Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

# Efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections: a systematic review and meta-analysis of randomized controlled trials

This article was published in the following Dove Press journal:
*Infection and Drug Resistance*



Shao-Huan Lan[1]
Chih-Cheng Lai[2]
Li-Chin Lu[3]
Shen-Peng Chang[4]
Hui-Ting Huang[4]

[1]School of Pharmaceutical Sciences and Medical Technology, Putian University, Putian, People's Republic of China; [2]Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Taiwan; [3]School of Management, Putian University, Putian, People's Republic of China; [4]Department of Pharmacy, Chi Mei Medical Center, Liouying, Taiwan

**Purpose:** To assess the clinical efficacy and safety of delafloxacin for treating acute bacterial skin and skin structure infections (ABSSSIs) in adult patients.

**Patients and methods:** The Cochrane Library, EBSCO, EMBASE, Ovid Medline, PubMed, and Web of Science databases were searched up to November 2018. Only randomized controlled trials (RCTs) that evaluated delafloxacin and other comparators for the treatment of ABSSSIs were included. The primary outcome was the clinical cure rate and the secondary outcomes were microbiological response and the risk of adverse events.

**Results:** Four RCTs were included. Overall, delafloxacin exhibited a clinical cure rate similar to the rates of the comparator drugs in the treatment of ABSSSI (OR, 1.05; 95% CI, 0.87–1.27, $I^2$=16%) and methicillin-resistant *Staphylococcus aureus* (MRSA)-associated ABSSSI (OR, 1.12; 95% CI, 0.71–1.77, $I^2$=0%). Delafloxacin had a microbiological eradication (documented and presumed) rate similar to the rates of the comparators in the treatment of ABSSSI (OR, 1.21; 95% CI, 0.58–2.50, $I^2$=0%) and MRSA-associated ABSSSIs (OR, 1.16; 95% CI, 0.37–3.60, $I^2$=0%). Delafloxacin and the comparators did not differ significantly in the risk of serious adverse events (AEs), treatment-emergent adverse events (TEAEs), and TEAEs related to the study drug. However, the risk of discontinuation of the study drug due to an AE was lower for delafloxacin than for the comparators (OR, 0.33; 95% CI, 0.15–0.74, $I^2$=0%).

**Conclusion:** The clinical efficacy of delafloxacin is as high as that of the comparator drugs in the treatment of ABSSSI, including MRSA-associated infections; furthermore, this antibiotic is as well-tolerated as the comparators.

**Keywords:** delafloxacin, acute bacterial skin and skin structure infections, MRSA, efficacy, safety

## Introduction

Acute bacterial skin and skin structure infection (ABSSSI) is a common type of infection in community and hospital settings.[1–3] Although the clinical outcomes of mild ABSSSIs are favorable, severe or complicated skin and soft tissue infections can be life-threatening, particularly without prompt and appropriate treatment. Appropriate antimicrobial therapy is the key to successful management of skin and skin structure infections; by contrast, inadequate empirical therapy is associated with a relatively high risk of treatment failure.[4,5] However,

Correspondence: Hui-Ting Huang
Department of Pharmacy, Chi Mei Medical Center, No.201, Taikang Taikang Vil., 73657, Liouying, Taiwan
Email kainesei@gmail.com

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/IDR.S202160

the incidence of infection by antibiotic-resistant bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), is increasing in the clinical setting of ABSSSI.[6,7] The antibiotics approved for treating ABSSSI when MRSA infection is suspected include vancomycin, linezolid, daptomycin, and tigecycline. In addition, several antibiotics, such as ceftaroline, dalbavancin, oritavancin, telavancin, and delafloxacin, which can be used to treat MRSA infection, have been developed to treat ABSSSIs.

Among these novel agents, delafloxacin is a new fluoroquinolone that has been developed in oral and intravenous forms and can facilitate the switch from intravenous to oral use in outpatient settings. In vitro studies[8–10] have demonstrated that delafloxacin is a broad-spectrum antibiotic that exhibits excellent activity against gram-positive pathogens, including MRSA, and gram-negative organisms. Therefore, delafloxacin can be considered a new therapeutic option for the treatment of ABSSSI. Several randomized controlled trials (RCTs)[11–14] have investigated the efficacy and safety of delafloxacin in the treatment of ABSSSIs in adult patients. However, a meta-analysis comparing the efficacy and safety of delafloxacin and other commonly used antibiotics for treating ABSSSI is not currently available. Therefore, we conducted a comprehensive meta-analysis to provide high-quality evidence on the efficacy and safety of delafloxacin in adult patients with ABSSSIs.

# Methods

## Data sources and search strategy

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses were used to search for articles and select studies and appraise article quality and data analysis procedures in this study.[15] The articles were searched systematically up to November 2018 from the Cochrane Library, EBSCO, EMBASE, Ovid Medline, PubMed, and Web of Science databases. The search terms "Baxdela" and "Delafloxacin" were used in the database search engines. Studies were included if they were RCTs, the participants in the experimental and control groups were adults (aged >18 years) with identical age distribution, the participants of the study exhibited ABSSSI, and the patients who received delafloxacin were in the experimental group and those who were treated with other antibiotic drugs were in the control group. The outcomes of interest included drug efficacy and safety, and dichotomous estimates were available for calculation. The diagnosis of ABSSSI included cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection and was characterized by ≥75 $cm^2$ of erythema, induration, or signs of system infection. Furthermore, we excluded articles if they were from

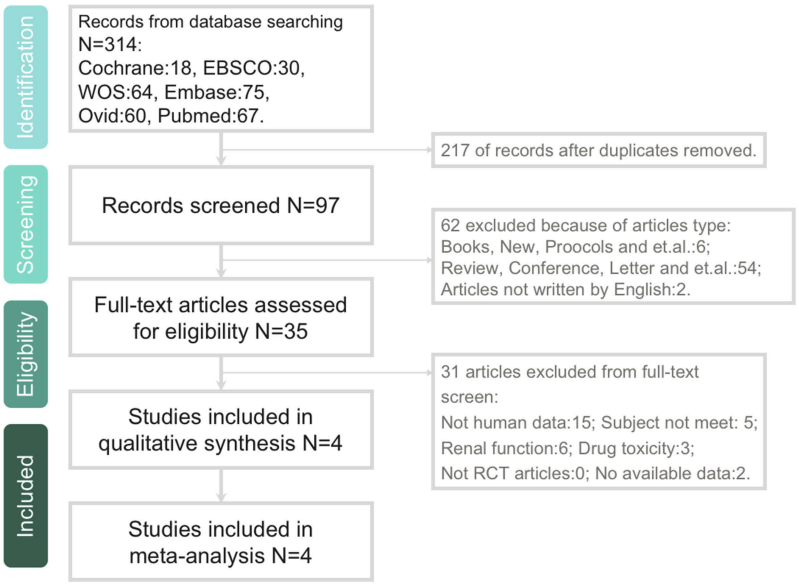


**Figure 1** Flowchart of the study selection process.
**Abbreviations:** WOS, Web of Science; RCT, randomized controlled trial.

books or newspapers; comprised only protocols; were reviews, opinion articles, articles from conferences; did not include human-related data; were on topics that did not match that of this study; were not RCTs; were about drug toxicity and renal function assessment; had some unavailable data; or were not written in English. Full texts of the included articles were reviewed by three investigators for final selection of experimental and control groups for meta-analysis. Three investigators (Lan, Chang, and Lu) reviewed the methods, study site and duration, study population, and regimen of treatments reported in the extracted articles. Initially, two authors (Lan and Chang) searched and examined the publications independently to avoid bias, and in case of a disagreement, the third author (Lu) resolved the issue.

## Definitions and outcomes

The primary outcome was overall clinical cure with complete resolution of clinical signs and symptoms of ABSSSI or without residual signs or symptoms, which were measured by the investigator assessment at follow-up visits. Secondary outcomes included the microbiological response rates and adverse events (AEs). A microbiological response was defined as documented eradication (absence of baseline pathogen) and presumed eradication (if an adequate source specimen was not available to culture, but the patient was assessed as clinically cured). Treatment-emergent adverse events (TEAEs) were recorded, irrespective of causality.

## Quality assessment and data analysis

The Cochrane Collaboration's criteria were used by the three investigators to assess the individual study design with respect to their methodological quality,[16] and the risk of study bias was assessed according to the guidelines developed by Higgins et al.[17] The criteria for appraisal of the studies were assessed by considering the design of RCTs with selection bias, performance bias, attrition bias, and detection bias, which were associated with low, unclear, and high risk. Differences in opinion of the three investors were resolved by voting and discussion. Meta-analysis (drug efficacy and safety) was conducted using Review Manager Software (RevMan, 5.3; Cochrane's Informatics & Knowledge Management Department). Heterogeneity of the studies was measured using the $I^2$ statistic and the Q test (heterogeneity $\chi^2$).[18,19] If the results of the Q test were $P<0.1$ or $I^2>50\%$, this indicated the presence of heterogeneity; consequently, a random-effects model (DerSimonian and Laird method) was used.[20] However, if heterogeneity was absent in a study, a fixed-effects model

**Table 1** Characteristics of included studies

| Study, year published | Study design | Study site | Study period | Study population | Number of patients | | Dose regimen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Delafloxacin | Comparator | Delafloxacin | Comparator |
| O'Riordan et al, 2015[13] | Multicenter, randomized, double-blind trial | 14 sites in USA | Between June and September 2008 | Complicated skin and skin structure infection | 49 (300 mg)<br>51 (450 mg) | 50 | Delafloxacin, 300 mg or 450 mg q12 h | Tigecycline 100 mg IV × 1, followed by 50 mg IV q12 h |
| Kingsley et al, 2016[11] | Multicenter, randomized, double-blind trial | 23 center in USA | Between February and November, 2011 | Acute bacterial skin and skin structureinfection (ABSSSI) | 81 (300 mg) | 77 (Linezolid)<br>98 (Vancomycin) | Delafloxacin 300 mg q12 h | Linezolid 600 mg or vancomycin 15 mg/kg |
| Pullman et al, 2017[14] | Multicenter, randomized, double-blind trial | 34 center in seven countries | Between April 2013 and June, 2014 | ABSSSI | 331 (300 mg) | 329 | Delafloxacin 300 mg q12 h | Vancomycin 15 mg/kg plus aztreonam 2 g q12 h |
| O'Riordan et al, 2018[12] | Multicenter, randomized, double-blind trial | 76 center in 16 countries | Between May 2014 and January, 2016 | ABSSSI | 423 (300 mg) | 427 | Delafloxacin 300 mg q12 h | Vancomycin 15 mg/kg plus aztreonam 2 g q12 h |

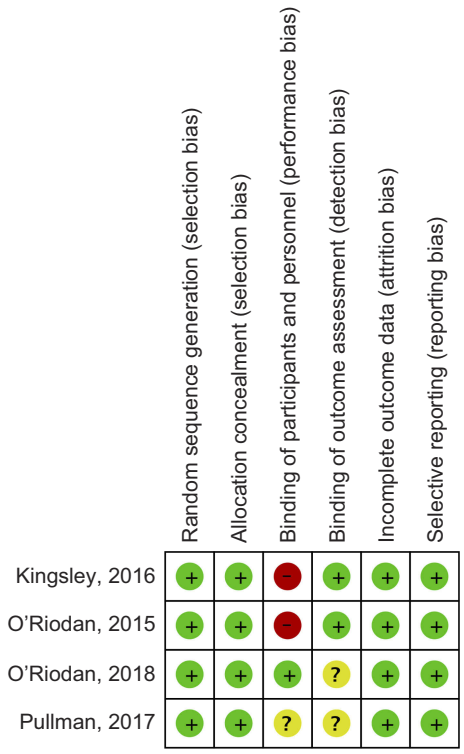


**Figure 2** Risk of bias per study and domain. Green color: low risk of bias; red color: high risk of bias; yellow color: unclear risk of bias.

(Mantel Haenszel method) was used.[21] Pooled ORs and 95% CIs were calculated for outcome analyses.

# Results

The search results yielded a total of 314 records from the online databases; 217 records were excluded because of duplication, 62 records were irrelevant when the title and abstract were screened (article type and language), 20 records were irrelevant when the full text was screened because they were experimental studies on animals (n=15) or because their objectives did not match that of the present study (n=5). Furthermore, nine articles investigated drug toxicity (n=3), and the studies evaluating renal function (n=6) were excluded. Finally, two articles that did not have available data in the results section were excluded. Overall, four RCTs were enrolled for the meta-analysis (Figure 1).

## Study characteristics and study quality

Four RCTs,[11–14] published between 2015 and 2018, met the inclusion criteria. All of the included studies were multicenter, double-blind, intention-to-treat analyses and RCTs (Table 1). Two studies[11,13] were conducted in only the United States and the other two studies[12,14] were conducted in multiple countries. Except for one study[13] that compared two doses of delafloxacin (300 mg and 450 mg) and comparators, the other three studies[11,12,14] used delafloxacin 300 mg in the experimental group. Two studies[12,14] used vancomycin and aztreonam as comparators, one[13] used tigecycline, and one[11] used linezolid or vancomycin. Overall, 935 and 981 patients comprised the experimental group treated with delafloxacin, and the control group, treated with comparators, respectively. The risk of bias of the included studies is presented in Figures 2 and 3, and only two studies[11,13] had a high risk of bias in the domain of blinding of participants and performance. Overall, cellulitis/erysipelas was the most common type of ABSSSI (45.6%, n=833), and 27.6% (n=504) of ABSSSIs were caused by MRSA (Table 2).

## Clinical efficacy

Overall, delafloxacin had a clinical cure rate similar to the comparators in the treatment of ABSSSIs (OR, 1.05; 95% CI, 0.87–1.27, $I^2$=16%, Figure 4). In the subgroup analysis according to the type of ABSSSI reported by three studies,[11,13,14] delafloxacin had a clinical cure rate similar to that of the comparators in the treatment of cellulitis/erysipelas (OR, 1.34; 95% CI, 0.85–2.03, $I^2$=0%), major cutaneous abscess (OR, 1.33; 95% CI, 0.79–2.22, $I^2$=0%), and wound

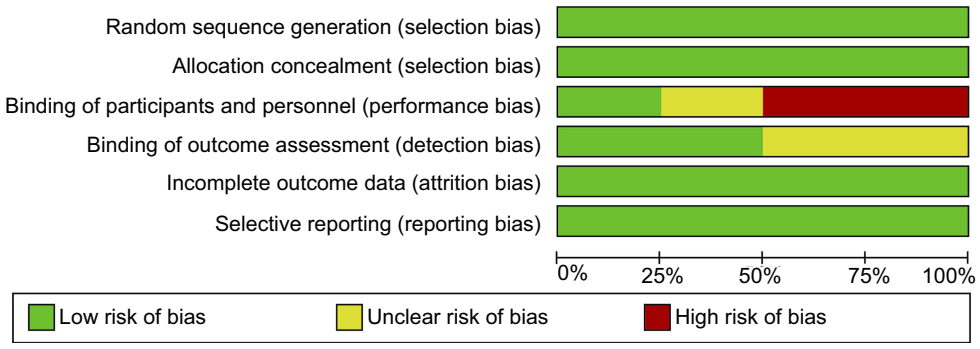


**Figure 3** Summary of risk of bias.

**Table 2** Characteristics of enrolled patients (intention-to-treat population)

| Studies | Number (%) of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | O'Riordan et al, 2015[13] | | Kingsley et al, 2016[11] | | Pullman et al, 2017[14] | | O'Riordan et al, 2018[12] | | Total | |
| Patients group | Delafloxacin, n=100 | Comparator, n=50 | Delafloxacin, n=81 | Comparator, n=175 | Delafloxacin, n=331 | Comparator, n=329 | Delafloxacin, n=423 | Comparator, n=427 | Delafloxacin, n=935 | Comparator, n=981 |
| Diagnosis | | | | | | | | | | |
| Cellulitis/erysipelas | 36 (36) | 18 (36) | 39 (48.1) | 76 (43.4) | 128 (38.7) | 128 (38.9) | 202 (47.8) | 206 (48.2) | 405 (43.3) | 428 (43.6) |
| Major cutaneous abscess | 34 (34) | 16 (32) | 21 (25.9) | 52 (29.7) | 84 (25.4) | 83 (25.2) | 106 (25.1) | 106 (24.8) | 245 (26.2) | 257 (26.2) |
| Wound infection | 30 (30) | 16 (32) | 19 (23.5) | 45 (25.7) | 116 (35.0) | 116 (35.3) | 111 (26.2) | 112 (26.2) | 276 (29.5) | 285 (29.5) |
| Burn infections | 0 (0) | 0 (0) | 2 (2.5) | 2 (1.1) | 3 (0.9) | 2 (0.6) | 4 (0.9) | 3 (0.7) | 9 (0.01) | 7 (0.7) |
| Methicillin-resistant *Staphylococcus aureus* | 48 (48) | 20 (40) | 34 (42.0) | 72 (41.1) | 78 (23.6) | 91 (27.7) | 66 (15.6) | 108 (25.3) | 226 (24.2) | 291 (29.7) |

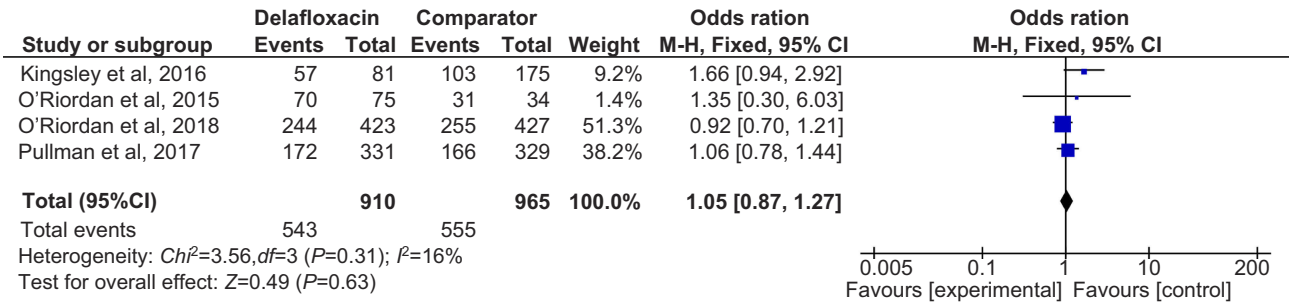


**Figure 4** Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

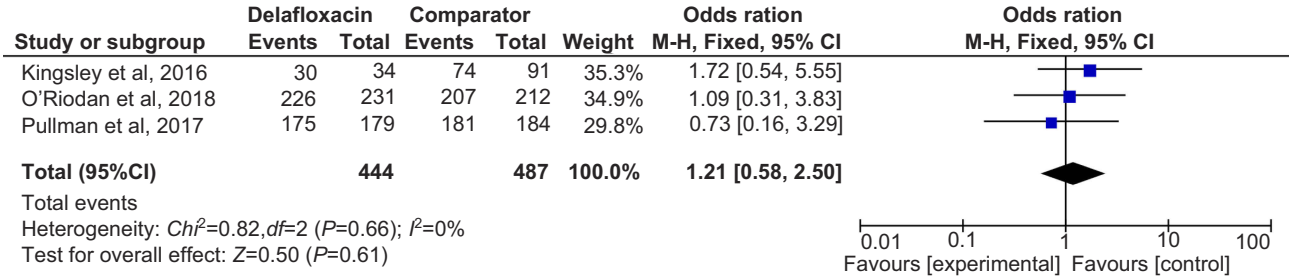


**Figure 5** Overall microbiological eradication rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

infection (OR, 0.77; 95% CI, 0.48–1.23, $I^2$=0%). In addition, all four studies[11–14] reported that the clinical cure rate of MRSA-associated ABSSSI was similar between delafloxacin and the comparators (OR, 1.12; 95% CI, 0.71–1.77, $I^2$=0%).

## Microbiological response

Delafloxacin had a microbiological eradication rate (documented and presumed) similar to comparators in the treatment of ABSSSIs (OR, 1.21; 95% CI, 0.58–2.50, $I^2$=0%, Figure 5) in the pooled analysis of three studies.[11,12,14] A similar trend was noted in MRSA-associated ABSSSIs (OR, 1.16; 95% CI, 0.37–3.60, $I^2$=0%). Two studies[12,14] reported objective responder rates among microbiologically evaluated populations; no statistical differences were observed between the group treated using delafloxacin and that treated using the comparators in terms of ABSSSI caused by *S. aureus* (OR, 1.07; 95% CI, 0.42–2.76, $I^2$=71%), MRSA (OR, 0.62; 95% CI, 0.28–1.40, $I^2$=21%), and methicillin-susceptible *S. aureus* (MSSA; OR, 1.46; 95% CI, 0.76–2.80, $I^2$=0%).

## AEs

No significant differences were evident in the risk of serious adverse events (SAEs) and TEAEs between delafloxacin and comparators (SAEs, OR, 0.96; 95% CI, 0.61–1.52, $I^2$=0%; TEAEs, OR, 0.85; 95% CI, 0.53–1.36, $I^2$=80%, Figure 6). The risks of TEAEs related to the study drug were similar between delafloxacin and comparators (OR, 0.94; 95% CI, 0.62–1.41, $I^2$=70%, Figure 6). Finally, the risk of discontinuation of the study drug due to an AE was lower for delafloxacin than for the comparators (OR, 0.33; 95% CI, 0.15–0.74, $I^2$=0%, Figure 6).

# Discussion

This meta-analysis based on four RCTs determined that delafloxacin has a clinical efficacy similar to comparators in the treatment of adult patients with ABSSSIs. First, the clinical cure rate of delafloxacin in treating ABSSSIs was as high as that of the comparators in the pooled populations of the four RCTs.[11–14] Second, subgroup analysis of various types of ABSSSIs, including cellulitis/erysipelas, major cutaneous abscess, wound infection, and MRSA-associated ABSSSI, exhibited no significant differences in the clinical efficacy between delafloxacin and comparators in the treatment of ABSSSI. Finally, the microbiological eradication rate of delafloxacin was similar to that of the comparators in the pooled analysis of the three RCTs.[11,12,14] A similar trend was observed in MRSA-associated ABSSSIs. Moreover, the objective responder rates among the microbiologically evaluated population were similar between delafloxacin and comparators for

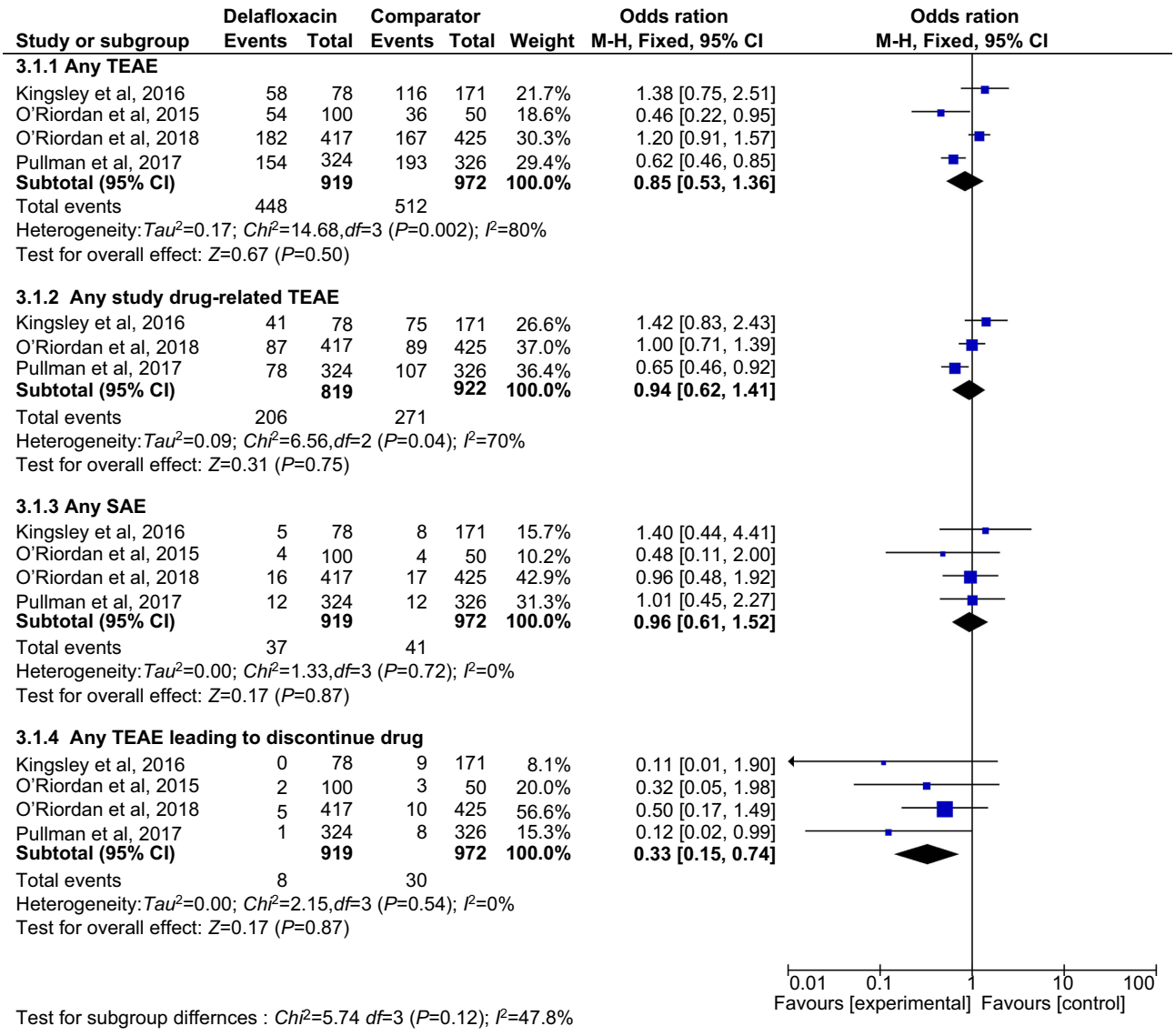


**Figure 6** Risk of adverse events between delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.
**Abbreviations:** TEAE, treatment-emergent adverse event; SAE, serious adverse event.

*S. aureus*-, MRSA-, and MSSA-associated ABSSSIs. These findings are supported by the results of in vitro investigations in an included study,[13] which showed that the minimum inhibitory concentration (MIC) of delafloxacin against *S. aureus*, including MRSA and MSSA, was low and that all *S. aureus* isolates were susceptible to delafloxacin. Studies[22,23] have demonstrated that delafloxacin exhibits excellent in vitro activity against *Staphylococcus*; the MIC for 90% inhibition ranged from 0.12 to 0.5 μg/mL for MRSA and 0.25 μg/mL for coagulase-negative *Staphylococcus*. In addition, ABSSSIs, including wound infections and abscesses, can be polymicrobial, and delafloxacin has a broader coverage than linezolid and vancomycin, both of which inhibit gram-positive bacteria only. Furthermore, delafloxacin is available in intravenous and oral forms, which facilitates treatment in the outpatient setting, and has broader coverage than linezolid and vancomycin, which inhibit only gram-positive bacilli. Overall, delafloxacin is suggested to play a crucial role in the treatment of adult patients with ABSSSIs compared with other available antibiotics with high *Staphylococcus* and MRSA coverage.

The risk of AEs is another important concern in the treatment of ABSSSIs with this antimicrobial agent. The most common AEs are nausea, diarrhea, and headaches. In this analysis, the pooled risks of TEAEs were similar

between delafloxacin and comparators. The risk of TEAEs due to study drugs and SAEs (the safety issue) did not differ significantly between delafloxacin and comparators. Moreover, delafloxacin was associated with a lower risk of discontinuation of study drug due to an AE than were the comparators. All these findings suggest that delafloxacin is as safe as the other comparators in the treatment of ABSSSIs in adult patients. Although the US Food and Drug Administration recently raised concerns about the risk of ruptures or tears in the aortic blood vessel associated with fluoroquinolone antibiotics, similar reports regarding delafloxacin-associated aortic aneurysm or dissection are scarce. Additional studies are needed to clarify this issue.

This meta-analysis has one major strength. Only double-blind RCTs were included, consequently, the risk of bias was minimized and the level of evidence was strong. However, this meta-analysis also has several limitations. First, we did not evaluate the specific association between in vitro activity and the in vivo response of different organisms, particularly the key pathogen MRSA. Second, the numbers of studies and patients were relatively low in this meta-analysis; therefore, the formal test for heterogeneity may have underestimated the degree of heterogeneity.

In conclusion, based on the findings of this meta-analysis of four RCTs, the clinical and microbiological efficacy of delafloxacin is as high as the comparator in the treatment of ABSSSIs, including MRSA-associated infections, and this antibiotic is as well-tolerated as the comparators. The statistical analysis result did not indicate any evidence of heterogeneity among four studies for all four endpoints. Therefore, delafloxacin can be recommended as an appropriate antibiotic therapy for ABSSSIs.

## Disclosure

The authors report no conflicts of interest in this work.

## References


1. Hersh AL, Chambers HF, Maselli JH, et al. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med*. 2008;168:1585–1591. doi:10.1001/archinte.168.21.2355
2. Garau J, Blasi F, Medina J, et al. Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. *BMC Infect Dis*. 2015;15:78. doi:10.1186/s12879-015-0822-2
3. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10–e52. doi:10.1093/cid/ciu296
4. Halilovic J, Heintz BH, Brown J. Risk factors for clinical failure in patients hospitalized with cellulitis and cutaneous abscess. *J Infect*. 2012;65:128–134. doi:10.1016/j.jinf.2012.03.013
5. Berger A, Oster G, Edelsberg J, Huang X, Weber DJ. Initial treatment failure in patients with complicated skin and skin structure infections. *Surg Infect (Larchmt)*. 2013;14:304–312. doi:10.1089/sur.2012.103
6. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med*. 2006;355:666–674. doi:10.1056/NEJMoa055356
7. Pallin DJ, Egan DJ, Pelletier AJ, et al. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant Staphylococcus aureus. *Ann Emerg Med*. 2008;51:291–298. doi:10.1016/j.annemergmed.2007.11.042
8. Pfaller MA, Sader HS, Rhomberg PR, et al. In vitro activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. *Antimicrob Agents Chemother*. 2017;61.
9. McCurdy S, Lawrence L, Quintas M, et al. In vitro activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and nonsusceptible *Staphylococcus aureus* isolates from two phase 3 studies of acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2017;61.
10. Flamm RK, Rhomberg PR, Huband MD, et al. In vitro activity of delafloxacin tested against isolates of *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. *Antimicrob Agents Chemother*. 2016;60:6381–6385. doi:10.1128/AAC.00941-16
11. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. *J Antimicrob Chemother*. 2016;71:821–829. doi:10.1093/jac/dkv411
12. O'Riordan W, McManus A, Teras J, et al. A comparison of the efficacy and safety of intravenous followed by oral delafloxacin with vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections: a phase 3, multinational, double-blind, randomized study. *Clin Infect Dis*. 2018;67:657–666. doi:10.1093/cid/ciy165
13. O'Riordan W, Mehra P, Manos P, et al. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. *Int J Infect Dis*. 2015;30:67–73. doi:10.1016/j.ijid.2014.10.009
14. Pullman J, Gardovskis J, Farley B, et al. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. *J Antimicrob Chemother*. 2017;72:3471–3480. doi:10.1093/jac/dkx066
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269, w264.
16. Shuster JJ. *Review: Cochrane Handbook for Systematic Reviews for Interventions, Version 5.1. 0, Published 3/2011*. Julian PT Higgins and Sally Green, Editors. Wiley Online Library; 2011.
17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. doi:10.1002/sim.1186
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi:10.1136/bmj.327.7420.895
20. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28:105–114. doi:10.1016/j.cct.2006.04.004
21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.

22. Remy JM, Tow-Keogh CA, McConnell TS, et al. Activity of delafloxacin against methicillin-resistant Staphylococcus aureus: resistance selection and characterization. *J Antimicrob Chemother*. 2012;67:2814–2820. doi:10.1093/jac/dks307

23. Nilius AM, Shen LL, Hensey-Rudloff D, et al. In vitro antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. *Antimicrob Agents Chemother*. 2003;47:3260–3269. doi:10.1128/AAC.47.10.3260-3269.2003