated the relationship between the duration of prophylaxis and the development of resistant recurrent UTIs. For every 10 days of exposure to prophylaxis, the odds of a multidrug-resistant UTI decreased by 5% (95% CI: 0.92–0.98).

TABLE 2 Characteristics of First Recurrent UTI Among Children With VUR

Study	Multidrug-Resistant UTI, *n* = 41 (18%)[a], *n* (%)	Total First Recurrent UTIs, *n* = 224	Total Patients, *n* = 1299
Pennesi et al[18] (Italy)	3 (9)	33	100
Roussey-Kesler et al[19] (France)	6 (25)	24	223
Craig et al[20] (Australia)	4 (17)	24	144
Brandström et al[21] (Sweden)	0 (0)	36	137
Hari et al[22] (India)	8 (62)	13	93
Hoberman et al[23] (United States)	20 (21)	94	602

[a] Percentages of total first recurrent UTIs.

DISCUSSION

Treating VUR patients with continuous antibiotic prophylaxis decreases the risk of developing a recurrent UTI, but when a recurrent UTI develops, there is an increased risk of multidrug resistance. Although this tradeoff has been previously considered, the benefit of prophylaxis cannot be established without quantifying the risk of resistance, which, to date, has not been thoroughly studied in this population.[20,23] In the current analysis, we demonstrate that among all patients with VUR, treating 21 patients with prophylaxis prevents 1 UTI. However, adversely, every 21 VUR patients treated with prophylaxis will result in 1 multidrug-resistant recurrent UTI. The probability of preventing a recurrent UTI while on prophylaxis is equal to that of developing a resistant UTI while on prophylaxis. Furthermore, among children who developed a recurrent UTI, the adjusted odds of the first recurrent infection being multidrug

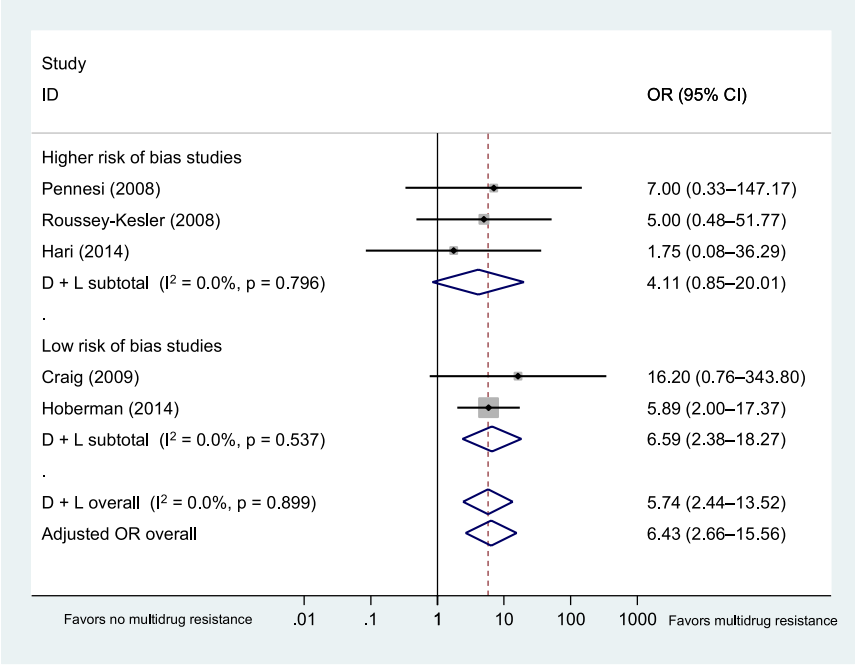

FIGURE 2
Forest plot for odds of multidrug-resistant first recurrent UTIs with antibiotic prophylaxis use among children with recurrent UTIs and VUR stratified by risk of bias. Squares with horizontal lines indicate the odds ratios with 95% CIs for a given study. Lateral tips of diamonds represent summary measures and associated 95% CIs. D + L, DerSimonian and Laird; ID, identification; OR, odds ratio.

resistant were 6.4 times greater than in those who were not treated with prophylaxis. These odds are further increased among patients whose enrollment UTI was multidrug resistant. These patients had 8.3 times the odds of the first recurrent UTI being multidrug resistant compared with those who were not treated with prophylaxis. These findings may be used to facilitate a more informed conversation with families when deciding on a management strategy for a child with VUR.

In this analysis, we not only highlight the increased risk of developing a resistant UTI, but we also emphasize that the increased prevalence of multidrug-resistant UTIs is problematic because antibiotic choice for these resistant infections may be challenging. Among patients treated with continuous antibiotic prophylaxis, broad-spectrum antibiotics may be indicated when therapy is initiated for a first recurrent UTI given the increased odds of multidrug resistance in this population. Our analysis revealed that broad-spectrum antibiotics were more frequently prescribed for treatment of recurrent UTIs if patients were in the prophylaxis group (68%) versus the control group (49%). We recognize that oral broad-spectrum antibiotics are often appropriate empirical choices for the management of recurrent UTIs given the risk for multidrug resistance; however, use of broad-spectrum antibiotics may potentiate the cycle of resistance because antibiotic use is a major risk factor for the development of antibiotic resistance.[25,26]

TABLE 3 Effects of Continuous Antibiotic Prophylaxis on First Recurrent UTIs Among All Children With VUR

Outcome	Risk (95% CI)				Number Needed to Treat
	Control Group, %	Prophylaxis Group, %	Risk Difference, %	Risk Ratio	
UTI	23.1 (19.9–26.5)	18.3 (15.3–21.4)	4.8 (0.5–9.2)	0.8 (0.6–1.0)	21
Multidrug-resistant UTI	1.5 (0.7–2.8)	6.4 (4.6–8.6)	4.9 (2.8–7.0)	4.2 (2.1–8.3)	21

There are other possible factors influencing the risk of a multidrug-resistant UTI, such as frequency of antibiotic intake for other illnesses. This could not be fully explored in the current study because researchers did not collect these data, but randomization has minimized the impact of such confounders. However, data in the current study do support the impact of regional practices on the prevalence of resistant UTIs as demonstrated by the substantial difference in the rate of multidrug resistance, which varied between 0% in the study by Brandström et al[21] in Sweden and 62% in the study by Hari et al[22] in India. In developing countries, antibiotics can be easily obtained from pharmacies without a prescription, leading to high rates of antibiotic consumption. To study patterns of antibiotic resistance rates in developing countries, the World Health Organization collaborated with Kotwani and Holloway to surveil antibiotic use patterns and found that 40% of patients in New Delhi, India receive at least 1 antibiotic when presenting to a pharmacy or clinic for care. This is in contrast to practices in Sweden, which has a governmental strategy to combat antibiotic resistance that is composed of 7 objectives that are focused not only on "responsible use of antibiotics" but also "increasing knowledge for preventing and managing antibiotic resistance."[27] These countries also have substantially different antibiotic resistance patterns. In 2014, India reported *E coli* with >80% resistance to fluoroquinolones whereas Sweden reports only 12%.[28] Of note, although Hari et al[22] had the highest

proportion of multidrug resistance in the first recurrent UTI, uropathogen sensitivity data of the enrollment UTI were not available for this study. Therefore, the data did not contribute to the analysis of the impact of multidrug-resistant enrollment UTI on recurrent UTI resistance. Thus, this exclusion may cause an underestimation of the impact of multidrug-resistant enrollment UTIs.

Despite evidence presented here for increased likelihood of developing multidrug resistance while being treated with prophylaxis, in our analysis, it was also suggested that the longer the patients are prescribed prophylaxis, the less likely they are to develop a multidrug-resistant UTI. There was a decrease in the odds of developing multidrug-resistant UTIs by over 5% for every 10 days of exposure to prophylaxis. This could be confounded by the reduced risk of a repeat UTI over time. Another explanation for this finding is that patients become less adherent with chronic medications over time. Decreased adherence to prophylaxis equates to decreased antibiotic exposure. Thus, nonadherent patients more closely resemble the control group and have decreasing odds of developing a multidrug-resistant UTI.

Poor adherence to prophylaxis has been identified by researchers in previous studies. Using a large pharmacy claims database, Copp et al[29] previously determined only a 40% adherence rate among children with VUR being treated with continuous antibiotic prophylaxis. Similarly, other researchers evaluating adherence among children prescribed continuous antibiotic prophylaxis have consistently demonstrated adherence rates <30%, which is significantly lower than adherence rates published in many trials in which authors evaluated response to prophylaxis.[30–32] Finally, literature in which researchers evaluated adherence to other long-term therapies such as combination antiretroviral therapy for HIV, airway clearance therapy for cystic fibrosis, and regimens for pediatric rheumatic diseases reveals that adherence is a dynamic process, and many patients demonstrate decreased adherence over time.[33–35] The uncertainty regarding adherence certainly confounds the results of researchers evaluating the impact of prophylaxis. Unfortunately, the assessment of adherence in the 6 included studies was varying and suboptimal. This issue was appreciated in the design of the Hoberman and co-workers[36] study, which recognized the importance of adherence as a potential effect modifier. Because the true prophylaxis adherence rate is unclear in these studies, its impact on resistant UTIs also remains unclear.

This study should be interpreted in the context of its limitations. Relevant variables that may contribute to antimicrobial resistance such as medication adherence and other antibiotic exposure before and during the study period could not be evaluated because they were not adequately captured by the primary studies. Moreover, 2 RCTs were excluded from this analysis because their authors were unable to contribute uropathogenic data on recurrent UTIs for individual patients.[16,17] Some included studies were also determined to have a risk for significant bias, particularly as patients in 3 of the included studies were not blinded, introducing performance and detection bias. However, these biases are not likely to impact the findings of this analysis because laboratory technicians assessing uropathogen sensitivity profiles are blinded to prophylaxis status. In this analysis, a substantial percentage of UTIs (42%) were contributed by 1 study. Although, the addition of the other studies contributed the majority of patients (58%) to the analysis. Lastly, this analysis was focused on first recurrent UTIs rather than all recurrent UTIs. Although the median number of recurrent UTIs per patient was 1.38, a minority of patients (34%) had more than 1 recurrent UTI, with some studies including patients with more than 20 recurrent UTIs. This may reflect differences in urine capture methods and UTI definitions. Therefore, limiting analysis to the first recurrent UTI minimizes variability that could be due to individual study and/or patient differences.

CONCLUSIONS

Continuous antibiotic prophylaxis increases the risk of acquired antibiotic multidrug resistance among recurrent UTIs. One multidrug-resistant recurrent UTI would develop for every 21 VUR patients treated with prophylaxis. These results have important implications in the selection of empirical treatment of breakthrough UTIs in continuous antibiotic prophylaxis patients and in the risk-benefit assessment of continuous antibiotic prophylaxis as a management option for prevention of recurrent UTIs. Additional study of other commonly used antimicrobial prophylactic agents and further investigation of risk factors related to the development of uropathogen resistance are necessary.

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ABBREVIATIONS

CI: confidence interval
RCT: randomized controlled trial
UTI: urinary tract infection
VUR: vesicoureteral reflux

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