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REVIEW

Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: A meta-analysis of randomized controlled trials

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Summary *Background:* Acute uncomplicated cystitis is one of the most common bacterial infections in women and is conventionally treated with antibiotics. However, emergence of resistant uropathogens forces physicians to reconsider the prescription of antibiotics for acute uncomplicated cystitis in non-pregnant young women.
Objective: To evaluate the effectiveness of antibiotics in the treatment of acute uncomplicated cystitis.
Methods: We searched PubMed, the Cochrane Central Register of Controlled Trials and Scopus database.
Results: Five randomized controlled trials (RCTs) involving non-pregnant, non-immunocompromised adult women with clinically and microbiologically documented acute uncomplicated cystitis were included. Clinical success was significantly more likely in women treated with antibiotics versus those treated with placebo [4 RCTs, 1062 patients, random effects model (REM), odds ratio (OR) = 4.81, 95% confidence intervals (CI) = 2.51—9.21]. Antibiotics were also superior to placebo, regarding cure (4 RCTs, 1062 patients, REM, OR = 4.67, 95%CI = 2.34—9.35); microbiological eradication at the end of treatment (3 RCTs, 967 patients, REM, OR = 10.67, 95%CI = 2.96—38.43); after the end of treatment (3 RCTs, 738 patients, REM, OR = 5.38, 95%CI = 1.63—17.77), and microbiological reinfection or relapse (5 RCTs, 843 patients, REM, OR = 0.27, 95%CI = 0.13—0.55). However, adverse events were more likely to occur in antibiotic-treated patients versus placebo-treated women (4 RCTs, 1068 patients, REM, OR = 1.64, 95%CI = 1.10—2.44). No difference was found between the

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compared treatment arms regarding study withdrawals from adverse events, the development of pyelonephritis and emergence of resistance.
Conclusion: Antibiotics are superior to placebo regarding both clinical and microbiological success in adult non-pregnant women with microbiologically confirmed acute uncomplicated cystitis. However, they are associated with more adverse events.
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Introduction

Acute uncomplicated cystitis is one of the commonest bacterial infections, mainly encountered in young sexually active women without anatomical abnormalities of the urinary tract.[1–4] It is reported that approximately the one-third of women up to 24 years of age will have at least 1 episode of urinary tract infection (UTI) that will require antibiotic therapy.[2] Since acute uncomplicated cystitis may be considered as a relatively easy to cure type of infection, many factors should be taken into consideration when prescribing antibiotics for the treatment of this clinical entity.

Cystitis is accompanied by disturbing symptoms as dysuria, frequency and urgency for urination. These symptoms preclude women from keeping up with their daily activities and thus reduce their quality of life. The above-mentioned symptoms are the main reason for which women with cystitis seek medical advice. As a result, cystitis is associated with a considerable economical burden, in terms of both direct medical costs and indirect costs.[2] According to the guidelines, a three-day treatment with trimethoprim/sulphamethoxazole (co-trimoxazole) is considered as the baseline treatment for acute uncomplicated cystitis in areas where the resistance rate is less than 10–20%.[5] Emergence of uropathogens resistant to co-trimoxazole, has led to a shift of the physicians' prescription pattern to fluoroquinolones in several settings[6–13]; but emergence of resistance to these drugs is also reported.[14,15] Acute cystitis has also been associated with acute pyelonephritis.[16] On the other hand, spontaneous resolution of cystitis' symptoms has been reported to occur in almost half of the episodes after two to four weeks.[17]

Taking these considerations into account, we aimed to compare the effectiveness and safety profile of antibiotic treatment versus placebo in non-pregnant women with acute uncomplicated cystitis by performing a meta-analysis of relevant randomized controlled trials.

Methods

Literature search

The clinical trials included in our meta-analysis were retrieved from searches performed in PubMed database, the Cochrane Central Register of Controlled Trials (both up to 07/11/2008), and Scopus (up to 12/11/2008) as well as by hand-searching the bibliographies of relevant articles. The PubMed search strategy used was: ''(cystitis OR lower urinary tract infection) AND (placebo OR antibiotics) AND (treatment) NOT review[pt] NOT case reports[pt]''. The search strategy applied on both the Cochrane Central Register of Controlled Trials and Scopus was: ''(cystitis OR lower urinary tract infection) AND (placebo OR treatment)''. Two reviewers (I.K.K. and E.K.V.) independently performed the literature search, the evaluation of retrieved studies for the eligibility for inclusion in the meta-analysis as well as the data extraction.

Study selection criteria

A study was regarded as eligible for inclusion in our meta-analysis if it represented a randomized placebo-controlled trial (RCT) and involved women with documented uncomplicated cystitis (with either a positive dipstick test and/or a positive urine culture) that were treated either with antibiotics or placebo. In addition, in order to be included in our meta-analysis, studies should have involved women with cystitis that were not pregnant and that were not immunocompromised. Abstracts in scientific conferences, commentaries, editorials, letters to the editor or studies published in languages other than English, Spanish, French, German, Italian, or Greek, were excluded from our meta-analysis.

Data extraction

Data extracted from each one of the RCTs included in this meta-analysis referred to the type of study design, the quality assessment of each RCT, the characteristics of the study population, the diagnostic inclusion and the exclusion criteria used, the two compared treatment arms, any concomitantly administered antibiotic therapy, as well as specific outcomes assessed at the respective evaluations.

Definitions and outcomes of the meta-analysis

Effectiveness outcomes

Acute uncomplicated cystitis was defined as the presence of symptoms suggestive of urinary tract infection (UTI), such as painful urination (dysuria), or frequent or urgent need to urinate, along with detected pyuria and/or positive urine culture for a bacterial organism (uropathogen) in non-pregnant immunocompetent women without anatomical abnormalities of the urinary tract. *Clinical success* was defined as the complete (cure) or non-complete (improvement) of symptoms at the first evaluation after the end of treatment. Persistence of symptoms was defined as the presence of symptoms after at least one day of treatment. *Bacteriological success* (eradication) was defined as the presence of a negative urine culture at the end of treatment and at the first follow-up assessment after the end of treatment. *Microbiological reinfection or relapse* was defined as the presence of a positive urine culture at long term follow-up assessment, regardless of the presence of a sterile urine culture at a previous evaluation. Specifically,

relapse was defined as a positive urine culture with the same microorganism as the one identified at the initial culture, whereas reinfection was defined as a positive urine culture with a different than the initially isolated microorganism. Development of *pyelonephritis* during or after therapy was defined as a complication of cystitis consisting of a clinical syndrome of fever and flank pain. *ITT population* was defined as the number of patients that were randomly allocated in the compared treatment arms.

Safety outcomes

Adverse events were defined as any adverse events reported by the study participants during the study period. *Study withdrawals due to adverse events* were defined as any withdrawal from the study that was attributed to adverse events and occurred at any time during the study.

Quality assessment

The assessment of the methodological quality of the included RCTs was performed with the use of the Jadad criteria. According to these criteria, one point is assigned to a comparative trial for the presence of the randomization, blinding, and data regarding study withdrawals, respectively. In addition, one point is awarded or subtracted, depending on the appropriateness of the randomization and blinding procedures, respectively. The maximum score that can be attributed to a trial is 5 points. Trials assigned to a Jadad score higher than 2 points are considered as trials of adequate methodological quality.[18,19]

Statistical analysis

When the outcomes analyzed were expressed as dichotomous variables, we used a random effects model,[20] to estimate pooled odds ratios and 95% confidence intervals. In addition, the presence of statistical heterogeneity between the trials included in our study was assessed by the χ^2-test. Regarding the χ^2-test, a p value less than 0.1 was used to denote the presence of significant heterogeneity among the evaluated trials. We used the Review Manager (RevMan) v.5.0 Software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008) to perform all statistical analyses.

Results

Selected studies

The search strategy identified 1605 PubMed citations, 780 Cochrane central registry of control trials, and 3170 Scopus. From these articles, 5 individual RCTs were considered as eligible for inclusion in our meta-analysis.[21–25] The detailed procedure of selection of trials eligible for inclusion is depicted in Fig. 1 (Flow diagram).

Characteristics of the included RCTs

In Table 1 we present the main characteristics of the 5 RCTs included in this meta-analysis. All 5 included RCTs had a double-blind design.[21–25] Two of the 5 included RCTs were multicenter.[21,22] Two of the 5 included RCTs were assigned to a Jadad score of 2,[23,24] two a score of 3,[21,22] and the remaining 1 RCT was assigned a score of 4.[25] In Tables 2 and 3 we present data from the included RCTs regarding the effectiveness and safety outcomes of this meta-analysis, respectively.

Characteristics of the included populations

All 5 RCTs were conducted at European countries.[21–25] Three out of the 5 RCTs enrolled adult women, specifically age ranged between 18 and 84 years among these 3 RCTs.[21,23,24] Regarding the remaining 2 included RCTs, the age of the enrolled women ranged from 15 to 75 years.[22,24] All 5 RCTs enrolled adult women with clinical symptoms suggestive of a lower urinary tract infection.[21–25] In all 5 included studies, the enrolled patients had documented bacteriuria.[21–25] In 1 out of these 3 studies, a group of the included women had symptoms and detected pyuria without documented bacteriuria.[22]

Antimicrobial regimens

In 2 of the 5 included studies, all patients were treated with the same antibiotic and with the same dosage schedule; the antibiotics used were nitrofurantoin,[22] and co-trimoxazole,[25] respectively. In 2 RCTs, the patients that received antibiotic treatment were allocated into 3 groups.[21,23] Specifically, in 1 out of these 2 RCTs, the patients allocated in all 3 antibiotic treatment groups were treated with the same antibiotic agent but according to different dosage schedules,[21] whereas in the other study, the patients allocated in the 3 antibiotic-treated groups were treated with different antibiotic agents and with different dosage schedules.[23] In the remaining RCTs the antibiotic-treated patients were allocated in 2 groups and were treated with different antibiotic agents.[24]

Regarding the duration of antibiotic treatment, in 2 of the 5 included RCTs patients received a single dose of antibiotic treatment,[23,24] in 1 RCT patients received a 3-day antibiotic course,[22] whereas in the remaining 2 RCTs patients received a 7-day antibiotic course,[21,25] with the exception of the patients in 1 out of these 2 studies that were allocated in a 3-day antibiotic course, followed by 4 days of placebo treatment.[21] In all 5 included RCTs, the patients allocated in the placebo treatment arms were treated with placebo for the same duration as the patients allocated in the respective antibiotic treatment arms.[21–25]

Concomitant treatment

In four of the five studies where information was provided, patients did not receive concomitant antimicrobial treatment.[21–25] The remaining 1 study did not provide relevant data.[21]

Follow-up

The duration of follow-up varied between 3 days after treatment institution and 3 months after the end of treatment among the 5 included RCTs.[21–25]

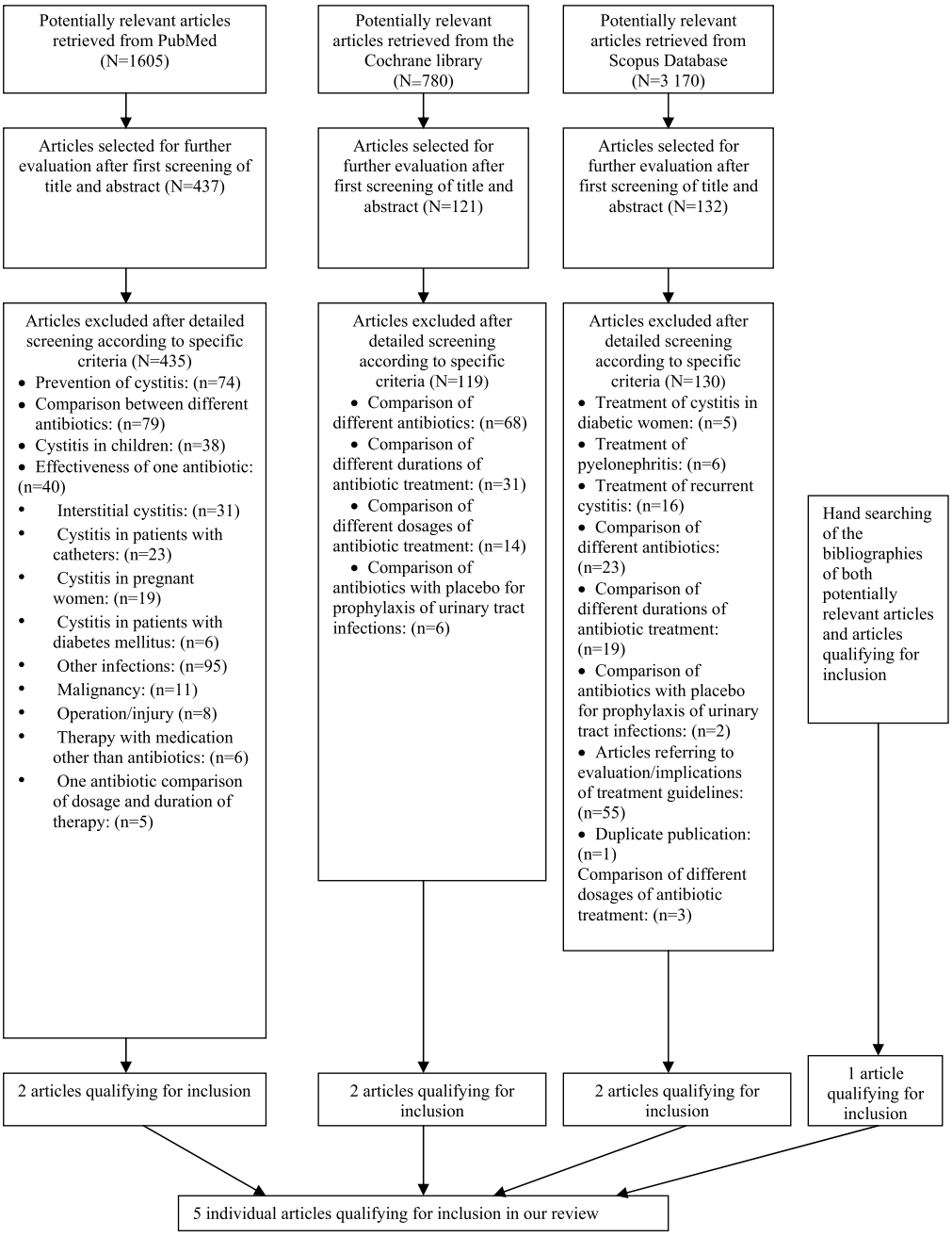

Figure 1 Flow diagram of the detailed process of selection of articles for inclusion in our review.

Outcomes of the meta-analysis

Effectiveness outcomes

Clinical success was significantly more likely in patients treated with antibiotics versus those treated with placebo [4 RCTs, 1062 patients, random effects model (REM), odds ratio (OR) = 4.81, 95% confidence intervals (CI) = 2.51–9.21].[21–24] Cure was significantly more likely in patients treated with antibiotics versus those treated with placebo (4 RCTs, 1062 patients, REM, OR = 4.67, 95%CI = 2.34–9.35), [21–24] (Fig. 2.) Microbiological success at the end of treatment was significantly more likely in patients treated with antibiotics versus those treated with placebo (3 RCTs, 967 patients, REM, OR = 10.67, 95%CI = 2.96–38.43),[21,22,24] (Fig. 3). The endpoints where the above-mentioned 3 outcomes were evaluated, ranged from day 3 up to day 17 among the respective RCTs. Microbiological success after the end of treatment was significantly more likely in patients treated with antibiotics versus those treated with placebo (3 RCTs, 738 patients, REM, OR = 5.38, 95%CI = 1.63–17.77),[21–23] (Fig. 3). Microbiological reinfection or relapse after the end of treatment was significantly more likely in patients treated with placebo versus those treated with antibiotics (5 RCTs, 843 patients, REM, OR = 0.27,

Table 1 Main characteristics of the randomized controlled trials included in the meta-analysis.

First author, year	Study design, Location	Jadad score	Study population	Inclusion criteria	Exclusion criteria	Antibiotic treatment, dosage, duration	Placebo	Concomitant antibiotic treatment	Follow-up
Ferry, 2007[21]	Multicenter, double-blind RCT, Northern Sweden	3	Non-pregnant women ≥18 y with uncomplicated UTI	Urgency, dysuria, suprapubic or loin pain[b] + significant bacteriuria[c]	Antibiotics for UTI during the last mo, known or suspected penicillin allergy, participation in other studies during the last 3 mo, genital infection, diabetes, abnormality of the urinary tract, ≥1 sings of pyelonephritis, urine incontinence and catheter or pads requiring, pregnancy or planned pregnancy, previous participation in the study	p.o pivmecillinam Group I: 200 mg tid, 7d Group II: 200 mg bid, 7 dGroup III: 400 mg bid, 3d + placebo, 4 d	Placebo, 7 d	NR	Day 8—10 Day 35—49
Christiaens, 2002[22]	Multi-center, double-blind RCT, Belgium	3	Non-pregnant women 15—54 y with uncomplicated UTI	Group A: clinically suspected UTI: (acute dysuria, urinary frequency or urgency + detected pyuria) Group B: bacteriologically proven UTI: (symptoms + pyuria + bacteriuria: $\geq 10^5$ cfu/ml)	Fever >38 °C (axillary), known nephrological or neurological problems, diabetes, other immuno compromising diseases, recurrent UTI (>3 occurrences/y during the past year or 1 episode in the past 3 mo), gynaecological complaints, symptom's duration >7 d, antibiotics during the past 4 w, known allergy to nitrofurantoin	p.o nitrofurantoin, 100 mg qid, 3 d	Placebo, 3 d	None	Day 3 Day 5 2 w after the start of treatment
Asbach, 1991[23]	Double-blind RCT, Germany	2	Non-pregnant women 18—35 y with uncomplicated UTI	Clinical history and presenting symptoms (dysuria, frequency and urgency) and physical examination and presence of leucocyturia + culture	Signs of upper urinary tract involvement, diabetes	p.o single dose Group I: cefixime 400 mg Group II: co-trimoxazole (160 mg/800 mg) Group III: ofloxacin 200 mg	Placebo single dose	None	Day 3—5 Day 14—17
Dubi, 1982[24]	Double-blind RCT France	2	Non-pregnant women 18—84 y with uncomplicated UTI	Uncomplicated UTI bacteriologically confirmed organism counts in urine: $\geq 10^5$/ml	Internees, women with pyelonephritis, anatomic abnormalities of the urinary tract, diabetes, interstitial nephritis, impaired renal function, allergy in the medications used in the study	p.o single dose Group I: co-trimoxazole (480/2400 mg) Group II: amoxicillin (750 mg)	Placebo single dose (Na-bicarbonate)	None	NR

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Table 1 (*continued*)

First author, year	Study design, Location	Jadad score	Study population	Inclusion criteria	Exclusion criteria	Antibiotic treatment, dosage, duration	Placebo	Concomitant antibiotic treatment	Follow-up
Brooks, 1972[25,a]	Double-blind RCT England	4	Non-pregnant >15 y and <75 y women with uncomplicated UTI	Dysuria and frequency, organism counts in urine: $\leq 10^4$/ml	Renal, cardiac or hepatic failure, concurrent antibacterial therapy	p.o co-trimoxazole (40 mg/200 mg)4 tb the 1st d +2 tb qid until 7th day, 7 d	Placebo, 7 d	None	Day 2 Day 9 6 w, 3 mo after the end of treatment

Abbreviations: y = years, mo = months, d = days, w = weeks, UTI = urinary tract infection, tb = tablets, LUTI = lower urinary tract infection, CRP = C-reactive protein, bid = twice daily, tid = three times a day, qid = four times daily.

[a] This study also had another part which involved women with dysuria, frequency and with $\geq 10^5$ organism counts in their urine who where treated with co-trimoxazole or sulphadimidine.

[b] The severity of each symptom was graded as none, light, moderate, or severe (scores 0–3), and a total symptom score of ≥ 2 was required for inclusion.

[c] Significant bacteriuria was defined as 10^3 cfu/ml for primary pathogens, 10^4 cfu/ml for secondary pathogens, and as 10^5 cfu/ml for doubtful pathogens, and as 10^5 cfu/ml for all species in patients without symptoms.

95%CI = 0.13–0.55).[21–25] The endpoints during which these outcomes were evaluated ranged from day 7 to day 49 among the respective RCTs.

In the 2 RCTs that reported relevant data, the incidence of pyelonephritis in women treated with antibiotics ranged from 0% to 0.15%, whereas in women treated with placebo ranged from 0.4% to 2.6%.[21,22]The difference observed between patients treated with antibiotics versus those treated with placebo was non-significant (2 RCTs, 962 patients, REM, OR = 0.33, 95%CI = 0.04–2.70).[21,22]

In the 3 RCTs that provided data for emergence of resistance, emergence of resistant pathogens in women treated with antibiotics ranged from 0% to 45.4%, whereas in women treated with placebo resistance ranged from 0% to 20%. The difference regarding this outcome between patients treated with antibiotics versus those treated with placebo was non-significant (3 RCTs, 173 patients, REM, OR = 1.32, 95%CI = 0.50–3.48).[23–25]

Regarding persistence of symptoms and clinical relapse, data provided from the included RCTs were not solid in order to perform a meta-analysis.

Safety outcomes

Total adverse events

Adverse events were significantly more likely to occur in patients treated with antibiotics versus patients treated with placebo (4 RCTs, 1068 patients, REM, OR = 1.64, 95%CI = 1.10–2.44),[21,22,24,25] (Fig. 4). Regarding study withdrawals due to adverse events, the difference observed between patients treated with antibiotics versus those treated with placebo was non-significant (3 RCTs, 1007 patients, REM, OR = 1.57, 95%CI = 0.31–7.93).[21,22,25]

Discussion

The main finding of our study is that clinical success and microbiological success are more likely to occur in women with documented acute uncomplicated cystitis that was treated with antibiotics, in comparison with those treated with placebo. Antibiotics were also found to be superior to placebo regarding cure and microbiological failure at long term follow-up. Regarding the other effectiveness outcomes, development of pyelonephritis and emergence of resistance, antibiotics were found to confer no benefit over placebo. However, adverse events were found to occur more frequently in women treated with antibiotics.

Supportive data are provided from a placebo-controlled trial that did not fulfill all of our criteria in order to be included in our meta-analysis. Specifically, this study reported the superiority of a 3-day trimethoprim treatment to reduce the symptom of dysuria in women who had symptoms suggestive of urinary tract infection but had a negative dipstick test for both leucocytes and nitrites.[26] Another study that did not provide patient related data, thus did not fulfill all our inclusion criteria, reported that a significant proportion of placebo-treated women with cystitis (almost 80%) obtained sterilization of the urine culture within 5 months. However, a significant number of

Table 2 Data from the included randomized controlled trials regarding the effectiveness outcomes of the meta-analysis.

First author, year[(ref)]	Therapeutic arm	ITT population (*n*)	Persistence of symptoms	Clinical success	Cure	Microbiological success at the end of treatment	Microbiological success at the 1st assessment after the end of treatment	Microbiological reinfection or relapse	Clinical relapse
Ferry, 2007[21]	Antibiotic group I *n*/*N* (%)	281	Total percentage: (56.0)	132/213 (61.9)	132/213 (61.9)	198/213 (92.9)	153/172 (88.9)	19/172 (11.0)	124/172 (72.0)
	Antibiotic group II *n*/*N* (%)	289		137/214 (64.0)	137/214 (64.0)	207/214 (96.7)	155/187 (82.8)	32/187 (17.1)	122/187 (65.2)
	Antibiotic group III *n*/*N* (%)	285		119/216 (55.0)	119/216 (55.0)	185/216 (85.6)	141/164 (85.9)	23/164 (14.0)	112/164 (68.2)
	Placebo group *n*/*N* (%)	288	(88.0)	53/212 (25.0)	53/212 (25.0)	72/212 (33.9)	66/94 (70.2)	28/94 (29.7)	48/94 (51.0)
Christiaens, 2002[22]	Antibiotic group *n*/*N* (%)	40	NR	27/35 (77.1)	13/35 (37.1)	21/26 (80.7)	17/23 (73.9)	6/23 (26.0)	NR
	Placebo group *n*/*N* (%)	38	NR	19/35 (54.2)	7/35 (20.0)	5/25 (20.0)	9/22 (40.9)	13/22(59.0)[b]	NR
Asbach, 1991[23]	Antibiotic group I *n*/*N* (%)	20	NR	17/19 (89.4)	17/19 (89.4)	NR	17/19 (89.4)	2/19 (10.5)	NR
	Antibiotic group II *n*/*N* (%)	20	NR	17/19 (89.4)	17/19 (89.4)	NR	17/19 (89.4)	2/19 (10.5)	NR
	Antibiotic group III *n*/*N* (%)	20	NR	16/19 (84.2)	16/19 (84.2)	NR	16/19 (84.2)	3/19 (15.7)	NR
	Placebo group *n*/*N* (%)	20	NR	5/19 (26.3)	5/19 (26.3)	NR	5/19 (26.3)[a]	14/19 (73.6)	NR

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Table 2 (*continued*)

First author, year[(ref)]	Therapeutic arm	ITT population (*n*)	Persistence of symptoms	Clinical success	Cure	Microbiological success at the end of treatment	Microbiological success at the 1st assessment after the end of treatment	Microbiological reinfection or relapse	Clinical relapse
Dubi, 1982[24]	Antibiotic group I *n*/*N* (%)	21	NR	20/21 (95.2)	20/21 (95.2)	20/21 (95.2)	NR	1/21 (4.7)	NR
	Antibiotic group II *n*/*N* (%)	22	NR	10/22 (45.4)	10/22 (45.4)	10/22 (45.4)	NR	12/22 (54.5)	NR
	Placebo group *n*/*N* (%)	18	NR	8/18 (44.4)	8/18 (44.4)	8/18 (44.4)	NR	10/18 (55.5)	NR
Brooks, 1972[25]	Antibiotic group *n*/*N* (%)	25	6/24 (25.0)	NR	NR	NR	NR	6/24 (25.0)	NR
	Placebo group *n*/*N* (%)	20	8/20 (40.0)	NR	NR	NR	NR	7/20 (35.0)	NR

Abbreviations: ITT = intention to treat population; NR = not reported.

[a] Data refer to the 14–17 days after the end of treatment assessment.

[b] These data refer to patients that had significant bacteriuria but with a negative urine culture obtained at an earlier assessment.

Table 3 Data from the included randomized controlled trials regarding the safety outcomes of the meta-analysis.

First author, Year[(ref)]	Therapeutic arm	Adverse events	Study withdrawals due to adverse events
Ferry, 2007[21]	Antibiotic group I *n/N* (%)	37/217 (17.0)[a]	Total: 7/657 (1.0)
	Antibiotic group II *n/N* (%)	26/220 (11.8)[a]	
	Antibiotic group III *n/N* (%)	31/220 (14.0)[a]	
	Placebo group *n/N* (%)	27/227 (11.8)[a]	0/227 (0)
Christiaens, 2002[22]	Antibiotic group *n/N* (%)	9/40 (22.5)[b]	0/40 (0)
	Placebo group *n/N* (%)	10/38 (26.3)[b]	1/38 (2.6)
Asbach, 1991[22]	Antibiotic group I *n/N* (%)	NR	NR
	Antibiotic group II *n/N* (%)	NR	NR
	Antibiotic group III *n/N* (%)	NR	NR
	Placebo group *n/N* (%)	NR	NR
Dubi, 1982[23]	Antibiotic group I *n/N* (%)	2/21 (9.5)[c]	NR
	Antibiotic group II *n/N* (%)	3/22 (13.6)[c]	NR
	Placebo group *n/N* (%)	1/18 (5.5)[c]	NR
Brooks, 1972[25]	Antibiotic group *n/N* (%)	5/25 (20)[d]	2/25 (8.0)
	Placebo group *n/N* (%)	1/20 (5.0)[d]	1/20 (5.0)

Abbreviations: NR = not reported.
[a] Mild to moderate adverse events, most commonly were gastrointestinal reactions.
[b] The reported adverse events were gastrointestinal, headache, dizziness—fatigue, sleep disturbances, vaginal itching, dermatological problems and other.
[c] The reported adverse events were mainly epigastralgia and nausea.
[d] The reported adverse events were sore tongue, furred tongue, skin rash, vomiting and general malaise.

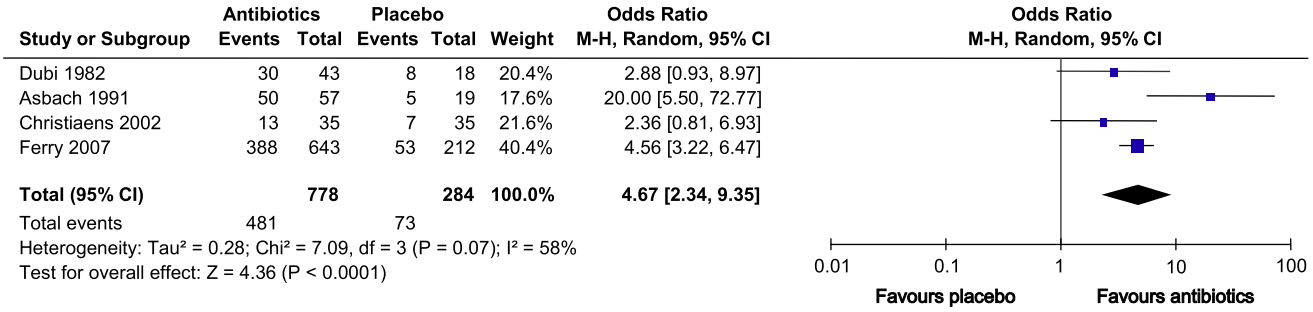

Figure 2 Clinical cure in women with acute uncomplicated cystitis who were treated with antibiotics compared to placebo. Vertical line indicates no difference between the compared treatment groups. Pooled odds ratios (95%CI) are shown by diamond shapes. 95%CIs are shown by horizontal lines. Squares indicate point estimates. The size of the squares indicates the weight of each individual study in the meta-analysis.

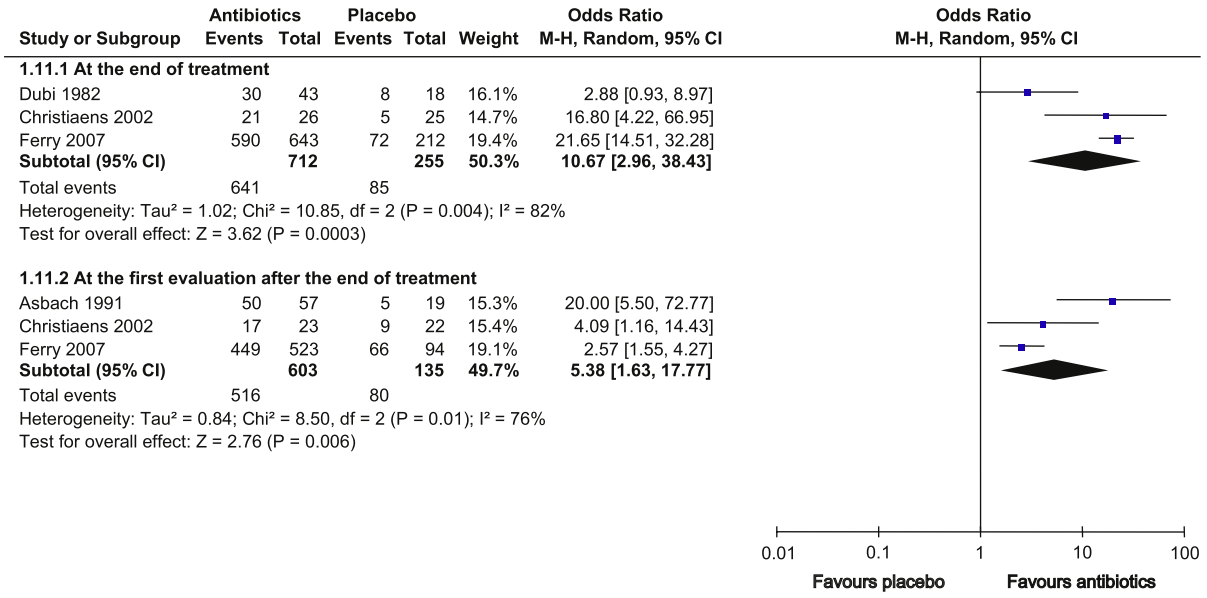

Figure 3 Microbiological success (eradication) at the end of treatment and at the first evaluation after the end of treatment in women with acute uncomplicated cystitis who were treated with antibiotics compared to placebo. Vertical line indicates no difference between the compared treatment groups. Pooled odds ratios (95%CI) are shown by diamond shapes. 95%CIs are shown by horizontal lines. Squares indicate point estimates. The size of the squares indicates the weight of each individual study in the meta-analysis.

these women (about one half) had a recurrent urinary tract infection within a year.[27]

According to our findings, antibiotic treatment was superior to placebo regarding the resolution of symptoms of cystitis. This finding was also consistent in terms of eradication of the causative pathogen in women with bacteriologically confirmed cystitis. However, in everyday clinical practice the main reason for which the majority of women with cystitis consult their doctor is the presence of symptoms suggestive of a urinary tract infection, as mentioned above. As a result, the clinical question that arises is whether or not to start empirical antibiotic treatment in these women without performing a dipstick test or a urine culture.[14,28] Treating women with symptoms of lower urinary tract infection (LUTI) without laboratory confirmation has advantages and drawbacks. Specifically, it can reduce the number of visits and the number of diagnostic tests performed and, consequently the medical costs deriving from these procedures. Current guidelines suggest that there is a possibility to treat symptomatic women empirically, and in the absence of clinical response after 48 h to perform a urine culture in order to identify the causative pathogen and tailor out antibiotic treatment.[28] However, in women with a history of recurrent bacteriologically confirmed LUTI who also recognize their symptoms, empirical treatment could start without laboratory documentation.[28]

On the other hand, treating dysuric women with antibiotics without bacteriological confirmation can result in increased observed adverse events and increased antibiotic resistance. The high rates of resistance to both co-trimoxazole and fluoroquinolones that have been observed among uropathogens necessitate a judicious use of antibiotics.[29–33] This factor, along with the increased costs deriving from antibiotic

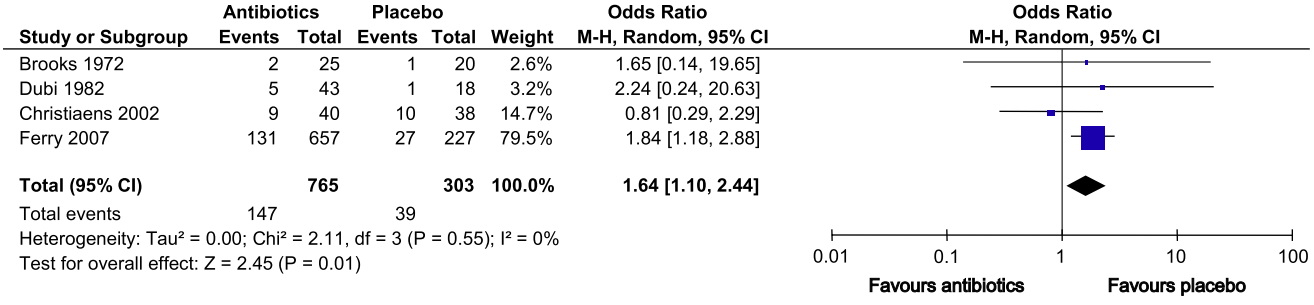

Figure 4 Total adverse events occurring in women with acute uncomplicated cystitis who were treated with antibiotics compared to placebo. Vertical line indicates no difference between the compared treatment groups. Pooled odds ratios (95%CI) are shown by diamond shapes. 95%CIs are shown by horizontal lines. Squares indicate point estimates. The size of the squares indicates the weight of each individual study in the meta-analysis.

prescriptions should be taken into consideration when deciding how to treat a woman with a clinical suspicion with a lower urinary tract infection. In our study adverse events were more likely to occur in women treated with antibiotics in comparison with those treated with placebo.

Our study has limitations that should be taken into consideration. Firstly, the number of the included RCTs is limited; this reflects the scarcity of RCTs assessing the comparison of antibiotic treatment to placebo in uncomplicated cystitis. In addition, the majority of women enrolled in the RCTs included in our meta-analysis have mild to moderate clinical symptoms. This should be taken in consideration in the extrapolation of our findings in women with more severe symptoms who are probably less likely to consent for enrollment in a placebo-controlled trial. Another limitation of our meta-analysis is that 4 out of the 5 included RCTs,[22–25] did not provide data regarding the number and/or the severity of cystitis symptoms. Only 1 of the included RCTs used a symptom score,[21] given that in almost all of the included RCTs no stratification of the enrolled women according to either the number or the severity of symptoms was performed at baseline, no correlation between the number and/or the severity of cystitis symptoms with any of the clinical and/or bacteriological outcomes could be attempted in this meta-analysis. Such a correlation might have shown that antibiotic treatment might confer more benefit to women with a greater number and more severe symptoms, in comparison with those that had fewer and less severe symptoms, bearing in mind that the risk for adverse events after antibiotic treatment is the same for all women that received antibiotic treatment. Additionally, antibiotics were found to confer no benefit regarding the development of pyelonephritis and emergence of resistant pathogens. However, the small number of women included in these analyses is a limitation that should be taken into consideration. Furthermore, the relative small time period in which emergence of resistance was evaluated in this meta-analysis is also a considerable limitation.

In conclusion, our meta-analysis showed that antibiotic treatment has greater clinical and microbiological effectiveness compared to placebo treatment in non-pregnant women with bacteriologically confirmed cystitis. However, antibiotic treatment was accompanied by more adverse events. Taking into consideration that the disturbing symptoms of cystitis are the main reason for which women with cystitis seek for medical advice, the data from this meta-analysis do suggest that physicians should continue prescribing antibiotic treatment to women complaining for such symptoms. However, the fact that antimicrobial treatment is also associated with adverse events, pressure for emergence of resistance, and cost may make clinicians to consider offering the wait and see option (without antibiotics), especially in women with minimal symptoms of cystitis. Finally, more RCTs focusing on potential correlations between the severity of symptoms with the clinical and bacteriological outcomes, along with a generally accepted symptom score for cystitis could make an important contribution in order to clarify which women with symptoms of acute cystitis could benefit the most from treatment, taking all relevant consideration into account.

Conflict of interest

None.

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