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Quinolones for uncomplicated acute cystitis in women (Review)

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[Intervention Review]

Quinolones for uncomplicated acute cystitis in women

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ABSTRACT

Background

Uncomplicated acute cystitis is one of the most common bacterial infections in adults. The percentage of women who have at least one episode of acute cystitis is estimated to be between 40% to 50%. Quinolones are recommended for acute cystitis in regions where the level of resistance to other antimicrobials namely co-trimoxazole is high. However the efficacy, safety and tolerance of quinolones needs investigation.

Objectives

To compare the efficacy, safety and tolerance of different quinolones in women with uncomplicated acute cystitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library* Issue 3, 2003), MEDLINE (1966 - September 2003), EMBASE (1988 - September 2003), reference lists of articles and abstracts from conference proceedings without language restriction. Reference lists of urology, infectious diseases and nephrology textbooks, review articles and relevant studies.

Selection criteria

Randomised and quasi-randomised controlled trials comparing two or more different quinolones in women (≥ 16 years) with uncomplicated acute cystitis were selected.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI).

Main results

We identified 11 studies enrolling 7535 women. There were no significant differences in clinical or microbiological efficacy between quinolones. Photosensitivity reactions were more frequently observed for sparfloxacin when compared to ofloxacin. Any adverse event, adverse events causing withdrawal, skin adverse events, photosensitivity reactions were more common for lomefloxacin when compared to norfloxacin. Any adverse event, adverse drug reactions, CNS adverse events were more common for ofloxacin when compared to ciprofloxacin. CNS adverse events and insomnia were more often reported for rifloxacin when compared to pefloxacin. Adverse drug reactions occurred frequently for ofloxacin than levofloxacin. Insomnia was reported more frequently for enoxacin than ciprofloxacin.

Authors' conclusions

We found no significant differences in clinical or microbiological efficacy between quinolones but some differences in occurrence and spectrum of quinolone safety.

PLAIN LANGUAGE SUMMARY

There is no evidence of difference in clinical and microbiological efficacy of quinolones for uncomplicated acute cystitis in women, but there is some evidence of differences in occurrence and range of adverse reactions.

Urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine. Bacterial cystitis (bacteria in the bladder, also called acute cystitis) can occur in men and women and the signs and symptoms include dysuria (pain on passing urine), frequency, cloudy urine, occasionally haematuria (blood in the urine), and is often associated with pyuria (high urine white blood cell count). There is an additional important distinction between complicated and uncomplicated UTI. Complicated UTIs are those associated with fever and/or back pain (indicating kidney infection), UTIs in men, UTIs associated with indwelling or intermittent urinary catheters, obstructive uropathy (any changes in the urinary tract due to obstruction), vesicoureteric reflux (urine travels from the bladder back up toward the kidneys) and other urological abnormalities. These types of infections require more intensive treatment. Uncomplicated acute cystitis is the most prevalent form of uncomplicated UTI in women. Quinolones are recommended as the drugs of choice for acute cystitis in regions where the level of resistance to other antimicrobials namely co-trimoxazole is high. The aim of this systematic review was to investigate which quinolone is most effective in treating uncomplicated acute cystitis and to also investigate safety and how well they are tolerated. Eleven studies (7535 women) were identified. No two studies compared the same quinolones. We found no significant differences in clinical or microbiological efficacy between quinolones. Several adverse events were reported in the individual studies. These included photosensitivity, insomnia, skin adverse events, central nervous system adverse events and adverse events leading to withdrawal to treatment. We were unable to determine which quinolone would be the safest or the most tolerated due to the lack of head-to-head data.

BACKGROUND

Urinary tract infections (UTIs) are common with an estimated annual global incidence of at least 250 million cases, and are costly to both patients and healthcare funding systems (Ronald 2001). Uncomplicated infections account for the greatest number of UTIs. The distinction between uncomplicated and complicated UTIs is important because of implications regarding pre- and post-treatment evaluation, type and duration of antimicrobial regimens and extent of evaluation of the urinary tract (Bacheller 1997). Acute cystitis is the most prevalent form of uncomplicated UTI. In the USA over seven million cases of acute cystitis are registered each year, equating to approximately one billion US dollars (Schappert 1994). The percentage of women who have at least one episode of acute cystitis is estimated to be between 40% to 50% (Kunin 1994). The organisms most often responsible for UTIs are the gram-negative bacteria of group Enterobacteriaceae. *Escherichia coli* (*E. coli*) causes approximately 80% of UTIs and *Staphylococcus saprophyticus* is the second most common pathogen, particularly in young women (Johnson 1989).

Factors that should be considered in selecting drugs for the treatment of uncomplicated acute cystitis include the antimicrobial activity (broad or narrow) of the agent, pharmacokinetics favouring wider dosing intervals, the prevalence of resistance in local urinary pathogens, the duration of adequate urinary antimicrobial levels, the effect on the faecal and vaginal flora, the potential for undesirable side effects and the cost of the treatment regimen (Hooton 1991; Hooton 1997; Neu 1992). People with acute cystitis are usually treated as outpatients and therefore tolerance and antimicrobial safety need to be carefully considered. Adverse reactions may result in non-compliance, administration of another drug and, in some cases, hospitalisation. These factors lead to cost increases and reduction in quality of life. Antimicrobials with proven efficacy in acute cystitis are co-trimoxazole, nitrofurantoin, quinolones (including fluoroquinolones) and fosfomycin trometamol (Naber 1999; Naber 2000a; Warren 1999). Increased resistance to co-trimoxazole however, may reduce its effectiveness in the treatment of uncomplicated acute cystitis as there has been shown to be a correlation between resistance and eradication of *E. coli* (Minassian 1998).

Quinolones have good activity against *E. coli*, achieve high urinary concentrations and have minimal effect on the natural vaginal protective flora (lactobacilli and anaerobes) (Anderson 1999). Once or twice-daily dose regimens may be used for administering these antimicrobials, providing the possibility of enhanced compliance. In addition, urinary pathogen resistance is rarer for quinolones when compared with co-trimoxazole. Treatment regimens for quinolones include single dose, three- or seven-day schedules, however single dose regimen is not considered suitable because of fewer cures and increased recurrence rates (Norrby 1990a). A seven-day course has greater potential for side effects, is more expensive and has not been shown to have an improved therapeutic effect. The short (three-day) course appears to offer the best combination of efficacy and decreased risk of side effects and toxicity (Warren 1999).

Recent reviews (Echols 1999; Warren 1999) have focused on the microbiological efficacy and factors influencing therapy outcomes of several different antimicrobials. But no author studied the

adverse reactions of quinolones. Hooton 1997 suggested that clinically significant differences in safety and tolerance may exist among different quinolones.

The aim of this systematic review is to evaluate the efficacy, safety and tolerance of different quinolones for the treatment of uncomplicated acute cystitis in women.

OBJECTIVES

To compare the efficacy, safety and tolerance of different quinolones in women with acute, uncomplicated cystitis.

METHODS

Criteria for considering studies for this review

Types of studies

We selected all randomised controlled trials (RCTs) and quasi-RCTs comparing two or more different quinolones in patients with uncomplicated acute cystitis. We selected studies that had included only women, and studies in which data were available separately for women. We contacted the authors of the studies in which both men and women were included but for which no details of the results for women were given to ask for the separate data about women patients.

Types of participants

Non-pregnant and non-lactating women ≥ 16 years old, with uncomplicated acute cystitis with the following criteria:

1. symptoms of acute cystitis (dysuria, urgency, frequency or suprapubic pain);
2. significant positive urine culture: ≥ 1000 colony forming units (cfu)/mL + pyuria ≥ 10 leukocytes/mm³ or positive urine culture ≥ 10000 cfu/mL alone (ECLM 2000).

Patients with symptoms of pyelonephritis (fever or flank pain) and with complicating factors such as indwelling or intermittent urinary catheters, obstructive uropathy, vesicoureteric reflux and other urological abnormalities, azotaemia due to intrinsic kidney disease or kidney transplantation were excluded. Patients with asymptomatic bacteriuria and UTIs in men were also excluded. Subgroup analyses including only women aged 16 to 60 years were to be performed where possible.

Types of interventions

All studies comparing effectiveness and/or safety and/or tolerability of two or more different oral quinolones (e.g. norfloxacin, ciprofloxacin, ofloxacin, pefloxacin, levofloxacin and others) in patients with uncomplicated acute cystitis given in equivalent treatment durations were included.

Types of outcome measures

1. Clinical response
 - a. Cure (complete disappearance of all baseline symptoms at test-of-cure visit).
 - b. Improvement (resolution of or reduction in the majority of the original signs and symptoms with no new or worsened symptoms at test-of-cure visit).
 - c. Failure (patients with initial signs and symptoms at test-of-cure visit development of new sign or symptoms or the need for intervention with other antimicrobial agents).
 - d. Patients without failure (no initial signs and symptoms at test-of-cure visit development of new sign or symptoms or the need for intervention with other antimicrobial agents).
 - e. Patients without recurrence (no reappearance of signs and symptoms at follow-up visit after cure or improvement at test-of-cure visit).
 - f. Clinical success (cure or improvement at test-of-cure visit).
 - g. Sustain clinical success (cure or improvement at test-of-cure visit and at follow-up visit).
2. Bacteriological response
 - a. Eradication (initial pathogen eliminated with no other pathogen isolated at test-of-cure visit).
 - b. Patients without persistence (initial pathogen eliminated at test-of-cure visit).
 - c. Persistence (initial pathogen does not eliminated at test-of-cure visit).
 - d. Patients without relapse (initial pathogen eliminated at test-of-cure visit and not re-isolated at follow-up visit).
 - e. Patients without reinfection (no significant growth of a new pathogen after eradication of the initial pathogen at any visit after treatment).
 - f. Sustained bacteriological success (eradication at test-of-cure visit and at follow-up visit).
3. Overall success
 - a. Clinical response (cure or improvement) + bacteriological response (eradication).
 - b. Sustained overall response (overall response at test-of-cure visit).
4. Adverse events
 - a. Any adverse event.
 - b. Organ or system specific adverse events.
 - c. Any serious adverse events (SAE) that are fatal, life-threatening, or requiring inpatient hospitalisation or prolongation of existing hospitalisation.
 - d. Any adverse event that result in significant disability or incapacity.
 - e. Any adverse event that require discontinuation of medication.
 - f. Any adverse event/reaction related to study drug (ADR).
 - g. Adverse laboratory events (ALE) (any laboratory abnormality).
5. Frequency of quinolones withdrawal due to clinical failure, adverse event or patient decision.
6. Development of pyelonephritis or urosepsis at any visit.
7. Long-term mortality (all-cause and related to UTI).
8. Average difference in the quality of life score (measured by any scale) between groups.

9. Number of people dropped out from the study after randomisation.

Search methods for identification of studies

The literature searching was performed independently by two authors.

Electronic searches

Relevant studies were obtained from the following sources without language restriction (see [Table 1 - Electronic search strategies](#)).

1. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 3, 2003).
2. MEDLINE (1966 - September 2003) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs ([Dickersin 1994](#)).
3. EMBASE (1980 - September 2003) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of randomised controlled clinical trials ([Lefebvre 1996](#)).

Searching other resources

1. Reference lists of urology, infectious diseases and nephrology textbooks, review articles and relevant studies.
2. Reference lists of abstracts from urology, infectious diseases and nephrology scientific meetings.
3. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

The reference lists of identified articles, reviews, books and book chapters on the treatment of uncomplicated acute cystitis was searched. Unpublished studies and data which were not included in bibliographical retrieval system were sought from identified authors as well as from pharmaceutical companies marketing antibiotics that were used for urinary tract infections.

Data collection and analysis

Study selection

The review was undertaken by three authors (VR, IA and ER). The search strategy described was used to obtain titles and abstracts of studies that were considered relevant to the review. The titles and abstracts were independently screened by VR and IA, who discarded studies that were irrelevant, although studies and reviews that included relevant data or information on studies were retained initially. Authors VR and IA independently assessed abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Critical appraisal

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.
- Unclear (B): Randomisation stated but no information on method used is available.
- 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.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment.
- No: Not reported and lack of intention-to-treat 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 were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated

Blinding

- Blinding of investigator
- Blinding of participant
- Blinding of outcome assessor

Completeness of follow-up

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

Data extraction

Data extraction was carried out by the same authors (VR and IA) independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Further information from the original author was obtained by written correspondence and any relevant information obtained in this manner was included in the review. Discrepancies were resolved in consultation with ER. In the case of duplicate publications, data were extracted from the most recent and/or the most complete report.

All data were to be analysed together, and then subgroup analyses performed to determine if the inclusion of lower quality studies affects the overall result. The following data were extracted systematically for each study;

- title
- trial design
- method of randomisation
- blinding (of participants, investigators and outcome assessor/s)
- Intention-to-treat analysis
- allocation concealment
- number of participants
- exclusions after randomisation
- duration of follow-up
- completeness of follow-up
- setting (community, long-stay institution, hospital)
- description of the trial population
- detailed description of the treatment used (substance, galenic form, dosage, duration of treatment)
- description and results of all measured outcomes

Where appropriate, the studies were to be subgrouped for meta-analysis according to the assessment of the above mentioned items and also for clinical heterogeneity.

Statistical analysis

For dichotomous outcomes (e.g. recurrence versus no recurrence) results were expressed as risk ratio (RR) with 95% confidence intervals (95% CI). Data were pooled using the random effects model. Where continuous scales of measurement were used to assess the effects of treatment (e.g. quality of life), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales have been used. We analysed all the primary and secondary outcomes under consideration. Where appropriate, the results were to be expressed as relative risk reduction (RRR), number needed to treat (NNT) and number needed to harm (NNH).

Statistical heterogeneity in trial results was to be assessed both by the inspection of graphical presentations ("funnel plot": plotting the study weight or sample size [on the Y axis] against the RR [on the X axis]) (Egger 1997), the Cochran Q test of N-1 degrees of freedom, with a probability of 0.05 used for statistical significance and the I^2 statistic (Higgins 2003). Three possible reasons for heterogeneity were pre-specified:

1. response differs according to the difference in the quality of the trial;
2. response differs according to sample size;
3. response differs according to clinical heterogeneity.

We also planned to used the funnel plot approach to assess the likelihood of publication bias.

RESULTS

Description of studies

We identified 7126 potential studies (Table 2 - Literature search results) and after screening of title and abstract, 84 were chosen for full text review. Eleven studies (7535 enrolled women) met our inclusion criteria (Henry 1998; Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993; Richard 2000; Richard 2002) (see Characteristics of included studies and Table 3 - Sources of included studies). Reasons for exclusion of the other studies were (Characteristics of excluded studies);

- narrative reviews (2)
- systematic reviews (3) or meta-analyses (5)
- not an RCT (27)
- mixed diagnoses and/or population e.g. acute pyelonephritis, complicated UTI, recurrent cystitis, nosocomial UTI or UTI in men (12)
- different treatment durations (16)
- different treatment doses of the same quinolone (4)
- laboratory inclusion criteria did not meet our inclusion criteria (4)

Baseline pathogen susceptibilities

Baseline pathogen susceptibilities to study drug is shown in Table 4.

Trial comparisons

All studies compared different quinolones.

1. sparfloxacin 200 mg/d versus ofloxacin 400 mg/d (Henry 1998)
2. lomefloxacin 400 mg/d versus norfloxacin 800 mg/d (Neringer 1992)
3. ciprofloxacin 200 mg/d versus ofloxacin 400 mg/d (McCarty 1999).
4. single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg (Jardin 1995).
5. rifloxacin 250 mg/d versus pefloxacin 400 mg/d (Richard 2000).
6. lomefloxacin 400 mg/d versus norfloxacin 800 mg/d (Nicolle 1993).
7. gatifloxacin 200 mg/d versus ciprofloxacin 200 mg/d (Richard 2002).
8. ciprofloxacin 500 mg/d versus norfloxacin 800 mg/d (Iravani 1995).
9. fleroxacin 200 mg/d versus ciprofloxacin 500 mg/d (Iravani 1993).
10. gemifloxacin 320 mg/d versus ciprofloxacin 500 mg/d (Naber 2000a).
11. conventional ciprofloxacin 500 mg/d versus extended-release ciprofloxacin 500 mg/d (Henry 2002).

Trial outcomes

Clinical outcomes

Cure was reported in five studies (Iravani 1993; Iravani 1995; Jardin 1995; Neringer 1992; Richard 2000), improvement in three (Iravani 1993; Jardin 1995; Richard 2000), patients without failure in five (Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; Nicolle 1993), patients without recurrence in five (Henry 1998; Henry 2002; Jardin 1995; Nicolle 1993; Richard 2002), clinical success in six (Henry 1998; Henry 2002; McCarty 1999; Nicolle 1993; Richard 2000; Richard 2002) and sustained clinical success in five (Henry 2002; McCarty 1999; Neringer 1992; Nicolle 1993; Richard 2002).

Bacterial outcomes

Bacteriological outcomes were the most commonly reported outcomes. Eradication was reported in all studies, patients without persistence in eight (Henry 2002; Iravani 1993; Iravani 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993; Richard 2002), patients without relapse in seven (Henry 1998; Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Richard 2000), patients without reinfection in eight (Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Neringer 1992; Nicolle 1993; Richard 2002) and sustained bacteriological success in eight (Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993). Overall success was reported only in one study (Henry 1998).

Adverse events

Reports about any adverse event were in nine studies (Henry 1998; Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Neringer 1992; Nicolle 1993; Richard 2000). Organ or system-specific adverse events were reported in nine (Henry 1998; Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Neringer 1992; Nicolle 1993; Richard 2002), serious adverse events in four (Henry 1998; McCarty 1999; Neringer 1992; Richard 2000),

adverse events that require discontinuation of medication in six (Henry 1998; Henry 2002; Jardin 1995; McCarty 1999; Neringer 1992; Neringer 1992; Nicolle 1993) and adverse reactions in six (Henry 1998; Henry 2002; Iravani 1995; McCarty 1999; Nicolle 1993; Richard 2000).

Some studies reported the outcomes at different time points. Where possible the outcomes were recalculated for common time points from the raw data. If this was not possible, the outcomes were to be pooled for short-term (test-of-cure visit (immediately after or up to two weeks post-treatment)) and long-term effects (follow-up visit (2 -6 weeks post-treatment) and late follow-up visit (> 6 weeks post-treatment)).

Risk of bias in included studies

See Table 5 - *Quality of included studies*

Allocation concealment

In 10 studies (Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Neringer 1992; Naber 2000a; Nicolle 1993; Richard 2000; Richard 2002) the assigned treatment was adequately concealed prior to allocation (centralised pharmacy-controlled randomisation). In one study (Henry 1998) the type of allocation concealment was not clearly described.

Randomisation method

The method of randomisation was described in 7/11 studies (computer generated schedule or code) (Henry 2002; Iravani 1993; Iravani 1995; McCarty 1999; Neringer 1992; Nicolle 1993; Richard 2000). In four studies (Henry 1998; Jardin 1995; Naber 2000a; Richard 2002) randomisation methods were not described clearly but it was unambiguously stated that randomisation was used.

Blinding

Ten studies (Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993; Richard 2000; Richard 2002) were double blind. The remaining trial was blinded to outcome assessors (Henry 1998).

Baseline characteristics

Baseline characteristics of the different treatment groups were described and compared in all 11 studies (Henry 1998; Henry 2002; Iravani 1993; Iravani 1995; Jardin 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993; Richard 2000; Richard 2002). In all of the included studies there was no statistically significant difference between the groups.

Sample size and power calculations

Five studies described a sample size and power calculation (Henry 1998; Henry 2002; Jardin 1995; McCarty 1999; Neringer 1992). The total number of patients enrolled in these studies ranged from 419 to 866 patients.

Intention-to-treat

In 8/11 studies data were analysed on an intention-to-treat basis (Henry 1998; Henry 2002; Jardin 1995; McCarty 1999; Naber 2000a; Neringer 1992; Nicolle 1993; Richard 2002).

Completeness of follow-up

In three studies patients lost to follow-up was less than 5% (Henry 1998; Jardin 1995; Neringer 1992), two studies varied between 5% and 10% (Nicolle 1993; Richard 2000) and the remaining six studies varied between 10% and 15% (Henry 2002; Iravani 1993; Iravani 1995; McCarty 1999; Naber 2000a; Richard 2002).

Effects of interventions

Eleven RCTs published in 11 papers were included in this review. None of 11 studies shared the same therapy and a quantitative synthesis of results was not feasible.

Sparfloxacin 200 mg/d versus ofloxacin 400 mg/d

Clinical success, eradication, overall success, frequency of any adverse event, ADR, nausea, diarrhoea, dizziness, headache, adverse events causing withdrawal, SAEs and ALE did not differ significantly between groups.

There was a significant increase in the relative risk of photosensitivity reactions when sparfloxacin was used in the one study identified (Analysis 1.4.4: RR 14.75, 95% CI 1.96 to 111.19).

Lomefloxacin 400 mg/d versus norfloxacin 800 mg/d

There were no significant differences in eradication, patients without reinfection, patients without persistence, sustained bacteriological success, sustained clinical success, cure, SAE, gastrointestinal adverse events, nausea, vomiting, diarrhoea, pruritus, CNS adverse event, headache, vertigo, dizziness, fatigue or vaginitis between groups.

The rates of any adverse event (Analysis 2.3.1: RR 1.73, 95% CI 1.23 to 2.43), adverse events causing discontinuation of medication (Analysis 2.3.2: RR 6.64, 95% CI 1.53 to 28.90), skin adverse events (Analysis 2.3.8: RR 13.29, 95% CI 3.20 to 55.12) and photosensitivity (Analysis 2.3.9: RR 46.51, 95% CI 2.85 to 760.22) were significantly higher for lomefloxacin when compared to norfloxacin.

Ciprofloxacin 200 mg/d versus ofloxacin 400 mg/d

There were no significant differences in eradication, patients without persistence, patients without reinfection, sustained bacteriological success, patients without relapse, clinical success, sustained clinical success, adverse events causing withdrawal, headache, nausea, CNS adverse events, insomnia, rash or SAEs between groups.

The rates of any adverse event (Analysis 3.3.1: RR 0.80, 95% CI 0.65 to 0.99), ADRs (Analysis 3.3.3: RR 0.72, 95% CI 0.57 to 0.92) and CNS adverse events (Analysis 3.3.7: RR 0.31, 95% CI 0.13 to 0.70) were significantly higher with ofloxacin therapy than with ciprofloxacin treatment.

Single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg

There were no significant differences in eradication, sustained bacteriological success, patients without relapse, cure, patients without reinfection, improvement, patients without recurrence, patients without failure, adverse events, adverse events causing withdrawal, gastrointestinal adverse events, skin/allergy, nausea, vomiting, dyspepsia, diarrhoea, flatulence, abdominal pain, dry

mouth, dizziness, headache, ataxia, sleepiness, hallucinations, tinnitus, pruritus, erythema or eczema between groups.

The rates of CNS adverse events (Analysis 4.3.11: RR 2.09, 95% CI 1.33 to 3.87) and insomnia (Analysis 4.3.14: RR 3.92, 95% CI 1.32 to 11.63) were significantly higher for rifloxacin compared to pefloxacin.

Levofloxacin 250 mg/d versus ofloxacin 400 mg/d

There were no significant differences in eradication, cure, improvement, patients without failure, clinical success, adverse events, SAE or patients without relapse between groups.

The rate of ADRs was significant higher with ofloxacin than with levofloxacin treatment (Analysis 5.3.2: RR 0.45, 95% CI 0.22 to 0.93).

Lomefloxacin 400 mg/d versus norfloxacin 800 mg/d

There was no significant differences in any outcome between lomefloxacin and norfloxacin (clinical success, patients without failure, patients without recurrence, sustain clinical success, eradication, patients without persistence, sustained bacteriological success, patients without reinfection, adverse events, ADR, adverse events causing withdrawal, nausea, headaches, vulvovaginal candidiasis).

Gatifloxacin 200 mg/d versus ciprofloxacin 200 mg/d

There were no significant differences in clinical success, sustained clinical success, recurrence, eradication, persistence, reinfection or vaginitis rate between groups.

Ciprofloxacin 500 mg/d versus norfloxacin 800 mg/d

There were no significant differences in eradication, patients without persistence, patients without reinfection, patients without relapse, cure, patients without failure, adverse events, ADR, vaginal moniliasis, abdominal pain, nausea, headache or dizziness between groups.

The rate of sustained bacteriological success was significant higher with norfloxacin than with ciprofloxacin treatment (Analysis 8.2.4: RR 0.89, 95% CI 0.79 to 0.99).

Fleroxacin 200 mg/d versus ciprofloxacin 500 mg/d

There were no significant differences in cure, improvement, patients without failure, eradication, patients without persistence, sustained bacteriological success, patients without reinfection, patients without relapse, adverse events, dry mouth, abdominal pain, headache, dizziness, nausea, diarrhoea, pruritus or vaginal candidiasis between groups.

The rate of insomnia was significant higher with fleroxacin than ciprofloxacin treatment (Analysis 9.3.7: RR 4.44, 95% CI 1.70 to 11.58).

Gemifloxacin 320 mg/d versus ciprofloxacin 500 mg/d

There were no significant differences in eradication, patients without persistence or sustained bacteriological success between groups.

Conventional ciprofloxacin 500 mg/d versus extended-release ciprofloxacin 500 mg/d

There were no significant differences in patients without failure, eradication, patients without persistence, sustained bacteriological success, patients without reinfection, patients without relapse, clinical cure, sustained clinical success, adverse events, ADR, adverse events causing withdrawal, headache, nausea or vaginal candidiasis between groups.

DISCUSSION

Acute cystitis is one of the most common illnesses for which antibiotics are prescribed in primary care. Specifically, the use of trimethoprim-sulfamethoxazole (TMP-SMX) as a first-line agent for uncomplicated cystitis is recommended only in areas where TMP-SMX resistance prevalence is 10% to 20% (Warren 1999). In areas where resistance to TMP-SMX exceeds this rate, alternative agents need to be considered such as quinolones. We identified 11 RCTs reporting clinical and microbiological outcomes in patients with uncomplicated acute cystitis treated with differing quinolones.

The results of any systematic review are totally dependent on obtaining a reasonable number of high quality studies. The methodological quality of all studies was relatively high. Ten of 11 studies had an adequate method of allocation concealment, 10/11 studies were double blinded (blinding of patients and outcome assessors) and one the outcome assessors were blinded. All studies showed results for bacteriological cure rate and clinically important outcomes such as cure of symptoms. Adverse events were described in 10 studies. Criteria for the diagnosis of uncomplicated acute cystitis was well described in all studies.

The lower age limit was 18 years in all studies, however the upper age limits varied from 55 (Richard 2000) to 75 years (Jardin 1995). In three studies (Iravani 1993; Iravani 1995; McCarty 1999) the upper age limit was not specified. Taking into account that in postmenopausal women UTIs, including acute cystitis, occur more frequently, the differences in premenopausal-to-postmenopausal women ratio may be a source of heterogeneity. It was impossible to do a subgroup analysis of postmenopausal women.

Another possible source of heterogeneity between studies is the different handling of patients with organisms resistant to the study drugs. In five studies such patients were excluded (Henry 1998; Iravani 1993; Iravani 1995; Jardin 1995; Richard 2000), in two studies they were not excluded (Neringer 1992; Richard 2002) and in the remaining four studies there was no information provided. However the number of patients excluded due to the above mentioned reason was not high.

Which quinolone/s should be used for uncomplicated acute cystitis? None of the eleven studies comparing different quinolones showed significant advantages for any drugs with respect to clinical

or bacteriological outcomes. Significant differences were found in the occurrence of adverse drug reactions. Differences in the safety and tolerability of quinolones are well recognized. For example, temafloxacin was withdrawn from use in June 1992, and the use of trovafloxacin was restricted to the management of only serious infections in June 1999. The safety profiles of these two drugs represent significant divergence from those of other agents in this class. Due to such difference in safety profiles, quinolones cannot be considered interchangeable or of equal safety.

We found more frequent occurrences of:

- Photosensitivity reactions when using sparfloxacin versus ofloxacin.
- Any adverse event, adverse events causing withdrawal, skin adverse events, photosensitivity reactions when using lomefloxacin versus norfloxacin.
- Any adverse event, adverse reactions, CNS adverse events when using ofloxacin versus ciprofloxacin
- CNS adverse events, insomnia when using rifloxacin compared to pefloxacin
- Adverse drug reactions when using ofloxacin versus levofloxacin
- Insomnia when using fleroxacin versus ciprofloxacin.

However as no two studies compared the same quinolones, we were unable to determine which quinolone should be used for uncomplicated acute cystitis in women.

AUTHORS' CONCLUSIONS

Implications for practice

The following implications for practice concerning management of uncomplicated acute cystitis in women with quinolones have been identified:

- There are no significant differences in efficacy between different comparable quinolones for uncomplicated acute cystitis.
- Some quinolones have significantly lower rate of adverse drug reactions (events) than others.

Implications for research

Further RCTs are required to determine the benefits and harms of quinolones for uncomplicated acute cystitis in women. Safety data are important outcomes and should be reported for in all studies comparing quinolones.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Henry 1998

Methods	Randomised, open-label, observer-blind Multicentre study: 29 centres across the United States An investigator blinded to the treatment assignments evaluated the patient's clinical response
Participants	Number: 419 women Age: 18-64 years Inclusion criteria: UAC
Interventions	GROUP 1 3-day sparfloxacin regimen (400 mg loading dose on day 1, followed by 200 mg/d on days 2 and 3) GROUP 2 3-day ofloxacin regimen (200 mg twice daily for 3 days)
Outcomes	Bacteriological Clinical Bacteriological + clinical response Adverse events
Notes	
Risk of bias	

Henry 1998 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Henry 2002

Methods	Randomised, double-blind, double-dummy Multicentre study: 58 centres across the United States
Participants	Number: 891 women Age: 18-65 years Inclusion criteria: UAC
Interventions	GROUP 1 3 days conventional ciprofloxacin (250 mg twice daily) GROUP 2 3 days extended release ciprofloxacin (500 mg once daily)
Outcomes	Bacteriological Clinical response Adverse events after 5-9 days and 28-45 days

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Iravani 1993

Methods	Randomised, double-blind Multicentre study: 18 centres across the United States
Participants	Number: 961 women Age: >18 years Inclusion criteria: symptomatic UAC
Interventions	GROUP 1 Single dose fleroxacin (400 mg) GROUP 2 7 days fleroxacin (200 mg once daily) GROUP 3 7 days ciprofloxacin (250 mg twice daily)
Outcomes	Bacteriological Clinical response Adverse events
Notes	Compared group 2 and 3

Quinolones for uncomplicated acute cystitis in women (Review)

Iravani 1993 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Iravani 1995

Methods	Randomised, double-blind Multicentre study
Participants	Number: 451 women Age: >18 years Inclusion criteria: symptomatic UAC
Interventions	GROUP 1 3 days ciprofloxacin (500 mg once daily) GROUP 2 5 days ciprofloxacin (500 mg once daily) GROUP 3 7 days norfloxacin (400 mg twice daily)
Outcomes	Bacteriological Clinical response Adverse events
Notes	Compared group 2 and 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Jardin 1995

Methods	Randomised, double-blind Multicentre study: 74 general practitioners in France during 1991 and 1992
Participants	Number: 463 women Age: 18-75 years Inclusion criteria: symptomatic UAC
Interventions	GROUP 1 Single oral dose of rifloxacin (400 mg) GROUP 2 Single oral dose of pefloxacin (800 mg)
Outcomes	Bacteriological Clinical response Adverse events

Quinolones for uncomplicated acute cystitis in women (Review)

Jardin 1995 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McCarty 1999

Methods	Randomized, double-blind Multicentre study: 16 centres across the United States
Participants	Number: 866 women enrolled, 688 evaluated Age: >18 years Inclusion criteria: UAC
Interventions	GROUP 1 3-day course of oral ciprofloxacin (100 mg twice daily) GROUP 2 3-day course of oral ofloxacin (200 mg twice daily) GROUP 3 Timetoprim/sulfamethoxazole (160/800 mg twice daily)
Outcomes	Bacteriological Clinical response Adverse events
Notes	Compared group 1 and 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Naber 2000b

Methods	Randomised, double-blind, double-dummy, placebo-controlled Multicentre study: 84 North American centres
Participants	Number: 688 women Age: 16-65 years Inclusion criteria: symptomatic UAC
Interventions	GROUP 1 3 days gemifloxacin (320 mg once daily) GROUP 2 3 days ciprofloxacin (250 mg twice daily)
Outcomes	Bacteriological response

Quinolones for uncomplicated acute cystitis in women (Review)

Naber 2000b (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Neringer 1992

Methods	Randomised, double-blind Multicentre study: 21 Swedish centres
Participants	Number: 703 women enrolled Age: 17-75 years Inclusion criteria: UAC GROUP 1 196 women GROUP 2 196 women GROUP 3 195 women
Interventions	GROUP 1 3 days lomefloxacin (400 mg once daily) GROUP 2 7 days lomefloxacin (400 mg once daily) GROUP 3 7 days norfloxacin (400 mg twice daily)
Outcomes	Bacteriological and clinical response Adverse events SAEs Events causing withdrawal
Notes	Compared group 1 and 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nicolle 1993

Methods	Randomised, double-blind double-dummy Multicentre study
Participants	Number: 165 women Age: 18-65 years

Quinolones for uncomplicated acute cystitis in women (Review)

Nicolle 1993 (Continued)

Inclusion criteria: UAC

Interventions	GROUP 1 3 days oral norfloxacin (400 mg twice daily) GROUP 2 3 days oral lomefloxacin (400 mg once daily)
Outcomes	Bacteriological and clinical response Adverse events Events causing withdrawal
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Richard 2000

Methods	Randomised, double-blind Multicentre study
Participants	Number: 594 women Age: 18-55 years Inclusion criteria: symptomatic UAC
Interventions	GROUP 1 3 days oral rifloxacin (250 mg once daily) GROUP 2 3 days oral pefloxacin (200 mg twice daily)
Outcomes	Bacteriological and clinical response Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Richard 2002

Methods	Randomised, double-blind
Participants	Number: 1334 women Age: >18 years Inclusion criteria: UAC

Quinolones for uncomplicated acute cystitis in women (Review)

Richard 2002 (Continued)

Interventions	<p>GROUP 1 Single dose gatifloxacin (400 mg)</p> <p>GROUP 2 3 days gatifloxacin (200 mg once daily)</p> <p>GROUP 3 3 days ciprofloxacin (100 mg twice daily)</p>
Outcomes	<p>Bacteriological and clinical response</p> <p>Adverse events</p>
Notes	<p>The dose of ciprofloxacin in this study was lower (100 mg twice daily) than usual (250 mg twice daily)</p> <p>Safety data were incompletely reported - only data for vaginitis incidence was reported but no data concerning overall AE rate or rate of other AE</p> <p>Compared group 2 and 3</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

UAC - uncomplicated acute cystitis

SAEs - serious adverse events

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abejar 1993	Not an RCT
Arav-Boger 1994	Patients with different colony counts were included.
Arcieri 1987	Systematic review, but it was impossible to extract any individual data or sufficiently evaluate individual data.
Auquer 2002	Different treatment durations (single dose 500 mg ciprofloxacin versus 3 days norfloxacin 400 mg twice daily).
Backhouse 1989	Both men and women were included in the study population.
Banya 1985	The study was not controlled.
Beringer 1997	The article does not describe original studies. It is impossible to separate data from UTI studies.
Bernal 2002	Different treatment durations of the same fluoroquinolone (3 days versus 7 days norfloxacin 400 mg twice daily).
Blomer 1986	Combines data from different studies of ofloxacin. Only one is a comparison between quinolones, but it is impossible to clarify if the study was randomised and to extract study description.
Bottino 1989	Different doses of the same fluoroquinolone (300 mg and 600 mg ofloxacin for 3 days).
Bouffieux 1982	<p>1. Both men and women were included in the study population.</p> <p>2. Patients with pyelonephritis were included.</p>

Quinolones for uncomplicated acute cystitis in women (Review)

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Study	Reason for exclusion
Boyko 1990	Patients with baseline pathogens resistance to study drugs were excluded.
Briedigkeit 1982	Not an RCT
Bucy 1981	Not an RCT
Cortes 1992	Study was not randomised although stated in the article. There were three arms in study (fos-fomycin versus pipemidic acid versus norfloxacin). The ratio of the patient in the groups was 49:36:21. The rate of this kind cannot be in randomised study. Microbiological criteria for patients inclusion into study was not been defined.
Cox 1982	The study was not comparative.
Craft 1991	Different treatment durations (3 days temafloxacin 400 mg once daily versus 7 days).
Dawani 1987	Not an RCT
De Miranda 1995	Not comparative study
Del Rio 1996	Different treatment durations of two fluoroquinolones (single dose rufloxacin 400 mg versus 3 days norfloxacin 400 mg twice daily).
Derevianko 1996	The study was not controlled.
Drylie 1981	1. Not an RCT 2. It is impossible to determinate if only uncomplicated UTI were included into the study.
Fujita 1993	Not comparative study.
Gallego Gomez 1987	Not an RCT
Giamarellou 1984	1. Both men and women were included in the study population. 2. Both patients with complicated and uncomplicated UTI were included.
Goldstein 1987	1. Both men and women were included in the study population. 2. Both patients with complicated and uncomplicated UTI were included. 3. Patients with baseline pathogens resistant to study drugs were excluded.
Goto 1999	1. It is impossible to determine if patients with uncomplicated UTI only were included. 2. There is not clearly description of the randomisation procedure.
Guibert 1997	Microbiological evaluation was absent. Urine culture was not used.
Henry 1999	Different treatment durations (single dose sparfloxacin versus 3 day sparfloxacin versus 7 day ciprofloxacin).
Hirose 1992	Different doses of the same fluoroquinolone (100 mg and 200 mg sparfloxacin for 3 days).
Huilin 2000	Nosocomial UTI were evaluated.
Iravani 1996	Different treatment durations were compared (single dose sparfloxacin versus 3 day sparfloxacin versus 7 day ciprofloxacin).
Iravani 1991	Results from 3 studies were summarized. In one study fluoroquinolone (temafloxacin) was compared with co-trimoxazole and it is impossible to separate the data from individual study.

Study	Reason for exclusion
Iravani 1992	1. Both men and women were included in the study population. 2. Patients with baseline pathogens resistant to study drugs were excluded.
Ishigami 1976	Not an RCT
Ishihara 1998	Different treatment durations of the same fluoroquinolone (3 days versus 7 days fleroxacin).
Kadiri 1999	1. Both men and women were included in the study population. 2. Microbiological evaluation as inclusion criteria was absent. 3. The randomisation procedure was not described.
Karachalios 1991	Included patients both with acute and recurrent cystitis.
Koyama 2000	Different treatment durations of the same fluoroquinolone (single dose versus 3 days levofloxacin).
Kumamoto 1983	Different doses of the same fluoroquinolone (800 mg, 400 mg, 200 mg and 100 mg cinoxacin for 3 days).
Leelarasamee 1995	Different treatment durations of the same fluoroquinolone (single dose of pefloxacin versus 3 days pefloxacin).
Leibovici 1991	Meta-analysis, quinolones were not compared.
Loran 1997	Not an RCT
Ludwig 1996	There are 4 studies in the article. Only one of them compares Fluoroquinolones, but they were used in different treatment durations (single dose ofloxacin versus 3 days ofloxacin) and the study is not randomised.
Malinverni 1988	Systematic review. References to some studies were used.
Martorana 1988	Not comparative study
Matsuura 1985	Not comparative study
Miano 1990	The study is a non-systematic review. The information from as comparative and non-comparative studies was combined. Both men and women were included in the study population.
Miyata 1987	Not comparative study
Naber 1994	The publication is a meta-analysis. Only one included study compares two quinolones but there are no mention if the randomisation taken place.
Naber 1996	1. Both men and women were included in the study population. 2. Both patients with complicated and uncomplicated UTI were included.
Nagai 1988	The trial was not comparative. The trial included the patients both with acute and chronic complicated cystitis
Nordic 1988	Different treatment durations of the same fluoroquinolone (3 days versus 7 days norfloxacin).
Norrby 1990b	Systematic review, quinolones were not compared.
Ohmori 1989	Not an RCT

Study	Reason for exclusion
Ohmori 1998	Not an RCT
Piipo 1990	Different treatment durations of the same fluoroquinolone (3 days versus 7 days norfloxacin).
Pimentel 1998	Different treatment dosage of the same fluoroquinolone (7-10 day norfloxacin 800 mg once daily versus 400 mg twice daily).
Pytel' 1996	Not controlled study
Raz 1989	The trial included the patients with as acute and recurrent cystitis.
Reeves 1984	1. Both men and women were included in the study population. 2. The appropriate differentiation between lower and upper UTI was absent, so patients with both lower and upper UTI could be included.
Rizk 1992	This systematic review described two studies of uncomplicated cystitis in women, but there were no bibliographic references to appropriate publications. Authors did not describe individual data and characteristics of each study.
Sagunur 1992	Different treatment durations of the same fluoroquinolone (standard dose versus 3 days norfloxacin).
Schaeffer 1987	Not comparative study
Stein 1992	Different treatment durations (3 days temafloxacin versus 7 days ciprofloxacin).
Trienekens 1993	Different treatment durations of the same fluoroquinolone (3 days norfloxacin versus 7 days norfloxacin).
Tsugawa 1999	Different treatment durations of the same fluoroquinolone (3 days versus 7 days gatifloxacin).
van Balen 1990	Different treatment durations (5 days norfloxacin versus single dose pefloxacin).
van Poppel 1988	This article combined data from ciprofloxacin studies in different UTI types and with different study designs. There is impossible to extract individual study data and description.
Vogel 1984	1. Not an RCT 2. Both men and women were included in the study population. 3. There was no appropriate differentiation between lower and upper UTI, so patients with both lower and upper UTI could be included.
Wang 1986	1. It is non systematic review. 2. There were no original data concerning current systematic review.
Wittenberger 1986	Not an RCT
Zerqueni 1984	Both men and women were included in the study population. Complicated UTI were also studied

RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. 200 mg/d sparfloxacin versus 400 mg/d ofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients without recurrence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Patients without relapses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Clinical + microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Overall success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Photosensitivity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.7 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.8 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.9 Adverse events causing withdrawal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.10 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.11 Laboratory adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 200 mg/d sparfloxacin versus 400 mg/d ofloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Sparfloxacin n/N	Ofloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 Success				
Henry 1998	89/93	74/81		1.05[0.97,1.13]
			Sparfloxacin 0.5 0.7 1 1.5 2 Ofloxacin

Analysis 1.2. Comparison 1 200 mg/d sparfloxacin versus 400 mg/d ofloxacin, Outcome 2 Microbiological efficacy.

Analysis 1.3. Comparison 1 200 mg/d sparfloxacin versus 400 mg/d ofloxacin, Outcome 3 Clinical + microbiological efficacy.

Analysis 1.4. Comparison 1 200 mg/d sparfloxacin versus 400 mg/d ofloxacin, Outcome 4 Safety.

Comparison 2. 400 mg/d lomefloxacin versus 800 mg/d norfloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Sustained clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Cure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events requiring discontinuation of medication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Gastrointestinal adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 Vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Skin adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.9 Photosensitivity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.10 Pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.11 CNS adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.12 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.13 Vertigo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.14 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.15 Fatigue	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.16 Vaginitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Lomefloxacin n/N	Norfloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.1.1 Sustained clinical success				
Neringer 1992	164/228	163/223		0.98[0.88,1.1]
2.1.2 Cure				
Neringer 1992	204/235	190/223		1.02[0.95,1.1]
			Lomefloxacin 0.5 0.7 1 1.5 2 Norfloxacin	

Analysis 2.2. Comparison 2 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 2 Microbiological efficacy.

Study or subgroup	Lomefloxacin n/N	Norfloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.2.1 Eradication				
Neringer 1992	182/196	181/195		1[0.95,1.06]
2.2.2 Patients without reinfection				
Neringer 1992	188/196	191/195		0.98[0.95,1.01]
2.2.3 Patients without persistence				
Neringer 1992	188/196	189/195		0.99[0.95,1.03]
			Lomefloxacin 0.5 0.7 1 1.5 2 Norfloxacin

Analysis 2.3. Comparison 2 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 3 Safety.

Comparison 3. 200 mg/d ciprofloxacin versus 400 mg/d ofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Sustained clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Patients without relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Adverse events requiring discontinuation of medication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 CNS adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9 Rash	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 200 mg/d ciprofloxacin versus 400 mg/d ofloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Ciprofloxacin n/N	Ofloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 Clinical success				
McCarty 1999	211/226	222/231		0.97[0.93,1.01]
3.1.2 Sustained clinical success				
McCarty 1999	184/203	186/208		1.01[0.95,1.08]

Analysis 3.2. Comparison 3 200 mg/d ciprofloxacin versus 400 mg/d ofloxacin, Outcome 2 Microbiological efficacy.

Study or subgroup	Ciprofloxacin n/N	Ofloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 Eradication				
McCarty 1999	215/228	224/230		0.97[0.93,1.01]
3.2.2 Patients without persistence				
McCarty 1999	219/228	224/230		0.99[0.95,1.02]
3.2.3 Patients without reinfection				
McCarty 1999	224/228	230/230		0.98[0.96,1]
3.2.4 Sustained bacteriological success				
McCarty 1999	173/228	175/230		1[0.9,1.11]
3.2.5 Patients without relapse				
McCarty 1999	214/228	210/230		1.03[0.98,1.08]

Analysis 3.3. Comparison 3 200 mg/d ciprofloxacin versus 400 mg/d ofloxacin, Outcome 3 Safety.

Study or subgroup	Ciprofloxacin n/N	Ofloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 Any adverse events				
McCarty 1999	90/228	113/230		0.8[0.65,0.99]
3.3.2 Serious adverse events				
McCarty 1999	0/228	1/230		0.34[0.01,8.21]

Comparison 4. Single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg

Quinolones for uncomplicated acute cystitis in women (Review)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events requiring discontinuation of medication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Gastrointestinal adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Dyspepsia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.9 Flatulence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.10 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.11 CNS adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.12 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.13 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.14 Insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.15 Ataxia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.16 Sleepiness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.17 Hallucinations	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.18 Tinnitus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.19 Skin adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.20 Pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.21 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.22 Eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg, Outcome 1 Clinical efficacy.

Analysis 4.2. Comparison 4 Single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg, Outcome 2 Microbiological efficacy.

Analysis 4.3. Comparison 4 Single dose rifloxacin 400 mg versus single dose pefloxacin 800 mg, Outcome 3 Safety.

Comparison 5. 250 mg/d levofloxacin versus 400 mg/d ofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Cure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Improvement	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Patients without failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 250 mg/d levofloxacin versus 400 mg/d ofloxacin, Outcome 1 Clinical efficacy.

Analysis 5.2. Comparison 5 250 mg/d levofloxacin versus 400 mg/d ofloxacin, Outcome 2 Microbiological efficacy.

Analysis 5.3. Comparison 5 250 mg/d levofloxacin versus 400 mg/d ofloxacin, Outcome 3 Safety.

Comparison 6. 400 mg/d lomefloxacin versus 800 mg/d norfloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients without recurrence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Sustained clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Patients without failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events requiring discontinuation of medication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Headaches	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Vulvovaginal candidiasis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Lomefloxacin n/N	Norfloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 Clinical success				
Nicolle 1993	57/63	56/59		0.95[0.86,1.05]
6.1.2 Patients without recurrence				
Lomefloxacin 0.5 0.7 1 1.5 2 Norfloxacin

Analysis 6.2. Comparison 6 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 2 Microbiological efficacy.

Analysis 6.3. Comparison 6 400 mg/d lomefloxacin versus 800 mg/d norfloxacin, Outcome 3 Safety.

Comparison 7. 200 mg/d gatifloxacin versus 200 mg/d ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Sustained clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Patients without recurrence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Vaginitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 200 mg/d gatifloxacin versus 200 mg/d ciprofloxacin, Outcome 1 Clinical efficacy.

Analysis 7.2. Comparison 7 200 mg/d gatifloxacin versus 200 mg/d ciprofloxacin, Outcome 2 Microbiological efficacy.

Analysis 7.3. Comparison 7 200 mg/d gatifloxacin versus 200 mg/d ciprofloxacin, Outcome 3 Safety.

Comparison 8. 500 mg/d ciprofloxacin versus 800 mg/d norfloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Cure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients without failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Patients without relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Vaginal moniliasis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 500 mg/d ciprofloxacin versus 800 mg/d norfloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Ciprofloxacin n/N	Norfloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 Cure				
Iravani 1995	143/148	135/139		0.99[0.95,1.04]
8.1.2 Patients without failure				
Iravani 1995	143/148	145/149		0.99[0.95,1.03]
Ciprofloxacin 0.5 0.7 1 1.5 2 Norfloxacin				

Analysis 8.2. Comparison 8 500 mg/d ciprofloxacin versus 800 mg/d norfloxacin, Outcome 2 Microbiological efficacy.

Study or subgroup	Ciprofloxacin n/N	Norfloxacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.2.1 Eradication				
Iravani 1995	134/149	133/141		0.95[0.89,1.02]
8.2.2 Patients without persistence				
Iravani 1995	142/149	135/141		1[0.95,1.05]
8.2.3 Patients without reinfection				
Iravani 1995	145/149	139/141		0.99[0.95,1.02]
8.2.4 Sustained bacteriological success				
Iravani 1995	91/114	99/110		0.89[0.79,0.99]
8.2.5 Patients without relapse				
Iravani 1995	106/114	104/110		0.98[0.92,1.05]
Ciprofloxacin 0.5 0.7 1 1.5 2 Norfloxacin				

Analysis 8.3. Comparison 8 500 mg/d ciprofloxacin versus 800 mg/d norfloxacin, Outcome 3 Safety.

Comparison 9. 200 mg/d fleroxacin versus 500 mg/d ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Cure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Improvement	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Patients without failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Patients without relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.9 Pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.10 Vaginal candidiasis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 200 mg/d fleroxacin versus 500 mg/d ciprofloxacin, Outcome 1 Clinical efficacy.

Analysis 9.2. Comparison 9 200 mg/d fleroxacin versus 500 mg/d ciprofloxacin, Outcome 2 Microbiological efficacy.

Analysis 9.3. Comparison 9 200 mg/d fleroxacin versus 500 mg/d ciprofloxacin, Outcome 3 Safety.

Comparison 10. 320 mg/d gemifloxacin versus 500 mg/d ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 320 mg/d gemifloxacin versus 500 mg/d ciprofloxacin, Outcome 1 Microbiological efficacy.

Comparison 11. 500 mg/d conventional ciprofloxacin versus 500 mg/d extended-release ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients without failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Sustain clinical success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Microbiological efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Eradication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients without persistence	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients without reinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Sustained bacteriological success	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Patients without relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events related to study drug	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Adverse events requiring discontinuation of medication	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Vaginal moniliasis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Vaginitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 500 mg/d conventional ciprofloxacin versus 500 mg/d extended-release ciprofloxacin, Outcome 1 Clinical efficacy.

Study or subgroup	Conventional ciprofloxacin	Extended-release ciprofloxacin	Risk Ratio	
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
11.1.1 Clinical success				
Henry 2002	204/220	189/198		0.97[0.93,1.02]
			Conventional ciprofloxacin	Extended-release ciprofloxacin

Analysis 11.2. Comparison 11 500 mg/d conventional ciprofloxacin versus 500 mg/d extended-release ciprofloxacin, Outcome 2 Microbiological efficacy.

Analysis 11.3. Comparison 11 500 mg/d conventional ciprofloxacin versus 500 mg/d extended-release ciprofloxacin, Outcome 3 Safety.

ADDITIONAL TABLES

Table 1. Electronic search strategies

Database	Search terms
CENTRAL (Issue 3 2003)	(urinary tract infections[MH] OR UTI*[TIAB] OR acute cystitis[TIAB] OR cystitis[MH] OR Escherichia coli Infections[MH]) AND (Quinolone[MH] OR Anti-Infective Agents, Urinary[MH] OR Quinolone*[TIAB] OR Fluoroquinolone*[TIAB] OR (ciprofloxacin OR norfloxacin OR lomefloxacin OR levofloxacin OR ofloxacin OR pefloxacin OR rufloxacin OR moxifloxacin OR gatifloxacin OR sparfloxacin OR fleroxacin OR enoxacin OR Nalidixic Acid)[TIAB])
MEDLINE (1966 - Sep 2003)	((randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("Latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) AND (urinary tract infections[MH] OR UTI*[TIAB] OR acute cystitis[TIAB] OR cystitis[MH] OR Escherichia coli Infections[MH]) AND (Quinolone[MH] OR Anti-Infective Agents, Urinary[MH] OR Quinolone*[TIAB] OR Fluoroquinolone*[TIAB] OR (ciprofloxacin OR norfloxacin OR lomefloxacin OR levofloxacin OR ofloxacin OR pefloxacin OR rufloxacin OR moxifloxacin OR gatifloxacin OR sparfloxacin OR fleroxacin OR enoxacin OR Nalidixic Acid)[TIAB])
EMBASE (1980 - Sep 2003)	1. (urinary tract infections).me,ti,ab. 2. UTI#.ti,ab. 3. (acute cystitis).ti,ab. 4. cystitis/ 5. (Escherichia coli Infections)/ 6. 1 or 2 or 3 or 4 or 5 7. Anti-Infective-Agents-Fluoroquinolone\$/ 8. Anti-Infective-Agents-Quinolone\$/ 9. Anti-Infective-Agents-Urinary/ 10. ciprofloxacin.ti,ab. 11. norfloxacin.ti,ab. 12. lomefloxacin.ti,ab. 13. levofloxacin.ti,ab. 14. ofloxacin.ti,ab. 15. pefloxacin.ti,ab. 16. rufloxacin.ti,ab.

Table 1. Electronic search strategies *(Continued)*

17. moxifloxacin.ti,ab.
18. gatifloxacin.ti,ab.
19. gemifloxacin.ti,ab.
20. sparfloxacin.ti,ab.
21. fleroxacin.ti,ab.
22. enoxacin.ti,ab.
23. nalidixic acid.ti,ab.
24. or/7-23
25. 6 and 24

Table 2. Literature search results

Database	Sys-tem/Me-dia	Articles identified	Title	Abstract	Final in-clusion
The Cochrane Library, Issue 3 2003	CD	198	29	29	11
MEDLINE (PubMed) 1966 - September 2003	Internet	2542	63	42	17
MEDLINE (Ovid) 1966 - September 2003	Internet	1382	40	31	16
EMBASE (Ovid) 1966 - September 2003	Internet	1733	65	41	19
Kidney Disease A Bibliography Of Randomised Controlled Trials. Issue 2, 2002	CD	4	3	2	2
Science@Direct - full text journal search	Internet	30	0	0	0
EBSCO-Publishing: Academic Search Premier + Health Source	Internet	320	0	0	0
Blackwell Synergy - full text journal search	Internet	221	1	1	1
Wiley InterScience - full text journal search	Internet	185	0	0	0
Abstracts of the 8, 9, 10, 11, 12, 13 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 1997, 1999, 2000, 2001, 2002, 2003	CD	233	2	1	1
Abstracts of the 35, 36, 37, 38, 39, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 1995- 2000	CD	253	2	2	2
Abstracts of the 21st International Congress of Chemotherapy (ICC) 1999	CD	3	1	1	0
Industry	Letters	20	3	3	3
Handsearching		2	2	0	0
Reference reviewing		-	4	4	4

Table 3. Sources of included studies

Included studies	CENTRAL	EMBASE	MEDLINE (OVID)	MEDLINE (PubMed)	Conferences	Industry	Others
Henry 1998	+	+		+			
Henry 2002		+	+	+			
Iravani 1993		+	+	+			
Iravani 1995			+	+			
Jardin 1995	+	+	+	+			
McCarty 1999	+	+	+	+		+	
Naber 2000b					+		
Neringer 1992	+	+	+	+			
Nicolle 1993	+	+	+	+			
Richard 2000		+				+	+
Richard 2002		+	+	+			

Table 4. Baseline pathogen susceptibilities to study drug

Study	Description
Henry 1998	To be bacteriologically evaluable a patient had to have susceptible pathogens to both study drugs
Henry 2002	Not sure
Iravani 1993	Only women with susceptible pathogens were eligible for enrolment
Iravani 1995	All patients in whom efficacy was evaluable had pretreatment pathogens that were susceptible to all study drugs
Jardin 1995	The isolated pathogens had to be susceptible to either drug
McCarty 1999	Not sure
Neringer 1992	The patients with resistance pathogens was not excluded from the study
Naber 2000b	Not sure
Nicolle 1993	Not sure
Richard 2002	The patients with resistance pathogens was not excluded from the study
Richard 2000	Only women with susceptible pathogens were eligible for enrolment

Table 5. Quality of included studies

Study	Allocation concealment	Randomisation method	Blinding	Baseline characteristics	Power calculation	Sample size	Intention-to-treat	Follow-up - complete
Henry 1998	B	n.s.	Blinding of outcome assessor	Yes, no difference	Yes	419	Yes	Efficacy - 98.9%. Safety - 100%.
Henry 2002	A	Computer generated code	Blinding of participants and investigators	Yes, no difference	Yes	891	Yes	Efficacy - 89.8%. Safety - 98%.
Iravani 1993	A	Computer generated randomisation list	Blinding of participants and investigators	Yes, no difference	No	961	NS	Efficacy - 88.7%. Safety - 97.5%.
Iravani 1995	A	Computer generated code	Blinding of participants and investigators	Yes, no difference	No	444	No	Efficacy - 98.2%. Safety - 99%.
Jardin 1995	A	n.s.	Blinding of participants and investigators	Yes, no difference	Yes	463	Yes	Efficacy - 98.6%. Safety - 96.3%.
McCarty 1999	A	Computer generated block design random code	Blinding of participants and investigators	Yes, no difference	Yes	866	Yes	Efficacy - 89.3%. Safety - 100%.
Naber 2000b	A	n.s.	Blinding of participants and investigators	Yes, no difference	No	688	Yes	Efficacy - 87.5. Safety - NA

Table 5. Quality of included studies *(Continued)*

Neringer 1992	A	Computer generated schedule	Blinding of participants and investigators	Yes, no difference	Yes	703	Yes	Efficacy - ?. Safety - 97.6%.
Nicolle 1993	A	Computer generated schedule	Blinding of participants and investigators	Yes, no difference	No	164	Yes	Efficacy - 93.8%. Safety - 97.6%.
Richard 2000	A	Computer generated schedule	Blinding of participants and investigators	Yes, no difference	No	594	Yes	Efficacy - 93.8%. Safety - 99.5%.
Richard 2002	A	n.s.	Blinding of participants and investigators	Yes, no difference	No	1334	No	Efficacy - 85.3%. Safety - 99%.

WHAT'S NEW

Date	Event	Description
18 March 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2006

Date	Event	Description
14 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review - VR, IA, ER
- Screening of titles and abstracts - VR, IA
- Assessment for inclusion - VR, IA
- Quality assessment - VR, IA
- Data extraction - VR, IA
- Data entry into RevMan - VR
- Data analysis - VR, IA, ER
- Disagreement resolution - ER

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Smolensk State Medical Academy, Not specified.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Infective Agents, Urinary [*therapeutic use]; Ciprofloxacin [therapeutic use]; Cystitis [*drug therapy]; Fluoroquinolones [therapeutic use]; Levofloxacin; Norfloxacin [therapeutic use]; Ofloxacin [therapeutic use]; Pefloxacin [therapeutic use]; Quinolones [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans