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REVIEW ARTICLE

Antibiotics for Preventing Recurrent Urinary Tract Infection: Systematic Review and Meta-analysis

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Recurrent urinary tract infections are a common health problem. The only comprehensive synthesis on antibiotic prophylaxis in the last 15 years has been a guideline-embedded meta-analysis. We conducted a systematic review and meta-analysis of randomized controlled trials published up to October 13, 2020, evaluating patients age ≥12 years with either ≥2 episodes of lower urinary tract infection (UTI) within 6 months or ≥3 in the past year. Placebo or antibiotics were allowed as comparators. Study quality was low. In the 11 placebo-controlled trials, the risk for developing UTI was 85% lower with prophylaxis in comparison with placebo (risk ratio [RR], 0.15; 95% CI, 0.08–0.29). In the 9 head-to-head trials, the efficacy of the antibiotic agents appeared similar: The pooled RR indicated no difference between nitrofurantoin and comparators (RR, 1.01; 95% CI, 0.74–1.37), nor trimethoprim (+/- sulfamethoxazole; RR, 1.34; 95% CI, 0.89–2.03) or norfloxacin and comparators (RR, 1.17; 95% CI, 0.43–1.70). Studies comparing intermittent (postcoital) with continuous strategies revealed intermittent application to be equally effective.

Keywords. antibiotic prophylaxis; recurrent urinary tract infection; meta-analysis; UTI; cystitis.

Urinary tract infections (UTIs) are a common health care problem, with 11% of women reporting having suffered at least 1 UTI in the previous year [1]; 20%–30% of these women will experience recurrent UTI (RUTI) [2]. In men, RUTIs are less common, often associated with prostatic hyperplasia, and generally not well studied [3].

Besides nonantibiotic measures, different antibiotic prophylaxis regimens have been studied as a strategy for RUTI prevention, like continuous or intermittent antibiotic prophylaxis and prophylactic antibiotics after UTI-promoting events such as sexual intercourse. However, preferable antibiotic choices are poorly characterized, and the scientific literature on RUTI prophylaxis randomized trials has only been screened systematically in the last 15 years in a guideline-embedded meta-analysis [4], 2 meta-analyses focusing on nitrofurantoin [5, 6], and 3 descriptive literature reviews without meta-analysis [7–9]. Reviews and meta-analyses to date have not reported outcomes restricted to clinical recurrences, thereby including asymptomatic bacteriuria as recurrences. The objective of this systematic review and meta-analysis was to systematically assess the efficacy and safety of antibiotic prophylaxis for the prevention of RUTI in adults.

METHODS

We conducted a systematic review and meta-analysis of published and unpublished randomized controlled trials (RCTs) on antibiotic prophylaxis for recurrent urinary tract infections. We have followed PRISMA reporting guidelines [10].

Data Sources and Searches

We used the search terms "recurrent" AND "urinary tract infection" OR "UTI" OR "cystitis," AND "prophylaxis" OR "antibiotic," among others. The Cochrane sensitivity-maximizing filter to identify randomized trials was applied [11]. The search syntax is reported in Supplementary Table 1. We screened MEDLINE (from 1964), EMBASE (from 1988), the Cochrane Library (CENTRAL), the website clinicaltrials.gov, and reference lists of retrieved articles. The date of last search for all sources was October 13, 2020.

Study Selection

Criteria for randomized controlled trials were participants (men or women) aged ≥12 years with either ≥2 episodes of lower UTI within the last 6 months or ≥3 in the course of the past year. We included any type of prophylaxis schedule (daily, weekly, monthly, or postcoital). The control group had to have received placebo or a comparator antibiotic. We

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excluded studies comparing an antibiotic with a nonantibiotic compound (with the exception of placebo) and studies that included pregnant and breastfeeding women, patients with a history of urological surgery, major urogenital abnormalities, severe urinary incontinence, permanent urinary catheters, spinal cord lesions, immunosuppression, and neurogenic bladder dysfunction or severe renal function impairment (glomerular filtration rate <30 mL/min). Comorbidities like history of urolithiasis, mild renal impairment, diabetes mellitus, mild urinary incontinence, minor urogenital abnormalities on pyelogram, cystoscopy, or radiography, single kidney, and temporary indwelling catheters were not reasons for exclusion.

Two reviewers (J.B., J.M.) independently selected the studies, applying inclusion and exclusion criteria. In case of disagreement, 1 of the coauthors was consulted.

Data Extraction and Quality Assessment

The following information was collected with a data extraction form and brought together in a database: study setting, study population (age, comorbidities, prior treatment), trial design, inclusion and exclusion criteria, description of the intervention(s), duration of the intervention(s), length of follow-up, methods used to assess outcomes (urine culture, clinical evaluation), number of dropouts, specifics of data analysis, type of outcomes collected, and results.

The quality of the included trials was assessed in terms of the randomization process, internal validity, and external validity, based on the criteria described by Guyatt et al. [12]. Three investigators (J.M., J.B., A.A.) independently rated the risk of bias using a modification of the Cochrane handbook quality assessment recommendations [11].

Types of Outcome Measures

The primary outcome was the number of UTI episodes *during* the observed period of prophylaxis intake. Recurrences that followed the period of antibiotic intake were captured as a secondary outcome, as well as adverse effects (AEs) of antibiotic administration, stratified by severity: AEs leading to discontinuation of the treatment were considered severe AEs; all others were considered nonsevere.

Recurrences could be measured on the one hand using microbiological criteria (microbiological recurrences), with confirmation by a positive urine culture of >100 000 bacteria/mL, or using symptoms consistent with UTI, pyuria and positive urine culture with >10 000 bacteria/mL. On the other hand, they could be identified using the clinical criteria dysuria, pollakisuria, hesitancy, and/or frequency (clinical recurrences).

Analysis of Studies With Trimethoprim ± Sulfamethoxazole as Comparator

Based on the study by Stamm et al. [13], who found trimethoprim alone (TMP) and its co-formulation with sulfamethoxazole (TMP-SMZ) to be equally efficacious for UTI prevention, and similar findings in therapeutic and pediatric studies, the single compound and its combinations with sulfamethoxazole were analyzed as 1 antibiotic group.

Data Synthesis and Analysis

For analysis, included studies were classified into 3 main groups: "placebo-controlled studies" (PC), "head-to-head studies" (HH), and "continuous vs intermittent approaches" (CI). One study [14] differed from all other studies in terms of design and is therefore discussed individually.

The meta-analysis of the PC studies was based on a comparison of pooled risk ratios (RRs) in the 2 arms. As microbial recurrences are now considered to be of minor relevance, a subanalysis restricted to reported clinical recurrences in the included studies was performed.

HH prophylaxis comparisons were based on the number of infections per person-year, also in terms of an RR calculation. Heterogeneity was evaluated using the Q and I^2 statistics and considered to be significant if the P value using the chi-square test was <.1 for Q and to be high if the I^2 value was ≥75%. Confidence intervals for I^2 were based on the Higgins and Thomson calculation [15]. All meta-analyses were performed using the statistical package *OpenMetaAnalyst* utilizing the *meta* and *metafor* packages in R (R Foundation for Statistical Computing, Vienna, Austria), based on random- and fixed-effects models. Where appropriate, the absolute risk reduction (ARR) was used to calculate the number needed to treat (NNT).

Publication bias was investigated using funnel plots [16, 17] and the arcsine test [18]. A sensitivity analysis was added to investigate the potential effects of publication bias based on the trim and fill method [19] and the Copas selection model [20, 21] and using the *metasens* package in R.

RESULTS

Description of Studies

We retrieved 2105 studies from the search strategy. Of this selection, 2082 studies did not meet the inclusion criteria or were excluded for reasons disclosed in Figure 1. The main characteristics of the included 23 RCTs (24 comparisons) are depicted in Supplementary Table 2. The time frame of publication of the included studies ranged from 1971 to 2014, with only 3 published in the past 20 years. Six trials studied cinoxacin, an obsolete antibiotic. Patients for the studies were mainly recruited in outpatient clinics (20/23 studies), in 1 study in private practices [22], and in another study from university students [14], whereas 1 study did not describe the study setting [23]. Most studies only included women, while 2 studies also allowed the inclusion of men [23, 24]. The prophylaxis period was 6 months in 13/23 studies, 12 months in 9/23 studies, and 3

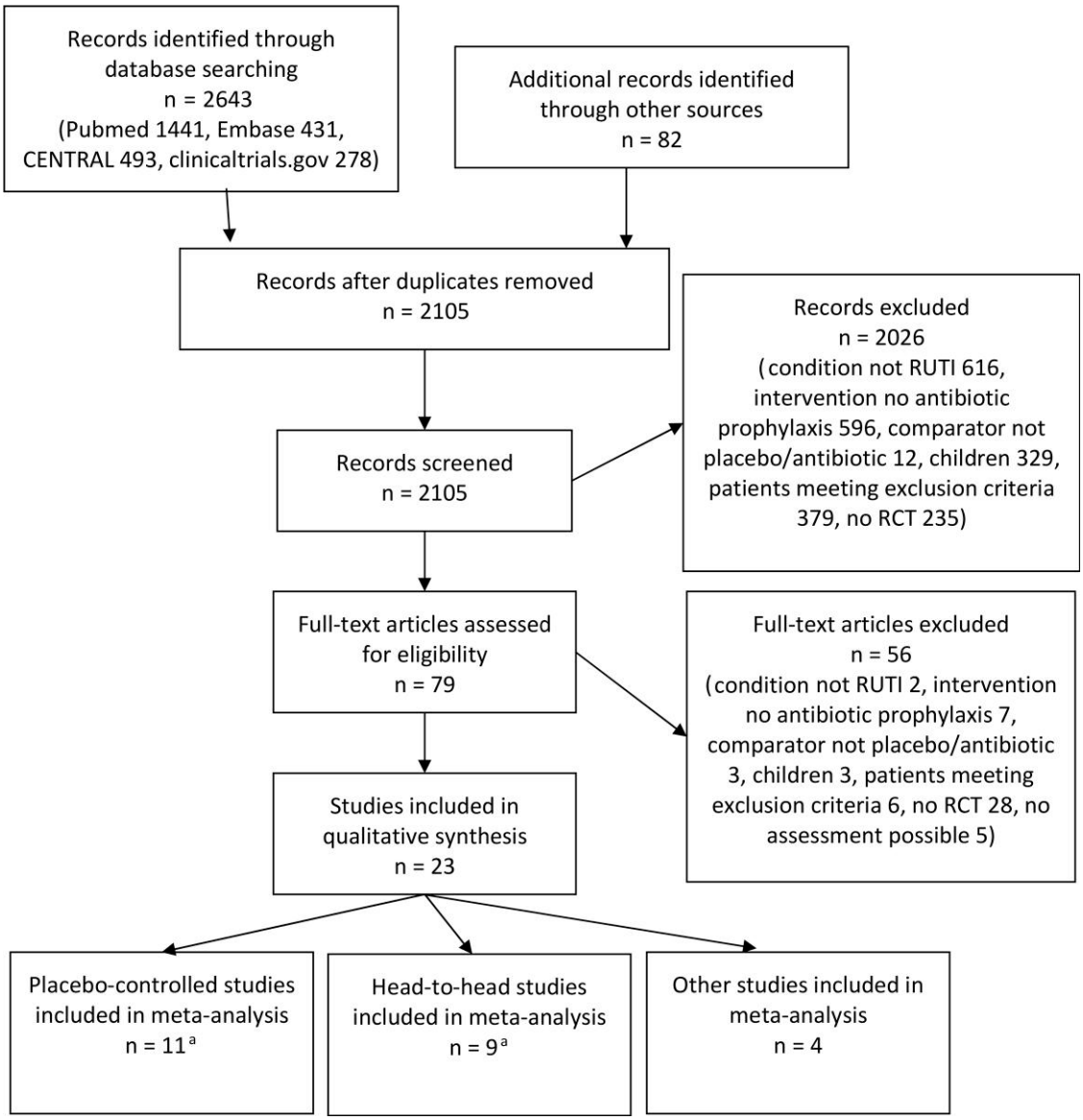

Figure 1. Study flowchart with reasons for exclusion of studies (not mutually exclusive). [a]Including overlap between studies with a placebo as well as an antibiotic comparator. Abbreviations: RCT, randomized controlled trial; RUTI, recurrent urinary tract infection.

months in 1 study [25]. Of note, some studies suspended the prophylaxis as soon as there was a recurrence.

Risk of Bias and Methodological Quality

Supplementary Figure 1 gives an overview of the risk of bias of included studies. Overall, study quality was low. For PC studies, the funnel plot indicated potential publication bias (Supplementary Figure 3), although this finding was not supported by a formal test of asymmetry (Arcsine test: $P = .49$). Heterogeneity, as measured by the I^2 statistic, was moderate at 57% (95% CI, 19.3%–76.6%), with the influence and contributions from each of the studies shown in the Baujat plot [26] in Supplementary Figure 2. Excluding the studies with cinoxacin, an obsolete antibiotic, the heterogeneity of the treatment effect between the studies was reduced ($I^2 = 22.9\%$; 0%–64.5%).

To further explore the discrepancy between the funnel plot and Arcsine test, an additional sensitivity analysis using a simple trim-and-fill method and a Copas selection model was performed. The trim-and-fill approach (Supplementary Figure 5) suggested adding 3 hypothetical studies to achieve relative symmetry, resulting in a slightly higher risk ratio, but still within the original confidence intervals for the random-effects model (RR, 0.23; 95% CI, 0.14–0.35; for trim and fill; vs RR, 0.15; 95% CI, 0.08–0.29). The Copas selection method (Supplementary Figure 6) produced an estimate slightly closer to that from

the original model ($P = .21$; .13–.32), suggesting that 1 additional study would be required to achieve symmetry. Thus, the sensitivity analysis indicated consistent estimates of the treatment effect with the original model.

For HH studies, there was little difference between the fixed- and random-effects models, the funnel plot (Supplementary Figure 4) was symmetric, and the formal test of asymmetry was nonsignificant at the 5% level. A sensitivity analysis was not deemed necessary in this case.

Funding of Studies

Only 8 of the 23 studies stated funding sources, 4/8 reported financial support from pharmaceutical companies, and 5/8 studies had pills or capsules provided by the pharmaceutical industry (Supplementary Table 3).

Effect of the Intervention

Table 1 summarizes the effect of interventions in the meta-analysis, divided by type of comparison. Further details are given below.

Placebo-Controlled Studies (Antibiotic vs Placebo)

In the 11 PC studies [13, 24, 27–35] including 805 patients (746 with efficacy assessment), the risk ratio for developing UTI was 0.15 (95% CI, 0.08–0.29; $P < .0001$) with antibiotic prophylaxis in comparison with placebo; the corresponding overall risk reduction was 55% (weighted average NNT, 1.81; 95% CI, 1.67–2.17), assuming relative homogeneity of the treatment effect (Figure 2). In absolute numbers, in the prophylaxis arm of trials, recurrences occurred in 33/400 patients (8%) during the observation period and in 225/346 patients (65%) in the placebo arm. Since 2004 (last Cochrane meta-analysis on this subject [36]), a single RCT comparing fosfomycin with placebo among 158 patients was published in 2005. This study reported an absolute UTI risk reduction of 68% (NNT, 1.5) [32]. The 6 RCTs that remained after excluding cinoxacin (n = 5), an obsolete antibiotic, showed a comparable risk reduction of 61% (NNT, 1.64; RR, 0.11; 95% CI, 0.07–0.17). As microbial recurrences nowadays are considered to be of minor relevance, a subanalysis restricted to reported clinical recurrences in placebo-controlled studies was performed (Figure 3). The risk ratio for having a clinical recurrence was 0.11 with antibiotic prophylaxis (95% CI, 0.07–0.17); therefore, the prophylactic effect against clinical recurrences was comparable to that against all recurrences (including microbial recurrences as described above).

A statistical analysis of UTI events after discontinuation of prophylaxis was not possible due to inconsistent reporting of the number of patients at risk in 2 of 3 studies that scrutinized the postprophylaxis period: One of these 2 studies [24] drew the conclusion that recurrences were infrequent even after discontinuation of prophylaxis, whereas the other reported no difference in recurrences after discontinuation of prophylaxis as compared with placebo [13]. The only study [37] that quantified events after discontinuation of the prophylaxis and reported both the number of events and the number of patients at risk found no difference in recurrences (59% in cinoxacin group, 39% in the placebo group, during a follow-up of ≥6 months after ending prophylaxis). This analysis was limited by the small number of included patients (n = 17 in the cinoxacin arm, 13 in the placebo arm).

Table 1. Summary of the Meta-analyses on Antibiotic Prophylaxis for Recurrent Urinary Tract Infections, Divided by Type of Comparison

Type of Comparison	No. of Studies	No. of Patients	Risk Ratio	95% CI	*P* Value
A. Placebo-controlled	11[a]	746	0.15	(0.08–0.29)	<.001
A1. Placebo-controlled excluding cinoxacin[b]	6	520	0.11	(0.07–0.17)	<.001
B. Head-to-head	9[a]	636			
B1. Nitrofurantoin vs other antibiotic	7	486	1.01	(0.74–1.37)	.97
B2. TMP (± SMZ) vs other antibiotic	4	176	1.34	(0.89–2.03)	.16
B3. Norfloxacin vs other antibiotic	3	239	1.17	(0.43–1.70)	.66
C. Continuous vs intermittent	3	564	1.78	(0.62–5.09)	.28
D. Intermittent vs placebo	1	25	0.15	(0.04–0.55)	.004

Abbreviations: SMZ, sulfamethoxazole; TMP, trimethoprim.

[a]Stamm et al. [13] was included in the placebo-controlled comparison (trimethoprim ± sulfamethoxazole vs placebo, nitrofurantoin vs placebo) and in the head-to-head comparison (trimethoprim ± sulfamethoxazole vs nitrofurantoin).

[b]Cinoxacin is an obsolete quinolone antibiotic.

Head-to-Head Studies (Antibiotic vs Antibiotic)

A total of 9 HH trials [13, 23, 25, 38–43] with 766 patients (636 with efficacy assessment) comparing different prophylactic antibiotics were included. Nitrofurantoin was the single most common comparator (to norfloxacin in 3 studies, to cefaclor in 1 study, and to trimethoprim [± sulfamethoxazole] in 3 studies); the pooled relative risk between nitrofurantoin and other comparator antibiotics indicated no significant difference (RR, 1.01; 95% CI, 0.74–1.37) (Supplementary Figure 7). Trimethoprim (± sulfamethoxazole) was studied in 4 HH studies, with no significant difference in the relative risk compared with the comparator antibiotic (RR, 1.34; 95% CI, 0.89–2.03). Similarly, there was no difference between norfloxacin and its comparators (3 studies; RR, 1.17; 95% CI, 0.43–1.70).

Continuous vs Intermittent Studies (eg, Postcoital)

Three studies [22, 44, 45] including 596 patients (564 with efficacy assessment) compared a continuous antibiotic strategy with intake of a prophylactic antibiotic dose either postintercourse [44] or after UTI-predisposing events such as micturition, diarrhea, constipation, traveling, and taking long walks [45]. One study in this group evaluated a monthly prophylactic

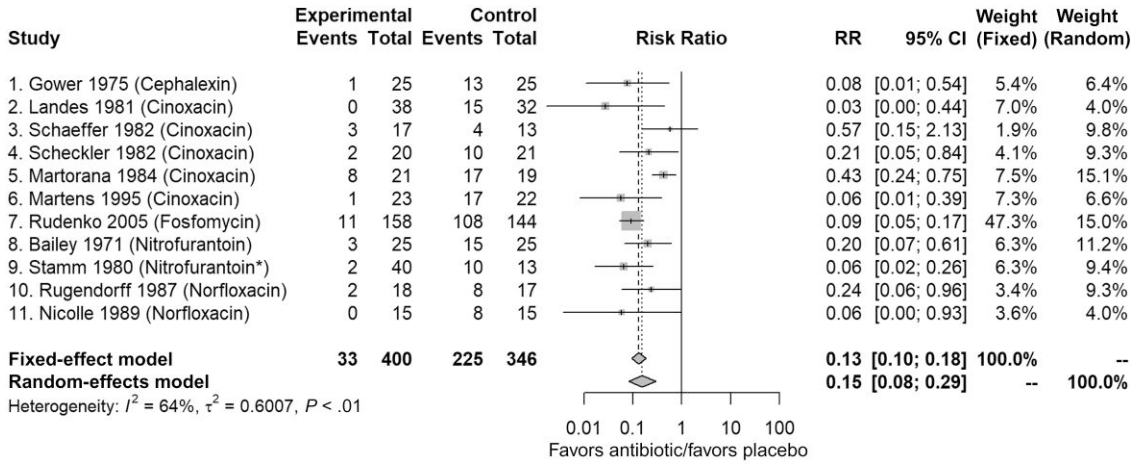

Figure 2. Forest plot of placebo-controlled studies for antibiotic prophylaxis of recurrent urinary tract infections. [a]Or trimethoprim ± sulfamethoxazole. Abbreviation: RR, risk ratio.

antibiotic dose without correlation to predisposing factors, which was considered intermittent application [22]. Even including the latter approach, there was no significant difference in efficacy between the continuous and intermittent prophylaxis approaches.

Intermittent (eg, Postcoital) vs Placebo Studies

Postcoital antibiotic prophylaxis compared with placebo was only examined in 1 included study [14], and its effect was in a comparable range (RR, 0.15; 95% CI, 0.04–0.55) to the placebo-controlled continuous antibiotic prophylaxis trials mentioned above.

Adverse Events

Reported adverse events (AEs) varied considerably in included trials and were not reported at all in 1 study [24]. Supplementary Table 4 gives an overview of described AEs. The pooled relative risk of nonsevere AEs with antibiotic prophylaxis was 3.42 (95% CI, 2.16–5.43; number needed to harm [NNH], 7.89), and the pooled relative risk of severe AEs was 3.22 (95% CI, 1.32–7.89; NNH, 30.97), favoring placebo over antibiotic prophylaxis.

The most commonly reported AEs with antibiotic prophylaxis were gastrointestinal complaints (including nausea) and oral or vaginal candidiasis. Allergic reactions or skin rashes were reported in 7 RCTs, mostly in patients receiving antibiotics; however, skin rashes were also reported in patients receiving placebo. Allergic reactions occurred with the following antibiotics: norfloxacin (5 patients), cinoxacin (3), nitrofurantoin (7), and trimethoprim-sulfamethoxazole/trimethoprim (2). Skin rashes were described with cinoxacin (4), nitrofurantoin (2), trimethoprim-sulfamethoxazole/trimethoprim (1), cephalexin (1), fosfomycin (1), a nonidentifiable antibiotic (5), and placebo (2).

Patients taking nitrofurantoin showed a higher number of dropouts, even though the number of reported side effects in the analyzed patients was comparable to that seen with other antibiotics. This might indicate some underreporting in AEs in the included studies, as an association of nitrofurantoin with nonsevere AEs has been described before [5].

Neither renal insufficiency nor *C. difficile* enterocolitis was mentioned as a possible AE in the included studies, also suggesting underreporting of AEs.

DISCUSSION

RUTIs are a common problem, causing morbidity and health care costs. A variety of prophylactic options, including but not limited to antibiotics, have been examined in either head-to-head or placebo-controlled trials. Our analysis includes 23 studies and confirms that antibiotic prophylaxis is effective for RUTI prevention when compared with placebo, with an NNT of only 1.81 (95% CI, 1.67–2.17). This finding is in line with what was reported in the last 2 comprehensive compilations of studies on this subject by Albert et al. [36] and Anger et al [4]. The NNT should be interpreted with caution though, as event rates varied between studies. The effect seems to be limited to the period of antibiotic intake [13, 24, 37], and the optimal duration of antibiotic prophylaxis to balance the preventive effect against potential toxicity or adverse effects remains unclear. Durations of prophylaxis >12 months have not been studied in a controlled setting, although 1 case series reported sustained efficacy over 5 years [46]. Head-to-head antibiotic comparisons were mainly published for nitrofurantoin vs comparators and showed no significant difference in recurrences, making nitrofurantoin, norfloxacin, and trimethoprim-sulfamethoxazole essentially interchangeable options. The strength of evidence on antibiotic interchangeability is

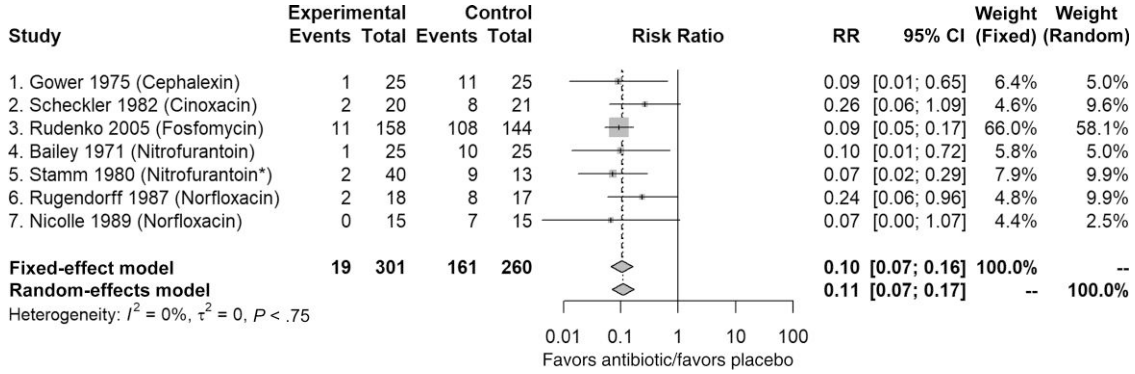

Figure 3. Forest plot of subanalysis of placebo-controlled studies restricted to reported clinical recurrences as events. [a]Or trimethoprim ± sulfamethoxazole. Abbreviation: RR, risk ratio.

tempered by the fact that only 3 of the studies were published in the past 20 years, and uropathogen resistance to fluoroquinolones and trimethoprim-sulfamethoxazole has increased greatly during that time period. In the small number of controlled trials comparing intermittent UTI prophylaxis after an activity that could precipitate UTI (such as sexual intercourse) vs continuous prophylaxis, both strategies appeared to be equally effective.

Of note, the systematically assessed study quality of the included RCTs was low, indicating that the results of the meta-analysis should be interpreted with caution. With studies dating back as far as the 1970s, this may reflect a lower reporting standard by today's expectations rather than low study quality. The placebo-controlled trial with the lowest methodological quality [37] was the only included study that yielded indifferent efficacy results, albeit with a very low rate of recurrence in both arms.

When reviewing the inclusion criteria, it is noteworthy that no uniform RUTI definition was employed in the included studies. Over the years, the definition of RUTI has changed from requiring 2 UTIs in the past 12 months (in earlier studies) to 3 or more UTIs within 1 year (in later studies). Also, the end points shifted from microbiological to clinical criteria, with the latter now being considered more relevant. Earlier studies considered asymptomatic bacteriuria to be the equivalent of a UTI. In the 3 head-to-head trials by Brumfitt et al. [38–40], UTI recurrences were defined as the presence of clinical symptoms without microbiological confirmation, and clinical recurrences were 5 times more common than microbiological ones, suggesting that most patients did not have UTIs by current definitions.

Antibiotic prophylaxis in RUTI prevention comes at a price, on the one hand in the form of AEs such as drug toxicity and on the other hand with the selection of antimicrobial resistance and alterations to the patient's microbiome. The considerable number of reported AEs (NNH, 30.97 for severe AEs leading to discontinuation; NNH, 7.89 for nonsevere AEs), even though there are indications of potential underreporting, must be weighed against the potential benefit for a patient when selecting a preventive strategy. Commonly reported AEs such as vaginal candidiasis were classified as nonsevere if they did not lead to discontinuation of prophylaxis, but may from the patient's perspective be just as undesirable as the prevented UTI episode.

Long-term antibiotic use is associated with resistance selection. High rates of resistance development under prophylactic antibiotics have been described for trimethoprim-sulfamethoxazole in particular (eg, [47]). A recent study shed light on the coexistence of antibiotic-resistant and -sensitive strains within the intestinal tract as a reservoir and major source for RUTI in a patient followed over a 5-year period using genomic analysis of urine and fecal strains [48]. Resistance development under prophylaxis complicates the treatment of future UTI episodes and contributes to the corresponding burden in a community. This collateral effect has also to be taken into consideration. Whether 1 antibiotic class is preferable to others in terms of risk of inducing resistance cannot be determined from this review; this should be clarified in future studies.

Nonantibiotic options were not the focus of this meta-analysis and have been discussed in detail elsewhere [49–51]. Patient-initiated antibiotic therapy at UTI symptom onset as an alternative to prophylaxis also has revealed satisfactory clinical response and low rates of overtreatment (treatment in symptomatic episodes with consecutively negative urine cultures), as long as the patient population can manage self-treatment [2, 52, 53].

Further research in the form of well-planned randomized controlled trials and long-term cohort studies is needed to clarify the role of antibiotic prophylaxis in relation to nonantibiotic preventive options for RUTI and to define the optimal and safe duration of antibiotic prophylaxis, taking into account the risk

of resistance selection. For the time being, this meta-analysis confirms that antibiotic prophylaxis is an effective prevention strategy for RUTIs and that a number of antimicrobial substances can be used with similar likelihood of success. The prophylactic effect seems, though, to be limited to the period of antibiotic intake, and the effectiveness of antibiotic prophylaxis should be weighed against concerns for resistance selection.

Supplementary Data

Supplementary materials Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study does not include factors necessitating patient consent.

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