Antimicrobial agents for treating uncomplicated urinary tract infection in women (Review)

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[Intervention Review]

Antimicrobial agents for treating uncomplicated urinary tract infection in women

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ABSTRACT

Background

Acute uncomplicated lower urinary tract infection (UTI) is one of the most common problems for which young women seek medical attention.

Objectives

To compare the efficacy, resistance development and safety of different antimicrobial treatments for acute uncomplicated lower UTI.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Renal Group's Specialised Register, MEDLINE, EMBASE and bibliographies of included studies.

Selection criteria

Randomised controlled trials (RCTs) comparing different classes of antimicrobials for acute uncomplicated UTI in women were included. The outcomes of interest were symptomatic and bacteriological cure at short and long-term follow-up, resistance development, number of days to symptom resolution, days of work loss, adverse events and complications.

Data collection and analysis

Two authors independently extracted the data and assessed study quality. Statistical analyses were performed using the random effects model and the results expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Trimethoprim-sulfamethoxazole (TMP-SMX) was as effective as fluoroquinolones in achieving short-term (RR 1.00, 95% CI 0.97 to 1.03) and long-term (RR 0.99, 95% CI 0.94 to 1.05) symptomatic cure. Beta-lactam drugs were as effective as TMP-SMX for short-term (RR 0.95' 95% CI 0.81 to 1.12) and long-term (RR 1.06' 95% CI 0.93 to 1.21) symptomatic cure. Short-term cure for

nitrofurantoin was similar to that of TMP-SMX (RR 0.99' 95% CI 0.95 to 1.04) as was long-term symptomatic cure (RR 1.01' 95% CI 0.94 to 1.09).

Fluoroquinolones were more effective than beta-lactams (RR 1.22, 95% CI 1.13 to 1.31) for short-term bacteriological cure. Rashes were more frequent in patients treated with TMP-SMX than with nitrofurantoin or fluoroquinolones and in patients treated with beta-lactam drugs compared to fluoroquinolones. Minimal data were available on the emergence of resistant strains during or after antimicrobial treatment.

Authors' conclusions

No differences were observed between the classes of antimicrobials included in this review for the symptomatic cure of acute uncomplicated UTI. Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological outcome, probably with little clinical significance. Individualised treatment should take into consideration the predictable susceptibility of urinary pathogens in local areas, possible adverse events and resistance development, and patient preference.

PLAIN LANGUAGE SUMMARY

Antimicrobial agents for treating acute uncomplicated urinary tract infection in women

Acute uncomplicated lower urinary tract infection (UTI), also know as cystitis, is characterised by burning on urination and frequent urination without fever or flank pain. It is a common event in otherwise healthy, non-pregnant adult women. A large range of antimicrobials are used in the treatment of cystitis. Twenty one good quality studies, enrolling 6016 participants, which used different classes of antimicrobials for treating acute cystitis in women for 3 up to 10 days, were included in this review. The classes of antimicrobials included in the review proved equally effective for the symptomatic cure. Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological cure, but the significance of this finding is doubtful. Fewer rashes developed in patients treated with fluoroquinolones. Nitrofurantoin caused fewer rashes than TMP-SMX while having similar rates of any adverse events. Given the small number of studies included in each comparison and for each outcome it is recommended that further randomised controlled trials be conducted.

BACKGROUND

Acute uncomplicated lower urinary tract infection (UTI) - also know as cystitis - in an otherwise healthy, non-pregnant woman is one of the most common problems for which young women seek medical attention (Baerheim 1997; Hooton 1997). More than 30% of all women will experience a UTI during their lifetime and the prevalence of UTI in women is approximately 50 times higher than in men (Henry 1999; Margariti 1997). In one cohort study the incidence of the disease was estimated to be 0.5 to 0.7/person-years (Hooton 1996).

Acute uncomplicated lower UTI is a superficial infection of the bladder mucosa. In the adult woman it should be considered uncomplicated if the patient is not pregnant or elderly, if there has been no recent instrumentation or antimicrobial treatment, and if there are no known functional or anatomic abnormalities of the genitourinary tract (Hooton 1997). Uncomplicated UTI is not considered a serious disease. It is not clear whether untreated UTI can progress to pyelonephritis, and if so how often. Progression to pyelonephritis probably occurs at a very low rate, while asymptomatic bacteriuria in young, healthy and non-pregnant women is not associated with renal damage (Stamm 1991).

All over the world the most common pathogens of uncomplicated UTI are similar: 80% to 90% *Escherichia coli*, 5% to 10% *Staphylococcus saprophyticus* and the remaining infections being caused by Proteus species and other Gram negative rods. Most are bacteria from the gut that colonise the perineum and than ascend through the urethra to infect the bladder mucosa. The infection causes specific symptoms, mainly the triad of dysuria (painful urination), urgency (the urgent need to void), and frequency (frequent urination). In randomised controlled trials (RCTs) the diagnosis is based on positive urine cultures in symptomatic subjects. In the past, the threshold for the diagnosis of UTI was > 100,000 colony forming units (CFU/mL) of voiding midstream urine (Stamm 1982). However, studies over the last 30 years have shown that in young symptomatic women with leucocyturia of 100 CFU/mL voided

midstream urine can establish the diagnosis (Kunin 1993; Stamm 1980; Stamm 1982).

A large range of antimicrobials in different doses are used in the treatment of UTI. Single-dose therapy has been advocated but doubts as to its use have been raised because of a high frequency of bacteriological recurrence (Leibovici 1991; Norrby 1990) and it is no longer common clinical practice. On the other hand, single-dose treatment probably achieves symptomatic relief more rapidly than seven days of treatment (Arav-Boger 1994). A systematic review that assessed different durations of antimicrobial therapy for uncomplicated UTI in women found that three days of treatment are similar to five to ten days of treatment in achieving symptomatic cure, while the longer treatment is more effective in obtaining a bacteriological cure but also has a higher rate of adverse effects (Milo 2005).

Treatment of uncomplicated lower UTIs in adult females is unique in comparison to other patient populations. Available guidelines for the management of symptoms of lower UTIs in women give conflicting recommendations and following guidelines for empirical treatment of uncomplicated UTIs is problematic (Flottorp 2000; Guay 2008; Miller 2004). Best practices and evidence-based research for treating lower UTIs in women were examined in a recent review; some practices were supported, others contraindicated, and gaps were identified (Jackson 2007).

Therapy for uncomplicated UTI usually begins before the results of microbiological tests are known. Furthermore, empirical therapy without a pre-therapy urine culture is often used. The rationale for this approach is based on the highly predictable spectrum of aetiological agents causing UTI and their antimicrobial resistance patterns. However, antimicrobial resistance among uropathogens causing community-acquired UTIs is increasing worldwide. Most important has been the increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX), the traditional first-line therapy for this disease (Gupta 2001). One study found that diabetes, recent hospitalisation and the use of antibiotics, particularly the use of TMP-SMX, were independent risk factors for TMP-SMX resistance (Wright 1999). Unfortunately, current data on regional resistance are often not readily available to physicians and regional variability in resistance remains largely unknown (Karlowsky 2001). Alternative use of other first-line agents including the fluoroquinolones and nitrofurantoin is increasing. Fluoroquinolones are an alternate therapy, but increasing resistance is reported from some countries, and widespread community use may promote resistance, limiting effectiveness of these agents for more serious infections (Nicolle 2003). Nitrofurantoin does not share cross-resistance with more commonly prescribed antimicrobials and its more widespread use is justified from a public health perspective as a fluoroquinolone-sparing agent. Beta-lactams and fosfomycin should be considered second-line agents for the empirical treatment of uncomplicated UTI (Hooton 2003). Antimicrobials may not be equivalent in curing UTI even if the pathogen is susceptible to them (Farrell 2003).

Both uncomplicated lower UTI and antibiotic treatment can affect QOL in a measurable way (Ernst 2005). While QOL is improved by treatment, those reporting adverse events have lower overall QOL.

The aim of this review was to compare different antimicrobials used for the treatment of acute uncomplicated UTI in women in terms of efficacy and adverse events and to assess whether the preferential use of one type or a specific class of antimicrobials is justified at present.

OBJECTIVES

To compare the efficacy and safety of different antibacterial treatments used for at least three days on relief of symptoms and bacteriuria in acute, uncomplicated lower UTI in otherwise healthy women aged 16 to 65 years. Specific objectives were:

- To assess the relative effectiveness of antibacterials from different classes or antibacterials within the same class on: relief of symptoms within two weeks of starting treatment; resolution of bacteriuria within two weeks of starting treatment; absence of symptoms or bacteriuria up to eight weeks after starting treatment.

- To assess the evidence for the development of resistance during treatment for antimicrobials from different classes (by comparing resistance of grown bacteria in urine before and after therapy). Data for vaginal, faecal or periurethral isolates were to be collected but not included in meta-analyses as we anticipated different methods of collecting and testing specimens, from different sites and many studies that won't report the site of collection.

- To assess the frequency of adverse events with the different antibacterial regimens.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing different antibacterials used for three days or more, with an identical duration of treatment in the two arms, for the treatment of uncomplicated UTI in women.

Types of participants

Inclusion criteria

- Outpatient, healthy women, aged 16 to 65 years, with uncomplicated UTI defined by the presence of urinary complaints (and the absence of upper UTI signs) and leucocyturia (as defined in the studies) or bacteriuria. Studies including subjects based only on clinical symptoms were considered for inclusion in the review and excluded subsequently if more than 30% of subjects did not have bacteriologically confirmed UTI and were excluded post-randomisation from the analyses, or separate data were not available for positive culture subjects.
- Uncomplicated UTI was defined in the absence of all of the following: costovertebral pain or tenderness, fever (> 37.8ºC), positive blood cultures.

Exclusion criteria

- Studies of the following groups of people having conditions complicating UTI were excluded from the review: multiple vomiting, sepsis, hospital acquired infection, pregnancy, indwelling urinary catheter, recent urinary tract instrumentation, known pathological functional or anatomic abnormality of the urinary tract, diabetes mellitus, immunocompromised patients (including AIDS, transplant recipients, hypogammaglobulinaemia, neutropenia, chemotherapy, haematological malignancies).
- Studies including more than 10% of the following were excluded: men, inpatients, women older than 65 years, participants less than 16 years old, upper UTI signs or with a drop-out rate of more than 30%.

Types of interventions

- Antibacterial treatment versus antibacterial treatment given by oral route for at least three days, for identical durations of treatment in both arms. The interventions studied included fluoroquinolones, nalidixic acid, beta-lactams, TMP-SMX and nitrofurantoin. Studies using ampicillin were excluded as this treatment is no longer used due to the high emergence of resistant strains in the past and only old studies available.
- Studies reporting combined interventions were included only if both treatment arms received the same co-treatment except for the antibacterials of interest.
- Studies comparing different types of fluoroquinolones have been assessed in a separate Cochrane review and were excluded (Rafalsky 2006).

Types of outcome measures

Primary outcomes

- Short-term symptomatic cure: the absence of urinary symptoms up to two weeks after start of treatment.
- Long-term symptomatic cure: the absence of urinary symptoms up to eight weeks after start of treatment.

Secondary outcomes

- Short-term bacteriological cure: a negative urine culture at the first follow-up within two weeks after start of treatment.
- Long-term bacteriological cure: a negative urine culture at up to eight weeks follow-up after start of treatment.
- Proportion of subjects that developed resistance (grown bacteria in urine) during the treatment period up to eight weeks after starting treatment.
- Number of days to symptom resolution.
- Days of work-loss.
- Any adverse event that necessitates discontinuation of treatment.
- Proportion of participants who develop rash during treatment.
- Proportion of participants who develop diarrhoea during treatment.
- Proportion of participants who develop any adverse event during treatment.
- Proportion of participants that have complications: pyelonephritis.

Search methods for identification of studies

We searched the following resources without language restriction.

Electronic searches

1. The Cochrane Renal Group's Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2010). Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings (Renal Group 2010).
2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) together with a search

strategy developed with input from the Cochrane Renal Group's Trials Search Co-ordinator.

3. EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a search strategy developed with input from the Cochrane Renal Group's Trials Search Co-ordinator.

See Appendix 1 for search terms used.

Searching other resources

We inspected the reference lists in all identified studies for further relevant studies and scrutinised the existing review literature. We contacted study authors for missing information. We considered studies using single-dose treatment to find articles that included more than two arms and also considered multi-day treatment comparisons.

Data collection and analysis

Selection of studies

We used the search strategy described to obtain titles and abstracts of studies that may have been relevant to the review. Two authors independently screened the titles and abstracts and discarded studies that were not applicable. We initially retained studies and reviews that included relevant data or information on studies. Two authors independently assessed retrieved abstracts and if necessary the full text) to determine which studies satisfied the inclusion criteria. We resolved disagreements in consultation with a third author.

Data extraction and management

Two authors extracted data using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study exists, reports were grouped together and we used the most recent or most complete dataset. Any discrepancies between published versions were highlighted. Disagreements were resolved in consultation with a third author. We documented justification for excluding studies in the Characteristics of excluded studies table. We extracted the following data:

- Characteristics of studies: date, location, period of data collection, year of publication, publication status, setting, design, sponsor of study, allocation concealment, blinding, case definition (symptomatic, bacteriological, both), bacteriologic definition (100 or 100,000 CFU/mL), definitions of cure (symptomatic, bacteriological or both).
- Characteristics of participants: number of participants in each group, age, previous antibiotic treatment and recurrent UTIs within the last year.
- Characteristics of interventions: type, dose, duration of antibacterial therapy, follow-up, compliance, co-interventions.
- Characteristics of outcome measures: number of patients with symptomatic/bacteriological cure in each group, number of patients with symptomatic/bacteriological recurrence, number of patients with adverse reactions related to the intervention, number of patients with resistant micro-organisms, loss to follow-up before the end of the study and reasons.

Assessment of risk of bias in included studies

Two authors assessed the methodological quality of studies fulfilling the inclusion criteria using the criteria described in the Cochrane Handbook (Higgins 2005), based on the evidence of a strong association between poor allocation concealment and overestimation of effect (Schulz 1995). The following quality items were assessed.

- Allocation concealment
- Blinding
- Intention-to-treat (ITT) analysis
- Completeness of follow-up

See Appendix 2 for the quality assessment checklist.

Measures of treatment effect

We analysed dichotomous data by calculating the risk ratio (RR) for each study with the uncertainty in each result being expressed as 95% confidence interval (CI). Comparisons made between the mean duration of symptoms in the two groups, when normally distributed, were analysed by using the mean and standard deviation of each study and calculating the mean difference (MD) and the 95% CI. We performed separate meta-analyses for groups of studies using different antimicrobials from the same class (e.g. different fluoroquinolones separately versus other antimicrobials) and from different classes where possible.

ITT analysis was performed considering all drop-outs in a study as failure to achieve symptomatic or bacteriological cure. We regarded only the randomised patients with positive urine cultures as the reference total patient number in the two study arms for the bacteriological cure. When the numbers of randomised women with positive cultures in the study groups were not available, we considered the total numbers of randomised patients for performing the ITT analysis for the symptomatic, but not for the bacteriological cure.

Dealing with missing data

Any further information required from the study authors was requested by written correspondence and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity in the results of the studies was assessed by inspection of the graphical presentation and by calculating the I^2 value (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We planned to examine funnel plots estimating the precision of studies (plots of RR for efficacy against the sample size) for potential asymmetry and publication bias.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We anticipated heterogeneity between the studies results for different doses of antimicrobials, different preparations used within the same class, different quality of studies, time lag between studies and for patients with pathogens susceptible to the allocated intervention at onset of treatment.

Sensitivity analysis

We considered performing sensitivity analyses for quality items and to stratify the data by decades to assess the influence of the time lag on the results of the studies (as increasing resistance of pathogens develops in time), if heterogeneity that could be attributed to these items was found.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See Characteristics of included studies.

We identified 835 references, of which we excluded 756 after inspection of the abstracts for one of the following reasons: not acute uncomplicated UTI, not randomised, observational studies, no intervention of interest, no relevant outcomes, repeated report of same study, review articles, complicated UTI, papers not fulfilling our inclusion criteria. We considered 80 reports potentially eligible for inclusion, but after inspection of the full papers we excluded 59 (see Characteristics of excluded studies table).

Included studies

Twenty-one studies with 6016 participants assigned to different antibiotics met the pre-stated inclusion criteria for this review. The studies were conducted in several European countries, USA, Canada, Japan and Korea. Different inclusion criteria were used in the studies; participants were considered for inclusion based on symptoms, symptoms and leucocyturia or symptoms and bacteriuria. Different thresholds for considering positive urine culture and bacteriological cure were used in the studies. Nine studies had more than two treatment arms, some using different periods of treatment or an intervention of no interest, and we included only the relevant treatment arms for the review (Boyko 1990; Ellis 1990; Goto 1999; Greenberg 1986; Hooton 1989; Hooton 1995; Iravani 1999; McCarty 1999; Spencer 1994).

Participants

Participants included in the studies were outpatient women with a diagnosis of acute uncomplicated lower UTI. A few studies included patients older than 65 years and gave no separate data for younger women. These studies were included in the review if the mean age and standard deviation suggested that the number of women older than 65 years was small (Goldstein 1985; Goto 1999; Hooton 1989; Iravani 1999; SUTISG 1995).

Interventions

- One study including 147 patients compared nalidixic acid to a beta-lactam (Kurokawa 1978).
- Five studies including 1898 patients compared a fluoroquinolone with a beta-lactam (Goto 1999; Hooton 2005; Naber 1993; Nicolle 2002; SUTISG 1995).
- Four studies including 1821 participants compared nitrofurantoin with TMP-SMX (Ellis 1990; Hooton 1995; Iravani 1999; Spencer 1994).
- Five studies including 956 patients compared TMP-SMX with a beta-lactam (Ellis 1990; Greenberg 1986; Guttmann 1977; Hooton 1995; Kavatha 2003).
- Eight studies including 1764 participants compared fluoroquinolones to TMP-SMX (Block 1987; Boyko 1990; Goldstein 1985; Henry 1986; Hooton 1989; McCarty 1999; Park 2007; Schaeffer 1985).
- Two studies including 570 participants compared nitrofurantoin to beta-lactam (Ellis 1990; Hooton 1995).

The numbers reported here consider the total numbers of patients included in the individual studies (including treatment arms excluded from this review for studies with multiple treatment arms), as not all the included studies with multiple arms reported separate

data for the numbers randomised in each group. The numbers of patients randomised to each treatment arm included in the review are reported in Characteristics of included studies where available. No other concomitant therapies were used in the studies. Treatment was started in the studies before the results of urine cultures were known.

The included studies for each comparison, the interventions, doses and durations of treatment are summarised in Table 1; Table 2; Table 3; Table 4; Table 5 and Table 6.

Table 1. Fluoroquinolones versus TMP-SMX

Study	Group 1	Group 2	Duration of treatment
Block 1987	Ofloxacin 100 mg bid	TMP-SMX 160/800 mg bid	3 days
Boyko 1990	Amifloxacin 200/400 mg bid	TMP-SMX 160/800 mg bid	10 days
Goldstein 1985	Norfloxacin 400 mg bid	TMP-SMX 160/800 mg bid	7-10 days
Henry 1986	Ciprofloxacin 250 mg bid	TMP-SMX 160/800 mg bid	10 days
Hooton 1989	Ofloxacin 200/300 mg bid	TMP-SMX 160/800 mg bid	7 days
McCarty 1999	Ofloxacin 200 mg bid	TMP-SMX 160/800 mg bid	3 days
McCarty 1999	Ciprofloxacin 100 mg bid	TMP-SMX 160/800 mg bid	3 days
Park 2007	Ciprofloxacin ER 500 mg qd	TMP-SMX 160/800 mg bid	3 days
Schaeffer 1985	Norfloxacin 400 mg bid	TMP-SMX 160/800 mg bid	10 days

bid - twice daily; qd - once daily; ER - extended release; TMP-SMX - trimethoprim-sulfamethoxazole

Table 2. Beta-lactam versus TMP-SMX

Study	Group 1	Group 2	Duration of treatment
Ellis 1990	Amoxicillin 250 mg tid	TMP-SMX 160/800 mg bid	7 days
Greenberg 1986	Cefadroxil 500 mg bid	TMP-SMX 160/800 mg bid	3 days
Guttmann 1977	Pivmecillinam 400 mg qid	TMP-SMX 160/800 mg bid	7 days
Hooton 1995	Amoxicillin 500 mg tid	TMP-SMX 160/800 mg bid	3 days
Hooton 1995	Cefadroxil 500 mg bid	TMP-SMX 160/800 mg bid	3 days

Table 2. Beta-lactam versus TMP-SMX (*Continued*)

Kavatha 2003	Cefpodoxime proxetil 100 mg bid	TMP-SMX 160/800 mg bid	3 days

bid - twice daily; qid - four times daily; tid - three times daily; TMP-SMX - trimethoprim-sulfamethoxazole

Table 3. Nitrofurantoin versus beta-lactam

Study	Group 1	Group 2	Duration of treatment
Ellis 1990	Nitrofurantoin 100 mg qid	Amoxicillin 250 mg tid	7 days
Hooton 1995	Nitrofurantoin 100 mg qid	Amoxicillin 500 mg tid	3 days
Hooton 1995	Nitrofurantoin 100 mg qid	Cefadroxil 500 mg bid	3 days

bid - twice daily; qid - four times daily; tid - three times daily

Table 4. Fluoroquinolones versus beta-lactam

Study	Group 1	Group 2	Duration of treatment
Goto 1999	Ciprofloxacin 200mg qd/bid	Cefpodoxime proxetil 200 mg qd	3 days
Hooton 2005	Ciprofloxacin 250 mg bid	Amoxicillin clavulanate 500/125 mg bid	3 days
Naber 1993	Ofloxacin 100 mg bid	Cefuroxime axetil 125 mg bid	3 days
Nicolle 2002	Norfloxacin 400 mg bid	Pivmecillinam 400 mg bid	3 days
SUTISG 1995	Norfloxacin 200 mg bid	Ritipenem acoxil 500 mg tid	5 days

bid - twice daily; qd - once daily; tid - three times daily

Table 5. Nitrofurantoin versus TMP-SMX

Study	Group 1	Group 2	Duration of treatment
Ellis 1990	Nitrofurantoin 100 mg qid	TMP-SMX 160/800 mg bid	7 days
Hooton 1995	Nitrofurantoin 100 mg qid	TMP-SMX 160/800 mg bid	3 days
Iravani 1999	Nitrofurantoin 100 mg bid	TMP-SMX 160/800 mg bid	7 days

Table 5. Nitrofurantoin versus TMP-SMX (*Continued*)

Spencer 1994	Nitrofurantoin 100 mg bid	TMP-SMX 160/800 mg bid	7 days

bid - twice daily; qid - four times daily; TMP-SMX - trimethoprim-sulfamethoxazole

Table 6. Nalidixic acid versus beta-lactam

Study	Group 1	Group 2	Duration of treatment
Kurokawa 1978	Nalidixic acid 500 mg qid	Pivmecillinam 50 mg qid	3 days

qid - four times daily

Outcomes

All the studies reported at least one of the outcomes included in the review. In addition, seven studies reported results for combined cure (symptomatic and bacteriological) and these were included in Table 7 (Ellis 1990; Goldstein 1985; Goto 1999; Henry 1986; Hooton 1995; Kurokawa 1978; Naber 1993). Two studies reported data for resistance development outside the urinary tract and were included in Table 8 (Hooton 1989; Schaeffer 1985).

Table 7. Mixed cure: clinical and bacteriological

Study	Intervention	Dose	Duration	Cured up to 2 weeks	Cured up to 8 weeks
Ellis 1990	Amoxicillin TMP-SMX Nitrofurantoin	250 mg tid 160/800 mg bid 100 mg qid	7 days 7 days 7 days	64% (16/25) 80% (16/20) 93% (26/28)	
Goldstein 1985	TMP-SMX Norfloxacin	160/800 mg bid 400 mg bid	7-10 days 7-10 days	86.4% (19/22) 91% (20/22)	
Goto 1999	Ciprofloxacin Cefpodoxime-proxetil	200 mg qd 200 mg qd	3 days 3 days	77.8% (21/27) 64.3% (18/28)	
Henry 1986	Ciprofloxacin TMP-SMX	250 mg bid 160/800 mg bid	10 days 10 days	93.5% 82.3%	
Hooton 1995	TMP-SMX Nitrofurantoin Cefadroxil Amoxicillin	160/800 mg bid 100 mg qid 500 mg bid 500 mg tid	3 days 3 days 3 days 3 days		82% (32/39) 61% (22/36) 66% (21/32) 67% (28/42)

Table 7. Mixed cure: clinical and bacteriological (*Continued*)

Kurokawa 1978	Pivmecillinam Nalidixic acid	50 mg qid 500 mg qid	3 days 3 days	62.5% (40/64) 57.6% (34/59)	
Naber 1993	Cefuroxime-axetil Ofloxacin	125 mg bid 100 mg bid	3 days 3 days	78.7% (52/67) 90.4% (56/62)	

bid - twice daily, qd - once daily; qid - four times daily; tid - three times daily; TMP-SMX - trimethoprim-sulfamethoxazole

Table 8. Resistance development outside the urinary tract

Study	Intervention	Dose	Duration	Resistance	Site
Hooton 1989	Ofloxacin TMP-SMX	200 mg bid 160/800 mg bid	7 days 7 days	0% (0/50) 19% (5/27)	rectal flora
Schaeffer 1985	Norfloxacin TMP-SMX	400 mg bid 160/800 mg bid	10 days 10 days	0% 11%	rectal vaginal flora

bid - twice daily; TMP-SMX - trimethoprim-sulfamethoxazole

Risk of bias in included studies

Allocation

All twenty-one studies were RCTs and used a parallel group design. Four studies described the randomisation process and allocation concealment was adequate (Hooton 2005; McCarty 1999; Naber 1993; Nicolle 2002). Five studies described the randomisation generation but concealment to allocated treatment was unclear (Greenberg 1986; Hooton 1989; Hooton 1995; Kurokawa 1978; SUTISG 1995). Twelve studies reported randomisation but the method of randomisation and concealment of allocation were not mentioned.

We contacted the authors of the included studies via e-mail if this was available for details on the randomisation process (see Characteristics of included studies).

Blinding

Eight studies were double-blind, four single-blind, five open. In four studies blinding was not mentioned (Goldstein 1985; Guttmann 1977; Hooton 1989; Hooton 1995).

Other potential sources of bias

Follow-up

Drop-outs in the included studies were less than 30% as stated in the protocol.

ITT analysis

Two studies mentioned ITT analysis (Iravani 1999; Nicolle 2002)

Effects of interventions

For numerical details and studies included in the meta-analyses (MA) see Data and analyses.

Fluoroquinolones versus TMP-SMX

Table 1

Short-term symptomatic cure

Fluoroquinolones and TMP-SMX were equally effective for all patients (Analysis 1.1 (5 studies, 927 participants): RR 1.00, 95% CI 0.97 to 1.03), and for those with susceptible pathogens (Analysis 1.2 (3 studies, 177 participants): RR 1.01, 95% CI 0.95 to 1.08).

Long-term symptomatic cure

McCarty 1999 reported there was no statistically significant difference between fluoroquinolone and TMP-SMX (Analysis 1.3).

Short-term bacteriological cure

Patients receiving fluoroquinolones had a modest advantage with borderline statistical significance (Analysis 1.4 (7 studies, 1253 participants): RR 1.03, CI 1.00 to 1.07; NNT (number needed to treat) = 20). For patients with susceptible pathogens the difference did not reach statistical significance (Analysis 1.5 (5 studies, 499 participants): RR 1.03, 95% CI 0.98 to 1.07).

Long-term bacteriological cure

A similar modest advantage to fluoroquinolones was shown with borderline statistical significance (Analysis 1.6 (6 studies, 884 participants): RR 1.06, 95% CI 1.00 to 1.12).

Isolation of resistant urinary pathogens during treatment

There was no statistically significant difference between fluoroquinolones and TMP-SMX (Analysis 1.7 (2 studies, 160 participants): RR 0.64, 95% CI 0.05 to 8.62).

Number of days to symptom resolution

No meta-analysis was performed for this outcome. Park 2007 reported a mean interval of 1.93 ± 0.55 days for fluoroquinolones and 2.92 ± 0.48 days for TMP-SMX, not specifying if the dispersion measure was the standard deviation (SD), and we had no reply from the author. Block 1987 reported a mean of 2.9 ± 1.6 days for fluoroquinolones and 3.2 ± 1.7 days for TMP-SMX. Boyko 1990 reported a similar mean for both groups (3 and 3.1 days), with no separate data for each group.

Days of work loss

No data were reported for this outcome.

Any adverse event requiring discontinuation of treatment

There was no statistically significant difference between fluoroquinolones and TMP-SMX (Analysis 1.8 (3 studies, 1063 participants): RR 0.37, 95% CI 0.12 to 1.14).

Adverse events

Any adverse event

There was no statistically significant difference between fluoroquinolones and TMP-SMX (Analysis 1.9.1 (7 studies, 1477 participants): RR 0.95, 95% CI 0.71 to 1.29).

Rash

Patients treated with fluoroquinolones were less likely to develop rash than those treated with TMP-SMX (Analysis 1.9.2 (2 studies, 1019 participants): RR 0.08, 95% CI 0.01 to 0.43).

Diarrhoea

There was no statistically significant difference between fluoroquinolones and TMP-SMX (Analysis 1.9.2 (3 studies, 1063 participants): RR 1.22, 95% CI 0.21 to 7.29).

Complications: pyelonephritis

Block 1987 reported one patient in each treatment group developed pyelonephritis (Analysis 1.10).

Beta-lactam drugs versus TMP-SMX

Table 2

Short-term symptomatic cure

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.1 (2 studies, 176 participants): RR 0.95, 95% CI 0.81 to 1.12).

Long-term symptomatic cure

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.2 (2 studies 138 participants): RR 1.06, 95% CI 0.93 to 1.21).

Short-term bacteriological cure

There was no statistically significant difference between beta-lactam and TMP-SMX in short-term bacteriological cure for all patients (Analysis 2.3 (5 studies, 389 participants): RR 0.95, 95% CI 0.88 to 1.04), or for those with susceptible pathogens (Analysis 2.4 (4 studies, 310 participants): RR 0.98, 95% CI 0.92 to 1.04).

Long-term bacteriological cure

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.5 (5 studies, 311 participants): RR 0.97, 95% CI 0.87 to 1.08).

Isolation of resistant urinary pathogens during treatment

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.6 (3 studies, 259 participants): RR 0.55, 95% CI 0.09 to 3.42).

Number of days to symptom resolution

No data were reported for this outcome.

Days of work loss

No data were reported for this outcome.

Any adverse event requiring discontinuation of treatment

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.7 (2 studies, 184 participants): RR 1.53, 95% CI 0.28 to 8.28).

Adverse events

Any adverse event

There was no statistically significant difference between beta-lactam and TMP-SMX (Analysis 2.8.1 (2 studies, 184 participants): RR 0.76, 95% CI 0.46 to 1.27)

Rash

Hooton 1995 reported 2.2% (1/46) of patients receiving TMP-SMX and 2.2% (2/92) of patients receiving beta-lactam developed a rash (Analysis 2.8.2).

Diarrhoea

Hooton 1995 reported no patients receiving TMP-SMX (0/46) and 2.2% of patients (2/92) receiving beta-lactam developed diarrhoea (Analysis 2.8.3).

Complications: pyelonephritis

No data were reported for this outcome.

Nitrofurantoin versus beta-lactam

Table 3

Short-term symptomatic cure

Ellis 1990 reported 92.9% (26/28) in the nitrofurantoin group and 78.3% (18/23) in the beta-lactam group were cured (Analysis 3.1).

Long-term symptomatic cure

Ellis 1990 reported no significant difference between nitrofurantoin and beta-lactam (RR 0.98, 95% CI 0.83 to 1.14).

Short-term bacteriological cure

There was no statistically significant difference between nitrofurantoin and beta-lactam in short-term bacteriological cure for all patients (Analysis 3.2 (2 studies, 170 participants): RR 1.09, 95% CI 0.75 to 1.58) or for those with susceptible pathogens (Analysis 3.3 (2 studies, 146 participants): RR 0.99, 95% CI 0.73 to 1.34).

Long-term bacteriological cure

There was no statistically significant difference between nitrofurantoin and beta-lactam (Analysis 3.4 (2 studies, 143 participants): RR 0.97, 95% CI 0.86 to 1.09).

Isolation of resistant urinary pathogens during treatment

Hooton 1995 reported no resistance development was found in either the nitrofurantoin or beta-lactam groups.

Number of days to symptom resolution

No data were reported for this outcome.

Days of work loss

No data were reported for this outcome.

Any adverse event requiring discontinuation of treatment

Hooton 1995 reported 4.3% (4/92) of patients receiving beta-lactam and no patient (0/42) receiving nitrofurantoin discontinued treatment because of adverse events (Analysis 3.5).

Adverse events

Any adverse event

Hooton 1995 reported 42.9% (18/42) in the nitrofurantoin group and 27.2% (25/92) in the beta-lactam group developed adverse events (Analysis 3.6.1).

Rash

Hooton 1995 reported 2.2% (2/92) in the beta-lactam group and no patient (0/42) in the nitrofurantoin group developed a rash (Analysis 3.6.2).

Diarrhoea

Hooton 1995 reported 7.1% (3/42) in the nitrofurantoin group and 2.2% (2/92) in the beta-lactam group had diarrhoea (Analysis 3.6.3).

Complications, pyelonephritis

No data were reported for this outcome.

Fluoroquinolones versus beta-lactam

Table 4

Short-term symptomatic cure

There was no statistically significant difference between fluoroquinolone and beta-lactam (Analysis 4.1 (2 studies, 1192 participants): RR 1.15, 95% CI 0.99 to 1.32).

Long-term symptomatic cure

Nicolle 2002 reported no difference in long-term symptomatic cure between the beta-lactam (90.8%; 297/327) and fluoroquinolone groups (91.4%; 318/348) (Analysis 4.2).

Short-term bacteriological cure

Patients treated with fluoroquinolones compared to beta-lactam were more likely to be cured (Analysis 4.3 (5 studies, 1289 participants): RR 1.22, 95% CI 1.13 to 1.31; NNT = 6), as were patients with susceptible pathogens (Analysis 4.4 (2 studies, 690 participants): RR 1.20, 95% CI 1.07 to 1.35).

Long-term bacteriological cure

There was no statistically significant difference between fluoroquinolone and beta-lactam (Analysis 4.5 (2 studies, 497 participants): RR 0.90, 95% CI 0.61 to 1.32).

Isolation of resistant urinary pathogens during treatment

Hooton 2005 reported 3.2% (5/156) in the beta-lactam group and 1.3% (2/155) in the fluoroquinolone group developed resistance (Analysis 4.6).

Number of days to symptom resolution

No data were reported for this outcome.

Days of work loss

No data were reported for this outcome.

Any adverse event requiring discontinuation of treatment

There was no statistically significant difference between fluoroquinolone and beta-lactam (Analysis 4.7 (4 studies, 1501 participants): RR 1.98, 95% CI 0.74 to 5.30).

Any adverse event

There was no statistically significant difference between fluoroquinolone and beta-lactam (Analysis 4.8.1 (4 studies, 1501 participants): RR 0.90, 95% CI 0.61 to 1.33).

Rash

Patients treated with fluoroquinolones were less likely to have rash than those treated with a beta-lactam (Analysis 4.8.2 (2 studies, 494 participants): RR 0.10, 95% CI 0.02 to 0.56).

Diarrhoea

Hooton 2005 reported 8% of patients in the beta-lactam group and 0.6% in the fluoroquinolone group developed diarrhoea.

Complications: pyelonephritis

Hooton 2005 reported 1.25% (2/160) in the beta-lactam group and no patient (0/162) in the fluoroquinolone group developed pyelonephritis (Analysis 4.9).

Nitrofurantoin versus TMP-SMX

Table 5

Short-term symptomatic cure

There was no statistically significant difference between nitrofurantoin and TMP-SMX (Analysis 5.1 (3 studies, 733 participants): RR 0.99, 95% CI 0.95 to 1.04).

Long-term symptomatic cure

There was no statistically significant difference between nitrofurantoin and TMP-SMX (Analysis 5.2 (2 studies, 338 participants): RR 1.01, 95% CI 0.94 to 1.09).

Short-term bacteriological cure

There was no statistically significant difference between nitrofurantoin and TMP-SMX for all patients (Analysis 5.3 (4 studies 668 participants): RR 0.97, 95% CI 0.87 to 1.08) or for patients with susceptible pathogens (Analysis 5.4 (3 studies, 463 participants): RR 0.95, 95% CI 0.84 to 1.08).

Long-term bacteriological cure

There was no statistically significant difference between nitrofurantoin and TMP-SMX (Analysis 5.5 (3 studies, 395 participants): RR 1.01, 95% CI 0.90 to 1.13).

Isolation of resistant urinary pathogens during treatment

Hooton 1995 reported no patient receiving nitrofurantoin (0/38) and 2.5% (1/40) receiving TMP-SMX developed resistance (Analysis 5.6).

Number of days to symptom resolution

No data were reported for this outcome.

Days of work loss

No data were reported for this outcome.

Any adverse event requiring discontinuation of treatment

There was no statistically significant difference between nitrofurantoin and TMP-SMX (Analysis 5.7 (3 studies, 921 participants): RR 0.69, 95% CI 0.34 to 1.41).

Adverse events

Any adverse event

There was no statistically significant difference between nitrofurantoin and TMP-SMX (Analysis 5.8.1 (3 studies, 921 participants): RR 0.96, 95% CI 0.79 to 1.17).

Rash

Patients treated with nitrofurantoin were less likely to develop rash than patients treated with TMP-SMX (Analysis 5.8.2 (3 studies, 921 participants): RR 0.17, 95% CI 0.04 to 0.76).

Diarrhoea

Hooton 1995 reported 7.1% (3/42) of patients receiving nitrofurantoin and no patient (0/46) receiving TMP-SMX developed diarrhoea (Analysis 5.8.3).

Complications: pyelonephritis

No data were reported for this outcome.

Nalidixic acid versus beta-lactam

Table 6

One study compared nalidixic acid and beta-lactam (Kurokawa 1978), and reported no significant differences between the treatment groups.

Sensitivity analyses

Where possible we performed sensitivity analysis by concealment of allocation to treatment. Concealment of allocation did not influence the results for short-term bacteriological cure in the fluoroquinolone versus beta-lactam treated patients (Analysis 4.11).

The years in which studies were performed did not seem to influence the individual results of the studies and no meta-analyses were performed for this item by decade, with insufficient studies available for each comparison. The individual study results were similar across the comparisons.

When analysed separately, the effects of specific fluoroquinolones, durations of treatment and ITT analyses (Analysis 1.11; Analysis 2.9; Analysis 4.10; Analysis 5.9) did not change the results.

The number of studies was insufficient for performing funnel plots.

DISCUSSION

UTIs are common bacterial infections, particularly in women. Antimicrobial therapy is seldom indicated for asymptomatic infection, but is usually indicated for amelioration of symptoms. In the few studies in which antibiotics were compared with placebo for uncomplicated UTI, antibiotics showed significant efficacy (Falagas 2009). Symptoms are usually severe and distressing enough to warrant starting antibiotic therapy immediately, without waiting for bacteriological confirmation.

Recently, the development of resistance to antimicrobial agents has become an increasing threat to successful treatment of UTI. An additional cause for concern is the number of severe adverse drug reactions following co-trimoxazole therapy (Spencer 1994).

In clinical practice the empirical management of uncomplicated UTI is to use antimicrobials effective against most *E. coli* strains, which are the predominant uropathogens, until the pathogens are

confirmed in urine culture. The decision to manage uncomplicated UTI is guided by the physician's perception of the symptom severity experienced by the patient, and by the highly predictable micro-organisms and relatively predictable local susceptibility to antimicrobials (Park 2007). Recommended empirical therapy for the treatment of acute uncomplicated UTI has evolved over the last few decades, primarily in response to the introduction of new agents and the increasing resistance of community *E. coli* to recommended empirical therapy (Nicolle 2002).

Desirable features of a good antimicrobial agent for the treatment of UTI are a wide spectrum of antibacterial activity which includes micro-organisms resistant to commonly used drugs, high urine levels of the drug, ease of administration and minimal side-effects and toxicity (Giamarellou 1983).

We included 21 studies of good quality (see Risk of bias in included studies) comparing different classes of antimicrobials in the review. Only two or three studies were found for inclusion in most of the meta-analyses that were performed. Individual study results were consistent within the different comparisons used in the review, no outliers were observed. We found no differences for the symptomatic cure between the classes of antimicrobials included in the review. Fluoroquinolones were more effective than beta-lactams for short-term bacteriological cure. More patients were also observed to be cured using fluoroquinolone compared to TMP-SMX for the short-term bacteriological cure and for the long-term bacteriological cure; however these results did not reach statistical significance. The results for all the comparisons did not change when we included only the patients with susceptible pathogens in the analyses. Fewer rashes were observed in patients treated with fluoroquinolones than with either beta-lactam drugs or TMP-SMX, but the risk for any adverse events were similar. Most study participants were infected with *E. coli*. Two studies reported resistance development outside the urinary tract to TMP-SMX but not to fluoroquinolones (Hooton 1989; Schaeffer 1985), but these were old studies and this finding may not be relevant today, when resistance to fluoroquinolones is widespread. A few studies reported a combined outcome (symptomatic and bacteriological) and their results support the results of the meta-analyses (see Table 7). Hooton 1995 found a better mixed cure for the TMP-SMX than nitrofurantoin treatment at the long-term follow-up, but not for the bacteriological cure alone.

Nitrofurantoin proved equally effective as TMP-SMX, was less likely to cause rash while having similar rates for any adverse event. Treatments were given for three days in one study and seven days in all other studies with these drugs (see Additional tables). There is also less concern about possible resistance development (Hooton 2003). Rare cases of severe idiosyncratic liver injury and acute pulmonary toxicity to nitrofurantoin were reported in the literature (Boelsterli 2006; Williams 2006). The incidence of these rare side effects is difficult to ascertain, and they are probably on the same order of magnitude (or less) than severe antibiotic associated diarrhoea caused by beta-lactam drugs or fluoroquinolones, or severe skin eruptions caused by TMP-SMX. Based on these findings nitrofurantoin should probably be considered the first drug of choice for treating uncomplicated UTI in women.

Fluoroquinolones were more effective for short-term bacteriological cure than beta-lactams and less likely to cause rash. However with regard to the main outcome that matters to patients, symptomatic relief, fluoroquinolones showed no advantage. We found no advantage for fluoroquinolones assessing long term bacteriological cure. No studies were found that compared nitrofurantoin to fluoroquinolones.

We conclude that fluoroquinolones have no added value over other antibiotic groups for the treatment of acute uncomplicated UTI. The questionable benefit in short term bacteriological eradication is probably offset by the potential impact of fluoroquinolone use on resistance.

Responsible use of antibiotics for UTI requires selection and administration of the right dosage of the most suitable antibiotic for an appropriate time period to eliminate pathogens quickly and successfully. The decision to consider an alternative first-line therapy for UTI should be driven by local resistance and susceptibility data (if known) and patient preference.

AUTHORS' CONCLUSIONS

Implications for practice

There were no differences between the classes of antimicrobials included in this review for the symptomatic cure of acute uncomplicated UTI. Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological cure, but the advantage was minor. Nitrofurantoin could be a good choice as a first line drug for treating uncomplicated UTI, with less risk of developing rash than TMP-SMX, as it does not share cross-resistance with commonly prescribed antibiotics and as a fluoroquinolone sparing agent. The individual treatment should take into consideration the susceptibility of urinary pathogens in local areas, possible adverse events and resistance development and patient preference.

Implications for research

Studies comparing nitrofurantoin to fluoroquinolones for a short duration of treatment (three to five days) should be performed. These studies should adhere to good methodological and reporting standards, namely reporting the methods of randomisation and concealment of allocation to treatment and the numbers of patients randomised and evaluated by study groups.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Block 1987

Methods	• Study design: parallel RCT
Participants	Inclusion criteria • Setting: outpatients department • Country: Norway • Adult, non-pregnant women; symptoms: frequency, dysuria and > 10 WBC/HPF • Number (ofloxacin/TMP-SMX): 125/125 • Mean age ± SD ○ Ofloxacin group: 41.2 ± 17 years ○ TMP-SMX group: 42.5 ± 17 years • Positive urine culture ($\geq 10^5$ CFU/mL) ○ Ofloxacin group: 82.4% (73.7% *E. coli*) ○ TMP-SMX group: 80% (78% *E. coli*) Exclusion criteria • Upper UTI; chronic disease; allergy to study drugs; use of warfarin, phenytoin, methotrexate, corticosteroids, other cytostatics
Interventions	• Ofloxacin group ○ 100 mg bid for 3 days • TMP-SMX group ○ 160/800 mg bid for 3 days
Outcomes	• Bacteriological elimination, relapse, reinfection, failure • Clinical cure/improvement, recurrence, failure • Time to symptom relief • Adverse events: assessed by interview during follow-up by spontaneous reporting and questionnaire • Definitions ○ Bacteriological cure: eradication of the infecting organism ○ Symptomatic cure: symptoms subsided
Notes	• Standard laboratory methods used • Follow-up at 4-6 and 18-20 days after treatment • Urinalysis before treatment • Not evaluable if lost to follow-up, treatment with other antibiotics, initially resistant pathogens • Patients without significant bacteriuria- acute urethral syndrome were only clinically assessed • Urine culture negative subjects excluded from the bacteriological assessment: ofloxacin group (22), TMP-SMX group (25) • Other reasons for exclusion and drop-outs ○ Ofloxacin group (6): pyelonephritis (1), lost to follow-up (4), resistant initially pathogen (1) ○ TMP-SMX (8): pyelonephritis (1), lost to follow-up (3), resistant initially pathogen

Block 1987 (*Continued*)

	(4)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated 'randomly allocated'
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double blind
Intention-to-treat (ITT) analysis?	No	No

Boyko 1990

Methods	• Study design: parallel RCT

Participants	Inclusion criteria
	• Setting: Multicentre; outpatient ambulatory and emergency care settings private, university, student health practices
	• Women > 18 years, UTI symptoms (dysuria, frequency, urgency, suprapubic pain) + bacteria in spun urinary sediment. UTI defined $\geq 10^5$ CFU/mL in clean-catch midstream or catheterised urine within 48 hours before treatment
	• Number (amifloxacin 200/amifloxacin 400/TMP-SMX): 52/54/47
	• Mean age
	  ○ Amifloxacin 200/400 mg groups: 27 years
	  ○ TMP-SMX group: 30 years
	• Positive urine culture ($\geq 10^5$ CFU/mL)
	  ○ Amifloxacin 200 mg group: 73% (73.7% *E. coli*)
	  ○ Amifloxacin 400 mg group: 72% (79.5% *E. coli*)
	  ○ TMP-SMX group: 74% (80% *E. coli*)
	Exclusion criteria
	• Recent UTI/frequent; pyelonephritis; other medical conditions

Interventions	• Amifloxacin 200
	  ○ 200 mg bid for 10 days
	• Amifloxacin 400
	  ○ 400 mg bid for 10 days
	• TMP-SMX
	  ○ 160/800 mg bid for 10 days

Outcomes	• Clinical cure at 5-9 days • Clinically improved at 5-9 days • Bacteriological cure/superinfection at 5-9 days • Bacteriological cure/relapse/reinfection at 4-6 weeks • Adverse events • Definitions

Boyko 1990 (*Continued*)

	○ Bacteriological cure: $\leq 10^4$ CFU/mL ○ Clinical cure: complete resolution of symptoms
Notes	• Susceptibility tested by standard methods • Patients with resistant organisms excluded post-randomisation • Included in efficacy analysis only those who complied with protocol requirements at the 5-9 day visits after end of treatment (evaluable) • All enrolled patients are included in the safety analysis • Follow-up: 2-4 days after start of treatment, 5-9 days and 4-6 weeks after end of treatment • Adverse events assessed by diary records by patients • Excluded post-randomisation ○ Urine culture negative: Amifloxacin 200 mg (14), Amifloxacin 400 mg (15), TMP-SMX group (12) • Other reasons for exclusion ○ Amifloxacin 200 group: resistance to treatment (3), drug noncompliance (1), noncompliance to follow-up (11), not urine culture (1); 37% drop-out excluding the 3 resistant strains ○ Amifloxacin 400 mg group: resistance to treatment (4), drug noncompliance (1), treatment other antibiotic (1), noncompliant with follow-up (8), not urine culture (1); 31% drop-out without 4 resistant strains ○ TMP-SMX group: resistance to treatment (1), drug noncompliance (3), noncompliant with follow-up (4; 20.6% drop out) ○ Drop-outs: 31 (29.8%) at 5-9 days follow-up for clinical/bacteriological evaluation in all the groups • Amifloxacin 200 and 400 mg groups considered together as one treatment arm in this review • E-mail sent to author for details of the randomisation: information not available • Funding: Grant from the Sterling Research Group N.Y.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double blind
Intention-to-treat (ITT) analysis?	No	Used for adverse events only

Ellis 1990

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Setting: General practitioners • Country: UK

Ellis 1990 (*Continued*)

	• Women 18-41 years with symptoms (frequency, dysuria)
	• Mean age (range)
	  ○ Amoxicillin group: 31.1 years (18.1-40.6)
	  ○ TMP-SMX group: 30.7 years (19-40.3)
	  ○ Nitrofurantoin group: 30.4 years (20.1-40.8)
	  ○ Trimethoprim group: 30.7 years (18.8-39.8)
	• Positive urine culture: > 10^5 CFU/mL (68.9% *E. coli*)
	Exclusion criteria
	• Flank pain; fever > 38°C; > 2 UTI in 12 months; pregnant; no menses in previous 6 weeks; allergy to drugs; bronchial; hepatic or renal disease

Interventions	• Amoxicillin
	  ○ 250 mg tid for 7 days
	• TMP-SMX
	  ○ 160/800 mg bid for 7 days
	• Nitrofurantoin
	  ○ 100 mg qid for 7 days
	• Trimethoprim
	  ○ 200 mg bid for 7 days

Outcomes	• Efficacy: < 10^5 CFU/mL + symptom free - combined cure
	• Symptomatic cure
	• Bacteriological cure
	• Recurrence
	• Side effects
	• Definitions
	  ○ Bacteriological cure: < 10^5 CFU/mL
	  ○ Symptomatic cure: symptom free

Notes	• Follow-up at 7 days and 4 weeks post-treatment
	• Urine culture at baseline and follow-up visits, < 10^5 excluded from the study at day 7
	• Diary card for symptom relief and 1st dose returned to the investigator
	• Patients lost to follow-up not included in the efficacy analysis
	• ITT for adverse events
	• 390 randomised, no separate data, no data for numbers excluded with negative urine culture and evaluated for adverse events by groups
	• 271 had negative urine culture and excluded post-randomisation
	• Other exclusions/drop-outs
	  ○ Amoxicillin (3): lost to follow-up (1), no data available (2)
	  ○ TMP-SMX (3): lost to follow-up (3)
	  ○ Nitrofurantoin (5): lost to follow-up (5)
	  ○ Trimethoprim (2): lost to follow-up (2)
	  ○ No data available for analysis: 3 patients

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated

Ellis 1990 (*Continued*)

Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Single blind
Intention-to-treat (ITT) analysis?	Yes	Used for adverse events only

Goldstein 1985

Methods	• Study design: Parallel RCT

Participants	Inclusion criteria
	• Women >18 years, frequency, urgency, dysuria, suprapubic pain, malodorous urine, >10 WBC/HPF, >10^5 CFU/mL on pretreatment urine culture
	• Number (TMP-SMX/norfloxacin): 22/23
	• Age range: 19-75 years
	• Positive urine culture (> 10^5 CFU/mL)
	  ○ TMP-SMX group: 100%
	  ○ Norfloxacin group: 95.6% (82% *E. coli in every group*)
	Exclusion criteria
	• Pregnancy; lactation; upper UTI; allergy to study drugs

Interventions	• TMP-SMX
	  ○ 160/800 mg bid for 7-10 days
	• Norfloxacin
	  ○ 400 mg bid for 7-10 days

Outcomes	• Early cure combined (clinical /bacteriological)
	• Long term bacteriological cure
	• Adverse events
	• Definitions
	  ○ Bacteriological cure: eradication of bacteriuria
	  ○ Clinical cure: absence of symptoms

Notes	• Standard methods used for urine culture, similar baseline characteristics • Patients evaluated at days 2-4 of treatment, 5-9 days and 4-6 weeks post treatment • Excluded post-randomisation ○ Negative urine culture: norfloxacin (1) • Adverse events reported by patients in daily diaries • Grant from Merck Sharp & Dohme Research Laboratories

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)

Goldstein 1985 (*Continued*)

Blinding?	Unclear	Not stated
Intention-to-treat (ITT) analysis?	No	No

Goto 1999

Methods	• Study design: Parallel RCT • Study duration: August 1993 to October 1994
Participants	Inclusion criteria • Setting: Multicentre • Country: Japan • Women, > 16 years, < 10 days symptoms (pain on urination) without fever > 37°C, WBC > 10/HPF, > 10^4 CFU/mL • Number ○ Ciprofloxacin 200 (1 day): 29 ○ Ciprofloxacin 200 (qd, 3 days): 30 ○ Ciprofloxacin 200 (bid, 3 days): 30 ○ Cefpodoxime proxetil: 31 • Mean age (range) ○ Ciprofloxacin 200 (1 day): 43.6 years (20-72) ○ Ciprofloxacin 200 (qd, 3 days): 48.5 years (19-73) ○ Ciprofloxacin 200 (bid, 3 days): 46.2 years (18-74) ○ Cefpodoxime proxetil: 45.6 years (17-75) • Positive urine culture (> 10^4 CFU/mL): 91.6% (all groups) ○ *E. coli* ◇ Ciprofloxacin 200 (1 day): 80% ◇ Ciprofloxacin 200 (qd, 3 days): 78% ◇ Ciprofloxacin 200 (bid, 3 days): 85% ◇ Cefpodoxime proxetil: 78% Exclusion criteria • Allergy to study drugs; antibiotic use in preceding week; unusual isolates; systemic disease; pregnancy; breast-feeding; concomitant infections
Interventions	• Ciprofloxacin ○ 200 mg qd for 1 day • Ciprofloxacin ○ 200 mg qd for 3 days • Ciprofloxacin ○ 200 mg bid for 3 days • Cefpodoxime proxetil ○ 200 mg qd for 3 days
Outcomes	• Bacteriological eradication • Overall combined cure clinical efficacy (excellent, moderate, poor): symptomatic and bacteriological • Adverse events • Definition of bacteriological cure: bacteriological elimination

Goto 1999 (*Continued*)

Notes	• Standard methods used for urine culture • 117 completed study (3 did not return to follow-up, no separate data) • 107 evaluated for efficacy (after excluding 10 negative culture) • Follow-up 2-3 weeks; first assessment at 5 days • 10 culture negative excluded from efficacy analysis, no separate data • ITT for adverse events • Arms 3 and 4 considered for this review

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	No	Open
Intention-to-treat (ITT) analysis?	No	For adverse events only

Greenberg 1986

Methods	• Study design: Parallel RCT • Study duration: April 1983 to November 1994

Participants	Inclusion criteria
	• Setting: ED/medicine clinic physician at St. Louis City Hospital
	• Country: USA
	• Nonpregnant women, > 12 years, with urgency, frequency, dysuria, suprapubic pain and tenderness, pyuria or haematuria (at least one of them) and $>10^5$ CFU/mL
	• Number (cefadroxil-3 days/TMP-SMX-3 days): 26/26
	• Mean age (cefadroxil-3 days/TMP-SMX-3 days): 32/34 years
	• Positive urine culture ($>10^5$ CFU/mL)
	  ○ Cefadroxil 3 days: 96%
	  ○ TMP-SMX 3 days: 92%
	Exclusion criteria
	• Upper UTI; allergy to study drugs; urinary abnormality; chronic diseases; pregnant; nursing, other antimicrobials used

Interventions	• Cefadroxil
	  ○ 500 mg bid for 3 days
	• TMP-SMX
	  ○ 160/800 mg bid for 3 days
	• Other intervention groups (not analysed)
	  ○ Cefadroxil: 1000 mg qd for 1 day
	  ○ Cefadroxil: 500 mg bid for 7 days
	  ○ TMP-SMX: 320/1600 mg qd for 1 day

Greenberg 1986 (*Continued*)

Outcomes	• Cure • Failure • Reinfection, relapse • Adverse events • Definition bacteriological cure: negative urine culture at that visit and all previous visits
Notes	• Subjects with resistant pathogens were enrolled in the study • Follow-up within 3 days of end of treatment, 2 weeks and 4 weeks post treatment with urine culture • Standard bacteriologic methods used • Similar baseline characteristics between groups • Excluded post-randomisation ○ Cefadroxil 3 days (6): refused (1), another drug inadvertently (2), negative urine culture (1), no urine culture at post treatment visit (2) ○ TMP-SMX 3 days (6): lost to follow-up (3), pelvic infection (2), no follow-up at 4 weeks (1) • Adverse events assessed by interview and examination at each follow-up visit • E-mail sent to the author for details of the randomisation and blinding • Funding: Grant from Bristol Research Laboratories

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation generated by a computer
Allocation concealment?	Unclear	Subjects assigned to treatment based on the order they were enrolled (B)
Blinding?	No	Open
Intention-to-treat (ITT) analysis?	No	No

Guttmann 1977

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Setting: 14 general practitioners, urban and rural • Country: UK • Women 15-55 years, not pregnant, no upper UTI, urinary frequency or pain on voiding • Number (pivmecillinam/TMP-SMX): 46/51 • Age range: 15-55 years • Positive urine culture (>10^5 CFU/mL) ○ Pivmecillinam group: 56.5% (61% *E. coli*) ○ TMP-SMX group: 53% (74% *E. coli*) • Complete follow-up (pivmecillinam/TMP-SMX): 23/23

Guttmann 1977 (*Continued*)

	Exclusion criteria • Abnormalities urinary tract; sensitivity to study drugs; frequent or recurrent UTI
Interventions	• Pivmecillinam ○ 400 mg qid for 7 days • TMP-SMX ○ 160/800 mg bid for 7 days
Outcomes	• Bacteriological cure • Relapse • Adverse events • Definition of bacteriological cure: elimination of urinary pathogen
Notes	• Standard methods for urine culture • Urine culture before treatment, 1st day of treatment, 2 days and 6 weeks post-treatment • If infection not confirmed stopped treatment • Similar groups except for % of previous UTI • Excluded post-randomisation ○ Pivmecillinam group: negative urine culture (20), not complete follow-up (3) ○ TMP-SMX group: negative urine culture (24), not complete follow-up (4) • 13% lost to follow-up • Funding: Research grant

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Unclear	Not stated
Intention-to-treat (ITT) analysis?	No	No

Henry 1986

Methods	• Study design: Parallel RCT • Duration: May 1985 to April 1986
Participants	Inclusion criteria • Country: USA • Women, positive urine culture >10^4 CFU/mL susceptible to both drugs and symptoms dysuria, haematuria, frequency and/or pyuria • Number (ciprofloxacin/TMP-SMX): 31/34 • Mean age ○ Ciprofloxacin: 37.6 years ○ TMP-SMX: 37 years

Henry 1986 (*Continued*)

	• Positive urine culture (> 10^4 CFU/mL): 69.3%, no separate data ○ *E. coli*: ciprofloxacin (90%); TMP-SMX (91%) Exclusion criteria • Allergy to study drugs; bacteraemia; pregnancy; urinary tract obstruction; neurogenic bladder; indwelling urinary catheter; creatinine > 1.6/100 mL
Interventions	• Ciprofloxacin ○ 250 mg bid for 10 days • TMP-SMX ○ 160/800 mg bid for 10 days
Outcomes	• Eradication of pathogen/clinical resolution up to 9 days post treatment • Relapse at 4 weeks post treatment • Adverse events • Overall cure rates: combined cure • Definition of bacteriological cure: eradication of urinary pathogen up to 9 days post treatment • Definition of symptomatic cure: asymptomatic
Notes	• Standard methods used for urine culture • 3% and 6% in the ciprofloxacin and TMP-SMX groups had fever/chills • Follow-up 4 weeks post treatment • No data available for numbers randomised by groups, numbers of urine culture positive, drop-outs • Other exclusions by groups ○ Culture negative and excluded post-randomisation: 39 (30.7%), no separate data ○ Enrolled (127), evaluable (65), excluded (62): negative urine culture (39), resistant organism (1), not complete follow-up (22, 17%), no separate data

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double blind
Intention-to-treat (ITT) analysis?	No	No

Hooton 1989

Methods	• Study design: Parallel RCT • Duration: 1984-1986

Participants	Inclusion criteria
	• Setting: 3 centres, women from university student health services
	• Country: USA
	• Women 18-75 years, dysuria, frequency, urgency, suprapubic pain. Evaluable if > 100 CFU/mL of midstream urine, pyuria > 10 WBC/mL
	• Mean age
	  ○ Ofloxacin 200 mg (3 days): 26 years
	  ○ Ofloxacin 200 mg (7 days): 24 years
	  ○ Ofloxacin 300 mg: 24 years
	  ○ TMP-SMX: 24 years
	• % urine culture positive can not be estimated from available data, (urine culture positive >100 CFU/mL), 89% of positive urine culture were *E. coli*
	Exclusion criteria
	• Pregnant; not using contraception; upper UTI (fever > 37.5°C; flank pain; tenderness); abnormal urinary tract; UTI > 2 weeks prior to presentation; allergy to treatment drugs; GI complaints; alcoholism; drug abuse; other medical illness; antibiotic use in previous 30 days

Interventions	• Ofloxacin (arm 1, not analysed)
	  ○ 200 mg bid for 3 days
	• Ofloxacin (arm 2)
	  ○ 200 mg bid for 7 days
	• Ofloxacin (arm 3)
	  ○ 300 mg bid for 7 days
	• TMP-SMX (arm 4)
	  ○ 160/800 mg bid for 7 days

Outcomes	• Cure • Early recurrence, late recurrence • Failure • Adverse events • Definition of bacteriological cure: negative urine cultures at all follow-up visits
Notes	• Combined data from 2 studies with identical design and study population • Standard procedures for urine culture susceptibility testing • Similar baseline characteristics between groups • Follow-up at 4 days of treatment, 1 week and 4 weeks post treatment. • Only 2 arms included in review TMP-SMX 7 days and ofloxacin 200 mg 7 days • Emergence of rectal resistant coliforms: TMP-SMX (5) • 208 enrolled, 46 (22%) excluded post-randomisation and including the negative urine cultures. For 8 subjects reasons and groups not mentioned and no separate data for groups available. • Negative urine culture: arm 1 (2), arm 2 (8), arm 3 (7), arm 4 (11) • (≤ 10 WBC/mL): arm 1 (1), arm 2 (3), arm 3 (3), arm 4 (3), • Evaluated if 1 post-treatment visit: 162 (78%) • Adverse events recorded by patients in diary and revised at each follow-up visit • Grant from Ortho Pharmaceutical Corp Raritan N.J.

Hooton 1989 (*Continued*)

	• Arms 2 and 3 considered together as one treatment arm in the meta-analysis • E-mail sent to author for details on randomisation, missing data on numbers randomised, % of positive urine culture, reasons for drop-outs by groups, numbers evaluated for adverse events: no data available

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation list provided by Ortho Pharmaceutical Corp
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Unclear	Not stated
Intention-to-treat (ITT) analysis?	No	No

Hooton 1995

Methods	• Study design: Parallel RCT

Participants	Inclusion criteria
	• Setting: Student Health centre, Seattle
	• Country: USA
	• Women > 18 years, with symptoms of acute cystitis (dysuria, frequency, urgency, suprapubic pain)
	• Number
	  ○ TMP-SMX: 46
	  ○ Nitrofurantoin: 42
	  ○ Cefadroxil: 40
	  ○ Amoxicillin: 52
	• Mean age
	  ○ TMP-SMX: 24 years
	  ○ Nitrofurantoin: 24 years
	  ○ Cefadroxil: 24 years
	  ○ Amoxicillin: 23 years
	• Positive urine culture (> 100 CFU/mL): 91% (85% *E. coli*) no separate data
	Exclusion criteria
	• Pregnant; nursing; upper UTI; abnormal urinary tract; > 7 days symptoms of UTI; allergy to study drugs

Interventions	• TMP-SMX (arm 1)
	  ○ 160/800 mg bid for 3 days
	• Nitrofurantoin (arm 2)
	  ○ 100 mg qid for 3 days
	• Cefadroxil (arm 3)
	  ○ 500 mg bid for 3 days

Hooton 1995 (*Continued*)

	• Amoxicillin (arm 4) ○ 500 mg tid for 3 days
Outcomes	• Combined cure: resolution of symptoms and eradication of significant bacteriuria • Early recurrence, late recurrence • Failure • Adverse events • Definition of bacteriological cure: eradication of significant bacteriuria (> 100 CFU/mL with symptoms or $>10^5$ CFU/mL without symptoms at the last post treatment visit in subjects with no previous post treatment significant bacteriuria • Definition of symptomatic cure: resolution of symptoms
Notes	• Urine culture at initial visit and follow-up visits: 4-6 days after enrolment, 2 weeks and 4-6 weeks post-treatment (late post-treatment visit) • Standard methods used for urine culture • Similar baseline characteristics between groups • Adverse events evaluated for subjects who took the medication and returned to at least 1 follow-up visit • Treatment outcome evaluated for subjects that had also > 100 CFU/mL at enrolment • Excluded post-randomisation ○ Culture negative (16), no separate data ○ At 1st follow-up visit: not evaluable (22): TMP-SMX: (6); nitrofurantoin (4); cefadroxil (3); amoxicillin (9) ○ Did not return for at least 1 follow-up (6), no separate data for groups • At last post-treatment visit an additional 9 dropped-out ○ TMP-SMX: no follow-up (1) ○ Nitrofurantoin: no follow-up (1); no urinary culture data available (1) ○ Cefadroxil: no study antibiotics (4); no follow-up (1) ○ Amoxicillin: no urinary culture data available (1) • Side effects assessed by interview at each follow-up visit • Arms 3 and 4 considered together as one treatment arm in the meta-analysis • E-mail sent to author for details on randomisation, numbers of positive urine culture and numbers of excluded / drop-outs by groups: no data available

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Unclear	Not stated
Intention-to-treat (ITT) analysis?	Yes	ITT for adverse events only

Hooton 2005

Methods	• Study design: Parallel RCT • Duration: July 1998 to May 2002
Participants	Inclusion criteria • University student health centre or a health maintenance organisation • USA • Healthy women 18-45 years, with dysuria, frequency, and/or urgency • Number (amoxicillin-clavulanate/ciprofloxacin): 183/187 • Median age (range) ○ Amoxicillin-clavulanate: 22 (18-45) years ○ Ciprofloxacin: 22 (18-45) years • Positive urine culture (urine culture + >100 CFU/mL) ○ Amoxicillin-clavulanate: 90% ○ Ciprofloxacin: 89% ○ *E. coli*: 82% (groups not separated) Exclusion criteria • Pregnant; pyelonephritis; allergy to study drugs; chronic illness requiring supervision; abnormal urinary tract; antimicrobials within previous 14 days
Interventions	• Amoxicillin-clavulanate ○ 500/125 mg bid for 3 days • Ciprofloxacin ○ 250 mg bid for 3 days
Outcomes	• Clinical cure/persistent UTI/recurrent UTI/microbiological cure at 2 weeks • Vaginal *E. coli* colonisation at all post-treatment visits, the association of vaginal colonisation with persistent/recurrent UTI • Definition of bacteriological cure: asymptomatic + < 10^5 CFU/mL and at least 1-log drop in colony count compared with baseline culture/symptomatic + < 100 CFU/mL and not taking antibiotics at the time of urine culture • Definition of symptomatic cure: no symptoms
Notes	• Urine and vaginal specimen at initial visits and repeated at every 2 week follow-up visit, follow-up until end of study or until re-treatment for persistent or recurrent UTI up to 4 months median • Women included in analyses if they met the enrolment criteria, > 100 CFU/mL in urine, had at least 1 follow-up post-randomisation • Similar baseline characteristics between groups • Excluded post-randomisation ○ Urine culture negative: amoxicillin-clavulanate (18); ciprofloxacin (21) ○ Lost to follow-up (reasons not mentioned): amoxicillin-clavulanate (5); ciprofloxacin (4) • Adverse events assessed by open questions • Grant from National Institute of Diabetes and Digestive and Kidney Disease • E-mail sent to author for randomisation details and data for numbers evaluated for adverse events
Risk of bias	

Hooton 2005 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Blocked randomisation scheme with varying block sizes not revealed to clinic personnel. Randomised by the statistician
Allocation concealment?	Yes	Assignments placed in sealed, sequentially numbered envelopes, opened at the time of enrolment
Blinding?	Yes	Single blind
Intention-to-treat (ITT) analysis?	No	No

Iravani 1999

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Setting: Multicentre, 13 centres • Women, positive urine culture within 48 hours before treatment by clean-catch technique, $\geq 10^3$ CFU/mL and pyuria, positive dipstick or $\geq$ 10 WBC/mL uncentrifuged urine, clinical (dysuria, frequency < 10 days) • Number (ciprofloxacin/TMP-SMX/nitrofurantoin): 239/238/236 • Mean age, SD (range) ○ Ciprofloxacin: 34.5, 16.6 (18-82) years ○ TMP-SMX: 33.4, 15.3 (18-85) years ○ Nitrofurantoin: 34.2, 16.7 (18-85) years • Positive urine culture ($\geq 10^3$ CFU/mL *E. coli*) ○ Ciprofloxacin: 79% ○ TMP-SMX: 86.2% ○ Nitrofurantoin: 81.5% Exclusion criteria • Allergy to treatment; asymptomatic bacteriuria; pregnancy; lactation; bacteraemia; urinary tract obstruction; neurogenic bladder; urinary catheter; multiple organisms; antacids > 1 dose/day; prior treatment within 30 days with one of the study drugs; creatinine > 3 mg/dL; CrCl < 30 mL/min/1.73 m^2
Interventions	• Ciprofloxacin ○ 100mg bid for 3 days + placebo tid for 4 days • TMP-SMX ○ 160/800 mg bid for 7 days • Nitrofurantoin ○ 100 mg bid for 7 days Cointerventions: phenazopyridine permitted up to 24 hours following enrolment

Iravani 1999 (*Continued*)

Outcomes	• Bacteriological cure 4-10 days after treatment, persistence, superinfection/continued eradication, relapse, reinfection at 4-6 weeks after treatment • Clinical resolution at 4-10 days after treatment, failure/continued resolution, relapse at 4-6 weeks after treatment • Adverse events • Definition bacteriological cure: eradication < 10^3 CFU/mL at 4-10 days after end of treatment • Definition symptomatic cure: disappearance of signs and symptoms
Notes	• Similar baseline characteristics, clinical and bacteriological evaluation at entry, during treatment and 4-10 days and 4-6 weeks after treatment • Standard methods for laboratory determinations used • Safety analysis all who received treatment and had a follow-up visit • Evaluable for efficacy if: ○ diagnosis present: clinical + pretreatment ≥10^3 CFU/mL ○ follow-up culture at 4-10 days after treatment ○ drug taken for 7 days ○ no other antimicrobial concomitantly • Patients with resistant organisms not excluded if improving or had a negative culture during treatment. Patients < 7 days treatment not excluded for efficacy analysis if considered failure or had adverse events. • Follow-up: 7 weeks • Excluded post-randomisation ○ Urine culture negative: 128 (18%) culture negative excluded; no separate data for groups ○ Excluded other reasons and drop-outs ◇ Not valid for efficacy analysis: 192 (27%) ◇ Culture negative: 128 (18%) ◇ Other reasons (64; 9%): cultured not obtained (28), entry criteria violation (14), < 7 days treatment (12), < 10^3 CFU/mL (3), other antimicrobial use (3), noncompliant to treatment (2), no follow-up (1), organism resistant to treatment (1); similar rates between groups, no separate data ◇ Prematurely discontinued from treatment (56): adverse events (21), protocol violations (13), pretreatment negative cultures (11), resistant organisms pretreatment (2) • Adverse events assessed by clinical observations • E-mail sent to author for details on randomisation, data on excluded patients with negative urine culture and drop-outs by groups, no reply

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double blind, opaque gelatin capsules for all the treatment

Iravani 1999 (*Continued*)

Intention-to-treat (ITT) analysis?	Yes	ITT analysis for all who received the treatment for adverse events

Kavatha 2003

Methods	• Study design: Parallel RCT

Participants	Inclusion criteria
	• Setting: Outpatients, 4 centres
	• Country: Greece
	• Women 18-70 years, clinical symptoms of lower UTI, absence of fever/flank pain, > 8 WBC/mL in uncentrifuged urine and at least 10^3 CFU/mL urine culture within 48 hours before start of treatment
	• Number (cefpodoxime-proxetil/TMP-SMX): 81/82
	• Mean age (SD)
	  ○ Cefpodoxime-proxetil: 43.63 (15.25) years; range 29-59 years
	  ○ TMP-SMX: 42.23 (15.58) years; range 26-58 years
	• Positive urine culture ($\geq 10^3$ CFU/mL)
	  ○ Cefpodoxime-proxetil: 81.5% (92% *E. coli*)
	  ○ TMP-SMX: 90% (84.3% *E. coli*)
	Exclusion criteria
	• Serum creatinine > 1.8 mg%; permanent urinary catheter; diabetes; immunosuppressed; abnormally urinary tract; asymptomatic bacteriuria; contraindications or allergy to study drugs; upper UTI; history of acute pyelonephritis; UTI in the last month with TMP-SMX failure; symptoms > 3 days prior to presentation; antimicrobial treatment in the last 72 hours; any other antibiotic during study; pregnancy; breast-feeding; participation in a clinical trial in previous 2 weeks; failure to use contraception; malabsorption; hepatic dysfunction; suspicion of noncompliance; resistant urinary pathogens; inability to take oral drugs

Interventions	• Cefpodoxime-proxetil
	  ○ 100 mg bid for 3 days
	• TMP-SMX
	  ○ 160/800 mg bid for 3 days

Outcomes	• Clinical/bacteriological cure up to 7 and 28 days after discontinuation of treatment • Bacteriological failure • Adverse events • Definition of bacteriological cure: sterile urine at both follow-up • Definition of symptomatic cure: all symptoms subsided
Notes	• Monitored at baseline 4 to 7 and 28 days after discontinuation of treatment by clinical, urinalysis and urine culture • Similar baseline characteristics • Conventional methods for collecting urine samples, culture and susceptibility testing • Sponsor Hoechst-Roussel • Only those who returned for at least the 1st follow-up visit included in analysis • Excluded post-randomisation ○ Urine culture negative: cefpodoxime-proxetil (15), TMP-SMX (8) • Other exclusions

Kavatha 2003 (*Continued*)

	○ Cefpodoxime-proxetil ◇ 1st follow-up: neurogenic bladder (2), US chronic pyelonephritis (1) ◇ 2nd follow-up: reason not mentioned (8), urine culture not repeated (5) ○ TMP-SMX ◇ 1st follow-up: resistant isolated pathogens (4) ◇ 2nd follow-up: cultures not repeated (10), reasons not mentioned (10) • Adverse events assessed by interview at each follow-up, including specific questions • E-mail sent to author for data on allocation concealment and missing data for the adverse events, no reply

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	No	Open
Intention-to-treat (ITT) analysis?	No	No ITT

Kurokawa 1978

Methods	• Study design: Parallel RCT • Duration: October 1977 to February 1978
Participants	Inclusion criteria • Country: Japan • Women 16-59 year, acute simple cystitis, pain on urination, pyuria > 10 WBC/HPF, > 10^4 CFU/mL • Number (pivmecillinam/nalidixic acid): 75/72 • Age range: 16-59 years in the groups • Positive urine culture ($\geq 10^4$ CFU/mL) ○ Pivmecillinam: 92% (76.5% *E. coli*) ○ Nalidixic acid: 97% (81.3% *E. coli*) Exclusion criteria • Allergy to study drugs; convulsive disease; renal/hepatic function impaired; cerebral arteriosclerosis; pregnant
Interventions	• Pivmecillinam ○ 50 mg qid for 3 days • Nalidixic acid ○ 500 mg qid for 3 days
Outcomes	• Overall clinical response: combined cure • Improvement in symptoms and lab findings • Bacteriological response

Kurokawa 1978 (*Continued*)

	• Usefulness of treatment • Side effects • Definition of bacteriological cure: < 10^3 CFU/mL • Definition of symptomatic cure: pain on urination disappeared

Notes	• No other medication allowed during study (antibiotics, GI drugs, anti-inflammatory)
	• No significant differences between groups
	• Significant difference for age
	• Follow-up 5 days
	• Excluded post-randomisation
	  ○ Negative urine culture: pivmecillinam (6), nalidixic acid (2)
	• Other exclusions
	  ○ Pivmecillinam (5): no simple cystitis (1), lost to follow-up (3), lag in final day of rating (1)
	  ○ Nalidixic acid (11): no pyuria (1), lost to follow-up (7), side effects (2), lag in final day of rating (1)
	• Adverse events recorded by the physician at the 1st follow-up visit
	• Drugs supplied from Fakeda Chemical Industries
	• E-mail sent to the author for details of the randomisation, no reply

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random sequence, serially numbered drugs, patients consecutively numbered
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double-blind, indistinguishable appearance of treatment
Intention-to-treat (ITT) analysis?	No	No

McCarty 1999

Methods	• Study design: Parallel RCT • Duration: 1990

Participants	Inclusion criteria
	• Setting: 16 centres
	• Women > 18 years, dysuria, pyuria > 10 WBC/mL unspun urine, frequency < 10 days and urine culture > 1000 CFU/mL within 48 hour before treatment
	• Number (ciprofloxacin/ofloxacin/TMP-SMX): 284/288/294
	• Mean age ± SD
	  ○ Ciprofloxacin: 29.8 ± 12.2 years
	  ○ Ofloxacin: 30.8 ± 14.4 years
	  ○ TMP-SMX: 29.7 ± 13.9 years

McCarty 1999 (*Continued*)

	• Urine culture positive (> 1000 CFU/mL): 86% (no separate data) ○ *E. coli*: ciprofloxacin (82%), ofloxacin (79.5%); TMP-SMX (81%) Exclusion criteria • Asymptomatic bacteriuria; allergy to study drugs; pregnancy; lactation; bacteraemia; urinary tract obstruction; neurogenic bladder; cystostomy; urethrectomy; indwelling urinary catheter; multiple organisms; > 1 dose of antacid/day; investigational study drug use within 30 days of study entry; creatinine > 3 mg/dL; CrCl < 30 mL/min/ 1.73 m²
Interventions	• Ciprofloxacin ○ 100 mg bid for 3 days • Ofloxacin ○ 200 mg bid for 3 days • TMP-SMX ○ 160/800 mg bid for 3 days • Concomitant antimicrobials were not permitted
Outcomes	• Bacteriological eradication, persistence, superinfection, clinical resolution at end of treatment • Bacteriological continued eradication, relapse, recurrence, continued clinical resolution up to 6 weeks • Adverse events • Definition bacteriological cure: urine culture < 1000 CFU/mL • Definition symptomatic cure: absence of signs and symptoms
Notes	• Subjects evaluated pre-treatment, 3rd day, up to 10 days and 6 weeks after treatment • Standard laboratory procedures used • Valid for evaluation for drug efficacy if clinical signs and symptoms, single pathogen > 1000 CFU/mL, urine culture repeated up to 10 days after treatment, at least 3 days treatment, no other antimicrobials • If pre-treatment resistant pathogen subject completed study if improving or had negative culture at 3 days of treatment. • No significant differences between groups in baseline characteristics except for race. • Treatment prematurely discontinued (29): adverse events (12), protocol violation (6), noncompliance (3), consent withdrawn (2), lost to follow-up (2), no treatment response (1), miscellaneous (3). No separate data for groups. • Rates of exclusion similar between groups ○ Enrolled (866), excluded (178, 21%): culture negative (124), culture not obtained (18), entry criteria violation (17), inadequate duration of treatment (13), noncompliance (1), < 1000 CFU/mL (5). No separate data. • 688 (79%) evaluated for efficacy: 124 (14%) culture negative, no separate data • Adverse events assessed by clinical observation • Arms 1 and 2 considered together as one treatment arm in the meta-analysis • E-mail sent to author for details on ○ randomisation: available ○ numbers of positive urine culture and drop-outs by groups: not available

Risk of bias

Item	Authors' judgement	Description

McCarty 1999 (*Continued*)

Adequate sequence generation?	Yes	Block design random code computer-generated at Bayer
Allocation concealment?	Yes	Sealed envelopes opened only in emergency, site monitors determined that the envelopes remained sealed (A)
Blinding?	Yes	Double blind, all opaque gelatin capsules
Intention-to-treat (ITT) analysis?	Yes	ITT for adverse events

Naber 1993

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Setting: !4 centres • Country: Germany • Women > 18 years, symptoms of uncomplicated UTI (frequency, urgency, pain on micturition and > 10 WBC/ HPF) • Number (cefuroxime-axetil/ofloxacin): 85/78 • Mean age (cefuroxime-axetil/ofloxacin): 40.7/36.7 years • Positive urine culture (>10 ^{4} CFU/mL) ○ Cefuroxime-axetil: 96.5% ○ Ofloxacin: 99% ○ 76% *E. coli* Exclusion criteria • Upper UTI; abnormalities of urinary tract; pregnancy; breast feeding; allergy to study drugs; failure to use contraception; alcohol/drug abuse; suspicion of non-compliance; renal/ hepatic/clotting/cerebral disorders; pathogen resistant to treatment; antimicrobial used in previous72 hours; participation in clinical trial in past 3 weeks
Interventions	• Cefuroxime-axetil ○ 125 mg bid for 3 days • Ofloxacin ○ 100 mg bid for 3 days
Outcomes	• Elimination of bacteriuria, persistence, superinfection • Cure combined both symptomatic and bacteriological, improvement, failure • Adverse events • Definition of bacteriological cure: < 1000 CFU/mL • Definition of symptomatic cure: absence of clinical symptoms
Notes	• Standard methods used for urine culture and sensitivity • Urine obtained 48 hour prior to treatment, within 48 hour after treatment, up to 9 days post -treatment (1st follow-up visit), up to 6 weeks post treatment (2nd follow-up visit), • Negative urine culture and excluded post-randomisation (4) ○ Cefuroxime-axetil (3); ofloxacin (1)

Naber 1993 (*Continued*)

	○ Culture negative (2 pre-treatment and 2 post-treatment) from 129 compliant ○ Compliant subjects evaluated at early follow-up for bacteriological efficacy: 125/129 • Other exclusion and drop-outs ○ 1st follow-up: cefuroxime-axetil (18); ofloxacin (16) ○ 2nd follow-up: cefuroxime-axetil (52); ofloxacin (50) • Adverse events evaluated at follow-up visits • E-mail sent to author for details of the randomisation and blinding

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central computer generated list
Allocation concealment?	Yes	Sealed envelopes opened after the patient was enrolled in the study (A)
Blinding?	Yes	Single blind
Intention-to-treat (ITT) analysis?	Yes	ITT for adverse events only

Nicolle 2002

Methods	• Study design: Parallel RCT • Duration: January 1999 to November 1999
Participants	Inclusion criteria • Setting: outpatients • Countries: Austria, Belgium, Canada, Denmark, France, Ireland, The Netherlands, Switzerland, UK • Women 18-65 years, outpatients, > 1 of frequency, urgency, dysuria, suprapubic pain < 7 days, negative pregnancy test, contraception during study period • Number (pivmecillinam/norfloxacin): 483/481 • Mean age ± SD ○ Pivmecillinam: 38.5 ± 13.1 years ○ Norfloxacin: 38.1 ± 13.2 years • Positive urine culture (urine culture + > 1000 CFU/mL) ○ Pivmecillinam: 69.5% (79% *E. coli*) ○ Norfloxacin: 72% (82% *E. coli*) Exclusion criteria • Symptoms > 7 days; upper tract infection; abnormality urinary tract; treatment for UTI in previous 2 weeks; > 3 treatment for UTI in previous 12 months; any antimicrobial in previous 2 weeks; immunosuppressed; epilepsy; CNS disorders; STD; diabetes complications; G6PD deficiency; pregnant; breast feeding; allergy to study drugs; history of tendon rupture due to fluoroquinolones; women receiving different medication

Interventions	• Pivmecillinam ○ 400 mg bid for 3 days • Norfloxacin ○ 400 mg bid for 3 days
Outcomes	• Bacteriological cure early/late follow-up • Clinical cure/improvement at interview/early/late follow-up • Proportion of resistant isolates in culture positives at follow-up • Adverse events • Definition bacteriological cure: eradication or < 10^3 CFU/mL + pyuria or > 10^3 but < 10^5 CFU/mL without pyuria • Definition symptomatic cure: baseline symptoms resolved and no new symptoms
Notes	• Similar demographic characteristics between groups • Standard methods for urine culture and susceptibility testing used, urinalysis and culture at enrolment • Follow-up at day 4 + 1 by telephone (symptoms and adverse events), and visits at 11 + 2 days and 39 + 5 days after enrolment for symptoms, adverse events and urine specimens • Positive culture (> 1000 CFU/mL + pyuria or >100,000 CFU/mL without pyuria). • Excluded post randomisation ○ Negative urine culture: pivmecillinam (147); norfloxacin (133) • Other exclusions ○ Pivmecillinam: protocol violation (22); did not provide safety and efficacy data (4, reason not mentioned); no urine culture at baseline (3); no urine culture at early follow-up (9) ○ Norfloxacin: protocol violation (23); did not provide safety and efficacy data (4, reason not mentioned), no urine culture at follow-up (9) ○ Subjects receiving additional antimicrobials after the early follow-up visit were excluded from the final assessment. • Funding Leo Pharmaceutical Products Ballerup Denmark • Adverse events assessed by telephone interview and at follow-up visits • E-mail sent to the author for details on the randomisation

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation computer generated random number list done centrally
Allocation concealment?	Yes	Investigators on site not aware of the allocation (A)
Blinding?	Yes	Double blind, study medication identical aluminium blister packs
Intention-to-treat (ITT) analysis?	Yes	ITT and per protocol analyses for the clinical outcomes, and for the bacteriological outcomes subjects with negative urine cultures at enrol-

Nicolle 2002 (*Continued*)

		ment are excluded from analyses. Patients enrolled in the ITT analyses but not available for follow-up were considered failures.

Park 2007

Methods	• Study design: Parallel RCT • Duration: August 2005 to December 2005
Participants	Inclusion criteria • Country: Korea • Healthy women, 18-65 years, dysuria, frequency, urgency, absence of flank pain or fever • Number: 75 randomised • Median age (range) ○ Ciprofloxacin: 42 (21-65) years ○ TMP-SMX: 41 (22-63) years • Positive urine culture (100 ≥ CFU/mL) ○ Ciprofloxacin: 71.9% *E. coli* ○ TMP-SMX: 82% *E. coli* Exclusion criteria • Allergy to study drugs; abnormal urinary tract; antibiotics in previous 2 weeks
Interventions	• Ciprofloxacin extended-release ○ 500 mg qd for 3 days • TMP-SMX ○ 160/800 mg bid for 3 days
Outcomes	• Clinical cure • Bacteriological cure • Mean interval to improved clinical symptoms • Adverse events • Definition of bacteriological cure: absence of uropathogen or at least a 1-log drop in the colony count from the baseline level • Definition of symptomatic cure: absence of symptoms
Notes	• Urinalysis at initial visit and 7 days post-treatment, 10 urine culture negative, no separate data by groups • Grant from Ministry of Health • E-mail sent to the author for details of the randomisation, data on numbers randomised, drop-outs, exclusions, positive urine culture by study groups: no reply

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)

Park 2007 (*Continued*)

Blinding?	Yes	Single blind
Intention-to-treat (ITT) analysis?	Unclear	Not stated

Schaeffer 1985

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Women, good health, uncomplicated UTI, no urological disease, $>10^5$ CFU/mL, all women had symptomatic bacteriuria • Number (norfloxacin/TMP-SMX): 20/20 • Mean age (norfloxacin/TMP-SMX): 31/30 years • Positive urine culture ($>10^5$ CFU/mL): 100% in both groups (92.5% *E. coli)*
Interventions	• Norfloxacin ○ 400 mg bid for 10 days • TMP-SMX ○ 160/800 mg bid for 10 days
Outcomes	• Symptomatic cure • Bacteriological cure • Adverse events • Anal/vaginal resistance development • Definition of bacteriological cure: sterile urine • Definition of symptomatic cure: asymptomatic
Notes	• Urinalysis and culture 24 hour before treatment, 2-4 days on treatment, 5-9 days and 4-6 weeks post treatment • Acquired resistant anal/vaginal organism: TMP-SMX (2; 1 resistant strain, 1 no culture was obtained and excluded) • E-mail sent to the author for details of the randomisation

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated (B)
Blinding?	No	Open
Intention-to-treat (ITT) analysis?	No	ITT for adverse events only

Spencer 1994

Methods	• Study design: Parallel RCT
Participants	Inclusion criteria • Setting: 45 general practice centres • Country: UK • Women > 18 years, symptoms of uncomplicated UTI, burning, painful micturition, frequency, nocturia, urgency and blood and WBC in urine • Number (nitrofurantoin/TMP-SMX/trimethoprim): 178/181/179 • Mean age (nitrofurantoin/TMP-SMX/trimethoprim): 43.6/ 44.8/43.6 years • Positive urine culture (>10^7 CFU/L) ○ Nitrofurantoin: 60.1% (84% *E. coli*) ○ TMP-SMX: 61.3% (85% *E. coli*) ○ Trimethoprim: 63.1% (76% *E. coli*) Exclusion criteria • Flank pain; fever; catheterised; recent urological surgery; pregnant; lactating; not taking contraceptive; allergy to study drugs; renal, hepatic or bronchial disease; drugs that interfered with study drugs
Interventions	• Nitrofurantoin ○ 100 mg bid for 7 days • TMP-SMX ○ 160/800 mg bid for 7 days • Trimethoprim ○ 200 mg bid for 7 days
Outcomes	• Early symptomatic cure • Early bacteriological cure • Adverse events • Definition bacteriological cure: no urinary pathogen at visit 2 • Definition of symptomatic cure: relief from symptoms at visit 2
Notes	• Standard laboratory tests • No significant difference between study groups • Symptom relief assessed by patient and investigator and urine culture at 9-15 days visit • Excluded from the bacteriological outcome: nitrofurantoin (71), TMP-SMX (70), trimethoprim (66), had negative urine culture • Excluded other reasons ○ From the clinical evaluation (reasons not stated): nitrofurantoin (14), TMP-SMX (13), trimethoprim (9) ○ From the bacteriological evaluation (withdrawal/failure to provide urine culture): nitrofurantoin (11), TMP-SMX (16), trimethoprim (14) • Adverse events recorded at visit 2 • E-mail sent to the author for details of the randomisation and reasons for drop-outs, no reply

Risk of bias

Item	Authors' judgement	Description

Spencer 1994 (*Continued*)

Adequate sequence generation?	Unclear	Randomised on 1:1
Allocation concealment?	Unclear	Not stated (B)
Blinding?	No	Open
Intention-to-treat (ITT) analysis?	No	ITT for adverse events only

SUTISG 1995

Methods	• Study design: Parallel RCT • Duration: September 1991 to January 1993
Participants	Inclusion criteria • Setting: 15 primary health care centres • Country: Sweden • Women > 18 years with symptoms of uncomplicated acute cystitis, fever < 38°C, + nitrite or Gram positive bacteria in urine • Number ○ Ritipenem acoxil: 140 (included > 10% > 60 years, post-menopausal; no separate data) ○ Norfloxacin: 141 (included > 10% > 60 years, post-menopausal; no separate data) • Median age (range) ○ Ritipenem acoxil: 38 (18-84) years ○ Norfloxacin: 41 (18-81) years • Positive urine culture ($\geq 10^4$ CFU/mL): 90.4% ○ Ritipenem acoxil: 78% *E. coli* ○ Norfloxacin: 82% *E. coli* Exclusion criteria • Allergy to study drugs; pyelonephritis; chronic disease; complicating factors; antibiotics in preceding week; pregnancy; breast feeding; other infections
Interventions	• Ritipenem acoxil ○ 500 mg tid for 5 days • Norfloxacin ○ 200 mg bid for 5 days
Outcomes	• Clinical efficacy: cure, improvement, failure • Bacteriological efficacy: eradication, persistence, recurrence, reinfection 5-9 days and 4 weeks post treatment • Definition of bacteriological cure: < 1000 CFU/mL • Definition of symptomatic cure: disappearance of symptoms
Notes	• Follow-up 5-9 days after treatment and 3-4 weeks after end of treatment. • Standard methods for urine sample, pyuria > 5 WBC in sediment microscopy • Evaluable for bacterial efficacy if inclusion criteria met (> 10,000 CFU/mL, > 3 days treatment, at least 1 follow-up urine culture after treatment) ○ Only for this outcome separate data available for women > 60 years

SUTISG 1995 (*Continued*)

	• Evaluable for clinical efficacy if > 3 days treatment and seen at least once after treatment. • No separate data for safety analysis for premenopausal women • Greater than 2 bacterial strains: non-evaluable • and • Excluded post-randomisation (no separate data) ○ Urine culture negative (27) ○ Other exclusions (no separate data): no complete treatment (4); > 2 strains in urine culture (11); loss to follow-up (2); lack of compliance to treatment (1); all excluded from bacteriological evaluations • Side effects assessed by open ended questions, patient spontaneous reporting • Only outcomes for which separate data available for premenopausal women were included in the meta-analysis • E-mail sent to author for details of the randomisation and data for numbers of drop-outs, exclusions, positive urine culture, numbers randomised of premenopausal women by groups: no reply

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomly allocated in blocks of four stratified by study centre
Allocation concealment?	Unclear	Not stated (B)
Blinding?	Yes	Double-blind, placebo identical tablets
Intention-to-treat (ITT) analysis?	No	No

bid - twice daily; CFU - colony forming unit; CrCl - creatinine clearance; GI - gastrointestinal; HPF - high powered field; ITT - intention-to-treat; qd - once daily; qid - four times daily; tid - three times daily; TMP-SMX - trimethoprim-sulfamethoxazole; US - ultrasound; UTI - urinary tract infection; WBC - white blood cell

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbas 1989	High drop-out (37%), drop-out not described
Andrade-Villanueva 1992	Inclusion criteria: signs of upper UTI, no separate data for lower UTI
Arredondo-Garcia 2004	High drop-out (37%), criteria for diagnosing cystitis not mentioned
Bailey 1983	Included subjects with asymptomatic bacteriuria, no separate data for cystitis

(*Continued*)

Ballesteros 1988	Men (> 10%), fever (> 10%), no separate data available for women or lower UTI
Bresky 1977	Fever (> 10%)
Brumfitt 1972	Men (> 10%), no separate data for women, hospital patients included, criteria considered could include upper UTI
Buckert 1983	Complicated UTI (> 10%), male (> 10%), mean age 70-72 years, no separate data for women and uncomplicated cystitis
Butler 1983	Treatment: 3 days versus 5 days
Cai 2009	Not RCT
Castrillon 1991	Not RCT
Chan 1989	Complicated UTI (> 10%), no separate data for uncomplicated UTI
Corrado 1990	Men (> 10%), complicated UTI (> 10%), no separate data for women and uncomplicated UTI
Cox 1989	Men (> 10%), no separate data for women
de Almeida Claro 1994	Men (> 10%), no separate data for women
De Simone 1991	Men (> 10%), elderly
Fancourt 1984	Inpatients, hospital acquired infection, fever one of entry criteria
Giamarellou 1983	Men (> 10%), no separate data for women
Goldstein 1987	Men (> 10%), no separate data for women
Gower 1976	Complicated UTI (> 10%), included asymptomatic cases (> 10%), no separate data for acute simple cystitis
Grob 1977	Men (> 10%), no separate data for women
Grubbs 1992	Complicated UTI (> 10%), no separate data
Guerra 1983	Only 10/40 patients had cystitis, not mentioned if simple acute cystitis
Guibert 1992	Men (> 10%), elderly
Haase 1984	Upper UTI (> 10%), no separate data for acute cystitis
Henning 1982	Age of patients not mentioned, author was contacted but no data available

(*Continued*)

Hoffler 1978	Complicated UTI (> 10%), no separate data available for acute cystitis
Iravani 1986	Signs of upper UTI (> 10%), no separate data for acute cystitis
Iravani 1988	Men (> 10%), no separate data for women
Iravani 1991	Included three separate studies, one considered for inclusion but different periods of treatment
Karachalios 1985	Inpatients with complicated UTI
Karachalios 1987	Men (> 10%), no separate data for women, hospitalised patients
Khan 1981	Children included
Laplante 1975	Complicated UTI (> 10%), no separate data for acute cystitis
Levenstein 1982	Men (> 10%), UTI as general diagnosis, not acute cystitis
Levenstein 1986	Per cent of men not mentioned, no separate data for groups reported, diagnosis of cystitis presumptive, no complete treatment
Lightstone 1988	Three separate studies with independent randomisation and 3 days versus 7 days treatment
Lovestad 1976	Not RCT, men (> 10%)
Ludwig 1987	Treatment: 3 days versus 7 days
Mabeck 1971	Not RCT
Matts 1985	Hospitalised patients, men (> 10%), upper UTI (> 10%), no separate data for acute cystitis
Naber 1989	Inpatients, complicated UTI
Naber 1990	Single-dose comparison
Nahas 1990	High risk of bias (C), author contacted for translation of paper
Peddie 1981	Asymptomatic bacteriuria included, no separate data
Perez-Ruvalcaba 1988	Complicated UTI, men (> 10%)
Polubiec 1988	Men (> 10%), no separate data for women
Raz 1994	Postmenopausal women (> 40%), ages included 17-88 years
Reeves 1984	Signs of upper UTI (> 10%), no separate data for women with acute cystitis

(*Continued*)

Rous 1981	No separate data for groups available, criteria for diagnosing UTI, inclusion, exclusion missing
Sabbaj 1985	Men (> 10%), fever and flank pain (> 10%), no separate data for women and acute cystitis
Sabbour 1984	Men (> 10%), complicated UTI (> 10%), no separate data for women with acute cystitis
Seidmon 1990	Men (> 10%), complicated UTI, different durations of treatment
Spencer 1992	Men (> 10%), no separate data for women
UTISG 1987	Complicated UTI (> 10%), no separate data for acute cystitis
Watt 1984	Per cent of men not mentioned, definition of UTI not mentioned
Wong 1988	Men (> 10%), no separate data for women
Zhang 2007	Men (> 10%), complicated UTI (> 10%), no acute cystitis (> 10%)

UTI - urinary tract infection

DATA AND ANALYSES

Comparison 1. Fluoroquinolone versus TMP-SMX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term symptomatic cure	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All fluoroquinolones versus TMP-SMX	5	927	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.03]
1.2 Ciprofloxacin versus TMP-SMX	3	584	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.13]
2 Short-term symptomatic cure: susceptible pathogens	3	177	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.08]
3 Long-term symptomatic cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Short-term bacteriological cure	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 All fluoroquinolones versus TMP-SMX	7	1253	Risk Ratio (M-H, Random, 95% CI)	1.03 [1.00, 1.07]
4.2 Ciprofloxacin versus TMP-SMX	3	586	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.17]
4.3 Ofloxacin versus TMP-SMX	3	783	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.08]
4.4 3 days of treatment	3	940	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.14]
4.5 7-10 days of treatment	4	313	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]
5 Short-term bacteriological cure: susceptible pathogens	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 All fluoroquinolones versus TMP-SMX	5	499	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.07]
5.2 Ofloxacin versus TMP-SMX	2	322	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.08]
6 Long-term bacteriological cure	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All fluoroquinolones versus TMP-SMX	6	884	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.00, 1.12]
6.2 Norfloxacin versus TMP-SMX	2	72	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.87, 1.41]
6.3 Ofloxacin versus TMP-SMX	2	511	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.10]
6.4 Ciprofloxacin versus TMP-SMX	2	433	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.96, 1.26]
7 Resistance development	2	160	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.05, 8.62]
8 Any adverse event requiring discontinuation of treatment	3	1063	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.12, 1.14]
9 Adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Any adverse event	7	1477	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.71, 1.29]
9.2 Rash	2	1019	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.43]
9.3 Diarrhoea	3	1063	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.21, 7.29]
10 Complications: pyelonephritis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 ITT analyses	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

11.1 Short-term symptomatic cure	3	1059	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
11.2 Short-term bacteriological cure	3	355	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.15]
11.3 Long-term bacteriological cure	3	196	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.84, 1.39]

Comparison 2. Beta-lactam versus TMP-SMX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term symptomatic cure	2	176	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.12]
2 Long-term symptomatic cure	2	138	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.21]
3 Short-term bacteriological cure	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All beta-lactam versus TMP-SMX	5	389	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.04]
3.2 3 days of treatment	3	299	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
3.3 7-10 days of treatment	2	90	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.83, 1.22]
4 Short-term bacteriological cure: susceptible pathogens	4	310	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
5 Long-term bacteriological cure	5	311	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
6 Resistance development	3	259	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.09, 3.42]
7 Any adverse event requiring discontinuation of treatment	2	184	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.28, 8.28]
8 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Any adverse event	2	184	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.27]
8.2 Rash	1	138	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.09, 10.74]
8.3 Diarrhoea	1	138	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.12, 51.57]
9 ITT analyses	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Short-term bacteriological cure	4	291	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.15]
9.2 Long-term bacteriological cure	4	291	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.26]

Comparison 3. Nitrofurantoin versus beta-lactam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term symptomatic cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Short-term bacteriological cure	2	170	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.75, 1.58]
3 Short-term bacteriological cure: susceptible pathogens	2	146	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.73, 1.34]
4 Long-term bacteriological cure	2	143	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
5 Any adverse event requiring discontinuation of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

6 Adverse events	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Any adverse event	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 Rash	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Diarrhoea	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Fluoroquinolone versus beta-lactam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term symptomatic cure	2	1192	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.99, 1.32]
2 Long-term symptomatic cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Short-term bacteriological cure	5	1289	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.13, 1.31]
4 Short-term bacteriological cure: susceptible pathogens	2	690	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.35]
5 Long-term bacteriological cure	2	497	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.61, 1.32]
6 Resistance development	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Any adverse event requiring discontinuation of treatment	4	1501	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.74, 5.30]
8 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Any adverse event	4	1501	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.61, 1.33]
8.2 Rash	2	494	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.56]
9 Complications: pyelonephritis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 ITT analyses	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Short-term symptomatic cure	2	1334	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.99, 1.30]
10.2 Short-term bacteriological cure	3	1174	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.15, 1.31]
10.3 Long-term bacteriological cure	2	843	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.51, 1.65]
11 Sensitivity analysis: adequate allocation concealment	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Short-term bacteriological cure	3	1047	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.15, 1.30]

Comparison 5. Nitrofurantoin versus TMP-SMX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term symptomatic cure	3	733	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.04]
2 Long-term symptomatic cure	2	338	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]
3 Short-term bacteriological cure	4	668	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
4 Short-term bacteriological cure: susceptible pathogens	3	463	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
5 Long-term bacteriological cure	3	395	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
6 Resistance development	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

7 Any adverse event requiring discontinuation of treatment	3	921	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.34, 1.41]
8 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Any adverse event	3	921	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.17]
8.2 Rash	3	921	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.76]
8.3 Diarrhoea	1	88	Risk Ratio (M-H, Random, 95% CI)	7.65 [0.41, 143.89]
9 ITT analyses	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Short-term symptomatic cure	2	833	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.10]
9.2 Short-term bacteriological cure	2	274	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.24]

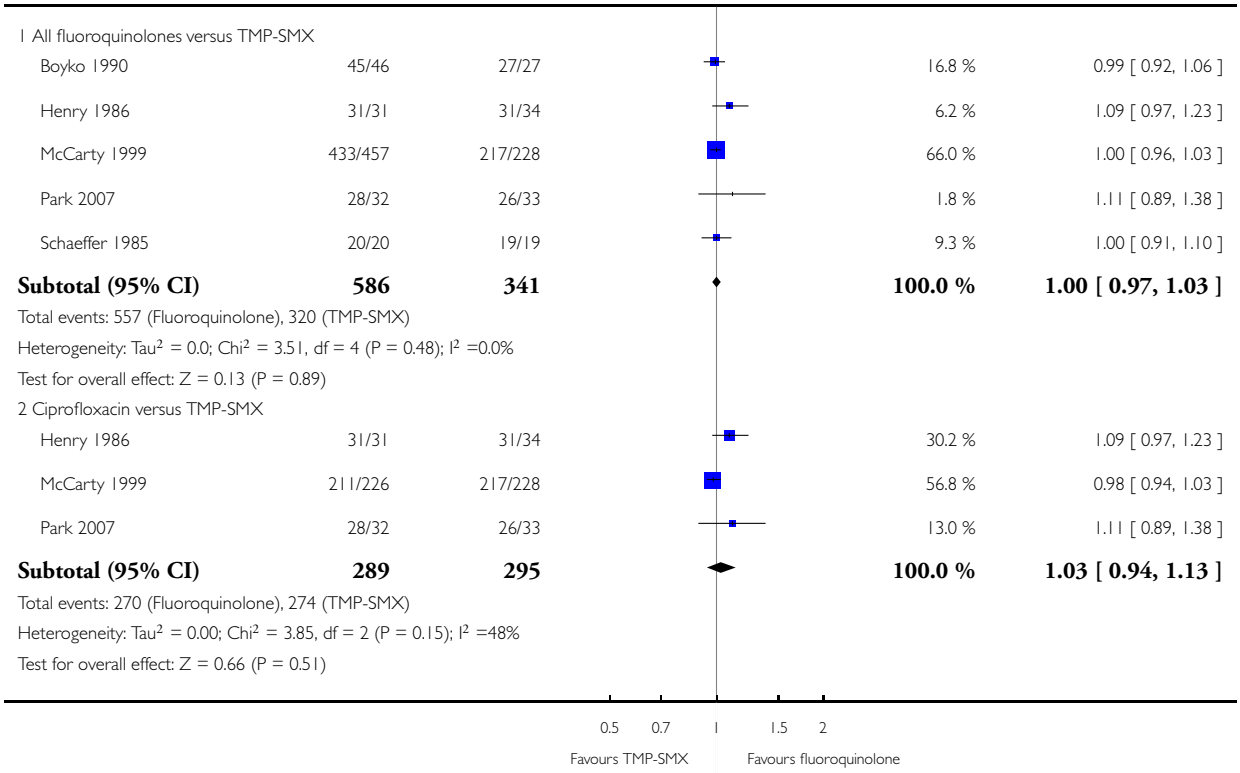
Analysis 1.1. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 1 Short-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 1 Short-term symptomatic cure

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All fluoroquinolones versus TMP-SMX					
Boyko 1990	45/46	27/27		16.8 %	0.99 [0.92, 1.06]
Henry 1986	31/31	31/34		6.2 %	1.09 [0.97, 1.23]
McCarty 1999	433/457	217/228		66.0 %	1.00 [0.96, 1.03]
Park 2007	28/32	26/33		1.8 %	1.11 [0.89, 1.38]
Schaeffer 1985	20/20	19/19		9.3 %	1.00 [0.91, 1.10]
Subtotal (95% CI)	**586**	**341**		**100.0 %**	**1.00 [0.97, 1.03]**
Total events: 557 (Fluoroquinolone), 320 (TMP-SMX)					
Heterogeneity: Tau² = 0.0; Chi² = 3.51, df = 4 (P = 0.48); I² =0.0%					
Test for overall effect: Z = 0.13 (P = 0.89)					
2 Ciprofloxacin versus TMP-SMX					
Henry 1986	31/31	31/34		30.2 %	1.09 [0.97, 1.23]
McCarty 1999	211/226	217/228		56.8 %	0.98 [0.94, 1.03]
Park 2007	28/32	26/33		13.0 %	1.11 [0.89, 1.38]
Subtotal (95% CI)	**289**	**295**		**100.0 %**	**1.03 [0.94, 1.13]**
Total events: 270 (Fluoroquinolone), 274 (TMP-SMX)					
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 2 (P = 0.15); I² =48%					
Test for overall effect: Z = 0.66 (P = 0.51)					



Analysis 1.2. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 2 Short-term symptomatic cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 2 Short-term symptomatic cure: susceptible pathogens

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Boyko 1990	45/46	27/27		46.9 %	0.99 [0.92, 1.06]
Henry 1986	31/31	31/34		22.3 %	1.09 [0.97, 1.23]
Schaeffer 1985	20/20	19/19		30.8 %	1.00 [0.91, 1.10]
Total (95% CI)	**97**	**80**		**100.0 %**	**1.01 [0.95, 1.08]**

Total events: 96 (Fluoroquinolone), 77 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.64$, df = 2 (P = 0.27); $I^2 = 24\%$

Test for overall effect: Z = 0.42 (P = 0.67)

Analysis 1.3. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 3 Long-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 3 Long-term symptomatic cure

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
McCarty 1999	370/411	184/203		0.99 [0.94, 1.05]

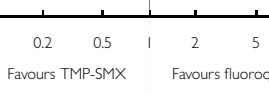
Analysis 1.4. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 4 Short-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 4 Short-term bacteriological cure

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All fluoroquinolones versus TMP-SMX					
Block 1987	89/97	81/92		9.6 %	1.04 [0.95, 1.15]
Boyko 1990	46/46	26/27		10.3 %	1.05 [0.95, 1.15]
Henry 1986	31/31	32/34		8.6 %	1.06 [0.96, 1.17]
Hooton 1989	75/81	51/55		9.6 %	1.00 [0.91, 1.10]
McCarty 1999	439/458	211/228		51.7 %	1.04 [0.99, 1.08]
Park 2007	25/32	18/33		0.7 %	1.43 [1.00, 2.06]
Schaeffer 1985	20/20	19/19		9.5 %	1.00 [0.91, 1.10]
Subtotal (95% CI)	**765**	**488**		**100.0 %**	**1.03 [1.00, 1.07]**
Total events: 725 (Fluoroquinolone), 438 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.96, df = 6 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 2.24 (P = 0.025)					
2 Ciprofloxacin versus TMP-SMX					
Henry 1986	31/31	32/34		37.8 %	1.06 [0.96, 1.17]
McCarty 1999	215/228	211/228		55.7 %	1.02 [0.97, 1.07]
Park 2007	25/32	18/33		6.5 %	1.43 [1.00, 2.06]
Subtotal (95% CI)	**291**	**295**		**100.0 %**	**1.06 [0.96, 1.17]**
Total events: 271 (Fluoroquinolone), 261 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.47, df = 2 (P = 0.11); I^2 =55%					
Test for overall effect: Z = 1.13 (P = 0.26)					
3 Ofloxacin versus TMP-SMX					
Block 1987	89/97	81/92		14.1 %	1.04 [0.95, 1.15]
Hooton 1989	75/81	51/55		14.0 %	1.00 [0.91, 1.10]
McCarty 1999	224/230	211/228		71.9 %	1.05 [1.01, 1.10]
Subtotal (95% CI)	**408**	**375**		**100.0 %**	**1.04 [1.01, 1.08]**
Total events: 388 (Fluoroquinolone), 343 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.97, df = 2 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 2.30 (P = 0.021)					
4 3 days of treatment					
Block 1987	89/97	81/92		34.7 %	1.04 [0.95, 1.15]



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Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
McCarty 1999	439/458	211/228		61.0 %	1.04 [0.99, 1.08]
Park 2007	25/32	18/33		4.4 %	1.43 [1.00, 2.06]
Subtotal (95% CI)	**587**	**353**		**100.0 %**	**1.05 [0.97, 1.14]**
Total events: 553 (Fluoroquinolone), 310 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.61$, df = 2 (P = 0.16); I^2 =45%					
Test for overall effect: Z = 1.29 (P = 0.20)					
5 7-10 days of treatment					
Boyko 1990	46/46	26/27		27.1 %	1.05 [0.95, 1.15]
Henry 1986	31/31	32/34		22.6 %	1.06 [0.96, 1.17]
Hooton 1989	75/81	51/55		25.3 %	1.00 [0.91, 1.10]
Schaeffer 1985	20/20	19/19		25.0 %	1.00 [0.91, 1.10]
Subtotal (95% CI)	**178**	**135**		**100.0 %**	**1.03 [0.98, 1.08]**
Total events: 172 (Fluoroquinolone), 128 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.14$, df = 3 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.01 (P = 0.31)					

Analysis 1.5. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 5 Short-term bacteriological cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 5 Short-term bacteriological cure: susceptible pathogens

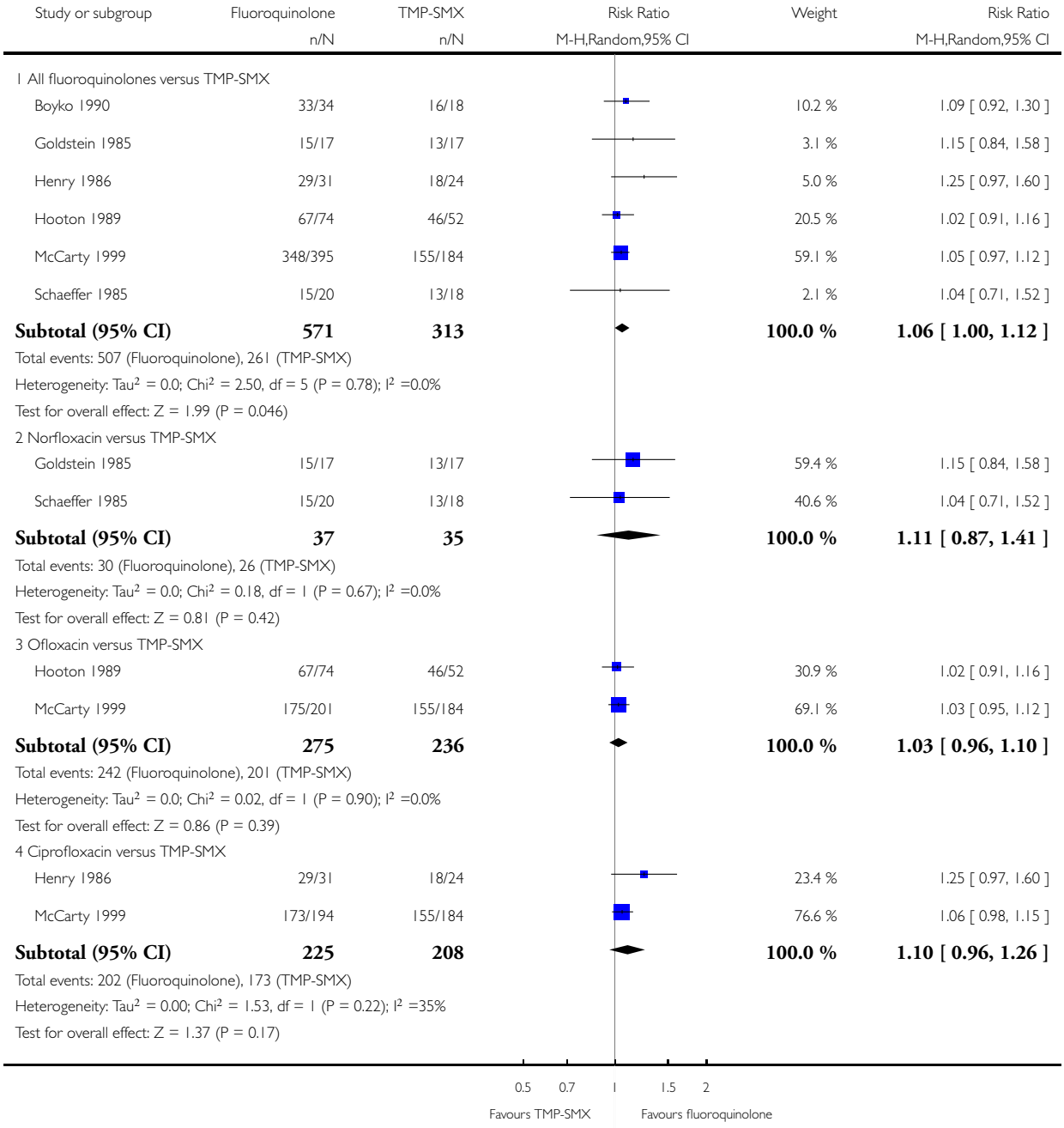
Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All fluoroquinolones versus TMP-SMX					
Block 1987	89/97	81/92		19.4 %	1.04 [0.95, 1.15]
Boyko 1990	46/46	26/27		20.7 %	1.05 [0.95, 1.15]
Henry 1986	31/31	32/34		17.3 %	1.06 [0.96, 1.17]
Hooton 1989	75/80	50/53		23.7 %	0.99 [0.91, 1.08]
Schaeffer 1985	20/20	19/19		19.0 %	1.00 [0.91, 1.10]
Subtotal (95% CI)	**274**	**225**		**100.0 %**	**1.03 [0.98, 1.07]**
Total events: 261 (Fluoroquinolone), 208 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.45$, df = 4 (P = 0.83); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.19 (P = 0.23)					
2 Ofloxacin versus TMP-SMX					
Block 1987	89/97	81/92		45.0 %	1.04 [0.95, 1.15]
Hooton 1989	75/80	50/53		55.0 %	0.99 [0.91, 1.08]
Subtotal (95% CI)	**177**	**145**		**100.0 %**	**1.02 [0.95, 1.08]**
Total events: 164 (Fluoroquinolone), 131 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.56$, df = 1 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.46 (P = 0.65)					

Analysis 1.6. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 6 Long-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 6 Long-term bacteriological cure



Analysis 1.7. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 7 Resistance development.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

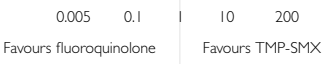
Outcome: 7 Resistance development

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Goldstein 1985	2/17	1/17		56.8 %	2.00 [0.20, 20.04]
Hooton 1989	0/74	2/52		43.2 %	0.14 [0.01, 2.88]
Total (95% CI)	**91**	**69**		**100.0 %**	**0.64 [0.05, 8.62]**

Total events: 2 (Fluoroquinolone), 3 (TMP-SMX)

Heterogeneity: $Tau^2 = 1.72$; $Chi^2 = 1.92$, df = 1 (P = 0.17); $I^2 = 48\%$

Test for overall effect: Z = 0.34 (P = 0.73)



Analysis 1.8. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 8 Any adverse event requiring discontinuation of treatment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 8 Any adverse event requiring discontinuation of treatment

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Boyko 1990	4/106	5/47		41.2 %	0.35 [0.10, 1.26]
Goldstein 1985	2/22	1/22		18.6 %	2.00 [0.20, 20.49]
McCarty 1999	3/572	9/294		40.2 %	0.17 [0.05, 0.63]
Total (95% CI)	**700**	**363**		**100.0 %**	**0.37 [0.12, 1.14]**

Total events: 9 (Fluoroquinolone), 15 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 3.29$, df = 2 (P = 0.19); $I^2 = 39\%$

Test for overall effect: Z = 1.74 (P = 0.083)

Analysis 1.9. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 9 Adverse events.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 9 Adverse events

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Any adverse event					
Block 1987	24/122	27/122		21.3 %	0.89 [0.54, 1.45]
Boyko 1990	37/106	11/47		17.3 %	1.49 [0.84, 2.66]
Goldstein 1985	3/22	5/22		4.7 %	0.60 [0.16, 2.21]
Henry 1986	3/31	10/34		5.5 %	0.33 [0.10, 1.09]
McCarty 1999	203/572	121/294		42.4 %	0.86 [0.72, 1.03]
Park 2007	9/32	5/33		7.8 %	1.86 [0.70, 4.94]
Schaeffer 1985	1/20	0/20		0.9 %	3.00 [0.13, 69.52]
Subtotal (95% CI)	**905**	**572**		**100.0 %**	**0.95 [0.71, 1.29]**
Total events: 280 (Fluoroquinolone), 179 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.92$, df = 6 (P = 0.18); $I^2 = 33\%$					
Test for overall effect: Z = 0.30 (P = 0.76)					
2 Rash					
Boyko 1990	0/106	3/47		34.0 %	0.06 [0.00, 1.22]
McCarty 1999	1/572	6/294		66.0 %	0.09 [0.01, 0.71]
Subtotal (95% CI)	**678**	**341**		**100.0 %**	**0.08 [0.01, 0.43]**
Total events: 1 (Fluoroquinolone), 9 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.92 (P = 0.0035)					
3 Diarrhoea					
Boyko 1990	3/106	0/47		36.7 %	3.14 [0.17, 59.61]
Goldstein 1985	0/22	1/22		32.1 %	0.33 [0.01, 7.76]
McCarty 1999	1/572	0/294		31.1 %	1.54 [0.06, 37.80]
Subtotal (95% CI)	**700**	**363**		**100.0 %**	**1.22 [0.21, 7.29]**
Total events: 4 (Fluoroquinolone), 1 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.07$, df = 2 (P = 0.58); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.22 (P = 0.82)					

Analysis 1.10. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 10 Complications: pyelonephritis.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 10 Complications: pyelonephritis

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Block 1987	1/120	1/123		1.03 [0.06, 16.20]

Analysis 1.11. Comparison 1 Fluoroquinolone versus TMP-SMX, Outcome 11 ITT analyses.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 1 Fluoroquinolone versus TMP-SMX

Outcome: 11 ITT analyses

Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short-term symptomatic cure					
Boyko 1990	45/106	27/47		11.7 %	0.74 [0.53, 1.03]
McCarty 1999	433/572	217/294		51.2 %	1.03 [0.94, 1.11]
Schaeffer 1985	20/20	19/20		37.0 %	1.05 [0.92, 1.20]
Subtotal (95% CI)	**698**	**361**		**100.0 %**	**1.00 [0.88, 1.13]**
Total events: 498 (Fluoroquinolone), 263 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.22$, df = 2 (P = 0.12); $I^2 = 53\%$					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 Short-term bacteriological cure					
Block 1987	89/103	81/100		42.4 %	1.07 [0.94, 1.21]
Boyko 1990	46/77	26/35		18.4 %	0.80 [0.62, 1.05]
Schaeffer 1985	20/20	19/20		39.1 %	1.05 [0.92, 1.20]
Subtotal (95% CI)	**200**	**155**		**100.0 %**	**1.01 [0.88, 1.15]**
Total events: 155 (Fluoroquinolone), 126 (TMP-SMX)					

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Study or subgroup	Fluoroquinolone n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.01; Chi² = 4.27, df = 2 (P = 0.12); I² =53%					
Test for overall effect: Z = 0.10 (P = 0.92)					
3 Long-term bacteriological cure					
Boyko 1990	33/77	16/35		31.8 %	0.94 [0.60, 1.46]
Goldstein 1985	15/22	13/22		30.9 %	1.15 [0.74, 1.81]
Schaeffer 1985	15/20	13/20		37.3 %	1.15 [0.77, 1.74]
Subtotal (95% CI)	**119**	**77**		**100.0 %**	**1.08 [0.84, 1.39]**
Total events: 63 (Fluoroquinolone), 42 (TMP-SMX)					
Heterogeneity: Tau² = 0.0; Chi² = 0.61, df = 2 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 0.60 (P = 0.55)					

Analysis 2.1. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 1 Short-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 1 Short-term symptomatic cure

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	18/23	18/20		26.1 %	0.87 [0.67, 1.13]
Kavatha 2003	62/63	70/70		73.9 %	0.98 [0.94, 1.03]
Total (95% CI)	**86**	**90**		**100.0 %**	**0.95 [0.81, 1.12]**
Total events: 80 (Beta-lactam), 88 (TMP-SMX)					
Heterogeneity: Tau² = 0.01; Chi² = 1.98, df = 1 (P = 0.16); I² =50%					
Test for overall effect: Z = 0.59 (P = 0.56)					

Analysis 2.2. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 2 Long-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 2 Long-term symptomatic cure

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	11/11	10/12		20.3 %	1.19 [0.89, 1.59]
Kavatha 2003	48/55	51/60		79.7 %	1.03 [0.89, 1.19]
Total (95% CI)	**66**	**72**		**100.0 %**	**1.06 [0.93, 1.21]**
Total events: 59 (Beta-lactam), 61 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					

Analysis 2.3. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 3 Short-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 3 Short-term bacteriological cure

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All beta-lactam versus TMP-SMX					
Ellis 1990	18/24	16/20		5.9 %	0.94 [0.68, 1.29]
Greenberg 1986	15/22	23/24		6.6 %	0.71 [0.53, 0.96]
Guttmann 1977	20/23	19/23		9.1 %	1.05 [0.82, 1.35]
Hooton 1995	74/80	39/40		34.1 %	0.95 [0.88, 1.03]
Kavatha 2003	62/63	70/70		44.3 %	0.98 [0.94, 1.03]
Subtotal (95% CI)	**212**	**177**		**100.0 %**	**0.95 [0.88, 1.04]**
Total events: 189 (Beta-lactam), 167 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.07, df = 4 (P = 0.09); I^2 =50%					
Test for overall effect: Z = 1.12 (P = 0.26)					

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Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 3 days of treatment					
Greenberg 1986	15/22	23/24		13.0 %	0.71 [0.53, 0.96]
Hooton 1995	74/80	39/40		40.8 %	0.95 [0.88, 1.03]
Kavatha 2003	62/63	70/70		46.2 %	0.98 [0.94, 1.03]
Subtotal (95% CI)	**165**	**134**		**100.0 %**	**0.93 [0.82, 1.05]**
Total events: 151 (Beta-lactam), 132 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.42, df = 2 (P = 0.01); I^2 =81%					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 7-10 days of treatment					
Ellis 1990	18/24	16/20		37.3 %	0.94 [0.68, 1.29]
Guttmann 1977	20/23	19/23		62.7 %	1.05 [0.82, 1.35]
Subtotal (95% CI)	**47**	**43**		**100.0 %**	**1.01 [0.83, 1.22]**
Total events: 38 (Beta-lactam), 35 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.33, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.08 (P = 0.93)					

Analysis 2.4. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 4 Short-term bacteriological cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 4 Short-term bacteriological cure: susceptible pathogens

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	12/14	13/15		4.3 %	0.99 [0.74, 1.32]
Greenberg 1986	9/13	23/24		2.7 %	0.72 [0.50, 1.05]
Hooton 1995	71/73	37/38		40.0 %	1.00 [0.94, 1.07]
Kavatha 2003	62/63	70/70		53.1 %	0.98 [0.94, 1.03]
Total (95% CI)	**163**	**147**		**100.0 %**	**0.98 [0.92, 1.04]**
Total events: 154 (Beta-lactam), 143 (TMP-SMX)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.97, df = 3 (P = 0.17); I^2 =40%					
Test for overall effect: Z = 0.58 (P = 0.56)					

Analysis 2.5. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 5 Long-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 5 Long-term bacteriological cure

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	11/11	11/13		12.4 %	1.17 [0.89, 1.53]
Greenberg 1986	11/19	14/16		5.6 %	0.66 [0.43, 1.01]
Guttmann 1977	18/20	18/19		22.7 %	0.95 [0.79, 1.14]
Hooton 1995	64/74	36/39		33.9 %	0.94 [0.82, 1.06]
Kavatha 2003	43/50	42/50		25.5 %	1.02 [0.87, 1.21]
Total (95% CI)	**174**	**137**		**100.0 %**	**0.97 [0.87, 1.08]**

Total events: 147 (Beta-lactam), 121 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.75$, df = 4 (P = 0.22); $I^2 = 30\%$

Test for overall effect: Z = 0.59 (P = 0.55)

Analysis 2.6. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 6 Resistance development.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 6 Resistance development

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Guttmann 1977	1/20	0/19		33.8 %	2.86 [0.12, 66.11]
Hooton 1995	0/80	1/40		33.1 %	0.17 [0.01, 4.05]
Kavatha 2003	0/50	1/50		33.1 %	0.33 [0.01, 7.99]
Total (95% CI)	**150**	**109**		**100.0 %**	**0.55 [0.09, 3.42]**

Total events: 1 (Beta-lactam), 2 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.69$, df = 2 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Analysis 2.7. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 7 Any adverse event requiring discontinuation of treatment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 7 Any adverse event requiring discontinuation of treatment

Study or subgroup	Beta-lactam n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Guttmann 1977	1/23	1/23		38.9 %	1.00 [0.07, 15.04]
Hooton 1995	4/92	1/46		61.1 %	2.00 [0.23, 17.39]
Total (95% CI)	**115**	**69**		**100.0 %**	**1.53 [0.28, 8.28]**

Total events: 5 (Beta-lactam), 2 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.69); $I^2 = 0.0\%$

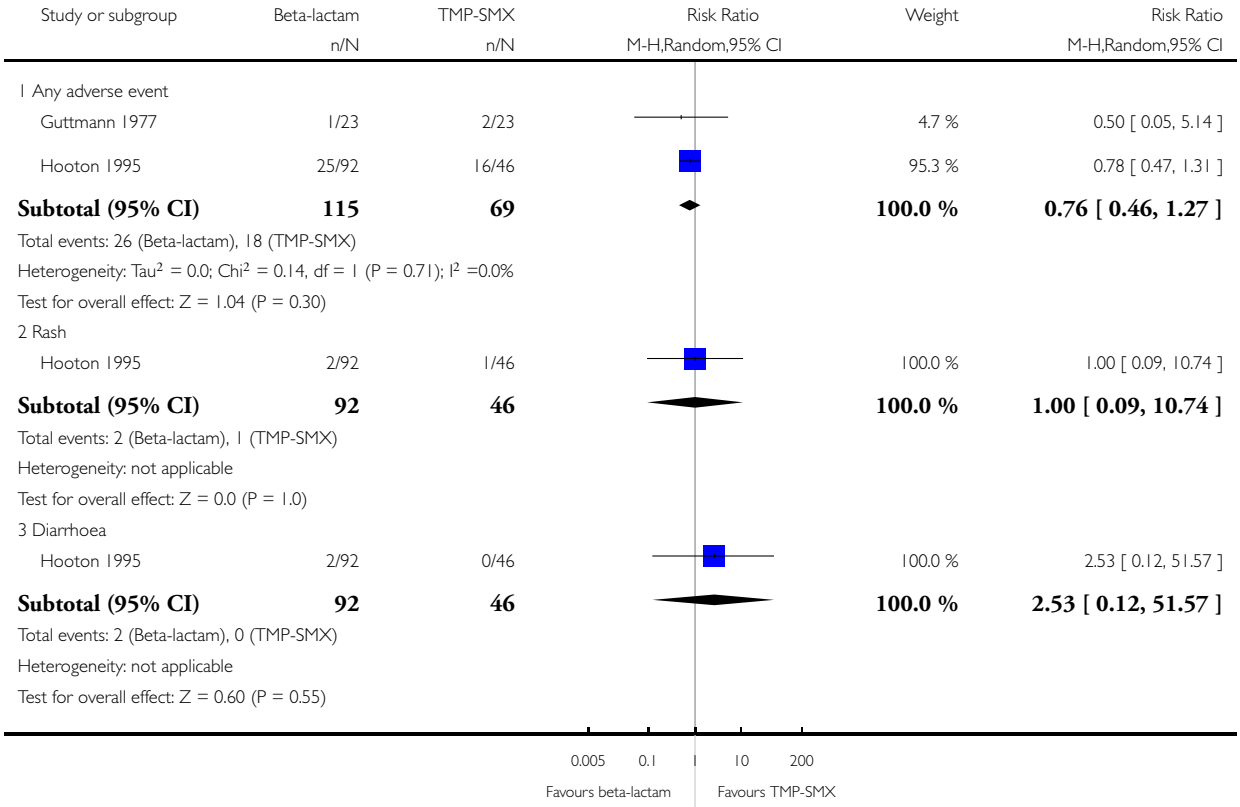
Test for overall effect: Z = 0.49 (P = 0.62)

Analysis 2.8. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 8 Adverse events.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 8 Adverse events

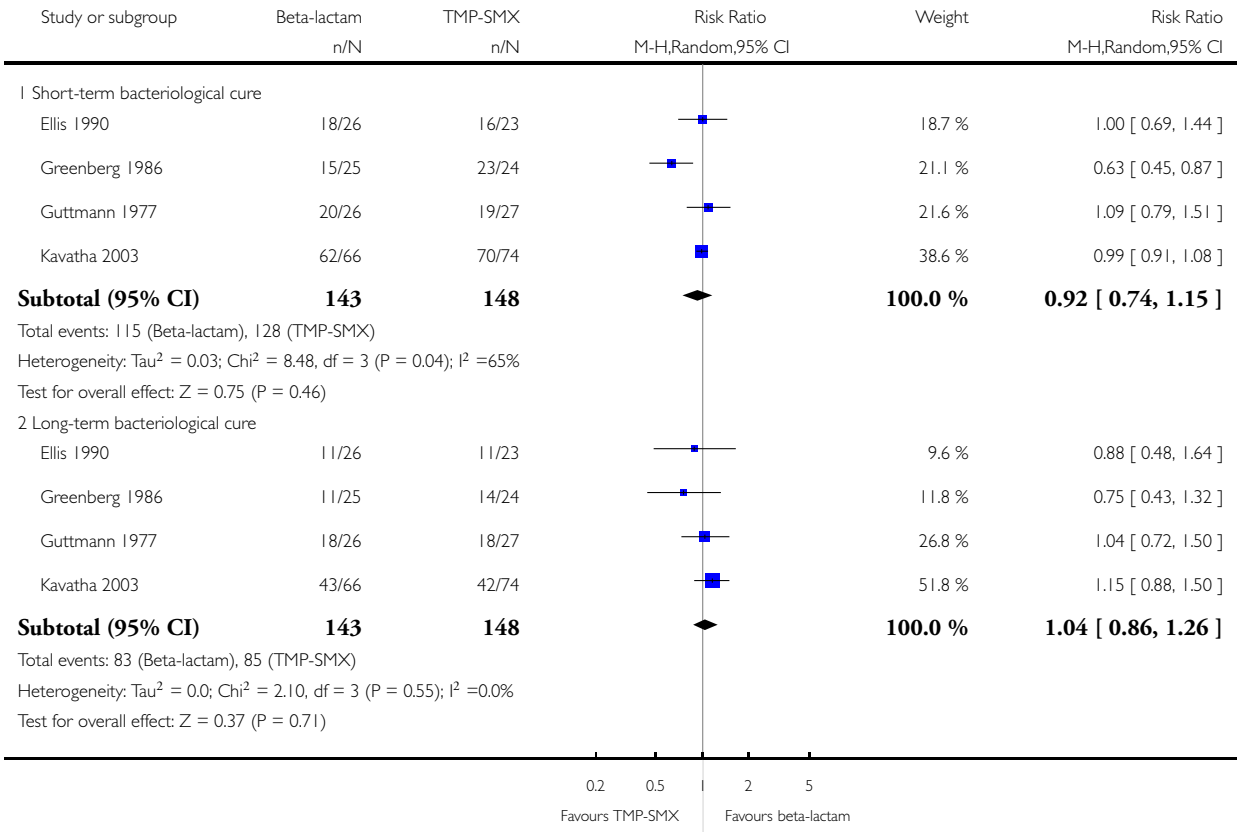


Analysis 2.9. Comparison 2 Beta-lactam versus TMP-SMX, Outcome 9 ITT analyses.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 2 Beta-lactam versus TMP-SMX

Outcome: 9 ITT analyses



Analysis 3.1. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 1 Short-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 1 Short-term symptomatic cure

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ellis 1990	26/28	18/23		1.19 [0.93, 1.51]

Analysis 3.2. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 2 Short-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 2 Short-term bacteriological cure

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	28/28	18/24		47.0 %	1.33 [1.05, 1.68]
Hooton 1995	32/38	74/80		53.0 %	0.91 [0.78, 1.06]
Total (95% CI)	**66**	**104**		**100.0 %**	**1.09 [0.75, 1.58]**

Total events: 60 (Nitrofurantoin), 92 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.99$, df = 1 (P = 0.01); $I^2 = 86\%$

Test for overall effect: Z = 0.44 (P = 0.66)

Analysis 3.3. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 3 Short-term bacteriological cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 3 Short-term bacteriological cure: susceptible pathogens

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	22/22	12/14		45.5 %	1.17 [0.93, 1.48]
Hooton 1995	31/37	71/73		54.5 %	0.86 [0.74, 1.00]
Total (95% CI)	**59**	**87**		**100.0 %**	**0.99 [0.73, 1.34]**

Total events: 53 (Nitrofurantoin), 83 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.81$, df = 1 (P = 0.03); $I^2 = 79\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Analysis 3.4. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 4 Long-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 4 Long-term bacteriological cure

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	21/22	11/11		53.5 %	0.98 [0.83, 1.14]
Hooton 1995	30/36	64/74		46.5 %	0.96 [0.81, 1.14]
Total (95% CI)	**58**	**85**		**100.0 %**	**0.97 [0.86, 1.09]**

Total events: 51 (Nitrofurantoin), 75 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Analysis 3.5. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 5 Any adverse event requiring discontinuation of treatment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 5 Any adverse event requiring discontinuation of treatment

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hooton 1995	0/42	4/92		0.24 [0.01, 4.36]

Analysis 3.6. Comparison 3 Nitrofurantoin versus beta-lactam, Outcome 6 Adverse events.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 3 Nitrofurantoin versus beta-lactam

Outcome: 6 Adverse events

Study or subgroup	Nitrofurantoin n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Any adverse event				
Hooton 1995	18/42	25/92		1.58 [0.97, 2.56]
2 Rash				
Hooton 1995	0/42	2/92		0.43 [0.02, 8.82]
3 Diarrhoea				
Hooton 1995	3/42	2/92		3.29 [0.57, 18.94]

Analysis 4.1. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 1 Short-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 1 Short-term symptomatic cure

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hooton 2005	159/162	127/160		47.8 %	1.24 [1.14, 1.34]
Nicolle 2002	381/433	360/437		52.2 %	1.07 [1.01, 1.13]
Total (95% CI)	**595**	**597**		**100.0 %**	**1.15 [0.99, 1.32]**
Total events: 540 (Fluoroquinolone), 487 (Beta-lactam)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.48$, df = 1 (P = 0.004); $I^2 = 88\%$					
Test for overall effect: Z = 1.85 (P = 0.064)					

Analysis 4.2. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 2 Long-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 2 Long-term symptomatic cure

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nicolle 2002	318/348	297/327		1.01 [0.96, 1.05]

Analysis 4.3. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 3 Short-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 3 Short-term bacteriological cure

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Goto 1999	23/27	23/28		9.0 %	1.04 [0.82, 1.31]
Hooton 2005	153/162	118/160		29.2 %	1.28 [1.16, 1.41]
Naber 1993	54/61	51/64		17.3 %	1.11 [0.95, 1.29]
Nicolle 2002	276/302	222/298		37.3 %	1.23 [1.14, 1.32]
SUTISG 1995	55/84	46/103		7.2 %	1.47 [1.12, 1.91]
Total (95% CI)	**636**	**653**		**100.0 %**	**1.22 [1.13, 1.31]**

Total events: 561 (Fluoroquinolone), 460 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.25$, df = 4 (P = 0.18); $I^2 = 36\%$

Test for overall effect: Z = 5.10 (P < 0.00001)

Analysis 4.4. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 4 Short-term bacteriological cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 4 Short-term bacteriological cure: susceptible pathogens

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Naber 1993	54/61	51/64		35.6 %	1.11 [0.95, 1.29]
Nicolle 2002	275/301	192/264		64.4 %	1.26 [1.16, 1.36]
Total (95% CI)	**362**	**328**		**100.0 %**	**1.20 [1.07, 1.35]**

Total events: 329 (Fluoroquinolone), 243 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.94$, df = 1 (P = 0.16); $I^2 = 48\%$

Test for overall effect: Z = 3.12 (P = 0.0018)

Analysis 4.5. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 5 Long-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 5 Long-term bacteriological cure

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Naber 1993	7/12	13/15		30.9 %	0.67 [0.40, 1.13]
Nicolle 2002	209/248	183/222		69.1 %	1.02 [0.94, 1.11]
Total (95% CI)	**260**	**237**		**100.0 %**	**0.90 [0.61, 1.32]**

Total events: 216 (Fluoroquinolone), 196 (Beta-lactam)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.50$, df = 1 (P = 0.11); $I^2 = 60\%$

Test for overall effect: Z = 0.55 (P = 0.58)

Analysis 4.6. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 6 Resistance development.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 6 Resistance development

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hooton 2005	2/155	5/156		0.40 [0.08, 2.04]

Analysis 4.7. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 7 Any adverse event requiring discontinuation of treatment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 7 Any adverse event requiring discontinuation of treatment

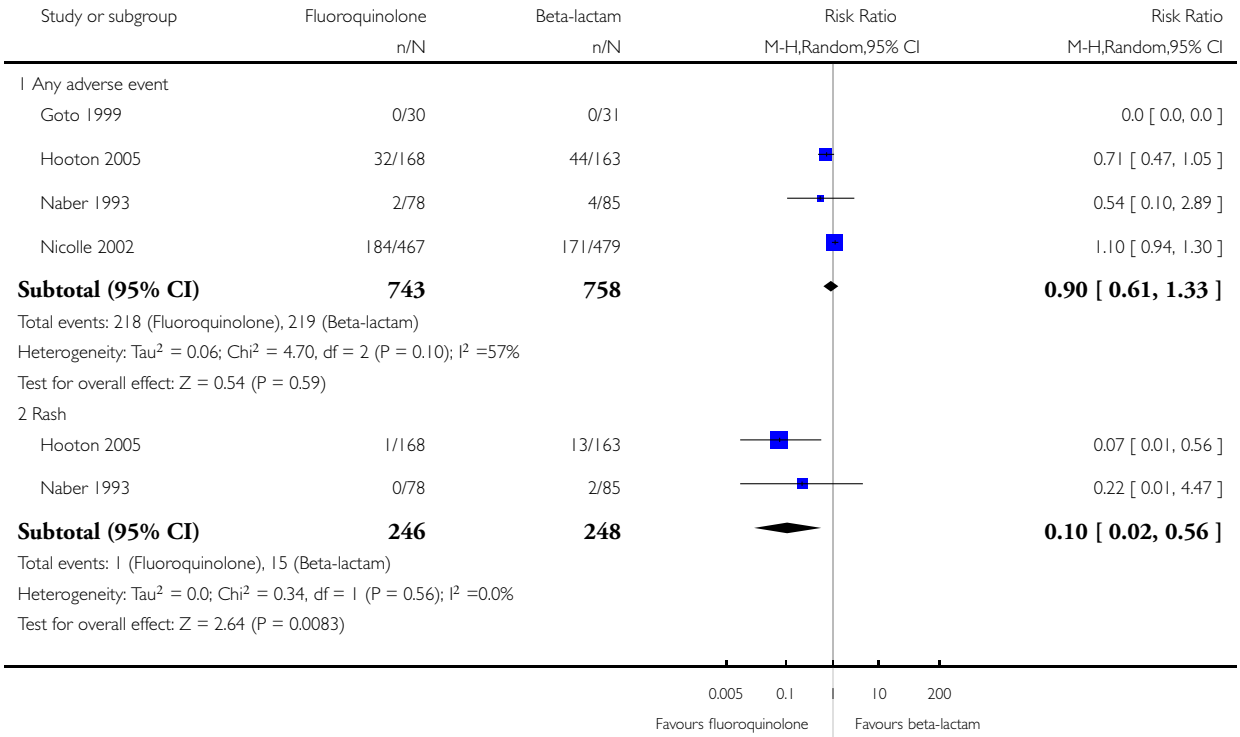
Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Goto 1999	0/30	0/31		0.0 [0.0, 0.0]
Hooton 2005	1/168	2/163		0.49 [0.04, 5.30]
Naber 1993	1/78	0/85		3.27 [0.13, 79.01]
Nicolle 2002	10/467	4/479		2.56 [0.81, 8.12]
Total (95% CI)	**743**	**758**		**1.98 [0.74, 5.30]**
Total events: 12 (Fluoroquinolone), 6 (Beta-lactam)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.62$, df = 2 (P = 0.45); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.35 (P = 0.18)				

Analysis 4.8. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 8 Adverse events.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 8 Adverse events

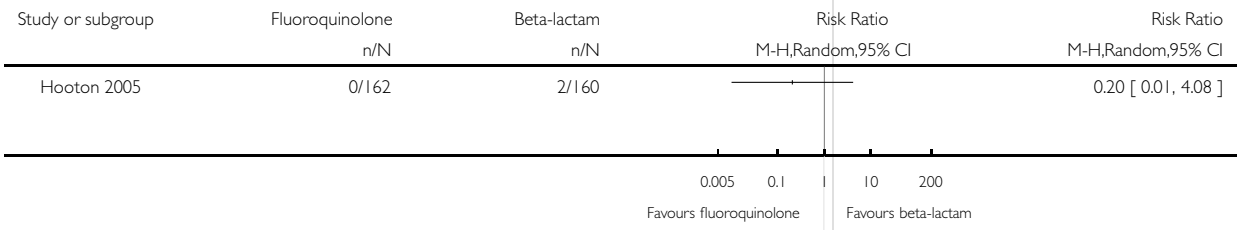


Analysis 4.9. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 9 Complications: pyelonephritis.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 9 Complications: pyelonephritis

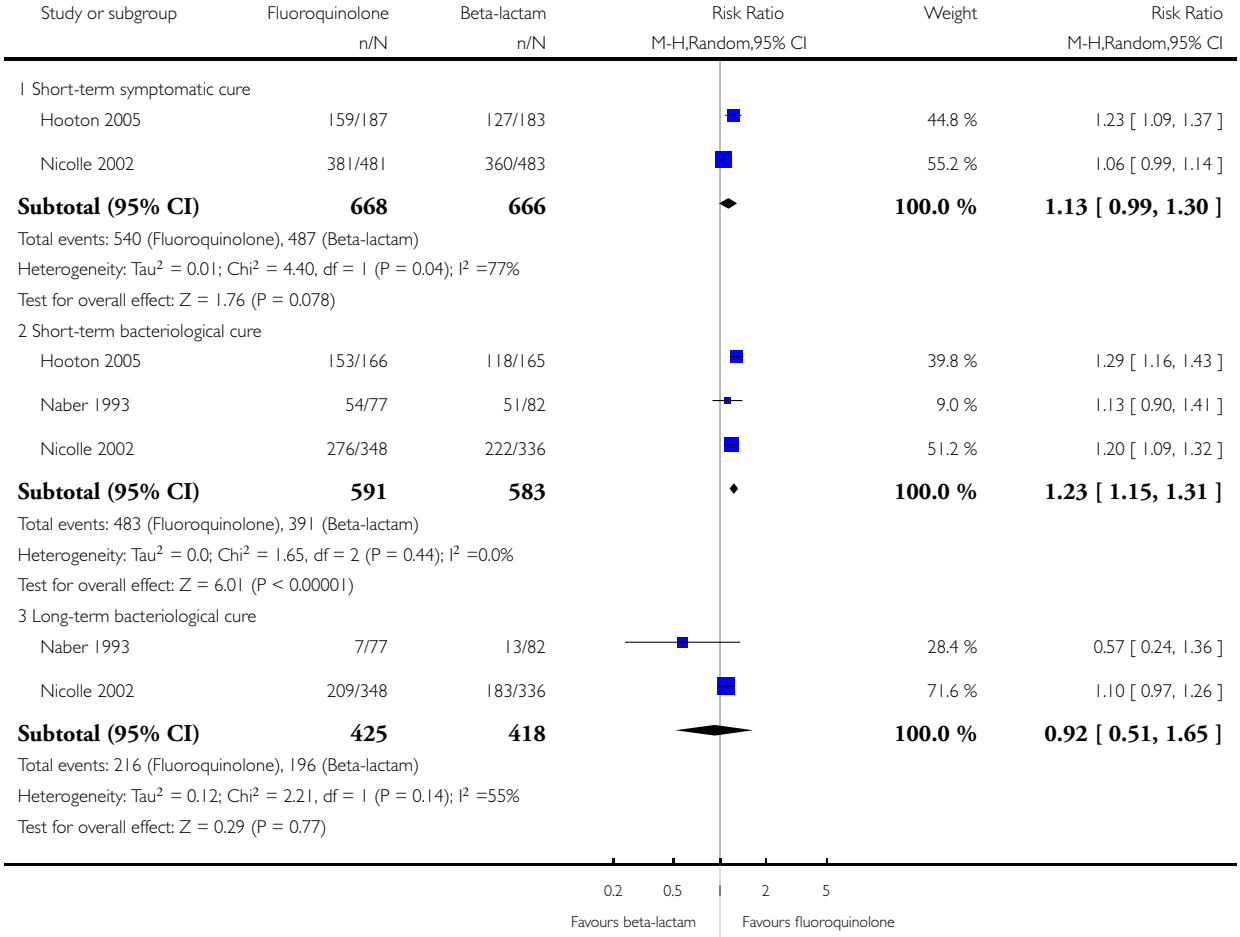


Analysis 4.10. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 10 ITT analyses.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 10 ITT analyses



Analysis 4.11. Comparison 4 Fluoroquinolone versus beta-lactam, Outcome 11 Sensitivity analysis: adequate allocation concealment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 4 Fluoroquinolone versus beta-lactam

Outcome: 11 Sensitivity analysis: adequate allocation concealment

Study or subgroup	Fluoroquinolone n/N	Beta-lactam n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short-term bacteriological cure					
Hooton 2005	153/162	118/160		32.8 %	1.28 [1.16, 1.41]
Naber 1993	54/61	51/64		15.2 %	1.11 [0.95, 1.29]
Nicolle 2002	276/302	222/298		52.0 %	1.23 [1.14, 1.32]

Analysis 5.1. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 1 Short-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 1 Short-term symptomatic cure

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	26/28	18/20		6.2 %	1.03 [0.86, 1.23]
Iravani 1999	166/179	165/174		68.1 %	0.98 [0.93, 1.03]
Spencer 1994	143/164	142/168		25.8 %	1.03 [0.95, 1.13]
Total (95% CI)	**371**	**362**		**100.0 %**	**0.99 [0.95, 1.04]**
Total events: 335 (Nitrofurantoin), 325 (TMP-SMX)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.39$, df = 2 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.23 (P = 0.82)					

Analysis 5.2. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 2 Long-term symptomatic cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 2 Long-term symptomatic cure

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	21/22	10/12		7.6 %	1.15 [0.88, 1.50]
Iravani 1999	135/151	137/153		92.4 %	1.00 [0.92, 1.08]
Total (95% CI)	**173**	**165**		**100.0 %**	**1.01 [0.94, 1.09]**

Total events: 156 (Nitrofurantoin), 147 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.93$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 0.23 (P = 0.81)

Analysis 5.3. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 3 Short-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 3 Short-term bacteriological cure

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	28/28	16/20		14.5 %	1.25 [1.00, 1.57]
Hooton 1995	32/38	39/40		23.7 %	0.86 [0.75, 1.00]
Iravani 1999	153/177	161/174		35.6 %	0.93 [0.87, 1.00]
Spencer 1994	79/96	79/95		26.2 %	0.99 [0.87, 1.13]
Total (95% CI)	**339**	**329**		**100.0 %**	**0.97 [0.87, 1.08]**

Total events: 292 (Nitrofurantoin), 295 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.92$, df = 3 (P = 0.05); $I^2 = 62\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Analysis 5.4. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 4 Short-term bacteriological cure: susceptible pathogens.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 4 Short-term bacteriological cure: susceptible pathogens

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	22/22	13/15		20.7 %	1.16 [0.93, 1.44]
Hooton 1995	31/37	37/38		31.2 %	0.86 [0.74, 1.00]
Iravani 1999	153/177	161/174		48.1 %	0.93 [0.87, 1.00]
Total (95% CI)	**236**	**227**		**100.0 %**	**0.95 [0.84, 1.08]**

Total events: 206 (Nitrofurantoin), 211 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.85$, df = 2 (P = 0.09); $I^2 = 59\%$

Test for overall effect: Z = 0.77 (P = 0.44)

Analysis 5.5. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 5 Long-term bacteriological cure.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 5 Long-term bacteriological cure

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ellis 1990	21/22	11/13		16.8 %	1.13 [0.88, 1.45]
Hooton 1995	30/36	36/39		30.8 %	0.90 [0.76, 1.07]
Iravani 1999	115/141	113/144		52.4 %	1.04 [0.93, 1.17]
Total (95% CI)	**199**	**196**		**100.0 %**	**1.01 [0.90, 1.13]**

Total events: 166 (Nitrofurantoin), 160 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.65$, df = 2 (P = 0.27); $I^2 = 24\%$

Test for overall effect: Z = 0.16 (P = 0.87)

Analysis 5.6. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 6 Resistance development.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 6 Resistance development

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hooton 1995	0/38	1/40		0.35 [0.01, 8.35]

Analysis 5.7. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 7 Any adverse event requiring discontinuation of treatment.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 7 Any adverse event requiring discontinuation of treatment

Study or subgroup	Nitrofurantoin n/N	TMP-SMX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hooton 1995	0/42	1/46		5.0 %	0.36 [0.02, 8.71]
Iravani 1999	7/236	11/238		58.1 %	0.64 [0.25, 1.63]
Spencer 1994	5/178	6/181		36.9 %	0.85 [0.26, 2.73]
Total (95% CI)	**456**	**465**		**100.0 %**	**0.69 [0.34, 1.41]**

Total events: 12 (Nitrofurantoin), 18 (TMP-SMX)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0.0\%$

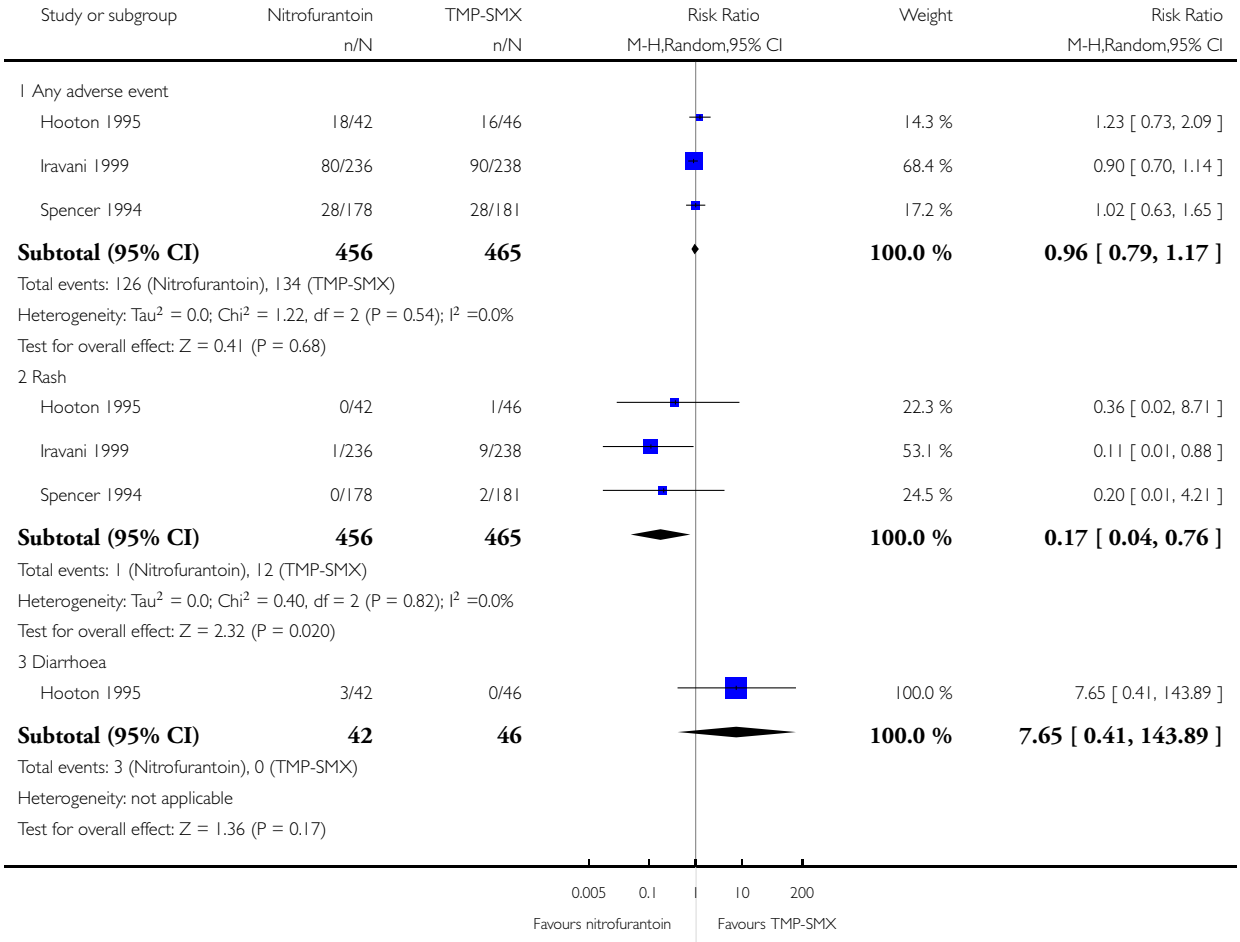
Test for overall effect: Z = 1.02 (P = 0.31)

Analysis 5.8. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 8 Adverse events.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 8 Adverse events

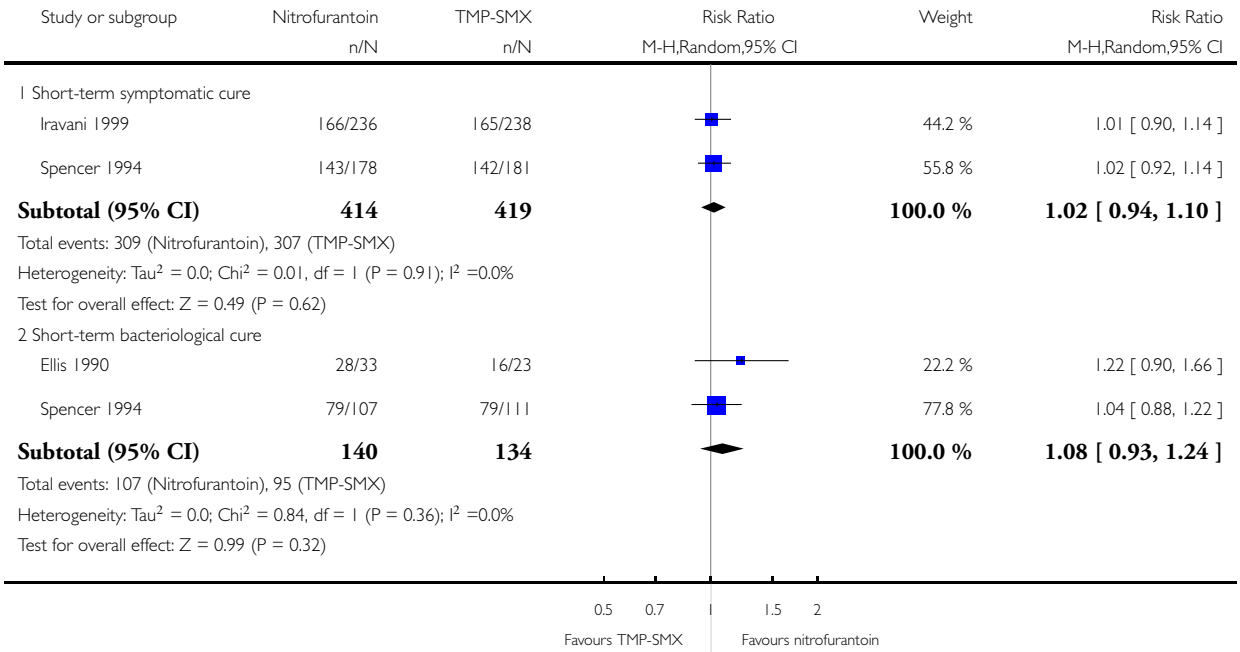


Analysis 5.9. Comparison 5 Nitrofurantoin versus TMP-SMX, Outcome 9 ITT analyses.

Review: Antimicrobial agents for treating uncomplicated urinary tract infection in women

Comparison: 5 Nitrofurantoin versus TMP-SMX

Outcome: 9 ITT analyses



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. urinary next tract next infection*:ti,ab,kw 2. bacteriuri*:ti,ab,kw 3. pyuri*:ti,ab,kw 4. cystitis:ti,ab,kw 5. (urinary near/2 infection*):ti,ab,kw 6. (uti or utis):ti,ab,kw 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 8. (male or males or men):ti,kw

(*Continued*)

	9. (female or females or women):ti,kw 10. (#8 AND NOT #9) 11. (#7 AND NOT #10)
MEDLINE	1. Urinary Tract Infections/ 2. Bacteriuria/ 3. Pyuria/ 4. Cystitis/ 5. (urinary adj2 infection$).tw. 6. (uti or utis).tw. 7. pyuri$.tw. 8. bacteriuri$.tw. 9. cystitis.tw. 10. or/1-9 11. male/ not female/ 12. 10 not 11 13. (exp Child/ or exp Infant/) not (Adolescent/ or exp Adult/) 14. 12 not 13 15. exp Anti-Infective Agents/ 16. and/14-15
EMBASE	1. Urinary Tract Infection/ 2. Bacteriuria/ 3. Pyuria/ 4. Cystitis/ 5. (urinary adj2 infection$).tw. 6. (uti or utis).tw. 7. pyuri$.tw. 8. bacteriuri$.tw. 9. cystitis.tw. 10. or/1-9 11. Male/ not Female/ 12. 10 not 11 13. exp Child/ not (Adult/ or Aged/) 14. 12 not 13 15. exp Antiinfective Agent/ 16. and/14-15

Appendix 2. Quality assessment checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (low risk of bias).
- Unclear (B): Randomisation stated but no information on method used is available (moderate risk of bias).
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group (high risk of bias).

We included studies in the review if they met the criteria (A) and (B).

Blinding

- Blinding of investigators: Yes/no/not stated.
- Blinding of participants: Yes/no/not stated.
- Blinding of outcome assessor: Yes/no/not stated.
- Blinding of data analysis: Yes/no/not stated.

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat (ITT) analysis

- Yes: Specifically reported by authors that ITT analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment.
- No: Not reported and lack of ITT analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or they were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated.

Completeness of follow-up

Per cent of participants excluded or lost to follow-up.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 10, 2010

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: AZ, JY, LL
- Develop a search strategy: AZ, LL
- Search for studies: AZ, MP
- Obtain copies of studies: AZ, HG
- Select which studies to include: AZ, HG, MP (arbiter)
- Extract data from studies: AZ, HG
- Enter data into RevMan: AZ
- Carry out the analysis: AZ
- Interpret the analysis: AZ, MP, LL
- Draft the final review: AZ, JY, LL
- Resolution of disagreements: LL

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We excluded studies using ampicillin in one of the treatment arms.