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

Alejandro G Gonzalez-Garay (✉ pegasso.100@hotmail.com)

Instituto Nacional de Pediatría <https://orcid.org/0000-0003-2342-8539>

Liliana Velasco-Hidalgo

Instituto Nacional de Pediatría

Eric Ochoa-Hein

Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran

Roberto Rivera-Luna

Instituto Nacional de Pediatría

Research article

Keywords: quinolones; urinary tract infection; network meta-analysis; therapy

Posted Date: August 2nd, 2019

DOI: <https://doi.org/10.21203/rs.2.12347/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at International Urogynecology Journal on February 24th, 2020. See the published version at <https://doi.org/10.1007/s00192-020-04255-y>.

Abstract

Background Uncomplicated urinary tract infection is considered an infection that occurs in healthy individuals who have a normal urinary tract, representing 5% of all annual medical visits. Several quinolones are available as second-line agents for treatment; however, we do not know which is the best antibiotic scheme for urinary tract infection; therefore, we conducted a network meta-analysis to hierarchize each quinolone according to its efficacy and safety. **Methods** MEDLINE, EMBASE and other databases were subjected to non-language-restricted searches up to 2018 for trials that included women treated with quinolones for uncomplicated urinary tract infection. Bias in the trials was assessed by two reviewers; the Cochrane Collaboration tool was used to analyze clinical and bacteriological remission, relapse, resistance, and adverse events. For direct comparisons, we obtained risk ratios and 95% confidence intervals by applying a fixed events model using Tau² and Q² tests to calculate the heterogeneity using trimethoprim/sulfamethoxazole as the common comparator across studies. For the network meta-analysis, we analyzed the indirect comparisons by Bucher's method. The results were summarized in a correlation matrix. **Results** We included 18 trials with 8765 women. For pre-menopausal women and treatment duration <3 days, norfloxacin and ofloxacin had a 57% of probability for achieving remission but with an 83% frequency of adverse events. For post-menopausal women, ciprofloxacin and ofloxacin were 82% more effective for remission with an 49% frequency of adverse events compared with other types of quinolones. **Conclusions** Compared with other quinolones, ofloxacin (200 mg) was more effective for remission, although with a high probability of adverse events; however, norfloxacin (400 mg) could be an alternative in treatment, due to its low probability of adverse events; even though additional trials are needed to confirm our findings, especially in treatment duration exceeds 3 days. PROSPERO registration CRD42015025886

Background

Urinary tract infection (UTI) is defined as the presence of symptoms due to infection of the urinary tract caused by pathogenic organisms, and it is often accompanied by leukocytes and inflammatory cytokines. If it affects the bladder (cystitis) and/or the urethra (urethritis), it is categorized as a low UTI; but if it also affects the kidneys (pyelonephritis), it is considered an upper UTI. [1,2]

Uncomplicated UTI (uUTI) is considered an infection that occurs in healthy individuals who have a normal urinary tract that has not been instrumented; on the other hand, complicated UTI (cUTI) occurs in hosts with immunocompromise, pregnancy or anatomical or functional abnormalities of the urinary tract. [1,2]

UTIs are regarded as infections with low morbidity and mortality in the community setting, but they have a high incidence, amounting to approximately 250 million cases annually at the global level and accounting for up to 5% of primary medical care visits. [2] In the United States alone, the National Epidemiological Surveillance System reported an incidence of 1,204,032 cases among individuals aged

25–44 years in 2006, mainly in women of reproductive age, which can progress to pyelonephritis if it does not receive adequate antibiotic treatment. [3–5]

This high incidence may be attributed in part to factors related to the age and sex of the patient: in pre-menopausal women, the recent use of a diaphragm, sexual activity and history of UTI in the last 12 months are frequent risk factors; whereas in post-menopausal women (> 65 years), the urinary incontinence, prolapse of pelvic organs and vaginal infections as a result of the change of the vaginal flora secondary to the decrease in estrogen levels; in elder men, diabetes mellitus, presence of prostatic hypertrophy, ureteral obstruction and invasive procedures of the urinary tract that alter the natural defense barriers are the most important risk factors [4,5,6]

Overall, the most frequent pathogens that cause uUTI 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, selection of antimicrobials for 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 scheme and associated complications. [4–7]

The Infectious Diseases Society of America guidelines have recommended the use of trimethoprim-sulfamethoxazole (TMP/SMX 160/800 mg twice for 3 days) and nitrofurantoin (100 mg twice for 5 days) as the empirical first-line agents for treatment of uUTI. [8] However, some low-income countries have reported resistance rates >20% for TMP/SMX, and the use of nitrofurantoin has shown poor effectiveness against *Proteus*, *Pseudomonas* and *Enterobacter* species. Consequently, researchers have tried to identify other line agents for treatment of uUTI.

The quinolones are a family of synthetic antibiotic agents that inhibit the activity of bacterial DNA gyrase and facilitate the fragmentation of genetic material. Although they are considered second-line agents, their efficacy is similar to that of empirical first-line agents if the etiologic agents remain susceptible, with the advantage of requiring short courses of treatment at a low cost. [9,10]

Some studies have analyzed the efficacy of the different types of quinolones compared with other quinolones or with TMP/SMX to identify the best antibiotic scheme for symptomatic remission of uUTI; however, the trials did not show no significant differences between the treatments, which has favored that sanitary personnel to prescribe the use of quinolones at convenience without taking into account their dose, the time of administration and adverse events, so it may be risky to assume that all quinolones are interchangeable for treating UTI. [11]

In order to test the comparative efficacy and safety of different types of quinolones against TMP/SMX, head to head trials would need to be conducted, although this would likely be an expensive and unlikely scenario. Fortunately, network meta-analysis allows simultaneous direct and indirect comparisons of events reported in multiple studies against each other; in the end, a ranking of interventions that facilitates decision making for sanitary personnel is generated, due to increased statistical power and precision of effect. [12,13]

Based on the aforementioned considerations, the present systematic review with network meta-analysis was carried out with the aim of analyzing the clinical and bacteriological efficacy, safety, relapse and resistance rates of ciprofloxacin and other types of quinolones compared with TMP/SMX in different clinical trials in order to rank them in order of best to worst for the treatment of uUTI. We believe this could help the healthcare staff with their decisions regarding treatment for patients with uUTI.

Methods

Search strategy

A reviewer (RRL) conducted a search of the following databases: CENTRAL (*The Cochrane Central Register of Controlled Trials 2018*), MEDLINE (PubMed up to 2018), EMBASE (Ovid up to 2018), LILACS, KoreaMed, and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (up to August 2018). 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 for 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 a quinolone compared with TMP/SMX (160/800 mg twice-daily) or against another quinolone in healthy adult women who had a normal urinary tract, had not been instrumented and were diagnosed with uUTI according to any of the following criteria: a) culture (>10,000 colony-forming units/ml); b) urinalysis (>20 leucocytes per field, >3 erythrocytes per field, and presence of nitrites); c) pyelonephritis; or d) the presence of bacteria in urine, positive results of Gram staining, and/or clinical symptoms (e.g., dysuria, urinary urgency, urinary frequency, or suprapubic pain). Studies published up to 2018 were included without language restriction.

The quinolones were adjusted in strata according to age (pre-menopausal versus post-menopausal), the dose and time of treatment (<3 days versus >3 days) and were compared with TMP/SMX (common comparator to generate the net) to evaluate the following outcomes: A) efficacy, according to symptom remission (clinical remission) and negative culture (bacteriological remission); B) safety, according to the frequency of any adverse events (e.g., gastrointestinal, allergic, genitourinary); and C) relapse and resistance rates.

A study was considered ineligible if the following occurred: the participants presented with immunosuppression, renal failure, chemotherapy, or pregnancy; prophylactic antibiotics or catheters were used; UTI was considered complicated (functional or structural abnormalities of the genitourinary tract);

or if the studies included drugs withdrawn by the FDA (sparfloxacin, lomefloxacin, gatifloxacin and temafloxacin). Crossover, quasi-experimental, non-inferiority, 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 as low, high or unclear for the following individual items: a) random sequence generation, b) allocation concealment, c) blinding of participants and personnel, d) incomplete data, and e) selective reporting of information. [12]

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

We presented an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram to show the process of trial selection (Figure 1) and the assessment of the risk of bias (Figure 2).

Data Extraction

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

Statistical analysis

Direct comparisons. For each pairwise comparison and each outcome, we obtained risk ratios (RRs) with 95% confidence intervals (CI 95%) as a measure of the association between the interventions, considering $RR < 1$ as a beneficial effect of the first treatment compared with the second treatment. Conventional meta-analyses were conducted using a fixed and random events 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 $> 50\%$. When we found heterogeneity, we attempted to determine the possible reasons for it by examining individual trials.

For the assessment of publication bias, we performed funnel plots to evaluate asymmetry and confirmed the findings using Egger’s test. [14]

For all outcomes, we considered all participants assigned to four patient groups according to age (pre-menopausal and post-menopausal); to the duration of treatment (< 3 days and > 3 days) and conducted an analysis according to the intention to treat; in cases where this information was not reported, we contacted the study authors.

Indirect comparisons. Due to the fact that a network meta-analysis is a method of synthesizing information from studies with same outcomes but different interventions, it requires information of direct and indirect comparisons between interventions in order 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).

First, we calculated the heterogeneity in the direct comparisons; when it was not important, we generated the net and analyzed transitivity considering study design and characteristics of participants, among other factors. Then 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 test; if all loops in the net had consistency, we performed a correlation matrix and obtained the Surface Under the Cumulative Ranking curve (SUCRA), which shows the cumulative probability of an intervention being among the best options, using STATA software v15.1. [13,15,16]

Results

Characteristics of the included studies

We identified 357 potential studies for inclusion; after screening the titles and/or abstracts and removing duplicates, 25 randomized controlled trials remained eligible. In this study, we included 18 trials with 8,765 participants [17–34]; 9 of these trials compared three arms [17,26–33] (Figure 1, Table 1).

The remaining 7 studies failed to comply with the selection criteria for this review and were excluded due: A) the comparator was fosfomycin or amoxicillin or cephalosporin and B) were trials of equivalence. [35–41]

Figure 1. Study flow diagram.

Table 1. Characteristics of the included studies.

We identified 7 different quinolone-based treatment schemes (ciprofloxacin 100, 250, and 500 mg; levofloxacin 250 mg; norfloxacin 400 mg; ofloxacin 200 and 400 mg). We created four patient groups according to age (pre-menopausal versus post-menopausal); to the duration of treatment (<3 days and >3 days) and generated a network meta-analysis using a common comparator (TMP/SMX 160/800 mg) for all groups.

Most of the trials included (86%) were considered to have either a low or unclear risk of bias; in the latter case, the lack of detailed descriptions for random sequence generation, allocation concealment and blinding of participants and personnel was frequent. We noted that 61% of trials had dropout rates >30%. In addition, 97% properly reported selective bias and other potential sources of bias (Figure 2). For details see Additional figure 1.

Figure 2. Summary graph of the risk of bias.

Of the 18 trials included in this review, ten trials (3187 participants) involved pre-menopausal women [17,18,22,24–26,28a,28b,30,33] (Figure 3) of which six studies (2445 participants) involved treatment duration <3 days [18,22,25,26,28b,30] and four trials (742 participants) involved treatment durations >3 days [17,24,,28a,33].

Figure 3. Network plot of uncomplicated UTI in pre-menopausal women

On the other hand, ten studies (5578 participants) involved post-menopausal women [19–21,23,27,28c,29,31,32,34] (Figure 4), of which eight trials (4356 participants) involved treatment durations <3 days [19–21,28c,29,31,32,34] and two studies (1222 participants) involved treatment durations >3 days [23,27].

Figure 4. Network plot of uncomplicated UTI in post-menopausal women

A) Treatment duration <3 days in pre-menopausal women.

Clinical remission

Of the six analyzed trials [18,22,25,26,28,30] involving 6 different types of interventions (ciprofloxacin 100, 250, and 500 mg; norfloxacin 400 mg; ofloxacin 200 and 400 mg), we calculated both direct and indirect comparisons with relative risks (RRs) and 95% Confidence Intervals (CIs) (Additional file 1) and generated a network plot with the cumulative ranking curve plots. The inconsistency factor (IF) was not significant ($p = 0.84$).

Overall, we did not observe a significant difference between schemes comparing different types of quinolones or TMP/SMX. The overall ranking curve plots the antibiotics most likely to yield a clinical remission of UTI were ofloxacin 200 mg and norfloxacin 400 mg with the best surface under ranking curve of 57.5% and 55.5% respectively (Table 2).

Bacteriological remission

The meta-analysis was performed with six trials and we generated a network plot with a non-significant IF ($p = 0.95$). This analysis did not show significant difference between either quinolones or TMP/SMX. The cumulative curve plots indicated that ofloxacin 200 mg was most likely to yield a bacteriological remission with a surface under curve of 63.2% (Table 2, Additional file 2).

Adverse events

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

[18,22,25,26,28,29]. In Additional file 3, we present the associated comparisons and a network plot with an IF of $p = 0.25$.

With exception of ciprofloxacin 100 and 250 mg (RR 0.74; 95% CI 0.58 to 0.94; $p = 0.015$ and RR 0.74; 95% CI 0.58 to 0.96; $p = 0.026$ respectively), the meta-analysis did not show a significant difference between schemes comparing different types of quinolones or TMP/SMX. The ranking curve plots reported that the antibiotics associated with a lower risk of develop any adverse events were ciprofloxacin (100 and 250 mg) and norfloxacin 400 mg with a surface under curve of 26.4% to 29.5% and 35.1%, respectively (Table 2).

Relapse and resistance

For relapse, the meta-analysis was performed with the same six trials with a non-significant IF ($p = 0.74$), in which we observed that ciprofloxacin (250 and 500 mg) and norfloxacin 400 mg were the antibiotics with most probability of relapse (77.7% to 80.4% and 61.9% respectively) (Table 2, Additional file 4). On the other hand, only three trials [22,28b,30] reported the resistance rate; so, we could not perform the analysis due to the inconsistency between the studies.

Finally, we compared the cumulative probabilities for each outcome to identify the overall efficacy and safety of the quinolone schemes, and we observed that ciprofloxacin 250 mg was the quinolone with best probability of clinical remission with low frequency of adverse events but with high relapse rate; on the other hand, ofloxacin 200 mg showed a high probability of clinical and bacteriological remission with low relapse rate, but it had the highest frequency of adverse events compared to other types of quinolones in pre-menopausal women treated for uUTI (Figure 5).

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

B) Treatment duration <3 days in post-menopausal women.

Clinical remission

Of the seven analyzed trials [20,21,28c,29,31,32,34] involving 6 different types of interventions (ciprofloxacin 100, 250, and 500 mg; levofloxacin 250 mg; norfloxacin 400 mg; and ofloxacin 200 mg), we generated a network plot which reported a non-significant IF ($p = 0.50$).

Overall, we did not observe a significant difference between schemes 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 UTI were ciprofloxacin 500 mg and ofloxacin 200 mg with a surface under ranking curve of 82.6% and 75.3% respectively. (Table 3, Additional file 5).

Bacteriological remission

We performed a meta-analysis with seven trials. We generated a network plot with a non-significant IF ($p = 0.68$). Ciprofloxacin 200 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 surface under curve plots indicated that ciprofloxacin 100 mg and norfloxacin 400 mg were most likely to yield a bacteriological remission with a cumulative probability of 79.6% and 55.1% respectively (Table 3, Additional file 6).

Adverse events

The adverse events in these trials were same as those reported in studies with pre-menopausal. The related network meta-analysis included seven trials [19,20,21,28c,29,32,34] which reported an IF of $p = 0.76$. Treatments associated with a lower risk of any adverse events were ofloxacin 200 mg (RR 0.56; 95% CI 0.36 to 0.88; $p = 0.013$) and levofloxacin 250 (RR 0.52; 95% CI 0.31 to 0.87; $p = 0.013$) compared with TMP/SMX. The cumulative curve plots reported that levofloxacin 250 mg and norfloxacin 500 mg were the quinolones with the smallest surface under curve to develop adverse events (28.6% and 33% respectively) (Table 3, Additional file 7).

Relapse and resistance

We only identified three trials [21,28c,29] with four interventions (ciprofloxacin 100, 250, 500 mg; and norfloxacin 400 mg) that reported the relapse rate; so, we could not perform the analysis due to the inconsistency between the studies. However, for resistance, we generated the meta-analysis with five trials [19,21,28c,29,32] with an IF of $p = 0.44$ and without difference between either quinolones or TMP/SMX. The treatment associated with a lower risk of resistance was ofloxacin 200 mg with a surface under curve of 0.8% (Table 3, Additional file 8).

Subsequently, we compared the surface under ranking curves for each outcome and we observed that ciprofloxacin 500 mg was the quinolone with best probabilities of clinical and bacteriological remission but with high frequency of adverse events and relapse rate; on the other hand, ofloxacin 200 mg showed a high probability of clinical remission with low resistance rate and frequency of adverse events compared to other types of quinolones in post-menopausal women treated for uncomplicated UTI (Figure 6).

With respect for the analysis of the duration of treatment >3 days, we could not generate a network in any age group and any outcome due to the inconsistency between the studies.

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

Discussion

Urinary tract infections are considered infections with low morbidity and mortality in the context of the community, but there is a high incidence in women of reproductive age. These are caused by a wide variety of pathogens and treatment depends mostly on the type of germ.

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 schemes.

Although quinolones share similar characteristics, some of them are associated with particular adverse events, so it may be risky to assume that they are interchangeable. Therefore, we conducted this network meta-analysis to analyze the efficacy and safety of different types of quinolones to hierarchize them and to identify the best treatment for patients with uUTI.

This review included 18 clinical trials with 8,765 participants in which 7 different types of quinolones were compared; we observed that a great variety of antibiotic schemes existed according to the dose and duration of use, so we divided the analysis into four groups (< 3 vs > 3 days of treatment and pre-menopausal vs post-menopausal women) according to the recommended duration use of TMP/SMX, as established by the Infectious Diseases Society of America, in order to reduce the heterogeneity between comparisons.

Overall, we observed that despite diversity among studies, 86% had a low or unclear risk of bias; as a result, we were able to generate network plots with transitivity and consistency. However, the lack of available evidence regarding schemes of treatment duration >3 days suggests a need for additional studies with adequate methodological quality in order to improve overall findings.

Overall, regarding the clinical and bacteriological remission rates, we did not observe significant differences for any type of quinolone compared with TMP/SMX (at a dose of 160/800 mg twice daily). Nonetheless, we observed that ofloxacin (at a dose of 200 mg) not exceeding 3 days of therapy duration was the most effective quinolones for clinical and bacteriological remission of uUTI in pre-menopausal women (57% and 63% respectively) with a low probability of relapse (35%) compared to other types of quinolones; however, it showed poor safety, as it reported an 83% probability of developing adverse effects such as dizziness, nausea, vomiting, and genital itching. So, we observed that an alternative that could be used for the treatment of uUTI is norfloxacin 400 mg, which has an effectiveness of 55% and 32% for clinical and bacteriological remission respectively, with a higher relapse rate than ofloxacin, but with a 35% probability of developing adverse events.

Regarding post-menopausal women, ofloxacin (at a dose of 200 mg) was found to yield the relatively best probabilities of clinical remission (75%) and low resistance rate and adverse effects (0.8% and 38% respectively); although it is worth mentioning that despite the fact that ciprofloxacin (at a dose of 500 mg) showed the best probability of clinical remission (80%), it reported a high probability of resistance (58%) and of developing adverse effects (50%).

These findings coincide with the findings of Gupta and Sotomayor [8,42] and the systematic review of Zalmanovici [10] in the sense that the use of these quinolones for short periods of time as an alternative for the treatment of uUTI would be recommended based on their effectiveness, albeit at a higher rate of adverse events. [8,11]

With the above, should make us think that the treatment schemes used by most physicians may not be the most appropriate; since although the last generation quinolones have a greater effectiveness for clinical and bacteriological cure, they also have a high risk of developing adverse events, which favors the abandonment of treatment and as a consequence the increase of bacterial strains resistant to antibiotic treatment.

We believe these findings could be taken into account when building a treatment strategy with second-line antibiotics in regions where resistance rates to TMP/SMX, pivmecillinam or nitrofurantoin monohydrate are high in the community. Nonetheless, performing new studies that also include cost analysis will be needed to emit a formal recommendation regarding a prioritized selection of quinolones. [8,11]

Notwithstanding current guideline recommendations, empirical first-line antibiotics for treatment of uUTI are not without disadvantages. Some first-line antibiotics would be prohibitively expensive for patients living in low-income countries (e.g., pivmecillinam and amoxicillin-clavulanate cost, on average, US\$124 and US\$132, respectively), others have high resistance rates (e.g., above 20% for TMP/SMX in some regions of the world) and others are not available in some countries (e.g., pivmecillinam). Quinolones remain useful because they are efficacious in settings with low resistance rates, have a relatively low cost (US\$28–40), and are available in many countries. According to a recently published model, first- and second-line agents for empirical treatment of uUTI seem to be comparable regarding total costs. However, relapse was not accounted for, and it is therefore currently unknown if any particular therapeutic regimen is economically advantageous. [43]

One mayor drawback of quinolones is their higher resistance rates as compared with the empirical first-line options, thereby relegating their use for directed therapy in most instances. However, the treating physician must keep in mind that prevalence of resistance cutoff points above which a particular antibiotic is no longer recommended is merely based on expert opinion and is probabilistic in nature (i.e., antibiotics with lower than 20% resistance rates in the community have a higher probability of being effective if the therapeutic decision is based solely on chance, leaving aside individual risk factors for resistance). Clinical decision making should also take into account other factors that may influence selection of a particular antibiotic, even though not depicted yet by evidence and not considered in current guidelines (such as adherence issues, costs and individual risk factors for resistance to an antibiotic). A one-size-fits-all approach is to be discouraged when selecting first- or second-line agents for treatment of uUTI. [44]

Furthermore, a word of caution must be exercised when attempting to infer community resistance rates from urinary cultures, since these are typically ordered for patients with complicated UTI for whom

factors associated with treatment failure are anticipated (e.g., resistant bacteria). It is currently unknown if reported resistance rates appropriately represent the community population with uUTI. [44]

Selection of first-line antibiotics assuming guideline recommendations is meant to provide an empiric treatment with the highest probability of being effective and well tolerated. Directed antibiotic therapy based upon culture results would be desirable, although this is not common practice in the ambulatory setting due to costs and delays in treatment initiation. Taking into account that uUTIs cannot be considered a medical emergency by definition, starting directed therapy once the results of etiologic agents and resistance profiles are known would be helpful to counter the rising resistance rates observed for all antibiotics.

We consider that a valuable contribution of this study is the suggestion of an orderly selection of quinolones based on efficacy, safety and resistance rates that will aid in clinical decision making when facing patients who are candidates for treatment with such antibiotics and to prevent abandonment of treatment, which favors the development of strains resistant to antibiotic therapy.

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 treatment of upper or lower uUTI. It would be advisable to carry out new studies that incorporate cost analyses to aid in the selection of particular quinolones.

Conclusions

In this study we did not observe significant differences for any type of quinolone compared with TMP/SMX. Nonetheless, we observed that, as compared with other quinolones, ofloxacin (at a dose of 200 mg) for treatment durations <3 days provides the highest clinical and bacteriological remission rates with lowest relapse and resistance rates for women with uUTI, albeit at a high probability of adverse events such as dizziness, nausea, vomiting, and genital itching. We consider that an alternative could be used for the treatment of uUTI is norfloxacin (at a dose of 400 mg) which has a low probability of developing adverse events in pre and post-menopausal women.

Additional trials with better methodological quality are needed for confirmation of these findings and improved data accuracy.

List Of Abbreviations

UTI: Urinary tract infection

uUTI: Uncomplicated urinary tract infection

cUTI: Complicated urinary tract infection

TMP/SMX: Trimethoprim-sulfamethoxazole

ICTRP: International Clinical Trials Registry Platform

RR: Risk ratio

CI 95%: 95% Confidence intervals

SUCRA: Surface under the cumulative ranking curve

Prospero: International Prospective Register of Systematic Reviews

Declarations

This review was registered and approved in the International Prospective Register of Systematic Reviews (CRD42015025886).

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors of 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.

Funding: This work was supported in the acquisition of articles by Senosiain Laboratories S. A. to conduct of this review. No authors have conflict of interest, no disclosures and received no compensation from Senosiain Laboratories S. A. for their work in the writing of this manuscript.

Authors' contributions: AGG, LVH, EOH and RRL contributed to the study design. RRL and AGG conducted the literature search. AGG, EOH and LVH participated in data collection, analysis and interpretation of results, and writing review, and approval of the manuscript.

Acknowledgements: We would like to thank Editage (www.editage.com) and Deborah H. S. for English language editing.

References

- [1] Rafalsky V, Andreeva I, Rjabkova E. Quinolones for uncomplicated acute cystitis in women (Review). Cochrane Database Syst Rev, 2006; 3: CD003597; doi: 10.1002/14651858.CD003597.pub2
- [2] Booth J, Mullen A, Thomson D, Johnstone C, Galbraith S, Bryson S, et al. Antibiotic treatment of urinary tract infection by community pharmacists: a cross-sectional study. Br J Gen Pract 2013; 63: e244–9; doi:

- [3] Alós J. Epidemiology and etiology of urinary tract infections in the community. Antimicrobial susceptibility of the main pathogens and clinical significance of resistance. *Enferm infecc Microbiol Clin* 2005; 23(4): 3–8; PMID: 16854352
- [4] Gupta K, Trautner B. Infecciones de vías urinarias, pielonefritis y prostatitis. In Longo D, Kasper D, Jameson J, Fauci A, Hauser S, Loscalzo J. *Harrison Principios de Medicina Interna*. Mc GrawHill Mexico, Ed 18, vol 2: 2387–95.
- [5] Orenstein R, Wong E. Urinary Tract Infections in Adults. *Am Fam Physician* 1999; 59(5): 1225–34; PMID: 10088877
- [6] Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2010, Issue 10. Art. No.: CD007182; doi: 10.1002/14651858.CD007182.pub2
- [7] Urinary Tract Infection In: Litwin MS, Saigal CS, editors. *Urologic Diseases in America*. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2012; NIH Publication No. 1265: 365–404.
- [8] Gupta K, Hooton T, Naber K, Wullt B, Colgan R, Miller L, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; 52(5): e103–20; doi: 10.1093/cid/ciq257
- [9] Andersson MI, MacGowan AP. Development of the quinolones. *J Antimicrob Chemother* 2003; 51(S1): 1–11; doi: 10.1093/jac/dkg212
- [10] Heeb S, Fletcher M, Chhabra S, Diggle S, Williams P, Cámara M. Quinolones: from antibiotics to autoinducers. *FEMS Microbiol Lett* 2011; 35(2): 247–74; doi: 10.1111/j.1574-6976.2010.00247.x
- [11] Henry N, Schultz H, Grubbs N, Muller S, Ilstrup D, Wilson W. Comparison of ciprofloxacin and co-trimoxazole in the treatment of uncomplicated urinary tract infection in women. *J Antimicrob Chemother* 1986; 18(Suppl D): 103–6; doi: 10.1093/jac/18.supplement_d.103
- [12] Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. London: The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org; doi:10.1002/9780470712184
- [13] Salanti G, Ades A, Lonnidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163–71; doi: 10.1016/j.jclinepi.2010.03.016

- [14] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7(3): 177–88; doi: 10.1016/0197–2456(86)90046–2
- [15] Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006; 101(474): 447–59; doi: 10.1198/016214505000001302
- [16] Habor RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006; 25(20): 3443–57; doi: 10.1002/sim.2380
- [17] Arredondo J, Figueroa R, Rosas A, Jáuregui A, Corral M, Costo A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *J Antimicrob Chemother* 2004; 54: 840–3; doi: 10.1093/jac/dkh414
- [18] Auquer F, Cordon F, Gorina E, Caballero J, Adalid C, Batlle J; Urinary Tract Infection Study Group. Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. *Clin Microbiol Infect*, 2002; 8: 50–4; doi: 10.1046/j.1198–743x.2001.00359.x
- [19] Basista MP. Randomized study to evaluate efficacy and safety of ofloxacin vs. trimethoprim and sulfamethoxazole in treatment of uncomplicated urinary tract infection. *Urology* 1997; 37(3): 21–7; doi: 10.1016/0090–4295(91)80092-L
- [20] Cox CE, Serfer HS, Mena HR, Briefer C, Childs SJ, Gordon SF, et al. Ofloxacin versus trimethoprim/sulfamethoxazole in the treatment of uncomplicated urinary tract infection. *Clin Ther* 1992; 14(3): 446–57; PMID: 1638586
- [21] Fourcroy J, Berner B, Chiang Y, Cramer M, Rowe L, Shore N. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. *Antimicrob Agents Chemother* 2005; 49(10): 4137–43; doi: 10.1128/AAC.49.10.4137–4143.2005
- [22] Garlando F, Rietiker S, Täuber M, Flepp M, Meier B, Lüthy R. Single-dose ciprofloxacin at 100 versus 250 mg for treatment of uncomplicated urinary tract infections in women. *Antimicrob Agents Chemother* 1987; 31: 354–56; doi: 10.1128/aac.31.2.354
- [23] Gomolin I, Siami P, Reuning J, Haverstock D, Heyd A, the Oral Suspension Study Group. Efficacy and safety of ciprofloxacin oral suspension versus trimethoprim-sulfamethoxazole oral suspension for treatment of older women with acute urinary tract infection. *J Am Geriatr Soc* 2001; 49: 1606–13; doi: 10.1046/j.1532–5415.2001.t01–1–49268.x
- [24] Henry N, Schultz H, Grubbs N, Muller S, Ilstrup D, Wilson W. Comparison of ciprofloxacin and co-trimoxazole in the treatment of uncomplicated urinary tract infection in women. *J Antimicrob Chemother* 1986; 18: 103–6; doi: 10.1093/jac/18.supplement_d.103

- [25] Henry D, Bettis R, Riffer E, Haverstock D, Kowalsky S, Manning K, et al. Comparison of once-daily extended-release Ciprofloxacin and conventional twice-daily Ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. *Clin Therap* 2002; 24: 2088–104; doi: 10.1016/S0149-2918(02)80099-6
- [26] Hooton T, Johnson C, Winter C, Kuwamura L, Rogers M, Roberts P, et al. Single-dose and three-day regimens of Ofloxacin versus Trimethoprim- Sulfamethoxazole for acute cystitis in women. *Antimicrob Agents Chemother* 1991; 35: 1479–83; doi: 10.1128/aac.35.7.1479
- [27] Iravani A. Multicenter study of single-dose and multiple-dose Fleroxacin versus Ciprofloxacin in the treatment of uncomplicated urinary tract infections. *Am J Med* 1993; 94(3A): 89S–96S; PMID: 8452189
- [28] Iravani A, Tice A, McCarty J, Sikes D, Nolen T, Gallis H, et al. Short-course Ciprofloxacin treatment of acute uncomplicated urinary tract infection in women: The minimum effective dose. *Arch Int Med*, 1995; 155: 485–94; doi: 10.1001/archinte.1995.00430050061007
- [29] Iravani A, Klimberg I, Briefer C, Munera C, Kowalsky S, Echols R, Urinary tract infection group. A trial comparing low-dose, short-course ciprofloxacin and standard 7 days therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother* 1999; 43(A): 67–75; doi: 10.1093/jac/43.suppl_1.67
- [30] McCarty J, Richard G, Huck W, Tucker R, Tosiello R, Shan M, et al.; the Ciprofloxacin urinary tract infection group. A randomized trial of short course Ciprofloxacin, Ofloxacin, or Trimethoprim/Sulfamethoxazole for the treatment of acute urinary tract infection in women. *Am J Med* 1999; 106: 292–9; doi: 10.1016/s0002-9343(99)00026-1
- [31] Naber K, Allin D, Clarysse L, Haworth D, James I, Raini C, Scheneider H, Wall A, Weitz P, Hopkins G, Ankel-Fuchs D. Gatifloxacin 400 mg as a single shot or 200 mg once daily for 3 days is as effective as ciprofloxacin 250 mg twice daily for the treatment of patients with uncomplicated urinary tract infections. *Int J Antimicrob Agents* 2004; 23: 596–605; doi: 10.1016/j.ijantimicag.2003.12.017
- [32] Pfau A, Sacks T. Single dose quinolone treatment in acute uncomplicated urinary tract infection in women. *J Urol*, 1993; 149: 532–4; doi: 10.1016/s0022-5347(17)36137-2
- [33] Richard G, Klimberg I, Fowler C, Callery-D´Amico C, Kim S. Levofloxacin versus Ciprofloxacin versus Lomefloxacin in acute pyelonephritis. *Urology*, 1998; 51: 51–5; doi: 10.1016/S0090-4295(98)00160-5
- [34] Richard G, DeAbate C, Rouff G, Corrado M, Fowler C, Morgan N. A double-blind, randomized trial of the efficacy and safety of short-course, once-daily Levofloxacin versus Ofloxacin twice daily in uncomplicated urinary tract infections. *Infect Dis Clin Pract (Baltim Md)* 1998; 9: 323–29
- [35] Ceran N, Mert D, Yuksel F, Erdem I, Adalati R, Ozyurek S, et al. A randomized comparative study of single-dose fosfomycin and 5-day ciprofloxacin in female patients with uncomplicated lower urinary tract

infections. *J Infect Chemother*, 2010; 16: 424–30; doi: 10.1007/s10156–010–0079-z

[36] García G, Fava E, Rubio V, Luna J. Infecciones urinarias no complicadas: comparación de una pauta con norfloxacin durante 7 días frente a norfloxacin durante 3 días. *Aten Primaria* 2002; 29(1): 148–9.

[37] Paparo S, De Rosa F, Marangi M, Polimeni A, Bertucci P, Terzaroli P, et al. Ciprofloxacin versus amoxicillin/clavulanic acid in the treatment of urinary tract infection. *Med J Infect Parasit Dis*, 1994; 9: 111–3.

[38] Piipo T, Pitkajarvi T, Salo SA. Three-day versus seven days treatment with norfloxacin in acute cystitis. *Curr Ther Res Clin Exp* 1990; 47(4): 644–53.

[39] Trienekens T, London N, Houben A, Dejong R, Stobberingh E. Treating acute urinary tract infections. An RCT of 3-day versus 7-day Norfloxacin. *Can Fam Physician* 1993; 39: 514–8; PMID: PMC2379759

[40] Vogel T, Verreault R, Gourdeau M. Antibiotic treatment for uncomplicated urinary tract infections in the elderly: A comparison of 3-day and 7-day courses. *CMAJ* 2004; 170: 469–73; PMID: 14970093

[41] Wagenlehner F, Umeh O, Steenbergen J, Yuan G, Daroviche R. Ceftolozane tazobactam compared with levofloxacin in the treatment of complicated urinary tract infections, including pyelonephritis: a randomized, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet*, 2015; 385: 1949–56; doi: 10.1016/S0140–6736(14)62220–0

[42] Sotomayor M, Ponce de León A, Guzmán J, Rosas E, Rodríguez F, González A, et al. Recomendaciones de expertos mexicanos en el tratamiento de las infecciones del tracto urinario en pacientes adultos, embarazadas y niños. *Rev Mex Urol* 2015; 75(2): 1–46.

[43] Rodríguez-Burbano L, Pio De La Hoz F, Leal-Castro A. Costo de infección de vías urinarias asociada a sonda vesical en un hospital universitario de Santander. *Rev Salud Publica* 2016; 1(18): 104–16; doi: 10.15446/rsap.v18n1.36905

[44] Fasugba O, Gardner A, Mitchell B, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect Dis* 2015; 15: 545; doi: 10.1186/s12879–015–1282–4

Tables

Table 1. Characteristics of the included studies.

Author / year	Sex / age	Intervention 1 N / dose	Comparator 1 N / dose	Comparator 2 N / dose	Outcomes
Arredondo 2004 [16] (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
Auquer 2002 [17] (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
Basista 1991 [18] (USA)	Women and men 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
Cox 1992 [19] (USA)	Women 18-80 years Men 37-46 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
Fourcroy 2005 [20] (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
Garlando 1987 [21] (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, relapse and adverse events
Gomolin 2001 [22] (Multicenter USA)	Women 80.5 (8.9)	N = 129 ciprofloxacin 250 mg,	N = 132 TMP/SMX 160/800 mg,	-	Clinical and bacteriological remission, relapse,

	years	orally, twice per day for 10 days	orally, twice per day for 10 days		resistance, and adverse events
Henry 1986 [23] (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
Henry 2002 [24] (USA)	Women 34.8 (12.6) years	N = 444 ciprofloxacin 500 mg, orally once per day for 3 days	N = 447 ciprofloxacin 250 mg, orally twice per day for 3 days	-	Clinical and bacteriological remission, relapse and adverse events
Hooton 1991 [25] (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
Iravani 1993 [26] (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
Iravani 1995 [27abc] (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
Iravani 1999 [28] (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
McCarty 1999 [29] (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

Naber 2004 [30] (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
Pfau 1993 [31] (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
Richard 1998 [32] (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
Richard 1998b [33] (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

Ages are presented as means (standard deviations).

N: number of participants

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

Quinolones (dosage)	Clinical remission	Surface under ranking curve (%)		
		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

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

Quinolones (dosage)	Clinical remission	Surface under ranking curve (%)		
		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

Supporting Information Legends

Additional figure 1: Summary graph of the risk of bias.

Additional file 1: Clinical remission for uUTI with <3 days of treatment in pre-menopausal women.

Additional file 2: Bacteriological remission for uUTI with <3 days of treatment in pre-menopausal women.

Additional file 3: Adverse events for uUTI with <3 days of treatment in pre-menopausal women.

Additional file 4: Relapse for uUTI with <3 days of treatment in pre-menopausal women.

Additional file 5: Clinical remission for uUTI with <3 days of treatment in post-menopausal women.

Additional file 6: Bacteriological remission for uUTI with <3 days of treatment in in post-menopausal women.

Additional file 7: Adverse events for uUTI with <3 days of treatment in in post-menopausal women.

Additional file 8: Resistance for uUTI with <3 days of treatment in in post-menopausal women.

Figures

Figure 1

Study flow diagram.

Figure 2

Summary graph of the risk of bias.

Figure 3

Network plot of uncomplicated UTI in pre-menopausal women

Figure 4

Network plot of uncomplicated UTI in post-menopausal women A) Treatment duration <3 days in pre-menopausal women.

Figure 5

Graph of surface under ranking curve of quinolones for treatment of uUTI in pre-menopausal women. B) Treatment duration <3 days in post-menopausal women.

Figure 6

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.xlsx](#)
- [supplement2.xlsx](#)
- [supplement3.xlsx](#)
- [supplement4.xlsx](#)
- [supplement5.doc](#)
- [supplement6.xlsx](#)
- [supplement7.xlsx](#)
- [supplement8.xlsx](#)
- [supplement8.xlsx](#)
- [supplement10.eps](#)