Infection and Drug Resistance

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ORIGINAL RESEARCH

Comparison of high-dose, short-course levofloxacin treatment vs conventional regimen against acute bacterial infection: meta-analysis of randomized controlled trials

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Objects: This meta-analysis aims to assess the efficacy and safety of high-dose, short-dose levofloxacin in comparison with conventional therapy on treating acute bacterial infection.

Methods: PubMed, Embase and Cochrane database were searched up to September 2018. Only randomized controlled trials (RCTs) evaluating high-dose, short-course levofloxacin and conventional regimen in the treatment of acute bacterial infection were included. The primary outcomes were clinical responses, microbiologic eradication and adverse effects.

Results: Seven RCTs of 3,731 patients (1,835 in the high-dose, short-course levofloxacin regimen group and 1,896 in the conventional regimen group) were included. Overall, no significant difference between the high-dose, short-course levofloxacin regimen group and the conventional regimen was found in terms of clinical response (risk ratio, RR: 1.01; 95% CI: 0.98–1.04, I^2=10%). In addition, the high-dose, short-course levofloxacin regimen had a similar microbiological eradication rate to conventional regimen (RR: 1.02; 95%CI: 0.98–1.06, I^2=0%). Moreover, the high-dose, short-course levofloxacin regimen had a similar incidence of treatment-emergent adverse events to conventional regimen (RR: 1.07; 95%CI: 0.99–1.17, I^2=0%). This trend was not affected by the different types of infections—community-acquired pneumonia, complicated urinary tract infection/acute pyelonephritis or acute sinusitis, different conventional regimen—levofloxacin (500 mg daily for 7–14 days) or ciprofloxacin (400 mg IV or 500 mg oral, twice daily for 10 days).

Conclusion: High-dose, short-course levofloxacin exhibits similar clinical success and microbiologic eradication rates with conventional regimen in the treatment of acute bacterial infection. Moreover, the high-dose, short-course levofloxacin regimen was well tolerated and had comparable safety profiles with the conventional regimen.

Keywords: levofloxacin, acute bacterial infection, community-acquired pneumonia, complicated urinary tract infection, acute sinusitis

Introduction

Effective antimicrobial agent with appropriate dosage and adequate duration is the cornerstone of the treatment of bacterial infection. However, the overuse of antibiotics may result in the emergence of antibiotic-resistant pathogens. To optimize the existing regimen for effectively treating bacterial infection with abbreviated duration of therapy, a strategy with high-dose, short-course antibiotic regimen has been developed.[1] Levofloxacin, one of fluoroquinolones, is a broad-spectrum

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antibiotic and exhibits concentration-dependent bactericidal activity. This anti-bacterial activity of this type of antibiotic is closely correlated with the ratio of the area under the concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) for the bacteria.[2–4] In addition, a high ratio of peak plasma concentration to MIC can help the emergence of antibiotic resistance. Theoretically, increasing the dose of fluoroquinolones under a tolerable dosage even with shortening the duration of antibiotic treatment can achieve at least similar clinical efficacy as a low-dose, long-course regimen. Since 2013, Dunbar et al[5] demonstrated the regimen of high-dose, short-course of levofloxacin (750 mg daily for 5 days) was as effective as the conventional regimen of levofloxacin (500 mg daily for 10 days) for the treatment of community-acquired pneumonia (CAP) in a randomized, double-blind investigation. The similar results were found in the further subgroup analyses of CAP patients with pneumonia severity index class III and IV,[6] aged ≥65 years,[7] with atypical pathogens.[8] In addition, a high-dose, short-course regimen was assessed in the setting of complicated urinary tract infection (cUTI), acute pyelonephritis (APN), and acute sinusitis.[9–12] But so far, there is no systematic review and meta-analysis comparing the efficacy and safety of high-dose, short-course levofloxacin and comparators for treating acute bacterial infections. Therefore, we performed a comprehensive meta-analysis to provide better evidence of the efficacy and safety of high-dose, short-course levofloxacin regimen on treating bacterial infections.

Methods

Study search and selection

All clinical studies were identified by a systematic review of the literature in the PubMed, Embase, and Cochrane databases until September 2018 using the following search terms: levofloxacin, bacterial, pneumonia, sinusitis, urinary tract infections, and random* (supplementary material). Only randomized controlled trials (RCTs) that compared the clinical efficacy and adverse effect of high-dose, short-course levofloxacin (750 mg daily for 5 days) and the conventional regimen were included. In addition, we searched all references in the relevant articles and reviews for additional eligible studies. Conference abstracts were not searched. Studies were excluded if they focused on in vitro activity or pharmacokinetic-pharmacodynamics assessment only. The articles of all languages of publication were included. Two authors (Cheng and Chen) searched and examined publications independently to avoid bias. When they disagreed, another author (Lai) resolved the issue. The following data including year of publication, study design and duration, type of infections, the antibiotic regimen of levofloxacin, and comparator, the outcomes, and adverse effects were extracted from every included study.

Definitions and outcome

The primary outcome was overall clinical success with the resolution of clinical signs and symptoms of acute bacterial infection at the end of therapy. Secondary outcomes included microbiologic eradication rate, and the adverse effect. Microbiologic eradication was defined as eradication of bacterial infections.

Data analysis

This study used Cochrane risk-of-bias assessment tool to evaluate the quality of enrolled studies and the risk of bias.[13] The statistical analyses was conduct using the software review manager, version 5.3. The degree of heterogeneity was evaluated with Q statistic generated from the chi-squared test. The proportion of statistical heterogeneity was assessed by I^2 measure. Heterogeneity was considered as significant when P-value was less than 0.10 or I^2 more than 50%. The fixed-effect model and the random-effects model were applied when the data was homogenous, and heterogeneous, respectively. The pooled risk ratio (RR) and 95%CI were calculated for outcome analyses.

Results

Study selection and characteristics

The search program yielded 5,700 references, including 796 from PubMed, 4,605 from Embase, and 299 from the Cochrane database. Then 4,010 articles were screened after excluding 1,690 duplicated articles. Finally, seven RCTs[5,9–12,14,15] fulfilling the inclusion criteria were included in this meta-analysis (Figure 1). All of studies were designed to compare the clinical efficacy and safety of high-dose, short-course levofloxacin with the conventional regimen for patients with bacterial infection (Table 1).[5,9–12,14,15] During the initial enrollment, the high-dose, short-course regimen and conventional regimen were applied for 1,835 and 1,896 patients, respectively. All of them were multicenter studies. Four studies were performed in the US,[5,9–11] and three studies were conducted in China.[12,14,15] Three studies[5,14,15] focused on CAP, and three studies focused on cUTI and APN.[9,10,12] Only one

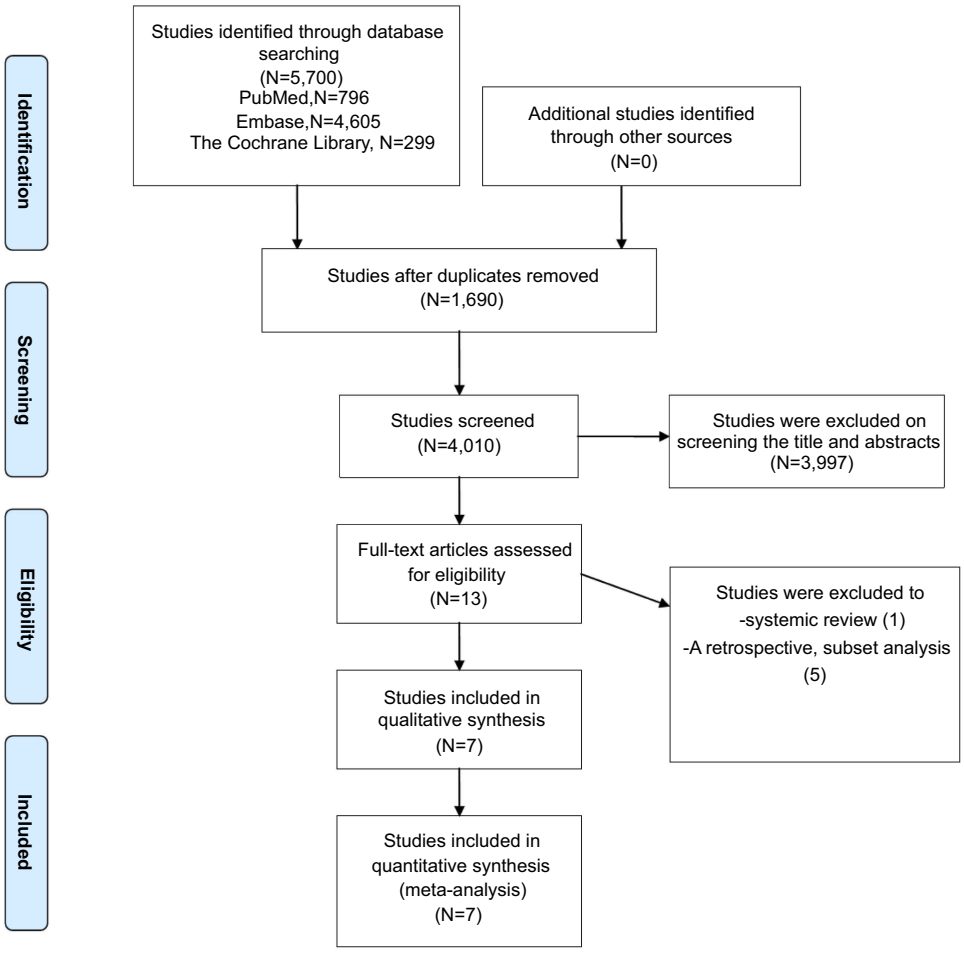

Figure 1 Flow diagram of the study selection process.

study investigated acute sinusitis.[11] Except one study that used ciprofloxacin regimen as a comparator,[9,10] the other six studies[5,9,11,12,14,15] used levofloxacin 500 mg for 7–14 days for comparison. Figures 2 and 3 show the analyses of risk of bias. Although most of the domains in the enrolled studies were classified as low risk of bias or uncertain risk of bias, three studies[12,14,15] carried high risk of bias in the domain of performance and detection bias (Figures 2 and 3).

Clinical success

Overall, the high-dose, short-course levofloxacin regimen had a similar clinical success rate to the conventional regimen (RR: 1.01; 95%CI: 0.98–1.04, I^2=10%, Figure 4). Sensitivity analysis after deleting individual study each time to reflect the influence of the single data set to the pooled RR showed similar findings. In the different subgroup of patients with CAP, cUTI/APN, and acute sinusitis, similar clinical success rates were noted between two different regimens (for CAP, RR: 0.98; 95%CI: 0.95–1.02, I^2=0%; for cUTI/APN, RR: 1.04; 95%CI: 0.99–1.10, I^2=0%; for acute sinusitis, RR: 1.03; 95%CI: 0.96–1.11). Five studies[5,11,12,14,15] compared the effect of high-dose, short-course levofloxacin (750 mg daily for 5 days) and conventional use of levofloxacin (500 mg daily for 7–14 days), and there was no difference in terms of clinical success rates between these two regimen (RR: 1.00; 95%CI: 0.97–1.03, I^2=0%). Another two studies[9,10] compared the high-dose, short-course levofloxacin regimen and the conventional regimen with ciprofloxacin (400 mg IV or 500 mg oral, twice daily for 10 days), their clinical success rates were similar (RR: 1.06, 95%CI: 0.99–1.13, I^2=0%)

Microbiologic eradication

High-dose, short-course levofloxacin regimen had a similar microbiological eradication rate to the conventional regimen (RR: 1.02; 95%CI: 0.98–1.06, I^2=0%, Figure 5). Sensitivity analysis showed the similar results. In the different subgroup of patients with CAP, cUTI/APN, and acute

Table 1 Characteristics of included studies

Study, published year, ref.	Study design	Country	Study period	Study population	No. of patients		Dose regimen	
					High-dose, short-course	Comparator	Levofloxacin	Comparator
Dunber et al, 2003[5]	Multicenter, randomized, double-blind, active treatment-controlled	United States		Mild to severe CAP	256	272	Levofloxacin, 750 mg per day for 5 days	Levofloxacin, 500 mg per day for 10 days
Poole et al, 2006[11]	Multicenter, randomized, open-label, controlled trial	United States		Acute sinusitis	389	391	Levofloxacin, 750 mg per day for 5 days	Levofloxacin, 500 mg per day for 10 days
Klausner et al, 2007[9]	Multicenter, randomized, double-blind	United States	2005–2006	APN	146	165	Levofloxacin 750 mg per day for 5 days	Ciprofloxacin 400 mg IV or 500 mg oral, twice daily for 10 days
Peterson et al, 2008[10]	Multicenter, double-blind, randomized study	United States		cUTI/APN	537	556	Levofloxacin 750 mg per day for 5 days	Ciprofloxacin 400 mg IV or 500 mg oral, twice daily for 10 days
Zhao et al, 2014[15]	Multicenter, randomized, open-label, controlled trial	China	2007–2008	CAP	121	120	Levofloxacin, 750 mg per day for 5 days	Levofloxacin, 500 mg per day for 7–14 days
Zhao et al, 2016[14]	Multicenter, randomized, open-label, controlled trial	China	2012–2014	CAP	221	227	Levofloxacin, 750 mg per day for 5 days	Levofloxacin, 500 mg per day for 7–14 days
Ren et al, 2017[12]	Multicenter, randomized, open-label, controlled	China	2012–2014	cUTI/APN	165	165	Levofloxacin, 750 mg per day for 5 days	Levofloxacin, 500 mg per day for 7–14 days

Abbreviations: CAP, community-acquired pneumonia; APN, acute pylonephritis; cUTI, complicated urinary tract infection.

sinusitis, similar microbiologic eradication rate were found for both regimens (for CAP, RR: 1.01; 95%CI: 0.96–1.06, I^2=0%; for cUTI/APN, RR: 1.03; 95%CI: 0.97–1.10, I^2=0%; for acute sinusitis, RR: 0.99; 95%CI: 0.94–1.05). While comparing high-dose, short-course levofloxacin (750 mg daily for 5 days) and conventional use of levofloxacin (500 mg daily for 7–14 days), the microbiologic eradication rate between these two regimens (RR: 1.01; 95% CI: 0.97–1.05, I^2=0%). The similar microbiologic eradication rate was noted between the high-dose, short-course levofloxacin regimen and the conventional regimen with ciprofloxacin (RR: 1.03, 95%CI: 0.96–1.11, I^2=0%).

Adverse events

Adverse events were recorded, irrespective of causality. Treatment-related adverse events are those ascribed by the investigator as having relationship to the study drug as well as those deemed not assessable. All studies[5,9–12,14,15] had

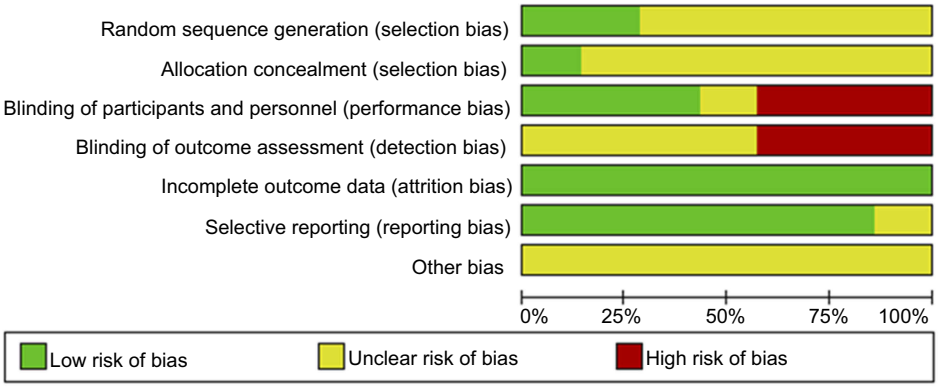

Figure 2 Summary of risk of biases.

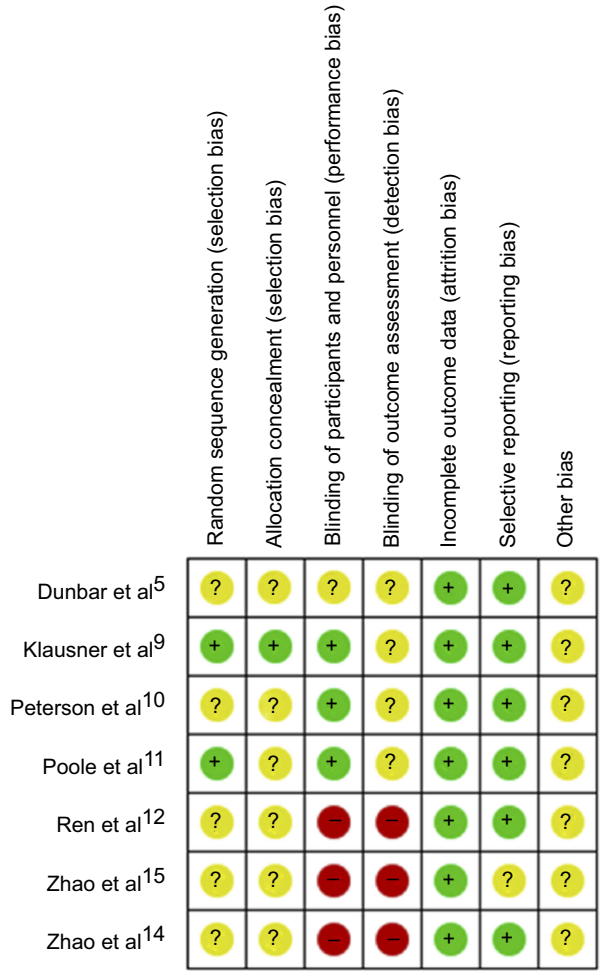

Figure 3 Risk of bias per study and domain.ors

reported the incidence of treatment-emergent adverse events, the high-dose, short-course levofloxacin regimen had a similar incidence to the conventional regimen (RR: 1.07; 95%CI: 0.99–1.17, I^2=0%, Figure 6). Five studies[5,9,11,14,15] reported the incidence of headache, the analysis showed the high-dose, short-course levofloxacin regimen had a similar incidence to the conventional regimen (RR: 1.45; 95%CI: 0.94–2.22, I^2=0%). In addition, the incidences of nausea, insomnia, diarrhea and vomiting were similar between these two regimens in the pooled analysis of four,[8,9,11,14] three,[8,11,14] two[11,14] and two[11,14] reports. Three studies[5,12,14] reported the drug-related adverse events, the incidences were similar between the high-dose, short-course levofloxacin regimen and the conventional regimen (RR: 1.23; 95%CI: 0.70–2.15, I^2=78%). Serious adverse events were reported in six studies,[5,9,10,12,14,15] the overall incidences were similar between these two regimens (RR: 0.73; 95%CI: 0.49–1.07, I^2=0%). Two studies[5,12] reported the risk of discontinuing drug due to adverse effects, the risk was similar between the high-dose, short-course levofloxacin regimen and the conventional regimen (RR: 0.84; 95%CI: 0.44–1.60).

Discussion

This meta-analysis based on seven studies found that high-dose, short-course levofloxacin had a similar clinical success rate of treating acute bacterial infections to the the conventional regimen. Similar findings were also noted in the microbiologic eradication rate. In addition, this result was not affected by the different types of infections—CAP, cUTI/APN or acute sinusitis, different conventional regimen—levofloxacin (500 mg daily for 7–14 days) or ciprofloxacin (400 mg IV or 500 mg oral, twice daily for 10 days). Although this meta-analysis did not assess the confounding effect of the disease severities, atypical pathogens, and patients' characteristics, several subgroup analyses helped resolve these issues. The subgroup analysis[6] of Dunber et al's trial[5] who belonged to PSI class III/IV—more severely ill CAP patients showed that both clinical success rate and microbiologic eradication

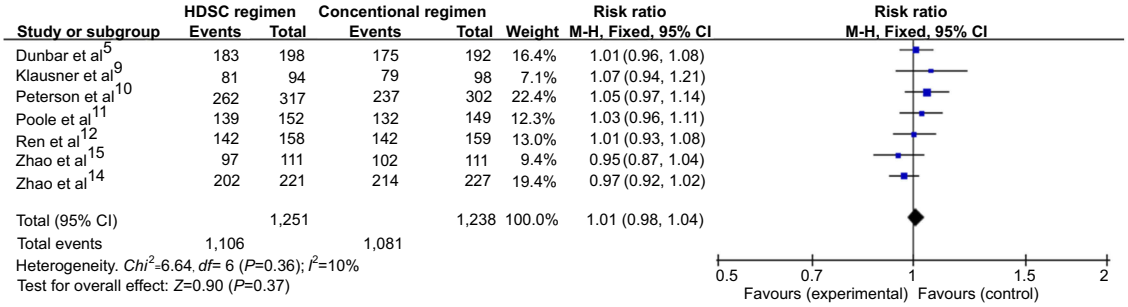

Figure 4 The overall clinical success between high-dose, short-course (HDSC) levofloxacin and conventional regimen in in the treatment of acute bacterial infections.

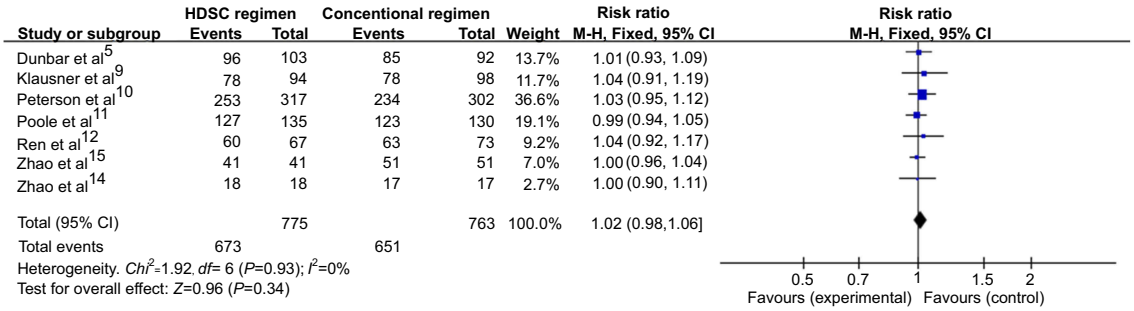

Figure 5 The overall microbiologic eradication rate between high-dose, short-course (HDSC) levofloxacin and conventional regimen in in the treatment of acute bacterial infections.

Figure 6 The risk of treatment-emergent adverse events between high-dose, short-course (HDSC) levofloxacin and conventional regimen in in the treatment of acute bacterial infections.

rate were comparable for the 750- and 500-mg regimens (for clinical success, 90.8% vs 85.5%, 95%CI: −15.9 to 5.4; for microbiologic eradication 88.9% vs 87.5%; 95% CI: −18.3 to 15.6). For patients with atypical CAP, a subgroup analysis[8] revealed that the clinical success rates were 95.5% (63/66) for the 750-mg group and 96.5% (55/57) for the 500-mg group (95%CI: −6.8 to 8.8). A post hoc, subgroup analysis[16] of Peterson et al's study[10] showed that clinical success rates between males and females were not statistically different between levofloxacin 750 mg once daily for 5 days and the ciprofloxacin 400/500 mg twice daily 10-day course group in either the modified intent-to-treat or microbiologically evaluable populations at end of treatment of cUTI/APN. Overall, these analyses confirm the role of high-dose, short-course levofloxacin in the treatment of acute bacterial infections is comparable with conventional regimen. Moreover, all of the enrolled studies were RCTs, and the risks of bias could be minimized. The enrolled studies were conducted in multicenters and in both Asia and Western countries. Therefore, the results of meta-analysis based on these studies should be convincing, and generalizable.

In addition to the assessment of clinical efficacy and microbiologic eradication, safety is another important concern in the treatment of acute bacterial infection by high-dose, short-course levofloxacin. In this analysis, the risks of

treatment-emergent adverse effects, common adverse effect, headache, serious adverse effect, and the risk of discontinuing drug due to adverse effects were similar between high-dose, short-course levofloxacin and conventional regimens. All of these findings should suggest that high-dose, short-course levofloxacin may be as safe as the conventional regimen in the treatment of acute bacterial infections.

Previous study[17] has demonstrated that a dose of 750 mg levofloxacin resulted in a greater proportion of patients with resolution of CAP symptoms by day 3 when compared with 500 mg therapy. Thus, it is possible for an earlier switch to oral medication for the 750 mg regimen. A similar trend was noted for patients with cUTI and APN, the total duration and dose of levofloxacin therapy was 50% shorter and 27% less for the high-dose, short-course regimen than the conventional regimen.[12] Although this meta-analysis did not evaluate the speed of symptom resolution and healthcare utilization, the short-course therapy is supposed to bring the additional benefit of shortening hospital stay, and reducing hospital cost based on previous reports.[1] However, further study is warranted to confirm this presumption.

Overall, this well-designed meta-analysis based on results of RCTs should be a valuable attempt at a systematic and comprehensive investigation to clarify the actual clinical relevance of a high-dose, short-course regimen of levofloxacin in the treatment of several common types of acute bacterial infections. Our results could potentially have a strong impact on prescribing in routine clinical practice due to demonstrated comparable efficacy and safety of high-dose short-course regimen of levofloxacin to conventional fluoroquinolone therapy, implying the possible improvement in health and economic outcomes if such a dosage regimen is used to treat relatively common infections.

This meta-analysis has several limitations. First, we did not evaluate the effect of high-dose, short-course regimens and conventional regimens against specific organism in each type of bacterial infection. Second, we did not assess the short-term outcomes, including re-infection, relapse or the emergency of resistance following antibiotic treatment, and also the long-term side effects, such as liver function impairment and kidney injury of high-dose short-course treatment. Further large-scale and long-term study is warranted to clarify these issues. Finally, most of the enrolled studies carry an unclear risk of bias in any of the explored domains, and almost half of the studies are identified as having a high risk of performance and detection bias, so the results should be carefully interpreted and cautiously implemented in clinical practice.

In conclusion, based on the analysis of seven RCTs, no differences in term of clinical success and microbiologic eradication rates were found between the high-dose, short-course levofloxacin and the conventional regimen in the treatment of acute bacterial infection. Moreover, the high-dose, short-course levofloxacin regimen was well tolerated and had comparable safety profiles as the conventional regimen. However, clinicians and health policy decision makers should also bear in mind the relatively rapid development of resistance to fluoroquinolones in a case of their widespread use and some issues including the use of healthcare, long-term outcomes and study bias remains unclear. Further studies are needed to confirm the role of high-dose short-course use of levofloxacin to treat acute bacterial infections.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

List of terms of the search strategy

PubMed

1. "levofloxacin" [MeSH Term]
2. "levofloxacin" [All Fields]
3. 1 or 2
4. "bacterial" [All Fields]
5. "sinusitis" [MeSH Terms]
6. "sinusitis" [All Fields]
7. Community-acquired [All Fields]
8. "pneumonia" [MeSH Terms]
9. "pneumonia" [All Fields]
10. "urinary tract infections" [MeSH Terms]
11. "urinary tract infections" [All Fields]
12. 4 OR 5 OR 6 OR 4 7 OR 8 OR 9 OR 10 OR 11
13. "randomized" [All Fields]
14. "randomised [All Fields]
15. 13 OR 14
16. 3 AND 12 AND 15

Embase

1. "levofloxacin"
2. "bacterial sinusitis"
3. "bacterial"
4. "sinusitis"
5. "Community-acquired"
6. "pneumonia"
7. "urinary"
8. "tract"
9. "infection"
10. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. 1 AND 10

Cochrane

1. levofloxacin
2. bacterial sinusitis
3. Community-acquired Pneumonia
4. Urinary tract infection
5. #2 or #3 or #4
6. #1 AND #5