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REVIEW ARTICLE

Efficacy and safety of quinolones for the treatment of uncomplicated urinary tract infections in women: a network meta-analysis

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Abstract

Introduction and hypothesis Uncomplicated urinary tract infection (uUTI) is defined as the presence of pathogenic organisms in the urinary tract without anatomical and functional abnormalities, is accompanied by inflammatory leukocytes and cytokines and may or may not develop clinical symptoms. The frequency of uncomplicated urinary tract infection is higher in young women. Several quinolone treatment regimens are available; however, since we do not know which is the best antibiotic regimen for the treatment of this urinary infection, we analyzed the published evidence and conducted a systematic review with network meta-analysis. The aim was to compare and hierarchize quinolones according to their efficacy and safety and to identify the best treatment for uncomplicated urinary tract infection in women through a systematic review with network meta-analysis.

Methods Medline, Embase, LILACS, Cochrane CENTRAL and other databases were searched for trials. Bias in the trials was assessed using the Cochrane Collaboration tool. To analyze efficacy and adverse events, for direct comparisons, we obtained risk ratios and 95% confidence intervals by applying a fixed-effects model using tau^2 and Q^2 tests to calculate the heterogeneity. For the network meta-analysis, we analyzed the indirect comparisons by Bucher's method.

Results We included 18 trials (8765 women). For premenopausal women, ofloxacin had a 57% probability of achieving remission but an 83% frequency of adverse events. For postmenopausal women, ofloxacin was 82% more effective for remission, with a 49% frequency of adverse events, compared with other types of quinolones.

Conclusions Compared with other quinolones, ofloxacin 200 mg once daily for a treatment duration < 3 days provides the highest clinical and bacteriological remission rates with the lowest relapse and resistance rates for the treatment of women with uUTIs. However, additional trials are needed to confirm our findings, especially when the treatment duration exceeds 3 days.

Keywords Quinolones · Urinary tract infection · Network meta-analysis · Therapy

Background

Urinary tract infection (UTI) is caused by pathogenic organisms, may or may not be symptomatic and is often accompanied by leukocytes and inflammatory cytokines. UTI is considered uncomplicated (uUTI) when the infection develops in the urinary tract without relevant anatomical or functional abnormalities or comorbidities and without catheterization [1, 2].

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UTIs are regarded as infections with low morbidity and mortality in the community environment, but they have a high incidence, with 250 million cases reported annually worldwide, are more frequent in young women (approximately 0.5 episodes per person per year) and represent up to 5% of primary medical health care visits [1, 3–5].

This high incidence may be attributed in premenopausal women to sexual activity and a history of UTI in the last 12 months and in postmenopausal women (> 65 years) to urinary incontinence, the prolapse of pelvic organs and vaginal infections as a result of the change in the vaginal flora secondary to the decrease in estrogen levels [4–6].

Overall, the most frequent pathogens that cause uUTIs are gram-negative bacilli (80% to 90% *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*), followed by group B *Streptococcus, Enterococcus faecalis* and *Staphylococcus saprophyticus*; however, the selection of antimicrobials for the treatment of uUTIs depends not only on the causative organism but also on the site of infection, dose and time of administration of the antibiotic regimen [4–7].

Due to the above, the guidelines of the Infectious Diseases Society of America recommend the use of TMP/SMX (160/800 mg twice daily for 3 days) or nitrofurantoin (100 mg twice daily for 5 days) as a first-line treatment for urinary tract infection [8]. However, some low-income countries have reported resistance rates > 20% for TMP/SMX; therefore, studies have been conducted to identify other effective antibiotics for the treatment of UTIs.

Several clinical trials have concluded that the administration of agents of the quinolone family is an appropriate therapeutic option [9, 10]. However, due to their variety, it has not been possible to identify which quinolone is most effective and safe for the treatment of uUTIs because it would be necessary to perform multiple head-to-head trials. Therefore, this has resulted in clinicians prescribing drugs as per convenience, without considering their dose, adverse effects and time of administration necessary for the healing of the patients [11–13].

Based on the above, we conducted this systematic review with a network meta-analysis to compare and hierarchize quinolones according to their efficacy and safety and to identify the best treatment for uUTIs in women.

Materials and methods

Search strategy

Two reviewers (RRL and AGG) conducted a search of the following databases: Medline, Embase, LILACS, Cochrane CENTRAL and the WHO International Clinical Trials Registry Platform. In addition, references cited in the identified studies and relevant abstracts presented at various conferences (e.g., Infectious Diseases Society of America, European Association of Urology and American Urological Association) were manually searched without language restriction. The search included the following MeSH terms: *((“urinary tract infections”[MeSH Terms] OR (“urinary”[All Fields] AND “tract”[All Fields] AND “infections”[All Fields]) OR “urinary tract infections”[All Fields]) AND (“ciprofloxacin”[MeSH Terms] OR “ciprofloxacin”[All Fields])) OR “quinolones”[All Fields] AND ((Randomized Controlled Trial[ptyp] OR systematic[sb]) AND “humans”[MeSH Terms] AND “adult”[MeSH Terms]).*

Study and participant selection criteria

We included any randomized controlled trial that examined the use of any quinolone in healthy adult women who had a normal urinary tract, had not been catheterized and had been diagnosed with a uUTI according to any of the following criteria: (1) culture (≥ 10,000 colony-forming units/ml); (2) urinalysis (≥ 20 leucocytes per field, ≥ 3 erythrocytes per field and the presence of nitrites); or (3) clinical symptoms (e.g., dysuria, urinary urgency, urinary frequency or suprapubic pain).

The quinolone regimens were adjusted according to age, dose and time of treatment to evaluate the following outcomes: (1) efficacy: ***clinical remission*** (the remission of the clinical symptoms such as dysuria, urgency and urinary frequency or suprapubic pain experienced by patients) and ***bacteriological remission*** (negative urine culture after treatment); (2) safety (according to the frequency of any ***adverse events***); and (3) ***relapse rate*** (the reappearance of signs and symptoms of a UTI from which the participant was convalescing) and ***resistance rate*** (continued presence of signs and symptoms of a UTI despite treatment).

A study was considered ineligible if the following occurred: the participants presented with immunosuppression, renal failure, pyelonephritis, chemotherapy or pregnancy; prophylactic antibiotics or catheters were used; UTI was considered complicated (functional or structural abnormalities of the genitourinary tract); or the studies included drugs withdrawn by the FDA (sparfloxacin, lomefloxacin, gatifloxacin and temafloxacin). Crossover, quasi-experimental, noninferiority, observational, narrative, case report and consensus studies were also excluded from this review.

Assessment of the risk of bias

Two independent reviewers (AGG, LVH) analyzed the study titles and abstracts to determine their inclusion; disagreements were resolved by discussion and consultation with a third reviewer (EOH). We used the Cochrane “risk of bias” assessment tool to judge the risk of bias for the following individual

items: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) incomplete data and (5) selective reporting of information [12].

Discrepancies were resolved by discussion with the third reviewer (EOH); for cases involving unclear information, the authors were contacted via email [12].

We present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to show the process of trial selection (Fig. 1) and the assessment of the risk of bias (Fig. 2, Supplementary Fig. 1) [14].

Data extraction

This process was performed independently by two researchers, who used a standardized form that included the following information: author's name, the year of publication, country, the number of participants included, treatment and dosage, the duration of follow-up, outcomes analyzed and findings obtained (Table 1).

Statistical analysis

Direct comparisons For each pairwise comparison and each outcome, we obtained RRs with 95% CI as a measure of the association between the interventions. Conventional meta-analyses were conducted using a fixed- and random-effects model, with the inverse variance for each outcome and comparison. We used the standard chi^2 test with a significance level of 0.1. Heterogeneity was considered important when the I^2 value was $\geq$ 50%.

For the assessment of publication bias, we formed funnel plots to evaluate asymmetry and confirmed the findings using Egger's test [15].

For all outcomes, we conducted an analysis according to the intention to treat; in cases where this information was not reported, we contacted the study authors.

Indirect comparisons Since a network meta-analysis is a method of synthesizing information from studies with the same outcomes but different interventions, it requires the information of direct and indirect comparisons between interventions to calculate a single effect size. An indirect comparison is the relative effect obtained from different treatments adjusted according to the results of their direct comparisons with a common comparator (transitivity).

To obtain indirect comparisons and to generate the network, it was necessary to use TMP/SMX (160/800 mg twice daily) as a common comparator because it was the most commonly used drug in the included clinical trials, it is not a quinolone and it is considered the conventional treatment for uUTIs according to the Infectious Diseases Society of America [8]. We calculated the indirect comparisons using Bucher's method, considering a cutoff value of 0.05.

Subsequently, we analyzed the inconsistency in each loop using the τ test; if all loops in the net had consistency, we performed a correlation matrix and obtained the SUCRA, which shows the cumulative probability of an intervention being among the best options, using STATA software v15.1 [13, 16, 17]. This review was registered and approved in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42015025886).

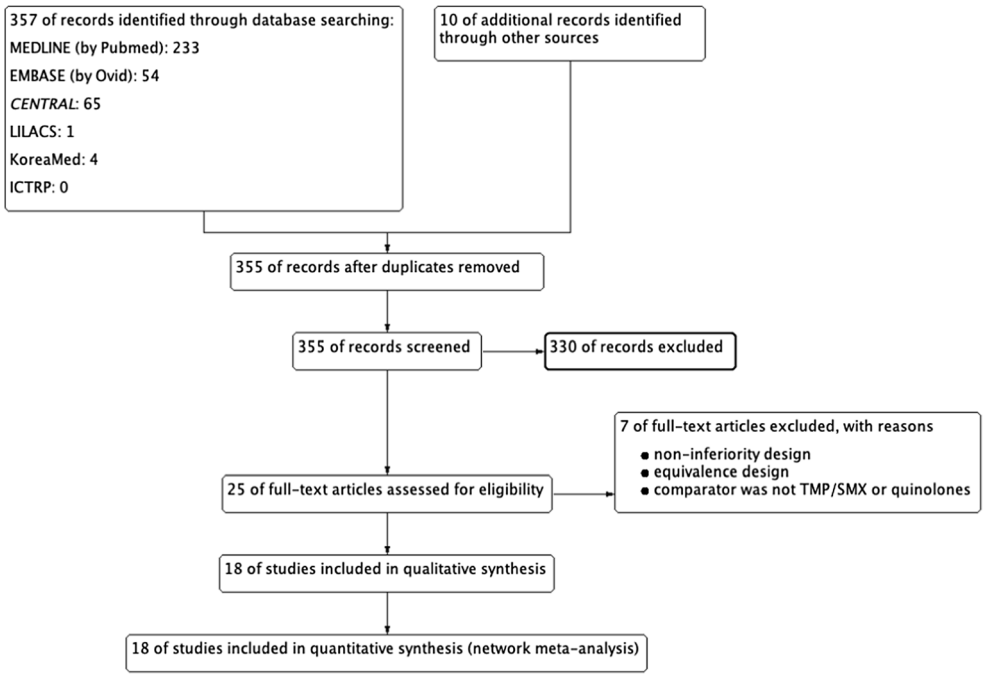

Fig. 1 Study flow diagram

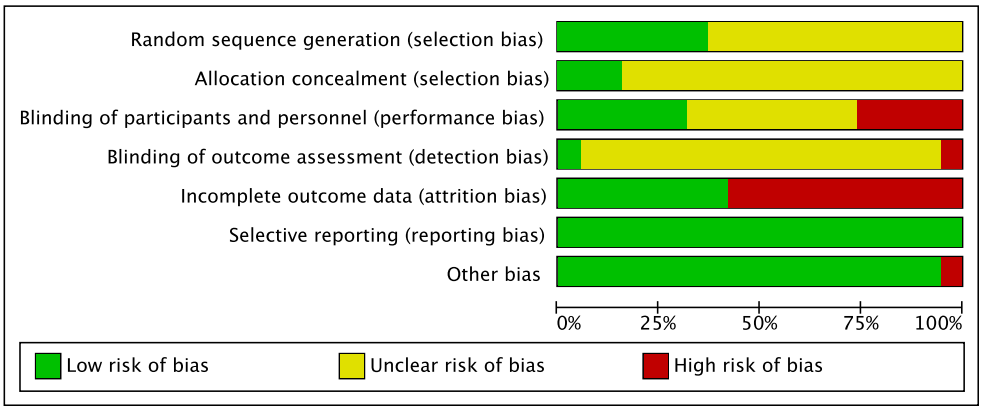

Fig. 2 Summary graph of the risk of bias

Results

Characteristics of the included studies

We identified 357 potential studies for inclusion; after we screened the titles and/or abstracts and removed duplicates, 25 randomized controlled trials remained eligible. In this study, we included 18 trials with 8765 participants [11, 18–34]; 9 of these trials compared three arms [18, 26–33] (Fig. 1).

The remaining seven studies failed to comply with the selection criteria for this review and were excluded because of (1) the comparator being fosfomycin, amoxicillin or cephalosporin and (2) trials of equivalence [35–41].

We identified seven different quinolone-based treatment regimens (ciprofloxacin 100, 250 and 500 mg; levofloxacin 250 mg; norfloxacin 400 mg; ofloxacin 200 and 400 mg) with different administration times (1 to 14 days) administered to women of different ages (18 to 80 years). Therefore, to reduce the heterogeneity, we grouped the population into four groups of patients according to age (pre- and postmenopausal) and the duration of treatment ($\leq$ 3 days and > 3 days), with which we could generate a network meta-analysis. For details, please see Table 1.

Fourteen percent of the trials were considered to have a high risk of bias due to the lack of detailed descriptions for random sequence generation, allocation concealment and blinding of participants and personnel. We noted that 61% of trials had dropout rates > 30%. However, 97% of the trials properly reported selective bias and other potential sources of bias (Fig. 2 and Supplementary Fig. 1).

Of the 18 trials included in this review, 10 (3187 participants) involved premenopausal women [11, 18, 19, 23, 25, 26, 28, 30, 33] (Fig. 3), of which 6 studies (2445 participants) involved a treatment duration $\leq$ 3 days [19, 23, 25, 26, 28, 30] and 4 trials (742 participants) involved a treatment duration > 3 days [11, 18, 28, 33].

On the other hand, ten studies (5578 participants) involved postmenopausal women [20–22, 24, 27–29, 31, 32, 34] (Fig. 4), of which eight trials (4356 participants) involved a treatment duration $\leq$ 3 days [20–22, 28, 29, 31–33] and two studies (1222 participants) involved a treatment duration > 3 days [24, 27].

(1) Treatment duration $\leq$ 3 days in premenopausal women

Clinical remission

The six analyzed trials [19, 23, 25, 26, 28, 30] involved six different types of interventions (ciprofloxacin 100, 250 and 500 mg; norfloxacin 400 mg; ofloxacin 200 and 400 mg) (for regimens of administration, see Table 1). We calculated both direct and indirect comparisons and generated a network plot with the cumulative ranking curve plots (Supplementary Table 1). The IF was not significant ($p = 0.84$).

Overall, we did not observe a significant difference between regimens when comparing different types of quinolones or TMP/SMX. The overall ranking curve plots the antibiotics most likely to yield a clinical remission of UTIs, such as ciprofloxacin 250 mg and ofloxacin 200 mg, with an area under the ranking curve of 58.5% and 57.5%, respectively (Table 2).

Bacteriological remission

The meta-analysis was performed with six trials, and we generated a network plot with a nonsignificant IF ($p = 0.95$). The cumulative curve plots indicated that ciprofloxacin 100 mg and ofloxacin 200 mg were most likely to yield bacteriological remission with an area under the ranking curve of 65.5% and 63.2%, respectively (Table 2, Supplementary Table 2).

Adverse events

The main adverse events reported in these trials were gastrointestinal issues (diarrhea, nausea and vomiting), dizziness, headache, rash and genital itching (for details, please see Table 1). The related network meta-analysis included six trials

Table 1 Characteristics of the included studies

Author/year	Sex/age	Intervention 1 N/dose	Comparator 1 N/dose	Comparator 2 N/dose	Outcomes	Findings
Arredondo 2004 (Multicenter: Mexico, Colombia, Ecuador, Venezuela,Salvador, Guatemala)	Women > 18 years	$N = 151$ Ciprofloxacin 250 mg, orally twice per day for 3 days	$N = 150$ TMP/SMX 160/800 mg, orally, twice per day for 7 days	$N = 154$ Norfloxacin 400 mg, orally twice per day for 7 days	Clinical and bacteriological remission, adverse events	Clinical remission: 86.4% TMP/SMX, 88.7% ciprofloxacin, 84.1% norfloxacin. Adverse events: 8.7% TMP/SMX, 4% ciprofloxacin, 3.9% norfloxacin (dyspepsia, headache, dizziness)
Auquer 2002 (Spain)	Women 18–65 years	$N = 114$ Ciprofloxacin 500 mg, orally once per day for 1 day	$N = 112$ Norfloxacin 400 mg, orally twice per day for 3 days	–	Clinical and bacteriological remission, relapse and adverse events	Clinical remission: 91.2% ciprofloxacin, 93.8% norfloxacin Bacteriological remission: 91.2% ciprofloxacin, 91.9% norfloxacin Adverse events: 12.7% ciprofloxacin, 11.3% norfloxacin (vulvar itching, central nervous system, gastrointestinal)
Basista 1991 (USA)	Women 18–84 years	$N = 49$ Ofloxacin 200 mg, orally once per day for 3 day	$N = 45$ TMP/SMX 160/800 mg, orally, twice per day for 7 days	–	Clinical and bacteriological remission and adverse events	Bacteriological remission: 86.2% ofloxacin, 80% TMP/SMX Adverse events: 8.2% ofloxacin, 15.6% TMP/SMX (nervous system, special senses, respiratory, gastrointestinal and genital system)
Cox 1992 (USA)	Women 18–80 years	$N = 101$ Ofloxacin 200 mg, orally once per day for 3 day	$N = 99$ TMP/SMX 160/800 mg, orally, twice per day for 7 days	–	Clinical and bacteriological remission and adverse events	Clinical remission: 89% ofloxacin, 76.6% TMP/SMX Bacteriological remission: 92% ofloxacin, 83.8% TMP/SMX Adverse events: 18.1% ofloxacin, 32% TMP/SMX (nervous, gastrointestinal and genital system)
Fourcroy 2005 (USA)	Women 18–89 years	$N = 524$ Ciprofloxacin 500 mg, orally once per day for 3 days	$N = 513$ Ciprofloxacin 250 mg, orally, twice per day for 3 days	–	Clinical and bacteriological remission, relapse, resistance and adverse events	Clinical remission: 93.4% ciprofloxacin 500 mg, 89.6% ciprofloxacin 250 mg Adverse events: 0.2–0.6% ciprofloxacin 500 mg, 1.4–2.2% ciprofloxacin 250 mg (nausea, diarrhea)
Garlando 1987 (Switzerland)	Women 25 (18) years	$N = 20$ Ciprofloxacin 100 mg, orally single dose	$N = 20$ Ciprofloxacin 250 mg, orally single dose	–	Clinical and bacteriological remission, resistance and relapse	Clinical and bacteriological remission: 84% ciprofloxacin 100 mg, 89% ciprofloxacin 250 mg
Gomolin 2001 (Multicenter USA)	Women 80.5 (8.9) years	$N = 129$ Ciprofloxacin 250 mg, orally, twice per day for 10 days	$N = 132$ TMP/SMX 160/800 mg, orally, twice per day for 10 days	–	Clinical and bacteriological remission, relapse, resistance and adverse events	Clinical remission: 97% ciprofloxacin, 85% TMP/SMX ($p = 0.009$) Bacteriological remission: 95% ciprofloxacin, 84% TMP/SMX ($p = 0.019$) Adverse events: 17% ciprofloxacin, 27% TMP/SMX ($p = 0.047$)
Henry 1986 (USA)	Women 37.6 years	$N = 31$ Ciprofloxacin 250 mg, orally, twice per day for 10 days	$N = 34$ TMP/SMX 160/800 mg, orally, twice per day for 10 days	–	Clinical and bacteriological remission, relapse and adverse events	Clinical remission: 93.5% ciprofloxacin, 82.3% TMP/SMX Adverse events: 29.4% TMP/SMX (nausea, anorexia, headache diarrhea, headache, myalgia, pruritus)
Henry 2002 (USA)	Women 34.8 (12.6) years	$N = 444$ Ciprofloxacin 500 mg, orally	$N = 447$ Ciprofloxacin 250 mg, orally	–	Clinical and bacteriological remission, relapse and adverse events	Clinical remission: 95.5% ciprofloxacin 500, 92.7% ciprofloxacin 250 mg. Bacteriological remission: 94.5% ciprofloxacin 500 mg, 93.7% ciprofloxacin 250 mg

Table 1 (continued)

Author/year	Sex/age	Intervention 1 N/dose	Comparator 1 N/dose	Comparator 2 N/dose	Outcomes	Findings
		once per day for 3 days	twice per day for 3 days			Adverse events: 10% ciprofloxacin 500 mg, 9% ciprofloxacin 250 mg (headache, nausea, diarrhea, vaginitis)
Hooton 1991 (USA)	Women 25 years	$N = 48$ Ofloxacin 400 mg, orally single dose	$N = 49$ Ofloxacin 200 mg, orally, once per day for 3 days	$N = 47$ TMP/SMX 160/800 mg, orally twice per day	Clinical and bacteriological remission, relapse and adverse events	Clinical remission: 81% ofloxacin 400 mg, 89% ofloxacin 200 mg, 98% TMP/SMX ($p = 0.03$) Relapse: 16% ofloxacin 400 mg, 7% ofloxacin 200 mg, 0% TMP/SMX Adverse events: 30% ofloxacin 400 mg, 32% ofloxacin 200 mg, 40% TMP/SMX (gastrointestinal and central nervous system, vaginitis, rash)
Iravani 1993 (USA)	Women 28.3(15) years	$N = 316$ Fleroxacin 400 mg, orally single dose	$N = 321$ Fleroxacin 200 mg, orally, once per day for 7 days	$N = 324$ Ciprofloxacin 250 mg, orally, twice per day for 7 days	Clinical and bacteriological remission, relapse, resistance and adverse events	Bacteriological remission: 88% fleroxacin 400 mg, 96% fleroxacin 200 mg, 96% ciprofloxacin Adverse events: 30% fleroxacin 400 mg, 31% fleroxacin 200 mg, 26% ciprofloxacin (nausea, headache, dizziness, insomnia, anxiety, rash)
Iravani 1995 (USA)	Women 27.5 (8.3) years	$N = 149$ Ciprofloxacin 100 mg, orally twice per day for 3 days	$N = 155$ Ciprofloxacin 250 mg, orally twice per day for 3 days	$N = 152$ Ciprofloxacin 250 mg, orally twice per day for 7 days	Clinical and bacteriological remission, resistance, relapse and adverse events	Bacteriological remission: 93% ciprofloxacin 100 mg, 90% ciprofloxacin 250 mg, 93% ciprofloxacin 250 mg for 7 days Adverse events: 23% ciprofloxacin 100 mg, 26% ciprofloxacin 250 mg, 23% ciprofloxacin 250 mg for 7 days (abdominal pain, nausea, headache, dizziness, vaginal moniliasis)
Iravani 1999 (USA)	Women 34.5 (6.6) years	$N = 168$ Ciprofloxacin 100 mg, orally twice per day for 3 days	$N = 174$ TMP/SMX 160/800 mg, orally twice per day for 7 days	$N = 179$ Nitrofurantoin 100 mg, orally twice per day for 7 days	Clinical and bacteriological remission, resistance, relapse and adverse events	Clinical remission: 95% ciprofloxacin, 95% TMP/SMX, 93% nitrofurantoin Bacteriological remission: 88% ciprofloxacin, 93% TMP/SMX, 86% nitrofurantoin Resistance: 12% ciprofloxacin, 6% TMP/SMX, 13% nitrofurantoin Adverse events: 29% ciprofloxacin, 38% TMP/SMX, 34% nitrofurantoin ($p = 0.093$) (nausea, headache, vaginitis)
McCarty 1999 (USA)	Women 30.8 (14.4) years	$N = 229$ Ciprofloxacin 100 mg, orally twice per day for 3 days	$N = 228$ Ofloxacin 200 mg, orally twice per day for 3 days	$N = 231$ TMP/SMX 160/800 mg, orally twice per day for 3 days	Clinical and bacteriological remission, resistance, relapse and adverse events	Clinical remission: 93% ciprofloxacin, 96% ofloxacin, 95% TMP/SMX Bacteriological remission: 94% ciprofloxacin, 97% ofloxacin, 93% TMP/SMX Relapse: 11% ciprofloxacin, 13% ofloxacin, 16% TMP/SMX Adverse events: 8% ciprofloxacin, 9% ofloxacin, 13% TMP/SMX (headache, nausea, central nervous system, insomnia, rash)
Naber 2004 (Germany)	Women 43.3 (16.1) years	$N = 371$ Gatifloxacin 400 mg, orally for 3 days	N = 371 Gatifloxacin 200 mg, orally once per day for 7 days	$N = 360$ Ciprofloxacin 250 mg, orally twice per day for 7 days	Clinical and bacteriological remission, resistance, relapse and adverse events	Bacteriological remission: 90.3% gatifloxacin 400 mg, 90.6% gatifloxacin 200 mg, 88.3% ciprofloxacin Resistance: 7.7% gatifloxacin 400 mg, 8.6% gatifloxacin 200 mg, 7.4% ciprofloxacin Relapse: 5.4% gatifloxacin 400 mg, 3.8% gatifloxacin 200 mg, 3.2% ciprofloxacin

Table 1 (continued)

Author/year	Sex/age	Intervention 1 N/dose	Comparator 1 N/dose	Comparator 2 N/dose	Outcomes	Findings
						Adverse events: 17.3% gatifloxacin 400 mg, 19.1% gatifloxacin 200 mg, 14.4% ciprofloxacin (nausea, headache, dizziness, diarrhea)
Pfau 1993 (Israel)	Women 27–64 years	*N* = 59 Ofloxacin 400 mg, orally single dose	*N* = 57 Norfloxacin 800 mg, orally single dose	*N* = 58 Ciprofloxacin 500 mg, orally single dose	Clinical remission and resistance	Clinical remission: 97% ofloxacin, 95.6% ciprofloxacin, 88% norfloxacin
Richard 1998 (USA)	Women 31 (20) years	*N* = 198 Levofloxacin 250 mg, orally once per day for 3 days	*N* = 196 Ofloxacin 200 mg, orally twice per day for 3 days	–	Clinical and bacteriological remission and adverse events	Clinical remission: 98.1% levofloxacin, 97% ofloxacin Bacteriological remission: 96.3% levofloxacin, 93.6% ofloxacin Adverse events: 3.4% levofloxacin, 7.5% ofloxacin (insomnia, headache, vomiting, abdominal and chest pain, sweating)
Richard 2002 (USA)	Women 18–71 years	*N* = 436 Gatifloxacin 400 mg, orally one dose	*N* = 443 Gatifloxacin 200 mg, orally once per day for 3 days	*N* = 244 Ciprofloxacin 100 mg, orally twice per day for 3 days	Clinical and bacteriological remission, relapse and adverse events	Clinical remission: 93% gatifloxacin 400 mg, 95% gatifloxacin 200 mg, 93% ciprofloxacin Bacteriological remission: 90% gatifloxacin 400 mg, 95% gatifloxacin 200 mg, 89% ciprofloxacin Adverse events: 5% gatifloxacin 400 mg, 1% gatifloxacin 200 mg, 2% ciprofloxacin (nausea, headache, diarrhea, vaginitis)

Ages are presented as means (standard deviations). N: number of participants

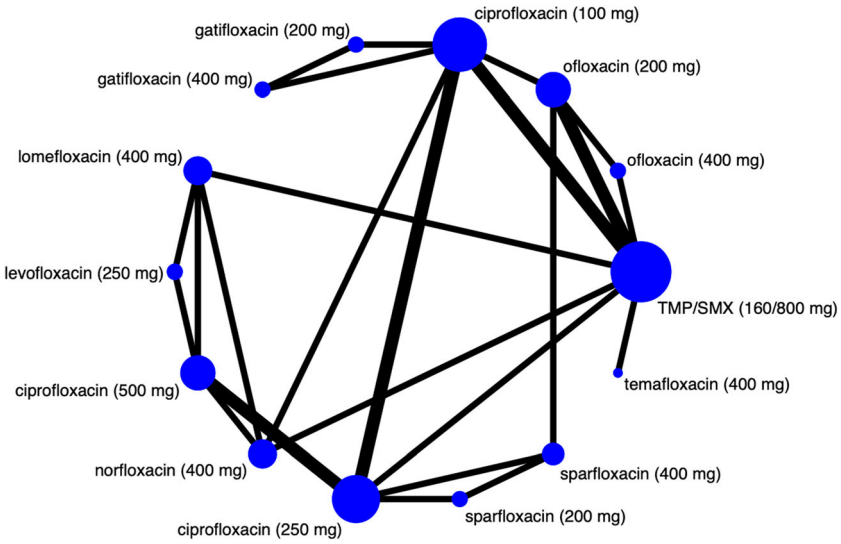

Fig. 3 Network plot of uncomplicated UTI in premenopausal women

with an IF of $p = 0.25$, which did not show a significant difference between quinolones and TMP/SMX (Supplementary Table 3) [19, 23, 25, 26, 28, 29]. The ranking curve plots reported that the antibiotic associated with a lower risk of developing any adverse events was ciprofloxacin (100 and 250 mg), with an area under the curve of 26.4% to 29.5% and 35.1%, respectively (Table 2).

Relapse and resistance

For relapse, a meta-analysis was performed with the same trials with a nonsignificant IF ($p = 0.74$), in which we observed that ciprofloxacin (250 and 500 mg) was the antibiotic with the highest probability of relapse (77.7% to 80.4%, respectively) (Table 2, Supplementary Table 4). For the resistance rate, we could not perform the analysis because of the heterogeneity among the studies.

Finally, we compared the cumulative probabilities for each outcome to identify the overall efficacy and safety of the quinolone regimens and observed that 200 mg ofloxacin once daily was the quinolone with better probability of clinical and bacteriological remission, with a low frequency of relapse rate but with the highest frequency of adverse events compared with the other types of quinolones (Fig. 5).

(2) Treatment duration ≤ 3 days in postmenopausal women

Clinical remission

Of the seven analyzed trials [21, 22, 28, 30–32, 34] involving six different types of interventions (ciprofloxacin 100, 250 and 500 mg; levofloxacin 250 mg; norfloxacin 400 mg; ofloxacin 200 mg) (for details, please see Table 1), we

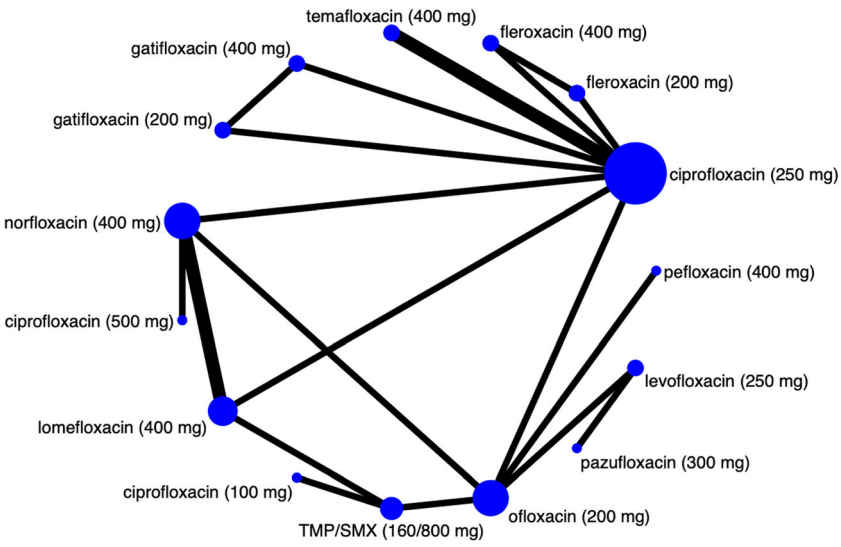

Fig. 4 Network plot of uncomplicated UTI in postmenopausal women

Table 2 Table of cumulative probabilities of each quinolone in pre-menopausal women (≤ 3 days of treatment)

Quinolones (dosage)	Surface under ranking curve (%)			
	Clinical remission	Bacteriological remission	Adverse effects	Relapse
Ciprofloxacin (100 mg)	28.4	65.5	26.4	60.2
Ciprofloxacin (250 mg)	58.5	32.1	29.5	80.4
Ciprofloxacin (500 mg)	34.6	31.5	53.3	77.7
Norfloxacin (400 mg)	55.5	32.3	35.1	61.9
Ofloxacin (200 mg)	57.5	63.2	82.8	35.5
Ofloxacin (400 mg)	47.7	61.3	43.5	31.0

generated a network plot that reported a nonsignificant IF ($p = 0.50$).

Overall, we did not observe a significant difference between regimens when comparing either quinolones or TMP/SMX, with the exception of ofloxacin 200 mg (RR 1.16; 95% CI 1.02 to 1.32; $p = 0.023$). In the ranking curve plots, the antibiotics most likely to yield a clinical remission of UTIs were ciprofloxacin 500 mg and ofloxacin 200 mg, with an area under the ranking curve of 82.6% and 75.3%, respectively (Table 3, Supplementary Table 5).

Bacteriological remission

We performed a network plot with a nonsignificant IF ($p = 0.68$). Ciprofloxacin 250 mg was the only quinolone that demonstrated a significant difference compared with TMP/SMX (RR 1.10; 95% CI 1.0 to 1.21; $p = 0.04$). The area under the curve plots indicated that ciprofloxacin 100 mg was most likely to yield bacteriological remission, with a cumulative probability of 79.6% (Table 3, Supplementary Table 6).

Adverse events

The adverse events in these trials were the same as those reported in studies with premenopausal women. The related network meta-analysis included seven trials [20–22, 28, 29, 32, 34] with an IF of $p = 0.76$ (for details, see Table 1). Treatments associated with a lower risk of any adverse event were ofloxacin 200 mg (RR 0.56; 95% CI 0.36 to 0.88; $p = 0.013$) and levofloxacin 250 mg (RR 0.52; 95% CI 0.31 to 0.87; $p = 0.013$) compared with TMP/SMX. The cumulative curve plots reported that 250 mg levofloxacin was the quinolone with the smallest area under the curve to develop adverse events (28.6%) (Table 3, Supplementary Table 7).

Relapse and resistance

We could not perform an analysis of relapse and resistance because of the heterogeneity among the studies. However, for resistance, we generated the network with five trials [20, 22, 28, 29, 32] with an IF of $p = 0.44$. The treatment associated with a lower risk of resistance was ofloxacin 200 mg, with an

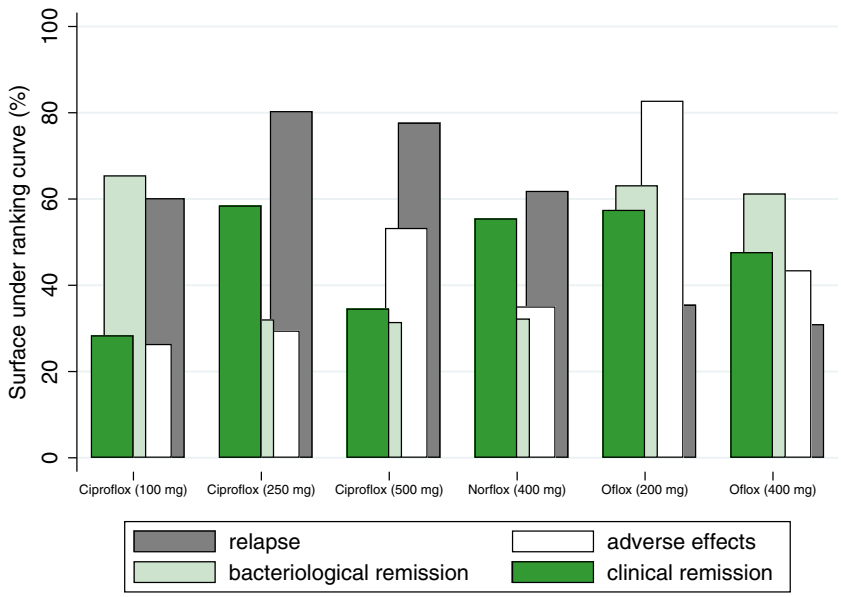

Fig. 5 Graph of the surface under ranking curve of quinolones for treatment of uUTI in pre-menopausal women

Table 3 Table of cumulative probabilities of each quinolone in post-menopausal women (≤ 3 days of treatment)

Quinolones (dosage)	Surface under ranking curve (%)			
	Clinical remission	Bacteriological remission	Adverse effects	Resistance
Ciprofloxacin (100 mg)	16.7	79.6	58.9	59.6
Ciprofloxacin (250 mg)	73.0	44.0	63.2	85.0
Ciprofloxacin (500 mg)	82.6	43.9	49.5	58.0
Levofloxacin (250 mg)	53.7	38.4	28.6	–
Norfloxacin (400 mg)	34.0	55.1	33.0	73.9
Ofloxacin (200 mg)	75.3	29.2	38.0	0.8

area under the curve of 0.8% (Table 3, Supplementary Table 8).

Subsequently, we compared the area under the ranking curves for each outcome and observed that ciprofloxacin 500 mg was the quinolone with the best probabilities of clinical remission but with a high frequency of adverse events compared with the other types of quinolones (Fig. 6).

With respect to the analysis of the duration of treatment > 3 days, we could not generate a network in any outcome because of the heterogeneity among the studies.

Discussion

UTIs are considered infections with low morbidity and mortality and are commonly caused by gram-negative bacilli; their treatment depends mostly on the type of bacteria. Currently, the Infectious Diseases Society of America recommends the use of TMP/SMX as a first-line antibiotic; however, resistance rates > 20% have been reported in some countries worldwide, encouraging a search for alternative drugs active in second-line regimens.

Although quinolones share similar characteristics, some of them are associated with specific adverse events, making it unsafe to assume that they are interchangeable. Therefore, we conducted this network meta-analysis to hierarchize the quinolones and to identify the best treatment for patients with uUTIs.

This review included 18 trials with 7 different treatment regimens (ciprofloxacin 100, 250 and 500 mg; levofloxacin 250 mg; norfloxacin 400 mg; ofloxacin 200 and 400 mg) with administration times from 1 to 14 days administered to 8765 women aged 18 to 80 years. In this study, we observed that despite diversity among the studies, only 14% had a high risk of bias due the lack of detailed descriptions for random sequence generation and high dropout rates.

Overall, regarding the clinical and bacteriological remission rates, we did not observe significant differences for any type of quinolone compared with TMP/SMX. Nonetheless, when comparing the efficacy and safety among quinolones, we observed that there were apparently disagreements in our

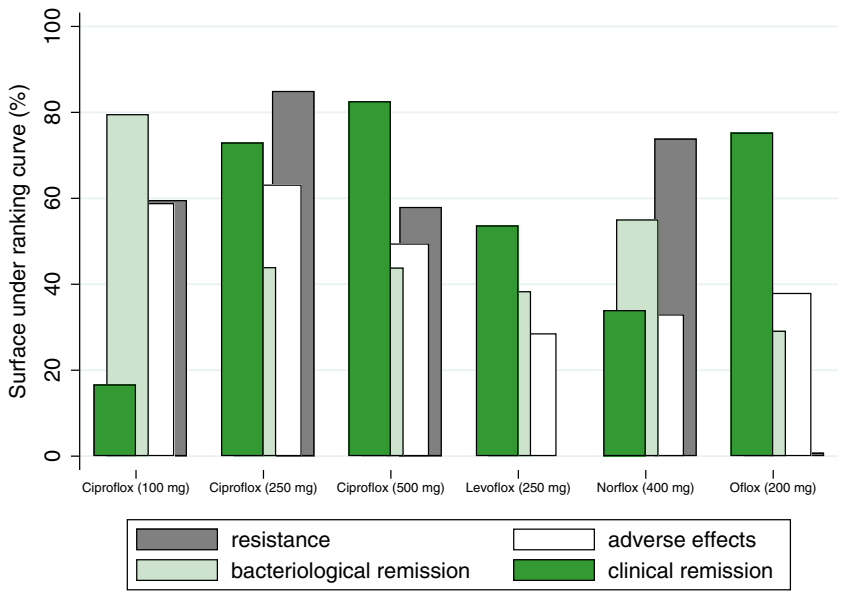

Fig. 6 Graph of the surface under ranking curve of quinolones for treatment of uUTI in post-menopausal women

findings since a higher dose of ciprofloxacin appeared to decrease the rate of bacteriological remission, while the use of higher doses of ofloxacin seemed to reduce the frequency of adverse events. This could be due to the high dropout rate of trial participants (> 30%) and some trials not being included in all quantitative network analyses, which limits comparisons between studies.

However, despite the above limitations, we observed that ofloxacin 200 mg once daily not exceeding 3 days of therapy duration was the most effective quinolone regimen for clinical and bacteriological remission of uUTIs in premenopausal women, with a low probability of relapse compared with other types of quinolones; however, a high probability of developing adverse effects (mainly dizziness, nausea and vomiting) was reported for this regimen. Therefore, an alternative that could be used for the treatment of uUTIs is norfloxacin 400 mg twice daily, which has good effectiveness for clinical and bacteriological remission, with a higher relapse rate than ofloxacin, but with a low probability of adverse events.

Regarding postmenopausal women, ofloxacin 200 mg was found to yield the best probabilities of clinical remission and low resistance rates and adverse effects. Although ciprofloxacin 500 mg once daily showed the best probability of clinical remission, a high probability of resistance and of developing adverse effects was reported; therefore, it might not be the best choice for the treatment of uUTIs.

These findings coincide with the results obtained in the studies of Gupta, Sotomayor and Zalmanovici [8, 10, 11, 42] in the sense that they recommend the use of these quinolones for short periods as an alternative for the treatment of UTIs.

It is worth mentioning that although the cost of TMP/SMX is lower (US $2.12 per 100 tablet) than that of ofloxacin (US $4.97 per 100 tablet) worldwide, there are more people allergic to TMP/SMX (3 to 5%) than to ofloxacin (0.4 to 2%) [43–46]. We hence consider that these findings could be taken into account when building an appropriate treatment strategy for uUTIs, without the need to use the latest-generation quinolones, which, although they are more effective, also have a high risk of causing adverse events, which favors the abandonment of treatment and the increase in bacterial strains resistant to antibiotic treatment.

Limitations of the review: Due to the great diversity of interventions in the trials included in this review, and as a consequence of the use of the age of the participants, different doses and administration times, we had to reduce the heterogeneity existing through the generation of subgroups. However, this limited the analysis of those studies that analyzed treatment durations > 3 days.

It is worth mentioning that despite these limitations, we were able to perform the network meta-analyses for all results without substantial inconsistency. However, we suggest additional studies in which there is a dropout rate < 30% to improve the findings.

Implications for practice: The results of this study suggest that ofloxacin would be a good option in terms of efficacy and safety if a quinolone is to be selected for the treatment of uUTIs. However, it would be advisable to carry out new studies that incorporate evidence on treatment regimen durations > 3 days and cost analysis studies to assist in the selection of a particular quinolone.

Conclusions

In this study, we did not observe significant differences for any type of quinolone compared with TMP/SMX. Nonetheless, we observed that, compared with other quinolones, ofloxacin 200 mg once daily for treatment durations $\leq$ 3 days provides the highest clinical and bacteriological remission rates, with the lowest relapse and resistance rates for women with uUTIs, albeit at a high probability of adverse events such as dizziness, nausea and vomiting. We consider norfloxacin 400 mg twice daily to be an alternative for the treatment of uUTIs, as it has a low probability compared with other quinolones of leading to adverse events in pre- and postmenopausal women.

Additional trials with treatment regimen durations > 3 days and cost analysis studies to assist in the selection of a particular quinolone are recommended.

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E Ochoa-Hein contributed to the conceptualization, validation, investigation, editing, visualization, supervision, writing review and editing of this manuscript.

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Compliance with ethical standards

Conflict of interest All authors of this review declare that we have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Abbreviations *CI 95%,* 95% confidence intervals; *DNA,* deoxyribonucleic acid; *IF,* inconsistency factor; *MeSH,* Medical Subject Headings; *NMA,* network meta-analysis; *RR,* risk ratio; *SUCRA,* surface under the cumulative ranking curve; *TMP/SMX,* trimethoprim-sulfamethoxazole; *UTI,* urinary tract infection; *uUTI,* uncomplicated urinary tract infection

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