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REVIEW ARTICLE

Efficacy and safety of ciprofloxacin treatment in urinary tract infections (UTIs) in adults: a systematic review with meta-analysis

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Abstract

Objectives and Design: *A systematic review with meta-analysis of randomized controlled trials (RCT) on the efficacy and safety of ciprofloxacin in the treatment of acute or complicated urinary tract infections in adults. Primary outcomes were bacteriological eradication, clinical cure, bacterial resistance, and adverse event rates.* **Results:** *Initially, 111 RCTs were identified. We excluded 81 studies due to low quality methodology. An analysis of the remaining RCTs identified therapeutic equivalence of ciprofloxacin against other antimicrobials in terms of bacterial eradication and clinical cure at the end of treatment and in subsequent stages. The percentage of bacterial resistance was similar in both groups, while the percentage of related adverse events was significantly lower in the groups treated with ciprofloxacin.* **Conclusions:** *We conclude that ciprofloxacin is a safe and effective therapeutic alternative for the treatment of acute or complicated urinary tract infections in adults.* (Gac Med Mex. 2015;151:210-28)

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Introduction

Urinary tract infections (UTIs) (upper urinary pathogenic bacteria levels higher than 100,000 colony-forming units per urine ml [CFU/ml], with or without associated symptoms) are one of the most common infectious diseases in all age groups and are among the medical conditions that most frequently require outpatient management. A global annual incidence of 250 million cases has been estimated, with significant direct and indirect costs[1]. The distinction between complicated and uncomplicated UTI is highly important due to implications related, among other aspects, to pre- and post-treatment assessment, type and duration of selected antimicrobial treatments and the length of urinary tract functionality and integrity assessment[2-4]. Organisms more commonly responsible for UTIs are gram-negative bacteria of the *Enterobacteriaceae* group*; Escherichia coli* is responsible for 80% of UTIs, followed by *Staphilococcus saprophyticus,* particularly in young women[5]. From the therapeutic point of view, one of the first meta-analysis intended to assess the effectiveness of antimicrobial treatment for UTIs in patients younger than 65 years of age was published in 2004. The use of antibiotics during the active phase of treatment was shown to significantly reduce the risk of bacterial recurrence by 79% (risk ratio [RR]: 0.21 [0.13-0.34]; p = 0.00001) and the risk of clinical recurrence by 85% (RR: 0.15 [0.08-0.28]; p = 0.00001), without significant differences between groups being observed

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after treatment conclusion. With regard to adverse events, the antibiotic-treated group had 58% more serious adverse events, although the difference between groups was not significant (RR: 1.6 [0.47-5.3]; p = non-significant [NS])[6]. A second systematic review was published in 2005, where optimal duration of antimicrobial therapy for the treatment of IVUs in non-pregnant woman from 18 to 65 years of age was assessed; 33 randomized controlled trials (RCTs) were included, with a total of 9,605 women. The short (3 days) was compared with the long treatment regimen (5 to 10 days). Overall, short-term failure was no different between both groups (RR: 1.06 [0.88-1.28]; p = 0.52), and no differences were observed when trials using the same antibiotics in both arms (RR: 1.15 [0.95-1.39]; p = NS) and those using different antibiotics (RR: 0.90 [0.62-1.29]; p = NS] were separately analyzed[7]. A third systematic review comparing different antibiotic routes of administration was published in 2007; 15 RCTs with different types of antimicrobials and treatment durations, most of them conducted in non-pregnant women, were included. The rates of clinical cure and reinfection were shown not to be significantly different between groups (RR: 1.01 [0.94-1.1] and RR: 0.76 [0.30-1.90]) with the use of "switch" therapy with initial intramuscular (IM) or intravenous (IV) administration followed by oral administration versus continuous IM or IV therapy[8]. With regard to theatment in subjects older than 65 years or in populations in special situations, two systematic reviews were identified as far as December 2009. The first was published in 2002 and included 15 RCTs with a total of 1,644 patients; it concluded that persistent UTI was less persistent in patients who received treatment for 3-6 days (RR: 2.01 [1.05-3.54]: p = 0.03), although this effect was not maintained after 2 weeks' follow-up (RR: 1.18 [0.59-2.3]. Patients treated with short regimens (< 7 days) showed higher risk of persistent UTI in the 2-week follow-up (RR: 1.93 [1.01-3.7]; p = 0.047), although not in the long-term (RR: 1.28 [0.89-1.84])[10]. The second review, without a meta-analysis, published in 2006 and conducted in extended care facilities residents, concluded that antibiotics were useful in reducing the rate of UTIs in these patients[9]. Currently known factors that have to be considered for the selection of UTI treatments include the agent's antimicrobial activity (broad or reduced), pharmacokinetic characteristics that enable their use for longer intervals, prevalence of uropathogens local resistence, antimicrobial urinary levels optimal duration, effect on fecal and vaginal flora, the potential for the development of unfavorable side-effects and treatment costs[11-13]. Antimicrobials with proven efficacy in the management of UTIs include co-trimoxazole (trimethoprim/sulfamethoxazole), quinolones (including fluoroquinolones) and fosfomycin, although the increase in co-trimoxazole resistance has reduced its therapeutic efficacy and, consequently, its use[14-17]. Since 1977, quinolones have become the cornerstone of treatment for different serious bacterial infections. These are nalidixic acid-related antibacterial structures, with excellent bioavailability, adequate tissue penetration and relatively reduced presence of adverse events. They have been used mainly in the treatment of UTIs and prostatitis, although there is also evidence of their use in enteral bacterial infections, biliary tree infections, sexually transmitted diseases and neutropenic immunosuppressed host prophylaxis. Of all quinolones, the most succesful and most widely used compound is with no doubt ciprofloxacin, which was patented in 1983 and approved for use in the USA by the Food and Drug Administration (FDA) in 1987. With regard to the use of ciprofloxacin for the management of UTIs, a significant number of RCTs have been conducted assessing the safety, efficacy and tolerability of this quinolone since 1986[23,127], but no systematic review with meta-analysis thoroughly assessing its efficacy and safety in the treatment of UTIs in adults has been published to this moment.

Methods

All published RCTs that had compared, in one of their treatment arms, ciprofloxacin against other antimicrobial in patients older than 18 years of age with positive urine culture (> 10^5 UFC/ml) regardless of the presence of acute cystitis (dysuria, urinary urgency, urinary frequency or suprapubic pain), allowing to clearly identify the presence or not of risk factors for the development of UTIs (indwelling or intermittent urinary catheters, obstructive uropathy, vesicoureteral reflux and other urological abnormalities) were selected, which later gave us opportunity to perform stratified analyses in patients with acute UTIs (non-complicated) or UTIs in patients with risk factors; additionally, efficacy, safety or tolerability of ciprofloxacin should have been clearly reported, regardless of the dose, route of administration and treatment duration. Bacteriological erradication at the end of treatment, persistence of bacterial erradication the days after treatment termination, presence of clinical cure the days after treatment termination, the rate of bacterial resistances and the frequency of related adverse events were considered the outcome measures. Two of the authors of this review independently identified articles published in English and Spanish. The consulted databases were: The Cochrane Central Register of Controlled Trials (CENTRAL) at The Cocharane Linrary;

Medline, using the highly sensitive search strategy developed by The Cocharane Collaboration for RCTs identification[130], and Embase, using the search strategy adapted by The Cochrane Collaboration for the search of RCTs in this database[131]. Specific MeSH descriptors used in this search were the following: (urinary tract infections[MH] OR UTI*[TIAB] OPR acute cystitis[TIAB] OR cystitis[MH] OR Escherichia coli Infections[MH] AND Quinolone[MH] OR Anti-Infective Agents, Urinary[MH] OR Quinolon*[TIAB] OR Fluoroquinolon*[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]). Additionally, a search for evidence was performed in Lilacs (from 1980 to 2010), in Artemisa (from 1999 to 2005) and in grey literature obtained through manual search or enquiry via e-mail. Evidence review was conducted in a blinded and independent fashion by three authors of this review who, after carefully analyzing each article, disregarded those considered not relevant for the purposes of the review. In case of disagreements between reviewers, agreement was reached by applying the panel of the Delphi method. Allocation schemes were classified as adequate (randomization methods that didn't allow for the investigator or the patient to know or influence on patient allocation), unclear (not sufficient information available to reach a judgement) or inadequate (description of randomization methods as non-opaque envelopes or presence of information allowing for a biased assignment of the study subject to some group in particular). Statistical analysis of the results was conducted using the STATA 11.0 statistical package for Mac, considering the sub-routines for the development of meta-analyses. For dichotomous outcomes (e.g., bacteriological erradication vs. no erradication), the results were expressed as the RR with a 95% confidence interval (95% CI), whereas for continuous measuring scales, data were expressed through the weighted mean difference (WMD). In the cases where primary exploration allowed for a heterogeneity value (I^2) higher than 60% to be identified, the decision was made to analyze the results using a random effects model (inverse of the variance). Statistical heterogeneity was explored using Egger's graphs, and publication bias was assessed using a funnel plot.

Results

One-hundred and eleven randomized controlled trials were identified and entirely reviewed; 81 articles were disregarded in the first evaluation for the reasons described in table 1 and 30 articles were selected for further analysis and for the development of the meta-analysis[20-130] (Tables 2, 3, 4 and 5). The analysis of relevant evidence allowed for therapeutical evidence of ciprofloxacin equivalence with the other antibiotics used as comparators to be identified in terms of becteriological erradication and clinical cure at the end of treatment (RR: 1.01 [0.99-1.03]; p = NS and RR: 0.99 [0.98-1.01]; p = NS, respectively), as well as in bacteriological erradication and clinical cure maintenance in stages following treatment finalization (RR: 1.03 [1.0-1.07]; p = 0.06 and RR: 0.99-1.0]; p = NS, respectively). The percentage of bacterial resistances was also similar in both groups (RR: 1.01 [0.80-1.27]; p = NS), while the percentage of observed adverse events was significantly lower in the groups of patients treated with ciprofloxacin (RR: 0.82 [0.75-0.91]; p = 0.0001) (Figs. 1 to 6). When the analysis of identified evidence in cases of UTIs in subjects with risk factors was conducted, therapeutic equivalence was observed between ciprofloxacin and the rest of antibiotics used as comparators with regard to bacteriological erradication and clinical cure at the end of treatment (RR: 1.0 [0.96-1.04]; p = NS and RR: 0.98 [0.96-1.01]; p = NS, respectively), as well as with bacteriological erradication and clinical cure maintenance in stages subsequent to treatment finalization (RR: 1.0 [0.94-1.05]; p = NS and RR: 0.97 [0.93-1.02]; p = NS, respectively). The percentage of bacterial resistances was also similar between groups (RR: 1.06 [0.78-1.4]; p = NS), whereas the percentage of observed adverse events was significantly lower in the groups of patients treated with ciprofloxacin (RR: 0.8 [0.67-0.96]; p = 0.01) (Figs. 7 to 12). When the analysis of evidence identified in acute UTIs cases (non-complicated) was performed, therapeutic equivalence was observed between ciprofloxacin and the other antibiotics used as comparators with regard to bacteriological erradication and clinical cure by the end of treatment (RR: 1.01 [0.99-1.04]; p = NS and RR: 1.0 [0.98-1.02]; p = NS, respectively). A discrete therapeutic superiority of ciprofloxacin was observed in the maintenance of bacteriological erradication in stages subsequent to treatment finalization (RR: 1.08 [1.01-1.16]; p = 0.01), whereas clinical cure maintenance was similar between groups (RR: 0.99 [0.97-1.02]; p = NS). The percentage of bacterial resistances was similar between groups (RR: 0.97 [0.67-1.3]; p = NS), whereas the percentage of observed adverse events was significantly lower in the groups op patients treated with ciprofloxacin (RR: 0.88 [0.81-0.96]; p = 0.003) (Figs. 13 to 18).

Table 1. Description of excluded trials

Authors	Reason for exclusion
Giamarellou rt al.[129]	Experience with ciprofloxacin *in vitro*
Gonzalez et al.[128], McCue et al.[81], Rao et al.[71]	Ciprofloxacin pharmacokinetics in healthy volunteers
Garlando et al.[126], Raz et al.[112], Karachalios et al.[107]	Comparison of different doses of ciprofloxacin
Kosmidis et al.[123]	Fleroxacin in UTI with no comparator
Shearman et al.[122], Hall et al.[77], Lukkarinen et al.[72]	Ciprofloxacin in prostatectomy prophylaxis
Cox [113]	Ciprofloxacin in transurethral surgery prophylaxis
Fass et al.[120], Gallis et al.[118], Levine et al.[119], Peacock et al.[117], Quintero-Perez et al.[115], Sifuentes-Osornio et al.[114], Villavicencio et al.[116], Paladino et al.[103]	Ciprofloxacin vs. ceftazidime for the tratment of non-urinary serious infections
Boyko et al.[109]	Amoxicillin vs. TMP in UTIs
Brouwer et al.[108]	Ciprofloxacin in vaginal hysterectomy
Van Poppel et al.[111]	Ciprofloxacin in transurethral maneuvers prophylaxis
Wolfhagen et al.[110]	Fleroxacin at 200 or 400
Iravani[102]	Efficacy of the use of temafloxacin
Lew et al.[105]	Ciprofloxacin for infection prophylaxis in subjects undergoing bone marrow transplantation
Bailey et al.[99]	Ciprofloxacin in pyelonephritis
Hibberd et al.[95]	TMP vs. ciprofloxacin in renal transplantation prophylaxis
Kalager et al.[101]	Ciprofloxacin vs. tobramycin + cefuroxime in serious infections
Vander der Wall et al.[97]	Prophylaxis for urinary catheter-associated infections
Childs[90], Pittman et al.[91], Pummer[89]	Fleroxacin vs. norfloxacin in complicated or uncomplicated UTIs
Cox[87]	Fleroxacin vs ceftazidime
Naber et al.[88]	Fleroxacin vs. ofloxacin in complicated UTIs
Whitby et al.[85]	Fleroxacin vs. amoxicillin
Biering-Sorensen et al.[84]	UTI prophylaxis in bone marrow injuries
Darouiche et al.[82]	Urodynamic studies prophylaxis
Pfau et al.[83]	Post-coital quinolone prophylaxis in recurrent UTIs
Gasser et al.[75]	Fleroxacin in transurethral surgery
Bierkens et al.[73]	Prophylaxis in lithotripsy
Lukkarinen et al.[79]	Antibiotic prophylaxis in transurethral prostatectomy
Moyses Neto et al.[69]	Prophylaxis in renal transplantation
Hsieh et al.[67]	Ciprofloxacin in cirrhosis
Kapoor et al.[65]	Prophylaxis in transrectal biopsy
Naber et al.[66]	Bactericidal activity of fleroxacin and pefloxacin in healthy volunteers
Tsugawa et al.[64]	Prophylaxis in urethrocystoscopy
Viitanen et al.[68]	Fleroxacin in transuterhral prostatectomy
Eickhoff et al.[58]	Ciprofloxacin in epididymitis

Continues

Table 1. Description of excluded trials (continued)

Authors	Reasons for exclusion
Mombelli et al.[63]	Oral ciprofloxacin vs. IV ciproploxacin for pyelonephritis
Naber et al.[56]	IV ciprofloxacin vs. oral ciprofloxacin bactericidal activity
Price et al.[57]	Assessment of CPGs in the mangement of infections in SICUs
Tsukamoto et al.[60]	Ciprofloxacin vs. ciprofloxacin + macrolide
Aron et al.[54]	Prophylaxis in prostate biopsy
Christiano et al.[55]	Prophylaxis in endourologic surgery
Henry et al.[59]	Use of ciprofloxacin OD or BID
Naber et al.[48]	Lomefloxacin vs. ciprofloxacin for prostatitis
Richard et al.[51]	Single dose vs. three + quinolones
Ulleryd et al.[46]	Use of ciprofloxacin from 2 to 4 weeks
Wagenlehner et al.[45]	Bactericidal activity in healthy volunteers
Dow et al.[37]	3 vs. 14-day treatment in UTI in bifid spine
Sabbagh et al.[39]	3 vs. 7-day prophylaxis in transrectal biopsy
Talan et al.[44]	Extended-release formulation every 24 h vs. twice daily
Valdevenito et al.[41]	Prophilaxis in prostate transurethral resection
Vogel et al.[43]	3 vs. 7 days
Wazait et al.[36]	UTI risk reduction after catheter removal
Wells et al.[40]	Ertapenem vs. ceftriaxone
Gupta et al.[34]	Treatment of resistant *E. coli* after prostatectomy
Bin et al.[31]	Comparison of ceftazidime, impinemem and cefoperazone
Esposito et al.[28]	Prevention of catheter-associated infections
Kartal et al.[32]	Prevention of bacteriuria after urodynamic study
Mariappan et al.[30]	Prevention of post-nephrolithotomy UTI
Wagenlehner et al.[45]	Pharmacokinetics in healthy volunteers
Wagenlehner et al.[33]	Bioavailability in healthy volunteers
Marcelin-Jimenez et al.[27]	Bioavailability and phenazopyridine
Peterson et al.[25]	Pre-treatment identification and susceptibility
Cam et al.[21]	Infection prevention in transrectal biopsy
Dybowski et al.[24]	Microbiology in acute cystitis
Tuncel et al.[22]	Post-prostatic biopsy complications reduction
Mirone et al.[19]	Comparison of ciprofloxacin extended vs. immediate release
Pfefferkorn et al.[20]	Infection prevention at urinary catheter removal

Table 2. Characteristics of studies included in the meta-analysis (acute UTI)

Author	Year	Treatment 1	Treatment 2	n1	n2	Multi-center	Blinding	Randomized
Naber et al.[38]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 400 mg SD	360	371	Yes	Double	Yes
Naber et al.[38]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 300 mg BID x 3 days	360	371	Yes	Double	Yes
Auqer et al.[50]	2002	Ciprofloxacin 500 mg SD	Norfloxacin 400 mg BID x 3 days	164	161	Yes	Double	Yes
Gomolin et al.[52]	2001	Ciprofloxacin 250 mg BID x 10 days	TMP 160/800 mg BID x 10 days	86	86	Yes	Oben label	Yes
Iravani et al.[61]	1999	Ciprofloxacin 100 mg BID x 3 days	TMP 160/800 mg BID x 7 days	168	174	Yes	Double	Yes
Iravani et al.[61]	1999	Ciprofloxacin 100 mg BID x 3 days	Nitrofurantoin 100 mg BID x 7 days	168	179	Yes	Double	Yes
Henry et al.[59]	1999	Ciprofloxacin 250 mg BID x 7 days	Sparflox 400 mg SD	386	395	Yes	Double	Yes
Henry et al.[59]	1999	Ciprofloxacin 250 mg BID x 7 days	Sparflox 200 mg OD x 3 days	386	394	Yes	Double	Yes
McCarty et al.[62]	1999	Ciprofloxacin 100 mg BID x 3 days	Ofloxa 200 mg BID x 3 days	229	228	Yes	Double	Yes
McCarty et al.[62]	1999	Ciprofloxacin 100 mg BID x 3 days	TMP 160/800 mg BID x 3 days	229	231	Yes	Double	Yes
Iravani et al.[80]	1996	Ciprofloxacin 500 mg BID x 5 days	Norfloxacin 400 mg BID x 5 days	249	227	Yes	Double	Yes
Iravani et al.[86]	1993	Ciprofloxacin 250 mg BID x 7 days	Fleroxacin 200 mg OD x 7 days	204	180	Yes	Double	Yes
Pfau et al.[92]	1993	Ciprofloxacin 500 mg SD	Ofloxacin 400 mg SD	59	59	No	Double	Yes
Pfau et al.[92]	1993	Ciprofloxacin 500 mg SD	Norfloxacin 800 mg SD	58	57	No	Double	Yes
Henry et al.[128]	1986	Ciprofloxacin 250 mg BID x 10 days	TMP/SMX 160/800 mg TID x 10 days	31	34	No	Double	Yes

NR: not reported

Table 3. Characteristics of the studies included in the meta-analysis (acute UTI)

Authors	Bacteriological erradication at the end of treatment with ciprofloxacin (%)	Bact. err. End Control (%)	Clinical cure at the end of treatment with ciprofloxacin (%)	Clin. cure End Control (%)	Maintenance of erradication after treatment with ciprofoxacin (%)	Bact. err. Post-Control (%)	Maintenance of clinical cure after treatment with ciprofoxacin (%)	Clin. cure Post-Control (%)	Bacterial resistance at the end of treatment with ciprofloxacin (%)	Bact. resist. Control (%)
Naber et al.[38]	0.49	0.48	0.84	0.81	0.48	0.45	0.86	0.82	0.05	0.04
Naber et al.[38]	0.49	0.56	0.84	0.85	0.48	0.46	0.86	0.88	0.05	0.05
Auqer et al.[50]	0.91	0.92	0.75	0.71	NR	NR	0.91	0.95	NR	NR
Gomolin et al.[52]	0.93	1.84	0.97	0.85	NR	NR	0.97	0.88	0.04	0.13
Iravani et al.[61]	0.88	0.93	0.95	0.95	0.91	0.78	0.90	0.95	0.12	0.06
Iravani et al.[61]	0.88	0.77	0.95	0.93	0.91	0.82	0.90	0.93	0.12	0.13
Henry et al.[59]	0.97	0.93	0.89	0.93	0.92	0.81	0.81	0.79	NR	NR
Henry et al.[59]	0.97	0.92	0.89	0.90	0.92	0.89	0.81	0.81	NR	NR
McCarty et al.[62]	0.94	0.93	0.93	0.95	0.89	0.84	0.91	0.91	1.04	0.07
McCarty et al.[62]	0.94	0.97	0.93	0.96	0.89	0.87	0.91	0.89	0.04	0.03
Iravani et al.[80]	0.90	0.94	0.97	0.97	0.80	0.90	0.89	0.95	0.05	0.04
Iravani[86]	0.89	0.96	0.98	0.97	0.93	0.89	NR	NR	NR	NR
Pfau et al.[92]	0.97	0.97	NR	NR	NR	NR	NR	NR	NR	NR
Pfau et al.[92]	0.97	0.88	NR	NR	NR	NR	NR	NR	NR	NR
Henry et al.[127]	1.00	0.94	NR	NR	NR	NR	NR	NR	NR	NR

NR: not reported

Table 4. Characteristics of studies included in the meta-analysis (complicated UTI)

Author	Year	Treatment 1	Treatment 2	n1	n2	Multi-center	Blinding	Randomized
Peterson et al.[23]	2008	Ciprofloxacin 400 mg BID x 5 days	Levofloxacin 750 mg OD x 10 days	391	391	Yes	Double	Yes
Klausner et al.[26]	2007	Ciprofloxacin 400 mg BID x 5 days	Levofloxacin 750 mg OD x 3 days	165	146	Yes	Double	Yes
Carmignani et al.[35]	2005	Ciprofloxacin 500 mg BID x 5 days	Prulifloxacin 600 mg OD x 10 days	130	127	Yes	Double	Yes
Naber et al.[42]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 400 mg SD	188	189	Yes	Double	Yes
Naber et al.[42]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 300 mg BID x 3 days	188	181	Yes	Double	Yes
Cox et al.[49]	2002	Ciprofloxacin 500 mg BID x 5-7 days	Gatifloxacin 400 mg OD x 5-7 days	183	189	Yes	Double	Yes
Raz et al.[53]	2000	Ciprofloxacin 250 mg BID x 7 days	Ofloxacin 200 mg BID x 7 days	214	213	Yes	Double	Yes
Frankenschmidt et al.[70]	1997	Ciprofloxacin 250 mg BID x 7 days	Fleroxacin 200 mg OD x 7 days	67	66	Yes	Open label	Yes
Frankenschmidt et al.[70]	1997	Ciprofloxacin 500 mg BID x 7 days	Fleroxacin 400 mg OD x 7 days	103	108	Yes	Open label	Yes
Naber et al.[78]	1996	Ciprofloxacin 500 mg BID x 10 days	Sparfloxacin 100 mg OD x 10 days	264	252	Yes	Double	Yes
Whitby et al.[74]	1996	Ciprofloxacin 500 mg BID x 10 days	Fleroxacin 400 mg OD x 10 days	65	68	No	Double	Yes
Schaeffer et al.[94]	1992	Ciprofloxacin 500 mg BID x 5 days	Norfloxacin 400 mg BID x 5 days	35	37	No	Open label	Yes
Abbas et al.[121]	1989	Ciprofloxacin 350 mg BID x 5 days	Amoxicillin/ clavulanic acid 250/125 mg TID x 5 days	102	87	No	Open label	Yes
Pisani et al.[76]	1996	Ciprofloxacin 500 mg BID x 15 days	Lomefloxacin 400 mg OD x 15 days	139	155	Yes	Double	Yes
Grubbs et al.[93]	1993	Ciprofloxacin 250 mg BID x 10 days	TMP/SMX 160/800 mg BID x 10 days	103	100	No	Double	Yes
Cox et al.[98]	1992	Ciprofloxacin 500 mg BID x 14 days	Lomefloxacin 400 mg OD x 14 days	75	75	No	Single	Yes
Stein et al.[100]	1992	Ciprofloxacin 250 mg BID x 3 days	Temafloxacin 400 mg OD x 3 days	207	197	Yes	Double	Yes
Ploubiec et al.[124]	1988	Ciprofloxacin 250 mg BID x 3 days	Cefalexin 1 g BID x 3 days	30	30	No	Double	Yes

Table 5. Characteristics of the studies included in the meta-analysis (acute UTI)

Authors	Bacteriological erradication at the end of treatment with ciprofloxacin (%)	Bact. err. End Control (%)	Clinical cure at the end of treatment with ciprofloxacin (%)	Clin. cure End Control (%)	Maintenance of erradication after treatment with ciprofoxacin (%)	Bact. err. Post-Control (%)	Maintenance of clinical cure after treatment with ciprofoxacin (%)	Clin. cure Post-Control (%)	Bacterial resistance at the end of treatment with ciprofloxacin (%)	Bact. Resist. Control (%)
Peterson et al.[23]	0.87	0.88	0.87	0.91	0.89	0.86	0.88	0.86	0.06	0.05
Klausner et al.[26]	0.88	0.95	0.89	0.99	0.88	0.96	0.89	0.99	0.01	0.02
Carmignani et al.[35]	0.93	0.98	NR	NR	NR	NR	NR	NR	0.07	0.02
Naber et al.[42]	0.69	0.76	0.70	0.69	0.65	0.66	NR	NR	0.15	0.11
Naber et al.[42]	0.69	0.72	0.70	0.70	0.65	0.64	NR	NR	0.15	0.13
Cox[50]	0.83	0.92	0.93	0.92	0.63	0.75	0.74	0.84	0.11	0.05
Raz et al.[53]	0.90	0.87	0.97	0.97	0.79	0.76	0.88	0.87		
Frankenschmidt et al.[70]	0.61	0.48	0.76	0.66	NR	NR	NR	NR	0.11	0.21
Frankenschmidt et al.[70]	0.80	0.81	0.89	0.80	NR	NR	NR	NR	0.04	0.04
Naber et al.[78]	0.81	0.73	0.85	0.89	0.67	0.63	0.85	0.86	NR	NR
Whitby et al.[74]	0.86	0.88	0.91	0.95	0.65	0.69	0.81	0.81	NR	NR
Schaeffer et al.[94]	0.66	0.57	NR	NR	NR	NR	NR	NR	0.03	0.08
Abbas et al.[121]	0.92	0.66	NR	NR	NR	NR	NR	NR	0.02	0.07
Pisani et al.[76]	0.81	0.87	0.76	NR	NR	NR	NR	NR		
Grubbs et al.[93]	0.91	0.91			NR	NR	NR	NR	0.09	0.09
Cox et al.[98]	0.96	0.97	0.96	0.97	NR	NR	NR	NR	0.04	0.03
Stein et al.[100]	0.96	0.97	0.95	0.90	NR	NR	NR	NR	0.01	0.01
Ploubiec et al.[124]	1.00	0.80			NR	NR	NR	NR	0.00	0.17

NR: not reported

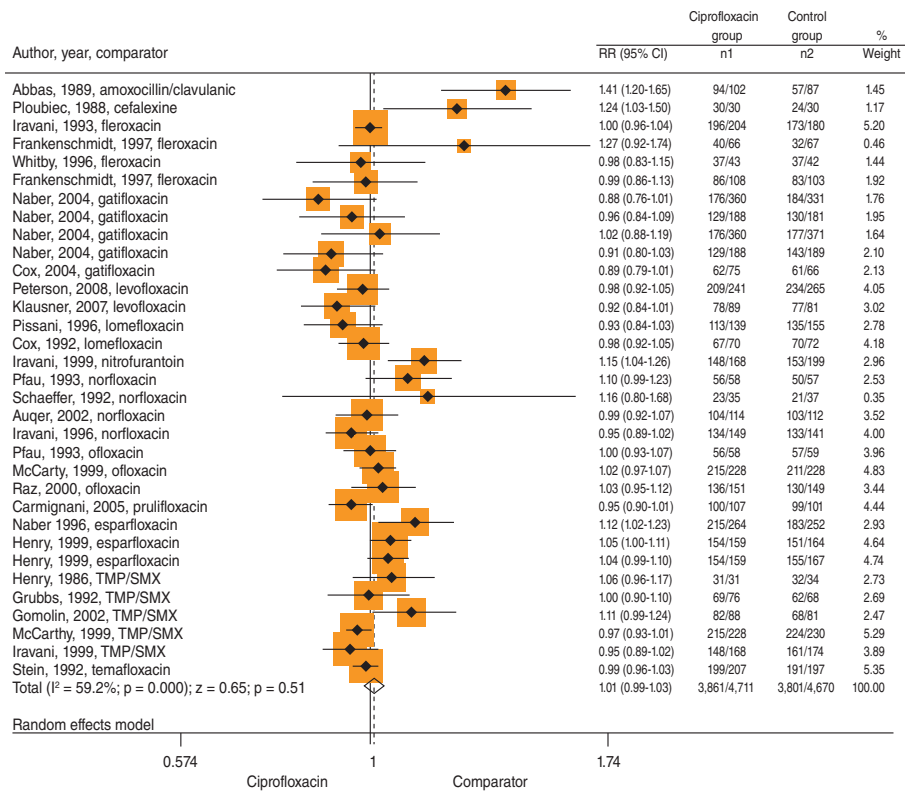

Figure 1. *Ciprofloxacin efficacy in adult UTIs: end-of-treatment bacteriological erradication (overall).*

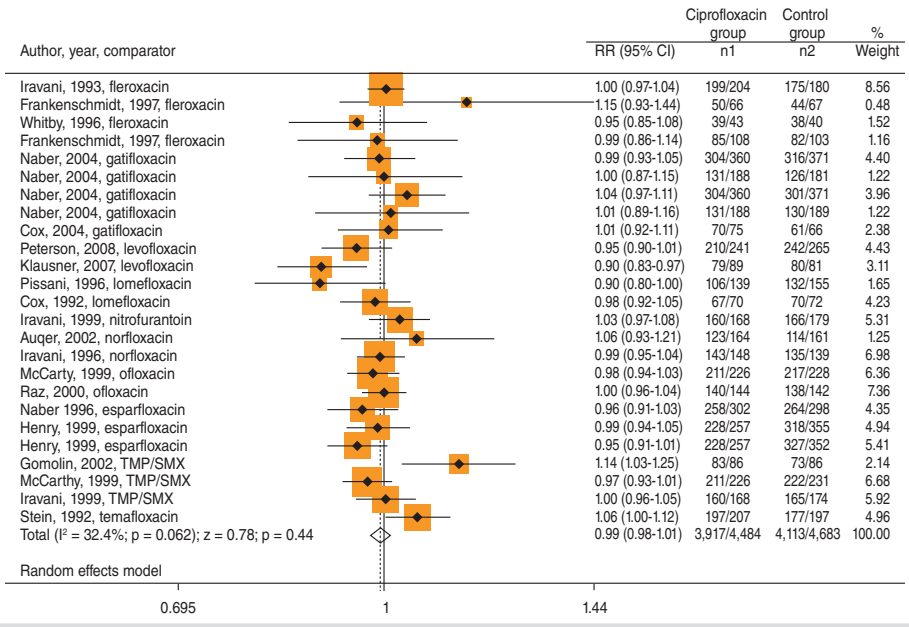

Figure 2. *Ciprofloxacin efficacy in adult UTIs: end-of-treatment clinical resolution (overall).*

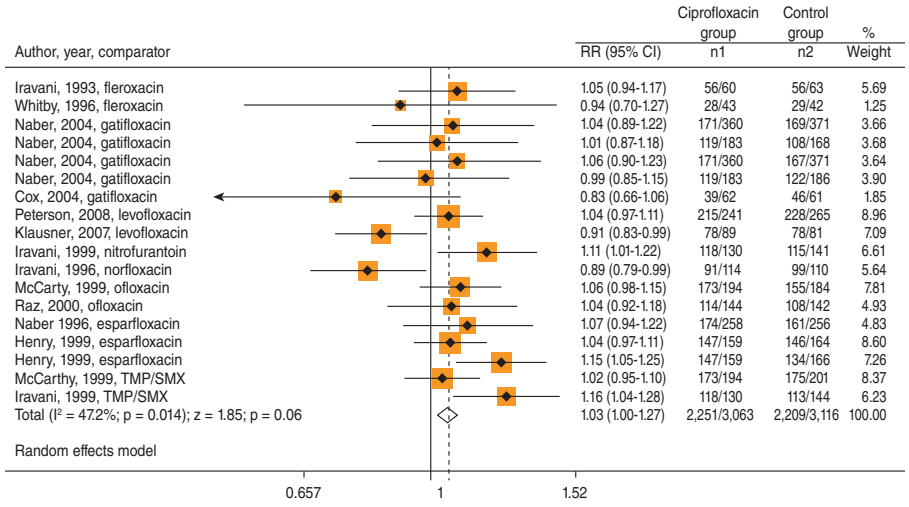

Figure 3. *Ciprofloxacin efficacy in adult UTIs: bacteriological erradication after treatment (overall).*

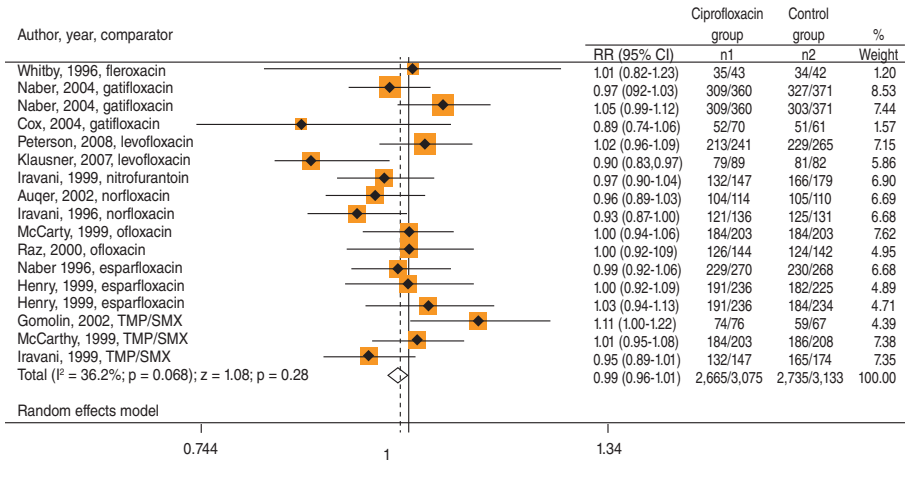

Figura 4. *Ciprofloxacin efficacy in adult UTIs: clinical resolution after treatment (overall).*

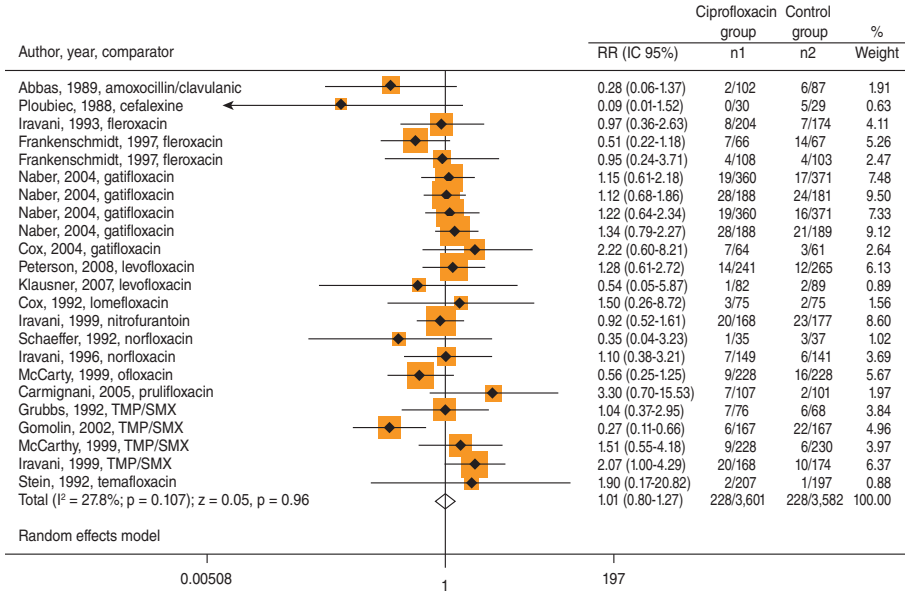

Figure 5. *Ciprofloxacin efficacy in adult UTIs: end-of-treatment bacterial resistances (global).*

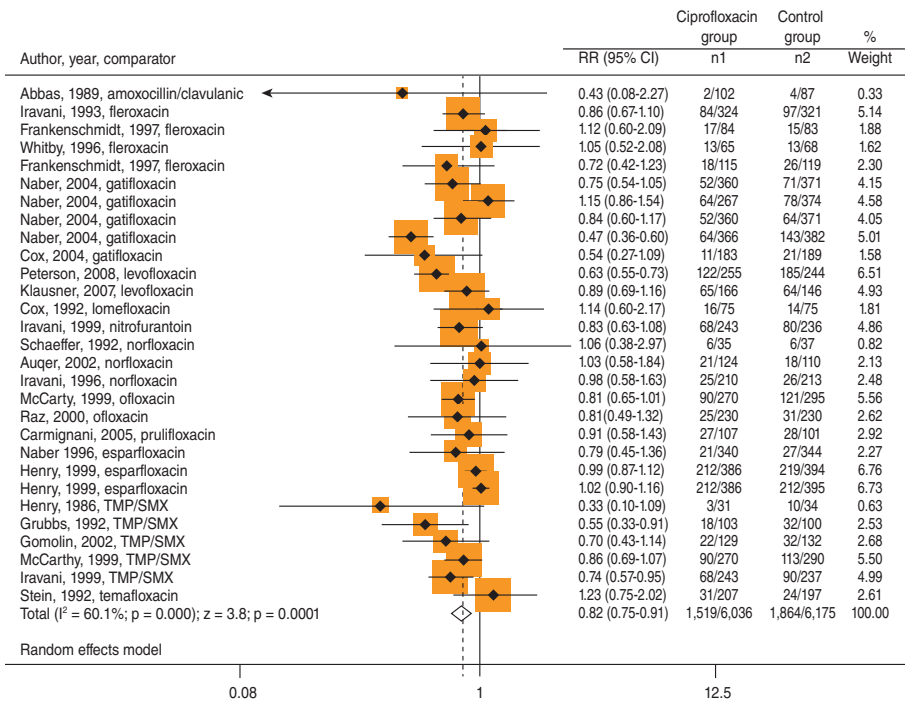

Figure 6. *Ciprofloxacin safety in adult UTIs: risk of adverse events (overall).*

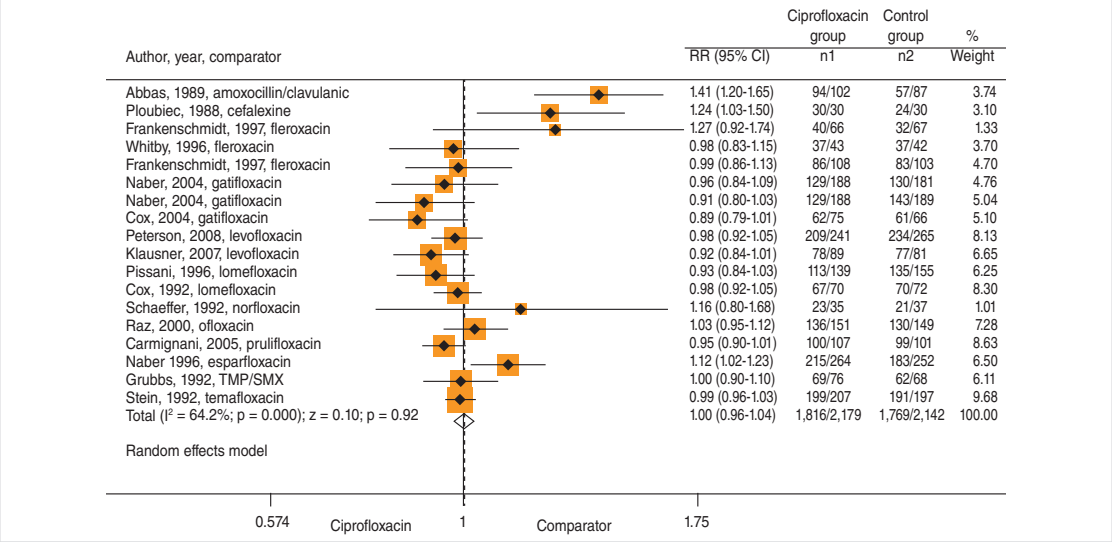

Figure 7. *Ciprofloxacin efficacy in UTIs in adults with risk factors: end-of-treatment bacteriological erradication (overall).*

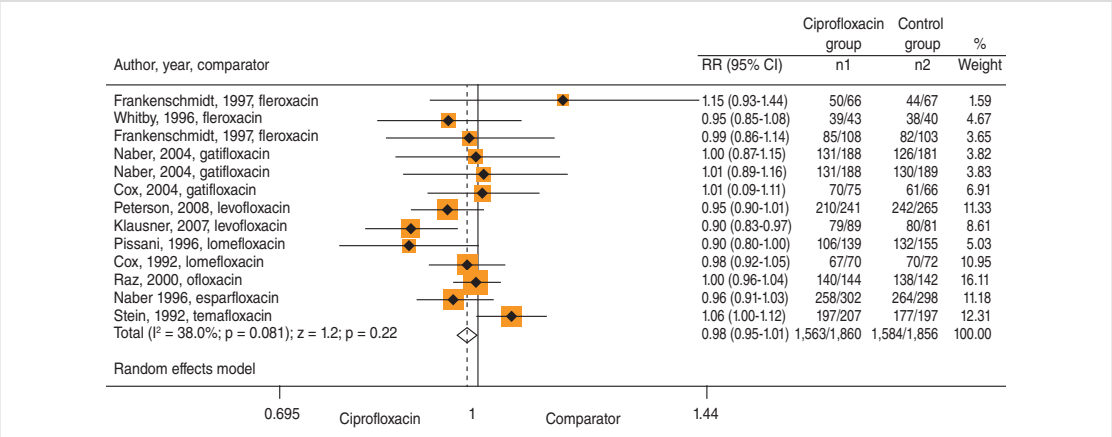

Figure 8. *Ciprofloxacin efficacy in UTIs in adults with risk factors: end-of-treatment clinical cure (overall).*

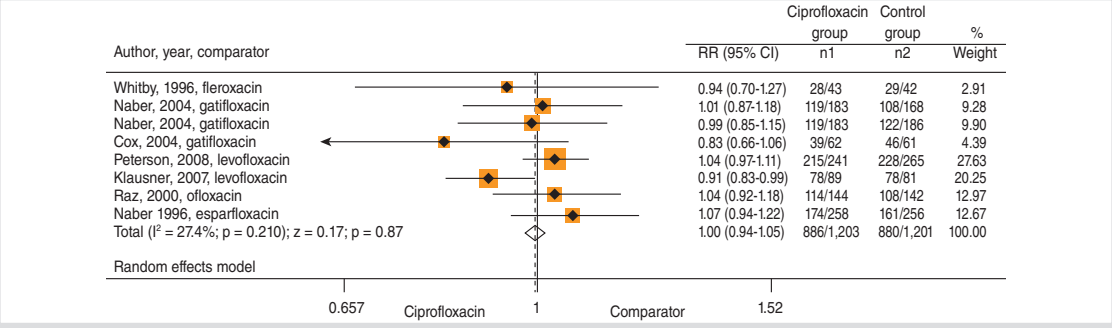

Figure 9. *Ciprofloxacin efficacy in UTIs in adults with risk factors: bacteriological erradication after treatment.*

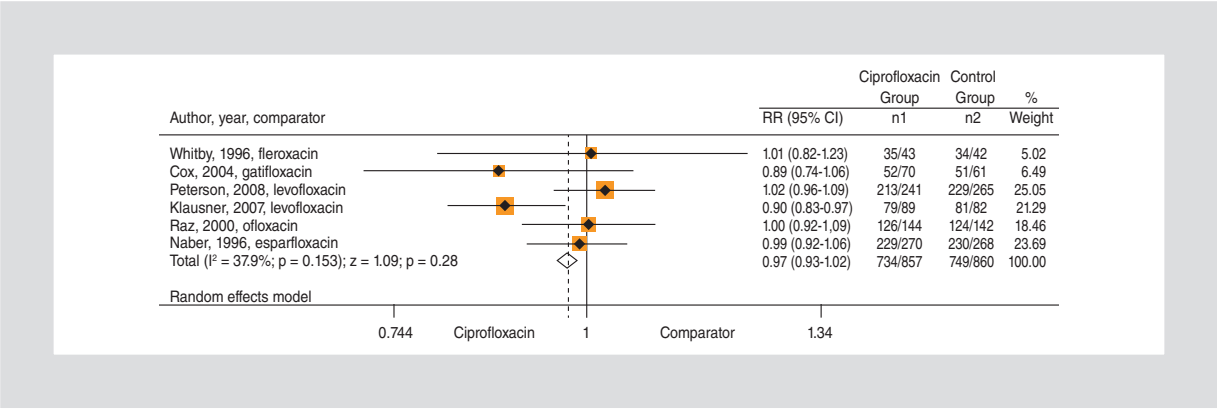

Figure 10. *Ciprofloxacin efficacy in UTIs in adults with risk factors: clinical cure after treatment.*

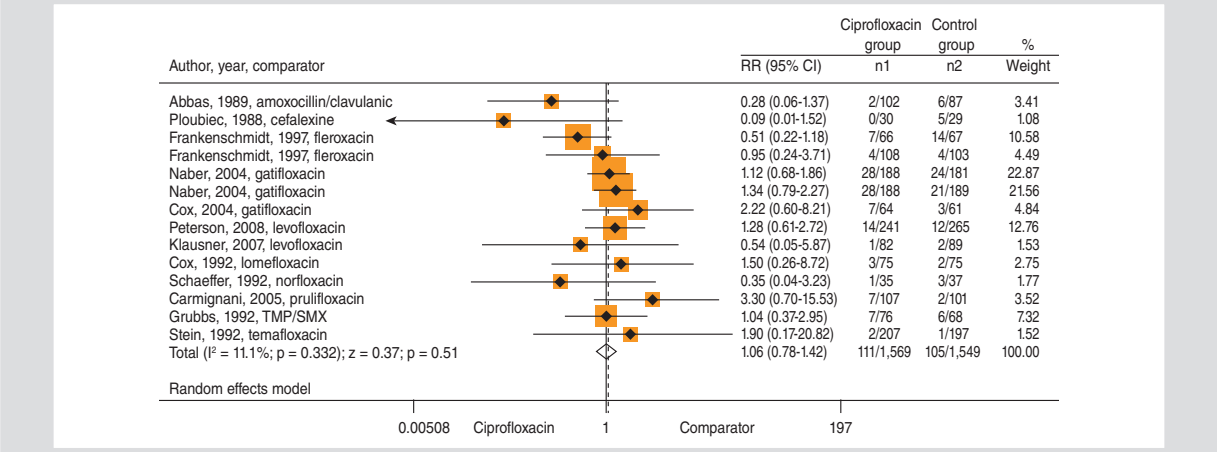

Figure 11. *Ciprofloxacin efficacy in UTIs in adults with risk factors: bacterial resistances.*

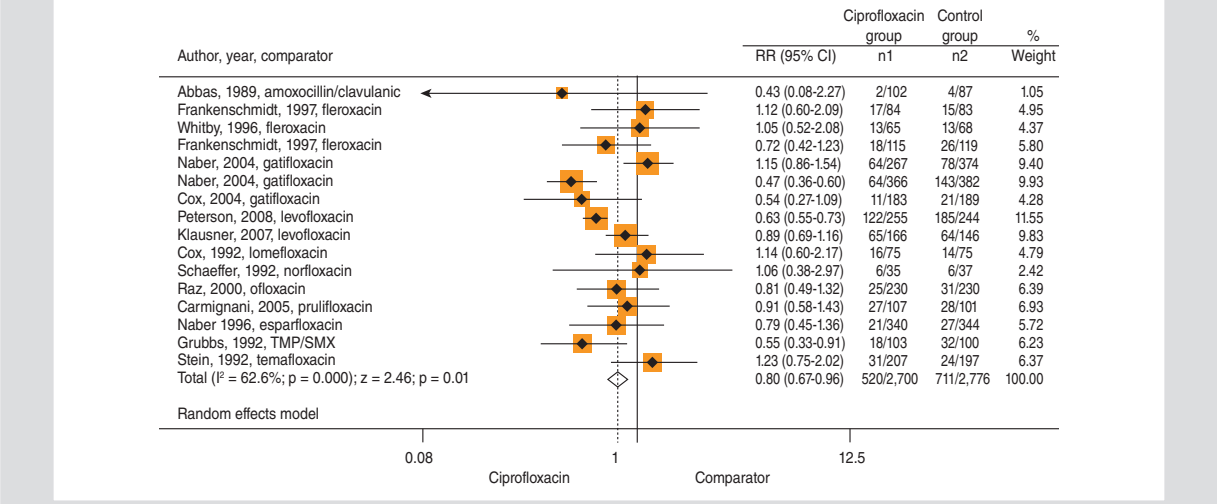

Figure 12. *Ciprofloxacin safety in UTIs in adults with risk factors: risk of related adverse events.*

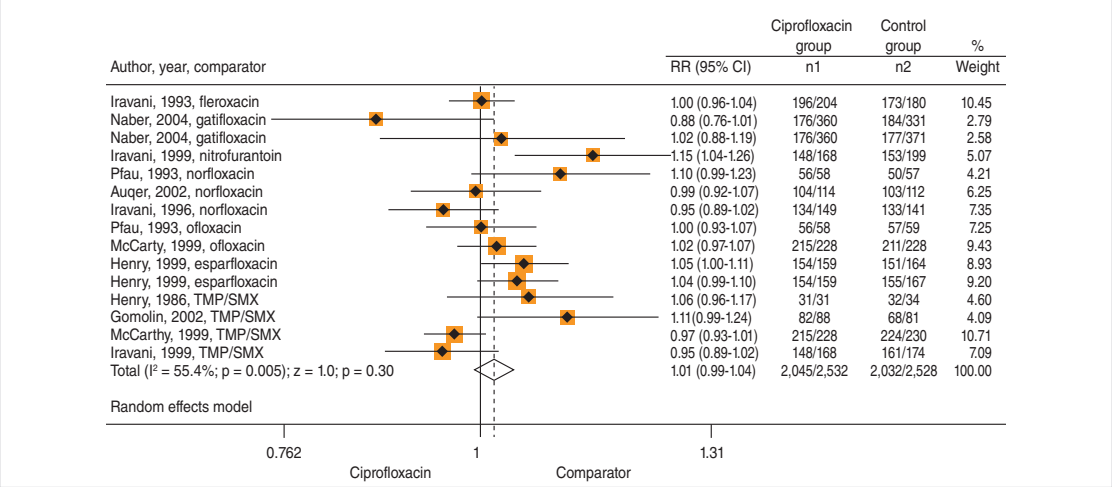

Figure 13. *Ciprofloxacin efficacy in acute UTIs in adults: end-of-treatment bacteriological erradication.*

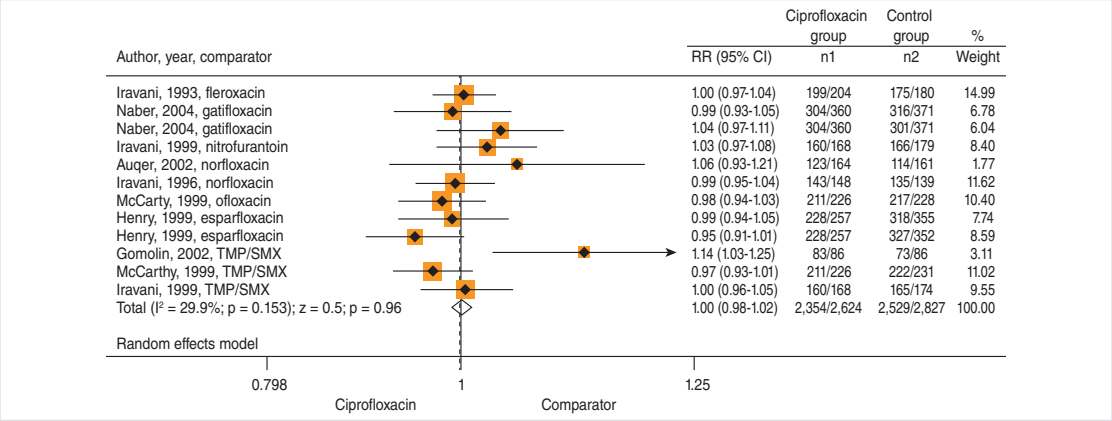

Figure 14. *Ciprofloxacin efficacy in acute UTIs in adults: end-of treatment-clinical cure.*

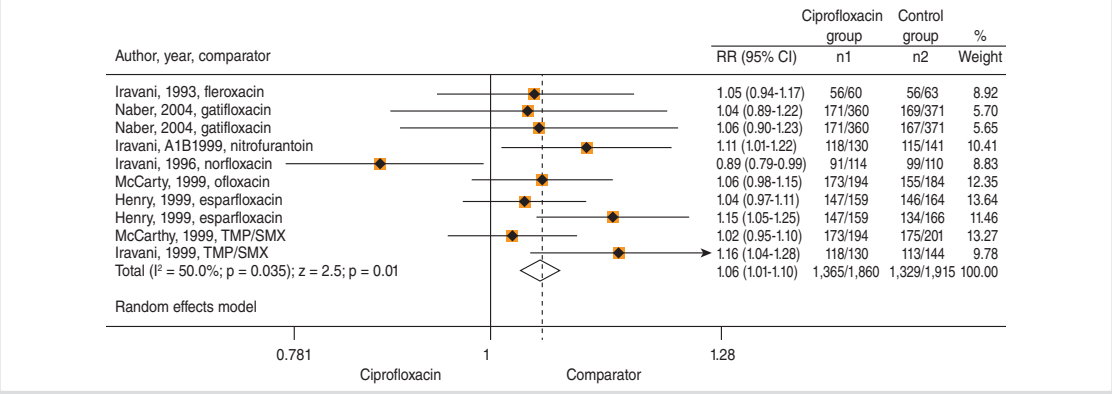

Figure 15. *Ciprofloxacin efficacy in acute UTIs in adults: bacteriological erradication after treatment.*

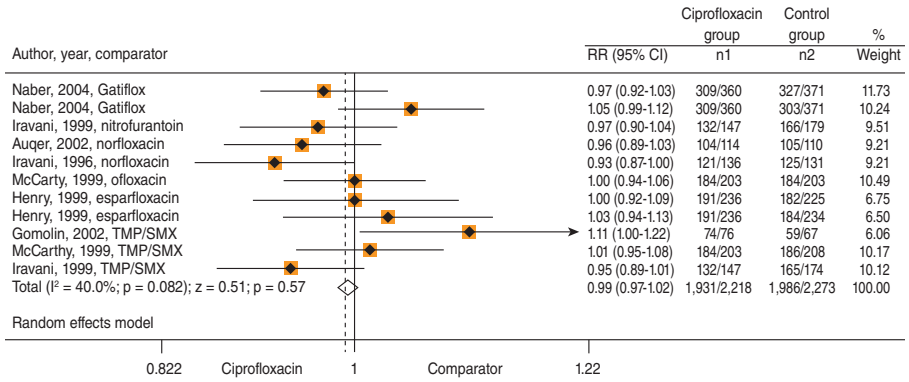

Figure 16. *Ciprofloxacin efficacy in acute UTIs in adults: clinical cure after treatment.*

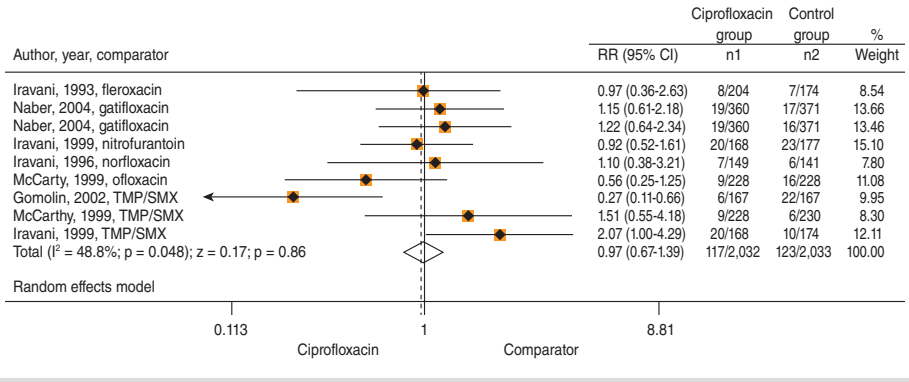

Figure 17. *Ciprofloxacin efficacy in acute UTIs in adults: bacterial resistances.*

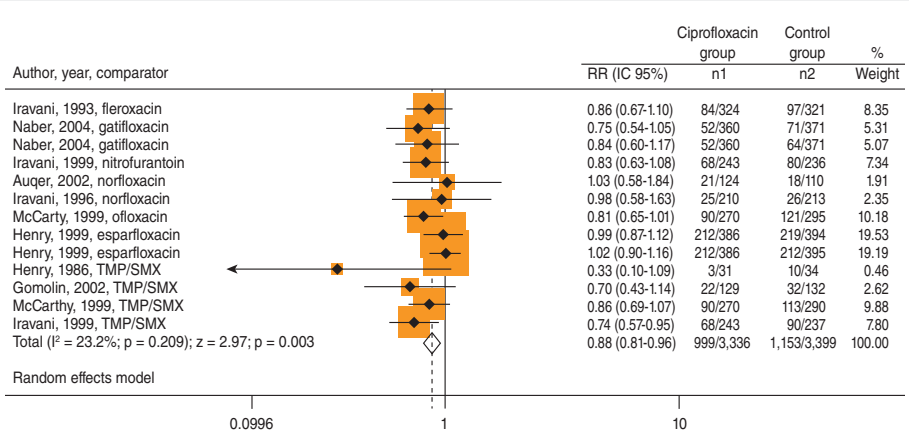

Figure 18. *Ciprofloxacin efficacy in acute UTIs in adults: risk of related adverse events.*

Discussion and conclusions

UTIs represent one of the most common conditions for which antibiotics are prescribed in primary care centers. Specifically, the use of co-trimoxazole as first-line agent is recommended in areas with prevalence of resistance to this medication lower than 20%; in areas where resistance exceeds this figure, treatment alternatives have to be considered[131]. Available evidence at this moment indicates that ciprofloxacin is a safe and efficacious alternative, with lower numbers of adverse events than other antimicrobials, for the treatment of acute or complicated UTIs (associated with risk factors). Methodological quality of the 30 studies included in the meta-analysis with adequate assignment of the maneuver (allocation concealment), most of them double-blinded, allows for this recommendation to be supported. The broad range of age in the groups (18-85 years), the inclusion of patients of both genders and the presence of different microorganisms, as well as the employed doses of different antimicrobials in both groups and its duration, generated a variable heterogeneity in the study, which, although partially adjusted by using random effects models (inverse of the variance), has to be accounted for. In summary, the analyzed evidence allows to conclude that, overall, there is therapeutic equivalence of ciprofloxacin with the rest of antimicrobials used for the treatment of acute or complicated UTIs, considering a similar capacity to that of other antimicrobials to achieve bacteriological erradication and clinical cure by the end of treatment and maintaining them in subsequent stages, as well as a percentage of bacterial resistances similar to that of other antimicrobials. The lower percentage of adverse events observed in the ciprofloxacin group both in patients with acute (non-complicated) UTIs and in patients with risk factors, allows continuing to recommend it as a superior alternative for the management of these patients.

References

1. Ronald AR, Nicolle LE, Stamm E, et al. Urinary tract infection in adults: research priorities and strategies. Int J Antimicrob Agents. 2001;17(4): 343-8.
2. Bacheller CD, Bernstein JM. Urinary tract infections. Med Clin North Am. 1997;81(3):719-30.
3. Schappert SM. National Ambulatory Medical Care Survey: 1992 summary. Adv Data. 1994;(253):1-20.
4. Kunin CM. Urinary tract infections in females. Clin Infect Dis. 1994;18(1):1-10.
5. Johnson JR, Stamm WE. Urinary tract infections in women: diagnosis and treatment. Ann Intern Med. 1989;111(11):906-17.
6. Albert X, Huertas I, Pereiro II, et al. Antibiotics for preventing recurrent urinarytract infection in non-pregnant women. Cochrane Database Syst Rev. 2004;(3):CD001209.
7. Milo G, Katchman EA, Paul M, et al. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2005;(2):CD004682.
8. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. Cochrane Database Syst Rev. 2007;(4):CD003237.
9. Regal RE, Pham CQ, Bostwick TR. Urinary tract infections in extended care facilities: preventive management strategies. Consult Pharm. 2006;21(5):400-9.
10. Lutters M, Vogt N. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Cochrane Database Syst Rev. 2002;(3):CD001535.
11. Hooton TM, Stamm WE. Management of acute uncomplicated urinary tract infection in adults. Med Clin North Ame. 1991;75(2):339-57.
12. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am. 1997;11(2):551-81.
13. Neu HC. Optimal characteristics of agents to treat uncomplicated urinary tract infection. Infection. 1992;20 Suppl 4:S266-71.
14. Naber KG. Short-term therapy of acute uncomplicated cystitis. Curr Opin Urol. 1999;9(1):57-64.
15. Naber KG. Treatment options for acute uncomplicated cystitis in adults. J Antimicrob Chemother. 2000;46 Suppl 1:23-7.
16. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis. 1999;29(4):745-58.
17. Minassian MA, Lewis DA, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. Int J Antimicrob Agents. 1998;10(1):39-47.
18. Sharma PC, Jain A, Jain S, Pahwa R, Yar MS. Ciprofloxacin: review on developments in synthetic,analytical, and medicinal aspects. J Enzyme Inhib Med Chem. 2010;25(4):577-89
19. Mirone V, Fusco F, Taglialatela D, et al. Efficacy and safety of ciprofloxacin XR 1000 mg once daily versus ciprofloxacin 500 mg twice daily in the treatment of complicated urinary tract infections. J Chemother. 2009;21(6):651-60.
20. Pfefferkorn U, Lea S, Moldenhauer J, Peterli R, von Floe M, Ackermann C. Antibiotic prophylaxis at urinary catheter removal prevents urinary tract infections: a prospective randomized trial. Ann Surg. 2009;249(4): 573-5.
21. Cam K, Kayikci A, Akman Y, Erol A. Prospective assessment of the efficacy of single dose versus traditional 3-day antimicrobial prophylaxis in 12-core transrectal prostate biopsy. Int J Urol. 2008;15(11):997-1001.
22. Tuncel A, Aslan Y, Sezgin T, Aydin O, Tekdogan U, Atan A. Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? Urology. 2008;71(6):1024-7; discussion 1027-8.
23. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology. 2008;71(1):17-22.
24. Dybowski B, JabÇonska O, Radziszewski P, Gromadzka-Ostrowska J, Borkowski A. Ciprofloxacin and furagin in acute cystitis: comparison of early immune and microbiological results. Int J Antimicrob Agents. 2008;31(2):130-4.
25. Peterson J, Kaul S, Khashab M, Fisher A, Kahn JB. Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. Clin Ther. 2007;29(10):2215-21.
26. Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Curr Med Res Opin. 2007;23(11):2637-45.
27. Marcelin-Jimenez G, Angeles AP, Martinez-Rossier L, Fernandez SA. Ciprofloxacin bioavailability is enhanced by oral co-administration with phenazopyridine: a pharmacokinetic study in a Mexican population. Clin Drug Investig. 2006;26(6):323-8.
28. Esposito S, Noviello S, Leone S, et al. A pilot study on prevention of catheter-related urinary tract infections with fluoroquinolones. J Chemother. 2006;18(5):494-501.
29. Wagenlehner FM, Kinzig-Schippers M, Sorgel F, Weidner W, Naber KG. Concentrations in plasma, urinary excretion and bactericidal activity of levofloxacin (500 mg) versus ciprofloxacin (500 mg) in healthy volunteers receiving a single oral dose. Int J Antimicrob Agents. 2006;28(6):551-9.
30. Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. BJU Int. 2006;98(5):1075-9.
31. Bin C, Hui W, Renyuan Z, et al. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamáse-producing Escherichia coli. Diagn Microbiol Infect Dis. 2006;56(4):351-7.
32. Kartal ED, Yenilmez A, Kiremitci A, Meric H, Kale M, Usluer G. Effectiveness of ciprofloxacin prophylaxis in preventing bacteriuria caused by urodynamic study: a blind, randomized study of 192 patients. Urology. 2006;67(6):1149-53.

33. Wagenlehner FM, Kinzig-Schippers M, Tischmeyer U, et al. Pharmacokinetics of ciprofloxacin XR (1000 mg) versus levofloxacin (500 mg) in plasma and urine of male and female healthy volunteers receiving a single oral dose. Int J Antimicrob Agents. 2006;27(1):7-14.
34. Gupta K, Hooton TM, Stamm WE. Isolation of fluoroquinolone-resistant rectal Escherichia coli after treatment of acute uncomplicated cystitis. J Antimicrob Chemother. 2005;56(1):243-6.
35. Carmignani G, De Rose AF, Olivieri L, Salvatori E, Rosignoli MT, Dionisio P. Prulifloxacin versus ciprofloxacin in the treatment of adults with complicated urinary tract infections. Urol Int. 2005;74(4):326-31.
36. Wazait HD, Patel HR, van der Meulen JH, et al. A pilot randomized double-blind placebo-controlled trial on the use of antibiotics on urinary catheter removal to reduce the rate of urinary tract infection: the pitfalls of ciprofloxacin. BJU Int. 2004;94(7):1048-50.
37. Dow G, Rao P, Harding G, et al. A prospective, randomized trial of 3 or 14 days of ciprofloxacin treatment for acute urinary tract infection in patients with spinal cord injury. Clin Infect Dis. 2004;39(5):658-64.
38. Naber KG, Allin DM, Clarysse L, et al. 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(6):596-605.
39. Sabbagh R, McCormack M, Piloquin F, et al. A prospective randomized trial of 1-day versus 3-day antibiotic prophylaxis for transrectal ultrasound guided prostate biopsy. Can J Urol. 2004;11(2):2216-9.
40. Wells WG, Woods GL, Jiang Q, Gesser RM. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy. J Antimicrob Chemother. 2004;53 Suppl 2:ii67-74.
41. Valdevenito Sepúlveda JP. [Antibiotics in transurethral resection of the prostate in patients with low risk of infectious complications: randomized prospective comparative study]. Arch Esp Urol. 2004;57(1):48-57.
42. Naber KG, Bartnicki A, Bischoff W, et al. Gatifloxacin 200 mg or 400 mg once daily is as effective as ciprofloxacin 500 mg twice daily for the treatment of patients with acute pyelonephritis or complicated urinary tract infections. Int J Antimicrob Agents. 2004;23 Suppl 1:S41-53.
43. Vogel T, Verreault R, Gourdeau M, Morin M, Grenier-Gosselin L, Rochette L. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. CMAJ. 2004;170(4):469-73.
44. Talan DA, Klimberg IW, Nicolle LE, Song J, Kowalsky SF, Church DA. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol. 2004;171(2 Pt 1):734-9.
45. Wagenlehner FM, Wydra S, Onda H, Kinzig-Schippers M, Sorgel F, Naber KG. Concentrations in plasma, urinary excretion, and bactericidal activity of linezolid (600 milligrams) versus those of ciprofloxacin (500 milligrams) in healthy volunteers receiving a single oral dose. Antimicrob Agents Chemother. 2003;47(12):3789-94.
46. Ulleryd P, Sandberg T. Ciprofloxacin for 2 or 4 weeks in the treatment of febrile urinary tract infection in men: a randomized trial with a 1 year follow-up. Scand J Infect Dis. 2003;35(1):34-9.
47. Henry DC Jr, Bettis RB, Riffer E, 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 Ther. 2002;24(12):2088-104.
48. Naber KG; European Lomefloxacin Prostatitis Study Group. Lomefloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis. Int J Antimicrob Agents. 2002;20(1):18-27.
49. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multicenter comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. Clin Ther. 2002;24(2):223-36.
50. Auquer F, Cordinn F, Gorina E, et al. Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. Clin Microbiol Infect. 2002;8(1):50-4.
51. Richard GA, Mathew CP, Kirstein JM, Orchard D, Yang JY. Single-dose fluoroquinolone therapy of acute uncomplicated urinary tract infection in women: results from a randomized, double-blind, multicenter trial comparing single-dose to 3-day fluoroquinolone regimens. Urology. 2002;59(3):334-9.
52. Gomolin IH, Siami PF, Reuning-Scherer J, Haverstock DC, Heyd A; 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(12):1606-13.
53. Raz R, Naber KG, Raizenberg C, et al. Ciprofloxacin 250 mg twice daily versus ofloxacin 200 mg twice daily in the treatment of complicated urinary tract infections in women. Eur J Clin Microbiol Infect Dis. 2000;19(5):327-31.
54. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int. 2000;85(6):682-5.
55. Christiano AP, Hollowell CM, Kim H, et al. Double-blind randomized comparison of single-dose ciprofloxacin versus intravenous cefazolin in patients undergoing outpatient endourologic surgery. Urology. 2000; 55(2):182-5.
56. Naber KG, Theuretzbacher U, Moneva-Koucheva G, Stass H. Urinary excretion and bactericidal activity of intravenous ciprofloxacin compared with oral ciprofloxacin. Eur J Clin Microbiol Infect Dis. 1999;18(11):783-9.
57. Price J, Ekleberry A, Grover A, et al. Evaluation of clinical practice guidelines on outcome of infection in patients in the surgical intensive care unit. Crit Care Med. 1999;27(10):2118-24.
58. Eickhoff JH, Frimodt-Miller N, Walter S, Frimodt-Miller C. A double-blind, randomized, controlled multicentre study to compare the efficacy of ciprofloxacin with pivampicillin as oral therapy for epididimytis in men over 40 years of age. BJU Int. 1999;84(7):827-34.
59. Henry DC, Nenad RC, Iravani A, et al. Comparison of sparfloxacin and ciprofloxacin in the treatment of community-acquired acute uncomplicated urinary tract infection in women. Sparfloxacin Multicenter Uncomplicated Urinary Tract Infection Study Group. Clin Ther. 1999;21(6): 966-81.
60. Tsukamoto T, Matsukawa M, Sano M, et al. Biofilm in complicated urinary tract infection. Int J Antimicrob Agents. 1999;11(3-4):233-6; discussion 237-9.
61. Iravani A, Klimberg I, Briefer C, Munera C, Kowalsky SF, Echols RM. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. J Antimicrob Chemother. 1999;43 Suppl A:67-75.
62. McCarty JM, Richard G, Huck W, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. Am J Med. 1999;106(3):292-9.
63. Mombelli G, Pezzoli R, Pinoja-Lutz G, Monotti R, Marone C, Franciolli M. Oral vs. intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. Arch Intern Med. 1999;159(1):53-8.
64. Tsugawa M, Monden K, Nasu Y, Kumon H, Ohmori H. Prospective randomized comparative study of antibiotic prophylaxis in urethrocystoscopy and urethrocystography. Int J Urol. 1998;5(5):441-3.
65. Kapoor DA, Klimberg IW, Malek GH, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology. 1998;52(4):552-8.
66. Naber KG, Theuretzbacher U, Kinzig M, Savov O, Sorgel F. Urinary excretion and bactericidal activities of a single oral dose of 400 milligrams of fleroxacin versus a single oral dose of 800 milligrams of pefloxacin in healthy volunteers. Antimicrob Agents Chemother. 1998;42(7):1659-65.
67. Hsieh WJ, Lin HC, Hwang SJ, et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. Am J Gastroenterol. 1998;93(6):962-6.
68. Viitanen J, Malminiemi K, Kallio J, Puolakka VM, Rajala P, Tammela TL. Transurethral prostatectomy in patients with preoperative bacteriuria: double-blind study with oral fleroxacin and cefalexin. Chemotherapy. 1998;44(1):69-75.
69. Moyses Neto M, Costa RS, Reis MA, et al. Use of ciprofloxacin as a prophylactic agent in urinary tract infections in renal transplant recipients. Clin Transplant. 1997;11(5 Pt 1):446-52.
70. Frankenschmidt A, Naber KG, Bischoff W, Kullmann K. Once-daily fleroxacin versus twice-daily ciprofloxacin in the treatment of complicated urinary tract infections. J Urol. 1997;158(4):1494-9.
71. Rao VV, Rambhau D, Rao BR, Srinivasu P. Circadian variation in urinary excretion of ciprofloxacin after a single-dose oral administration at 1000 and 2200 hours in human subjects. Antimicrob Agents Chemother. 1997;41(8):1802-4.
72. Lukkarinen O, Hellstrom P, Leppilahti M, Kontturi M, Tammela T. Antibiotic prophylaxis in patients with urinary retention undergoing transurethral prostatectomy. Ann Chir Gynaecol. 1997;86(3):239-42.
73. Bierkens AF, Hendrikx AJ, Ezz el Din KE, et al. The value of antibiotic prophylaxis during extracorporeal shock wave lithotripsy in the prevention of urinary tract infections in patients with urine proven sterile prior to treatment. Eur Urol. 1997;31(1):30-5.
74. Whitby M, Angus L, Nimmo G, Hill V. Complicated urinary infection in spinal injury patients: fleroxacin compared with ciprofloxacin. Chemotherapy. 1996;42(6):468-72.
75. Gasser TC, Wisard M, Frei R. Oral fleroxacin prophylaxis in transurethral surgery. J Urol. 1996;156(1):146-8.
76. Pisani E, Bartoletti R, Trinchieri A, Rizzo M. Lomefloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections: a multicenter study. J Chemother. 1996;8(3):210-3.
77. Hall JC, Christiansen KJ, England P, et al. Antibiotic prophylaxis for patients undergoing transurethral resection of the prostate. Urology. 1996;47(6):852-6.
78. Naber KG, di Silverio F, Geddes A, Guibert J. Comparative efficacy of sparfloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection. J Antimicrob Chemother. 1996;37 Suppl A:135-44.
79. Lukkarinen O, Hellstrom P, Leppilahti M, Kontturi M, Tammela T. Prospective randomized open study between ciprofloxacin and a combination of sulfadiazine and trimethoprim in antibiotic prophylaxis in connection with transurethral prostatectomy. Scand J Urol Nephrol. 1996; 30(1):33-6.
80. Iravani A, Tice AD, McCarty J, et al. Short-course ciprofloxacin treatment of acute uncomplicated urinary tract infection in women. The minimum

effective dose. The Urinary Tract Infection Study Group [corrected]. Arch Intern Med. 1995;155(5):485-94.
81. McCue JD, Gaziano P, Orders D. A randomised controlled trial of ofloxacin 200 mg 4 times daily or twice daily vs ciprofloxacin 500 mg twice daily in elderly nursing home patients with complicated UTI. Drugs. 1995;49 Suppl 2:368-73.
82. Darouiche RO, Smith MS, Markowski J. Antibiotic prophylaxis for urodynamic testing in patients with spinal cord injury: a preliminary study. J Hosp Infect. 1994;28(1):57-61.
83. Pfau A, Sacks TG. Effective postcoital quinolone prophylaxis of recurrent urinary tract infections in women. J Urol. 1994;152(1):136-8.
84. Biering-Sorensen F, Hiiby N, Nordenbo A, Ravnborg M, Bruun B, Rahm V. Ciprofloxacin as prophylaxis for urinary tract infection: prospective, randomized, cross-over, placebo controlled study in patients with spinal cord lesion. J Urol. 1994;151(1):105-8. Erratum in: J Urol. 1994;151(4):1032.
85. Whitby M, Brown P, Silagy C, Rana C. Comparison of fleroxacin and amoxicillin in the treatment of uncomplicated urinary tract infections in women. Am J Med. 1993;94(3A):97S-100S.
86. 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.
87. Cox CE. Comparison of intravenous fleroxacin with ceftazidime for treatment of complicated urinary tract infections. Am J Med. 1993;94(3A): 118S-125S.
88. Naber KG, Sigl G. Fleroxacin versus ofloxacin in patients with complicated urinary tract infection: a controlled clinical study. Am J Med. 1993;94(3A):114S-117S.
89. Pummer K. Fleroxacin versus norfloxacin in the treatment of urinary tract infections: a multicenter, double-blind, prospective, randomized, comparative study. Am J Med. 1993;94(3A):108S-113S.
90. Childs SJ. Fleroxacin versus norfloxacin for oral treatment of serious urinary tract infections. Am J Med. 1993;94(3A):105S-107S.
91. Pittman W, Moon JO, Hamrick LC Jr, et al. Randomized double-blind trial of high- and low-dose fleroxacin versus norfloxacin for complicated urinary tract infection. Am J Med. 1993;94(3A):101S-104S.
92. Pfau A, Sacks TG. Single dose quinolone treatment in acute uncomplicated urinary tract infection in women. J Urol. 1993;149(3):532-4.
93. Grubbs NC, Schultz HJ, Henry NK, Ilstrup DM, Muller SM, Wilson WR. Ciprofloxacin versus trimethoprim-sulfamethoxazole: treatment of community-acquired urinary tract infections in a prospective, controlled, double-blind comparison. Mayo Clin Proc. 1992;67(12):1163-8.
94. Schaeffer AJ, Anderson RU. Efficacy and tolerability of norfloxacin vs. ciprofloxacin in complicated urinary tract infection. Urology. 1992; 40(5):446-9.
95. Hibberd PL, Tolkoff-Rubin NE, Doran M, et al. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for the prevention of urinary tract infection in renal transplant recipients. A double-blind, randomized controlled trial. Online J Curr Clin Trials. 1992;Doc No 15:[4083 words; 46 paragraphs].
96. Peters HJ. Sequential therapy with ofloxacin in complicated urinary tract infections: a randomized comparative study with ciprofloxacin. Infection. 1992;20(3):172-3.
97. Van der Wall E, Verkooyen RP, Mintjes-de Groot J, et al. Prophylactic ciprofloxacin for catheter-associated urinary-tract infection. Lancet. 1992;339(8799):946-51.
98. Cox CE. A comparison of the safety and efficacy of lomefloxacin and ciprofloxacin in the treatment of complicated or recurrent urinary tract infections. Am J Med. 1992;92(4A):82S-86S.
99. Bailey RR, Lynn KL, Robson RA, Peddie BA, Smith A. Comparison of ciprofloxacin with netilmicin for the treatment of acute pyelonephritis. N Z Med J. 1992;105(930):102-3.
100. Stein GE, Philip E. Comparison of three-day temafloxacin with seven-day ciprofloxacin treatment of urinary tract infections in women. J Fam Pract. 1992;34(2):180-4.
101. Kalager T, Andersen BM, Bergan T, et al. Ciprofloxacin versus a tobramycin/cefuroxime combination in the treatment of serious systemic infections: a prospective, randomized and controlled study of efficacy and safety. Scand J Infect Dis. 1992;24(5):637-46. Erratum in: Scand J Infect Dis. 1993;25(2):271.
102. Iravani A. Treatment of uncomplicated urinary tract infections with temafloxacin. Am J Med. 1991;91(6A):124S-128S.
103. Paladino JA, Sperry HE, Backes JM, et al. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. Am J Med. 1991;91(5):462-70.
104. Fang GD, Brennen C, Wagener M, et al. Use of ciprofloxacin versus use of aminoglycosides for therapy of complicated urinary tract infection: prospective, randomized clinical and pharmacokinetic study. Antimicrob Agents Chemother. 1991;35(9):1849-55.
105. Lew MA, Kehoe K, Ritz J, et al. Prophylaxis of bacterial infections with ciprofloxacin in patients undergoing bone marrow transplantation. Transplantation. 1991;51(3):630-6.
106. Rapp RP, Billeter M, Hatton J, Young AB, Tibbs PA, Dempsey RJ. Intravenous ciprofloxacin versus ceftazidime for treatment of nosocomial pneumonia and urinary tract infection. Clin Pharm. 1991;10(1):49-55.
107. Karachalios GN, Georgiopoulos AN, Nasopoulou-Papadimitriou DD, Adracta DJ. Value of single-dose ciprofloxacin in the treatment of acute uncomplicated urinary tract infection in women. Drugs Exp Clin Res. 1991;17(10-11):521-4.
108. Brouwer WK, Hoogkamp-Korstanje JA, Kuiper KM. Antibiotic prophylaxis in vaginal hysterectomy. Three doses of cefuroxime plus metronidazole versus one dose of ciprofloxacin. Pharm Weekbl Sci. 1990;12(6A):292-4; discussion 294-5.
109. Boyko EJ, Iravani A, Silverman MH, Schelling DJ, Wright RA. Randomized, controlled trial of a 10-day course of amifloxacin versus trimethoprim-sulfamethoxazole in the treatment of acute, uncomplicated urinary tract infection. Amifloxacin Multi-Center Trial Group. Antimicrob Agents Chemother. 1990;34(4):665-7.
110. Wolfhagen MJ, Hoepelman AI, Verhoef J. Double-blind, dose-range-finding study of fleroxacin (RO 23-6240; AM-833) for treatment of complicated urinary tract infections. Antimicrob Agents Chemother. 1990;34(3):409-12.
111. Van Poppel H, Willemen P, Wegge M, Kraseman P, Chysky V, Baert L. Antibiotic cover of transurethral maneuvers with ciprofloxacin and susceptibility behavior of pathogens in patients with neurogenic bladder. Urol Int. 1990;45(6):342-5.
112. Raz R, Rottensterich E, Hefter H, Kennes Y, Potasman I. Single-dose ciprofloxacin in the treatment of uncomplicated urinary tract infection in women. Eur J Clin Microbiol Infect Dis. 1989;8(12):1040-2.
113. Cox CE. Comparison of intravenous ciprofloxacin and intravenous cefotaxime for antimicrobial prophylaxis in transurethral surgery. Am J Med. 1989;87(5A):252S-254S.
114. Sifuentes-Osornio J, Macas A, Amieva RI, Ramos A, Ruiz-Palacios GM. Intravenous ciprofloxacin and ceftazidime in serious infections. A prospective, controlled clinical trial with third-party blinding. Am J Med. 1989;87(5A):202S-205S.
115. Quintero-Perez NP, Andrade-Villaneuva JF, Leon-Garnica G, Bertin-Montano M, Rodriguez-Chagollan JJ, Rodriguez-Noriega E. Efficacy and safety of intravenous ciprofloxacin in the treatment of serious infections. A comparison with ceftazidime. Am J Med. 1989;87(5A):198S-201S.
116. Villavicencio J, Asensio de Fernandez ME, Ramirez CA. Intravenous ciprofloxacin or ceftazidime in selected infections. A prospective, randomized, controlled study. Am J Med. 1989;87(5A):191S-194S.
117. Peacock JE Jr, Pegram PS, Weber SF, Leone PA. Prospective, randomized comparison of sequential intravenous followed by oral ciprofloxacin with intravenous ceftazidime in the treatment of serious infections. Am J Med. 1989;87(5A):185S-190S.
118. Gallis HA, Brennan RO, Goodwin SD, Swinney V, Rumbaugh MM, Drew RH. Comparison of the safety and efficacy of intravenous ciprofloxacin and intravenous ceftazidime in the treatment of selected infections. Am J Med. 1989;87(5A):176S-180S.
119. Levine DP, McNeil P, Lerner SA. Randomized, double-blind comparative study of intravenous ciprofloxacin versus ceftazidime in the treatment of serious infections. Am J Med. 1989;87(5A):160S-163S.
120. Fass RJ, Plouffe JF, Russell JA. Intravenous/oral ciprofloxacin versus ceftazidime in the treatment of serious infections. Am J Med. 1989; 87(5A):164S-168S.
121. Abbas AM, Chandra V, Dongaonkar PP, et al. Ciprofloxacin versus amoxycillin/clavulanic acid in the treatment of urinary tract infections in general practice. J Antimicrob Chemother. 1989;24(2):235-9.
122. Shearman CP, Silverman SH, Johnson M, et al. Single dose, oral antibiotic cover for transurethral prostatectomy. Br J Urol. 1988;62(5): 434-8.
123. Kosmidis J, Gargalianos P, Adamis G, Petropoulou D, Makris D. Fleroxacin in single dose oral therapy of uncomplicated lower urinary tract infection. J Antimicrob Chemother. 1988;22 Suppl D:219-21.
124. Polubiec A, Weuta H, Stepka K, Ktos K, Strazynska R, Jorasz J. Bacterial infections of the lower urinary tract treated with ciprofloxacin or cefalexin--a comparative study. Infection. 1988;16 Suppl 1:S62-4.
125. Goldstein EJ, Kahn RM, Alpert ML, Ginsberg BP, Greenway FL, Citron DM. Ciprofloxacin versus cinoxacin in therapy of urinary tract infections. A randomized, double-blind trial. Am J Med. 1987;82(4A):284-7.
126. Garlando F, Rietiker S, Tiuber MG, Flepp M, Meier B, Lothy R. Single-dose ciprofloxacin at 100 versus 250 mg for treatment of uncomplicated urinary tract infections in women. Antimicrob Agents Chemother. 1987;31(2):354-6.
127. Henry NK, Schultz HJ, Grubbs NC, Muller SM, Ilstrup DM, Wilson WR. 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.
128. Gonzalez MA, Moranchel AH, Duran S, et al. Multiple-dose pharmacokinetics of ciprofloxacin administered intravenously to normal volunteers. Antimicrob Agents Chemother. 1985;28(2):235-9.
129. Giamarellou H, Efstratiou A, Tsagarakis J, Petrikkos G, Daikos GK. Experience with ciprofloxacin in vitro and in vivo. Arzneimittelforschung. 1984;34(12):1775-8.
130. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ. 1994;309(6964):1286-91.
131. Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Fourth International Cochrane Colloquium; 1996 Oct 20-24; Adelaide (Australia).