

Efficacy and safety of daptomycin for skin and soft tissue infections: a systematic review with trial sequential analysis

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Background: Skin and soft tissue infections (SSTIs) are significant indications for antibiotic treatment. Daptomycin, a novel antibiotic, has been registered and licensed to be used in the treatment of these infections. However, its efficacy and safety remain controversial.

Objective: The objective of this study was to conduct a systematic review with trial sequential analysis (TSA) to evaluate the efficacy and safety of daptomycin for the treatment of SSTIs and to analyze whether the available sample size has been large enough and is conclusive.

Methods: PubMed, the Cochrane Library, and EMBASE were searched for published randomized controlled trials (RCTs) that compared daptomycin with other antibiotics in adult patients with SSTIs up to February 2016.

Results: This meta-analysis included eight randomized controlled trials (n=2,002). There was no difference in either the clinical success rate (intention-to-treat population: relative risk [RR]=1.04, 95% confidence interval [CI]=0.99–1.10, P=0.12; clinically evaluable population: RR=1.00, 95% CI=0.97–1.04, P=0.82) or the microbiological success rate (RR=1.00, 95% CI=0.95–1.06, P=0.92) between the daptomycin and comparator groups for treating SSTIs, which was confirmed by TSA. Compared with vancomycin, daptomycin exhibited no advantage in increasing the clinical success rate (RR=1.03, 95% CI=0.95–1.13, P=0.47), and this was also confirmed by TSA. All-cause mortality, overall treatment-related adverse events, and creatine phosphokinase events were similar between these two groups.

Conclusion: Daptomycin and comparator drugs are equally efficacious with regard to clinical and microbiological success for patients with SSTIs, and TSA showed that no additional randomized controlled trials are required. Although daptomycin is a good alternative when other antibiotics are contraindicated for patients with SSTIs and it can serve as a first-line treatment for SSTIs, clinicians should be aware of potential adverse events, such as daptomycin-induced acute eosinophilic pneumonia and creatine phosphokinase, when treating patients with daptomycin.

Keywords: daptomycin, skin and soft tissue infections, vancomycin, meta-analysis, trial sequential analysis

Background

Most skin and soft tissue infections (SSTIs) are caused by *Staphylococcus aureus* or *β-haemolytic streptococci*,¹ and these are an important indication for antibiotic treatment. Vancomycin is the recommended standard therapy for the treatment of SSTIs when β -lactam antimicrobials cannot be used.² However, with the increase of minimum inhibitory concentrations in methicillin-resistant *S. aureus*, the treatment for SSTIs becomes increasingly challenging.

In recent years, a variety of novel antibiotics have been used for the treatment of SSTIs,¹ and several meta-analyses³⁻⁶ have been conducted to evaluate the efficacy of novel antibiotics in the treatment of SSTIs. The use of linezolid, among these antibiotics, has resulted in better clinical and microbiological cure rates.² However, its serious side effects that occur when the course of treatment exceeds 28 days, limit its clinical use.⁷ Further research is required to determine whether other drugs, including daptomycin, are more efficacious than the recommended standard therapy.

Daptomycin is a novel antimicrobial with *in vitro* bactericidal activity against most clinically relevant gram-positive bacteria. It was first cleared by the US Food and Drug Administration in 2003 for the treatment of SSTIs in adults at a dose of 4 mg/kg once per day for 7–14 days.^{8,9} To date, >70 countries and regions have approved this drug for the treatment of SSTIs. Several meta-analyses^{6,10} have evaluated the effect of daptomycin in the treatment of SSTIs. However, no significant differences were found between daptomycin and standard drugs. Recently, two related randomized controlled trials (RCTs)^{11,12} were published. In the present study, the effect of daptomycin on the treatment of SSTIs was evaluated by conducting this meta-analysis with trial sequential analysis (TSA) to analyze whether the available sample size is large enough and conclusive.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement methodology was used to perform this meta-analysis.¹³

Study selection

PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for relevant studies published up to February 2016. Search terms included “daptomycin,” “cubicin,” “lipopeptide,” “skin infection,” “soft tissue infection,” “SSRIs,” “cellulitis,” “wounds infection,” “abscess,” “erysipelas,” and “randomized controlled trial.” Retrieval was limited to humans, and language was not restricted.

Inclusion criteria

The selection criteria were as follows: 1) population: patients with SSTIs; 2) intervention: antibiotics; 3) comparison: daptomycin and other antibiotics; 4) outcome measure: clinical or microbiological success; and 5) study design: RCT.

Data extraction

Two investigators (CL and ZM) conducted the data extraction independently using a standardized, premade form.

Differences between the data from these two investigators were resolved through discussion or by consulting a third investigator (FZ). The standard form included the following information: first author, study design, publication year, mean age of patients, number of patients, and antimicrobial agents and their doses. The primary outcome was clinical success, and analyses were conducted for both intention-to-treat (ITT) and clinically evaluable (CE) groups of patients. Secondary outcomes were microbiological success, treatment-related adverse events, cases of elevated creatine phosphokinase (CPK), and all-cause mortality.

Quality assessment

The methodological quality of the included trials was assessed by two independent investigators (CL and ZM) according to the Cochrane Risk of Bias Tool. The standard criteria included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was classified as follows: “low risk,” “unclear risk,” or “high risk.” Eligible trials that met the low risk of bias criteria for all the key domains were regarded as being at a low risk of bias, whereas those that met the high risk of bias criteria for all the key domains were regarded as being at a high risk of bias. All other trials were considered to have an unclear risk of bias.

Grading quality of evidence

The overall quality of the evidence of the outcomes was evaluated using Grading of Recommendations Assessment, Development, and Environment (GRADE).¹⁴ The grades of evidence were classified into four categories: 1) high: RCTs with no limitations and with consistent, precise, and directly applicable results without evidence of reporting bias; 2) moderate (downgraded one level from high): RCTs with important limitations; 3) low (downgraded two levels from high): RCTs with very serious limitations; and 4) very low (downgraded three levels from high): RCTs with very serious limitations and inconsistent results.

Statistical analysis

Review Manager Version 5.1.2 (RevMan; The Cochrane Collaboration, Oxford, UK) and Stata Version 12.0 (Stata Corporation, College Station, TX, USA) were used to conduct the data analyses. Pooled relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes were calculated by using both fixed effects and random effects models. Statistical heterogeneity between eligible trials was evaluated by using the I^2 test. $I^2 > 50\%$ indicated significant

heterogeneity among trials,¹⁵ and the random effects model was used to conduct the meta-analysis. The fixed effects analytical model was used to pool the results with acceptable or no heterogeneity. Sensitivity analyses were conducted to test the robustness of the results. Publication bias was assessed using the Begg test and the Egger test. All *P*-values were two-sided, and a *P*-value <0.05 indicated a statistically significant difference.

Trial sequential analysis

In meta-analyses, it is important to minimize the risk of reaching a false-positive or false-negative conclusion. However, repeated significance tests of sparse and accumulated data are prone to yielding random errors, which increase the risk of type I errors.^{16,17} In order to determine whether the evidence from a meta-analysis is reliable and conclusive, TSA should be used. This method assesses the risk of random errors and helps determine whether there is a need for additional trials.¹⁸ TSA was obtained with $\alpha=0.05$ (two-sided), $\beta=0.20$ (power 80%), including the control event proportion observed in the comparator group or vancomycin group, and an RR reduction of 10% in outcomes.¹⁹ TSA was conducted using TSA Version 0.9 Beta (www.ctu.dk/tsa).²⁰

Results

Randomized trial characteristics

A total of 233 potentially relevant studies and nine trials were retrieved for detailed assessment. One trial²¹ was excluded because it used a high dose of daptomycin (10 mg/kg). In total, eight studies^{11,12,22–27} were included in this meta-analysis (Figure 1). Table 1 summarizes the characteristics of all

the included studies, which were published in English. These trials were published from 2004 to 2015. A total of 2,002 patients were included in this meta-analysis. All the included studies enrolled adult patients. The comparator drugs were vancomycin and semi-synthetic penicillin in two studies,^{22,27} vancomycin and teicoplanin in one study,²⁵ vancomycin in four studies,^{11,12,24,26} and telavancin in one study.²³

Quality of studies

Figure 2 shows the methodological quality assessments of the included trials. The allocation concealment was not clear. Because of the nature of the interventions, the studies were neither personnel-blinded nor participant-blinded. GRADE Working Group grades of evidence were moderate for the clinical and microbiological success rates and low for all-cause mortality and adverse events.

Primary outcome: clinical success rate on ITT and CE populations

Seven trials^{11,12,22,23,25–27} reported the clinical success rate of daptomycin versus comparator drugs in ITT and CE populations. In the ITT population, the overall success rate was 72.5% (1,372/1,892). In the daptomycin group, 73.7% (705/957) of patients reached clinical success, compared with 70.9% (663/935) in the comparator group. There was no significant difference in the clinical success rate between the two groups (RR =1.04, 95% CI =0.99–1.10, *P*=0.12, *I*²=0%; Figure 3A). TSA was conducted by using fixed effects mode, and the cumulative *Z*-curve did not cross the conventional boundary for benefit but did cross the required information size (RIS) boundary (Figure 3C).

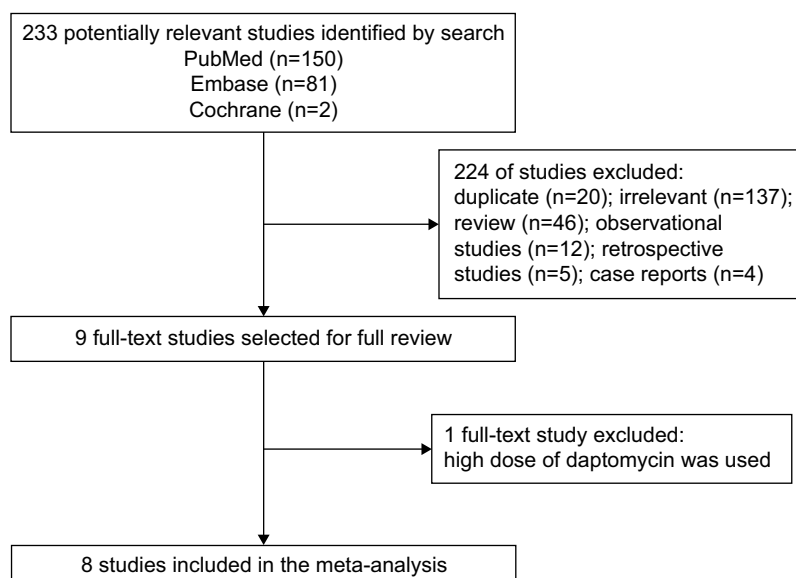


Figure 1 Flowchart of the study selection.

Table 1 Main characteristics of the included studies

Source	Country	Year	Setting	Population				Dose, treatment duration					
				Age		ITT, n		CE, n		D		C	
				D	C	D	C	D	C	D	C	D	C
Kauf et al ¹²	USA	2015	Prospective, open-label, multicenter study conducted at 36 sites	47.2±15.2 ^a	50.0±13.5 ^a	125	125	118	106	4 mg/kg, once daily, IV	Vancomycin was dosed at the investigator's discretion according to institutional protocol		
Shaw et al ¹¹	USA	2015	Prospective, randomized, controlled, single-site, open-label, noninferiority trial	42±12 ^a	38±13 ^a	50	50	39	39	4 mg/kg, once daily, IV, push > 1 to 2 minutes	Vancomycin given in a dose of 15 mg/kg at baseline and again at 12 hours by IV infusion to run > 1 to 2 hours for a maximum of two doses		
Konychev et al ²²	RUS	2013	Open-label, multicenter, randomized phase IIIb study conducted in 18 centers (in a hospital setting) from five countries	74.6±6.33 ^a	75.3±5.16 ^a	81	39	73	30	4 or 6 mg/kg, once daily, IV, for 5–14 or 10–28 days	Vancomycin, 1 g, twice daily for 5–14 or 10–28 days		
Aikawa et al ²⁴	JPN	2013	Randomized, open-label, active-comparator controlled, parallel-group, multicenter, phase III study conducted across 61 Japanese medical institutions	69.0 (22–92) ^b	70.0 (29–82) ^b	88	22	NR	NR	4 mg/kg, once daily, IV, push > 30 minutes for 7–14 days	Vancomycin, 1 g, twice daily, IV, 7–14 days		
Evers et al ²³	USA	2013	Prospective controlled, single-blinded, randomized study	69	65	20	20	20	20	4 mg/kg, once daily, IV	Telavancin, 10 mg/kg, once daily (average 8.2 mg/kg/day), IV, for 10–14 days		
Quist et al ²⁵	GER	2012	A phase IIIb, multicenter, comparative, randomized, assessor-blinded study conducted at 29 centers	NR	NR	97	92	58	47	4 mg/kg, once daily, IV	Vancomycin, 1 g, twice daily IV; teicoplanin 400 mg, once daily, IV		
Pertel et al ²⁶	USA	2009	Prospective, randomized, evaluator-blinded, multicenter trial	57 (22–79) ^b	55 (21–86) ^b	50	51	47	47	4 mg/kg, once daily, IV	Vancomycin was administered IV according to standard of care or SSP, 2 g, IV for 4 hours		
Arbeit et al ²⁷	USA	2004	Multicenter evaluator-blinded	51.5 (18–91) ^b	51.9 (17–94) ^b	534	558	446	456	4 mg/kg, once daily, IV, for 7–14 days	Penicillinase-resistant penicillin, 4–12 g, once daily, IV, or vancomycin 1 g, twice daily, IV		

Notes: ^aMean ± standard deviation; ^bmedian (range).

Abbreviations: C, comparator; CE, clinically evaluable; D, daptomycin; GER, Germany; ITT, intention-to-treat; IV, intravenously; JPN, Japan; NR, not reported; RUS, Russia; SSP, semi-synthetic penicillin.

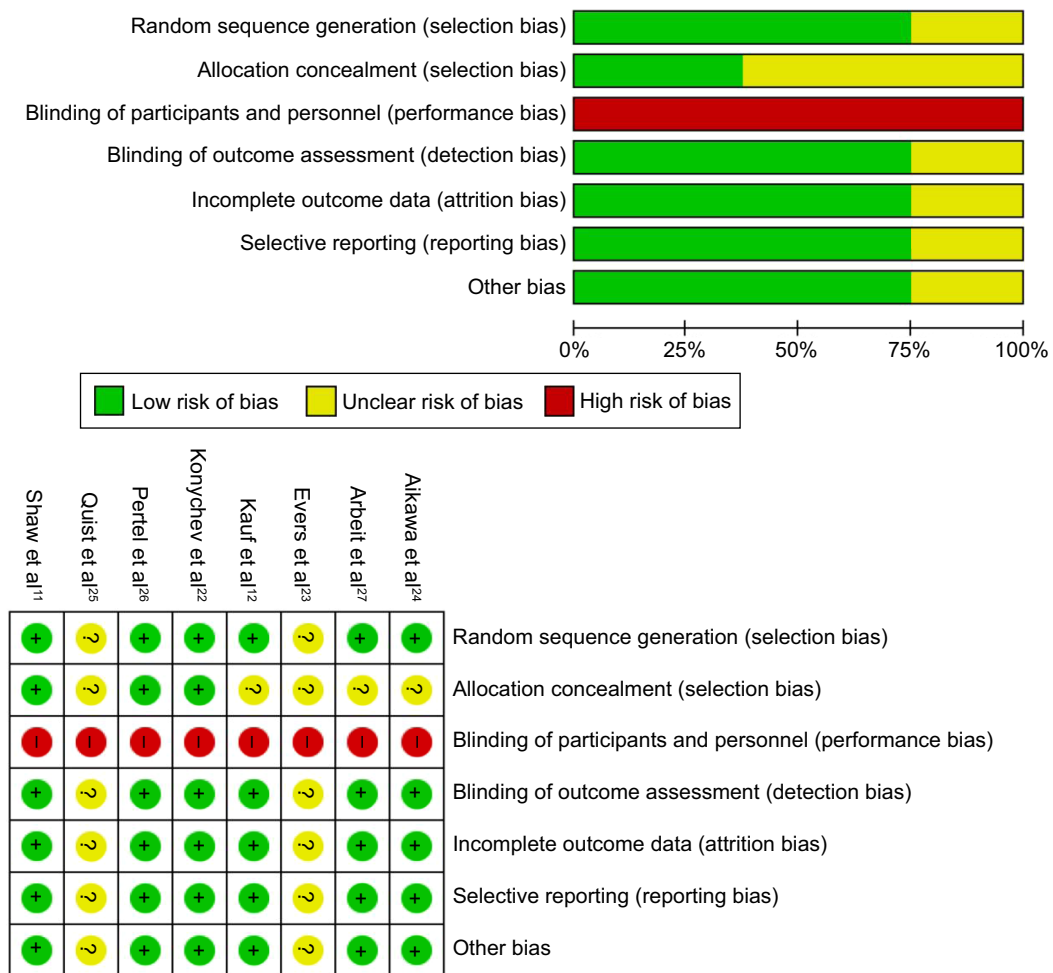


Figure 2 Assessment of the risk of bias.
Note: “+” indicates low risk of bias; “-” indicates high risk of bias; and “?” indicates unclear risk of bias.

These findings indicate that conclusive evidence was established, and further trials were not required. In the CE population, the overall success rate was 85.3% (1,319/1,546). In the daptomycin group, 85.6% (686/801) of patients reached clinical success, compared with 85.0% (633/745) in the comparator group. There was no significant difference in the clinical success rate between the two groups (RR=1.00, 95% CI=0.97–1.04, $P=0.82$, $I^2=0\%$; Figure 3B). TSA was conducted by using the fixed effects mode. The results were not renderable because the first information fraction exceeded 100% of the RIS boundary (Figure 3D). This result indicated that conclusive evidence was established and that further trials were not required. Six studies^{11,12,22,25–27} reported the clinical success rates of daptomycin and vancomycin in the CE population. As there was significant heterogeneity among studies ($\chi^2=23.25$, $df=5$, $P=0.0003$, $I^2=78\%$; Figure 4A), a random effects model was used to conduct the meta-analysis, and the results showed no significant difference in the clinical success rate between the two groups (RR =1.03,

95% CI=0.95–1.13, $P=0.47$; Figure 4A). In addition, the DerSimonian and Laird method for random effects analysis was also used to conduct TSA, and the cumulative Z-curve crossed the futility boundary, entered the futility area, and crossed the RIS boundary (Figure 4C). This result indicated that sufficient evidence was established and that further trials were not required.

Sensitivity analysis

Significant heterogeneity existed in the included studies between the daptomycin group and the vancomycin group ($I^2=78\%$), as shown in Figure 4A. After excluding the study conducted by Kauf et al¹² there was no heterogeneity among the remaining studies ($I^2=0\%$), and there was no significant difference in the clinical success rate between the two groups (RR =1.07, 95% CI =0.98–1.16, $P=0.12$; Figure 4B). The fixed effects model was used to conduct TSA, and the cumulative Z-curve did not enter the futility area and did not cross the conventional boundary (Figure 4D).

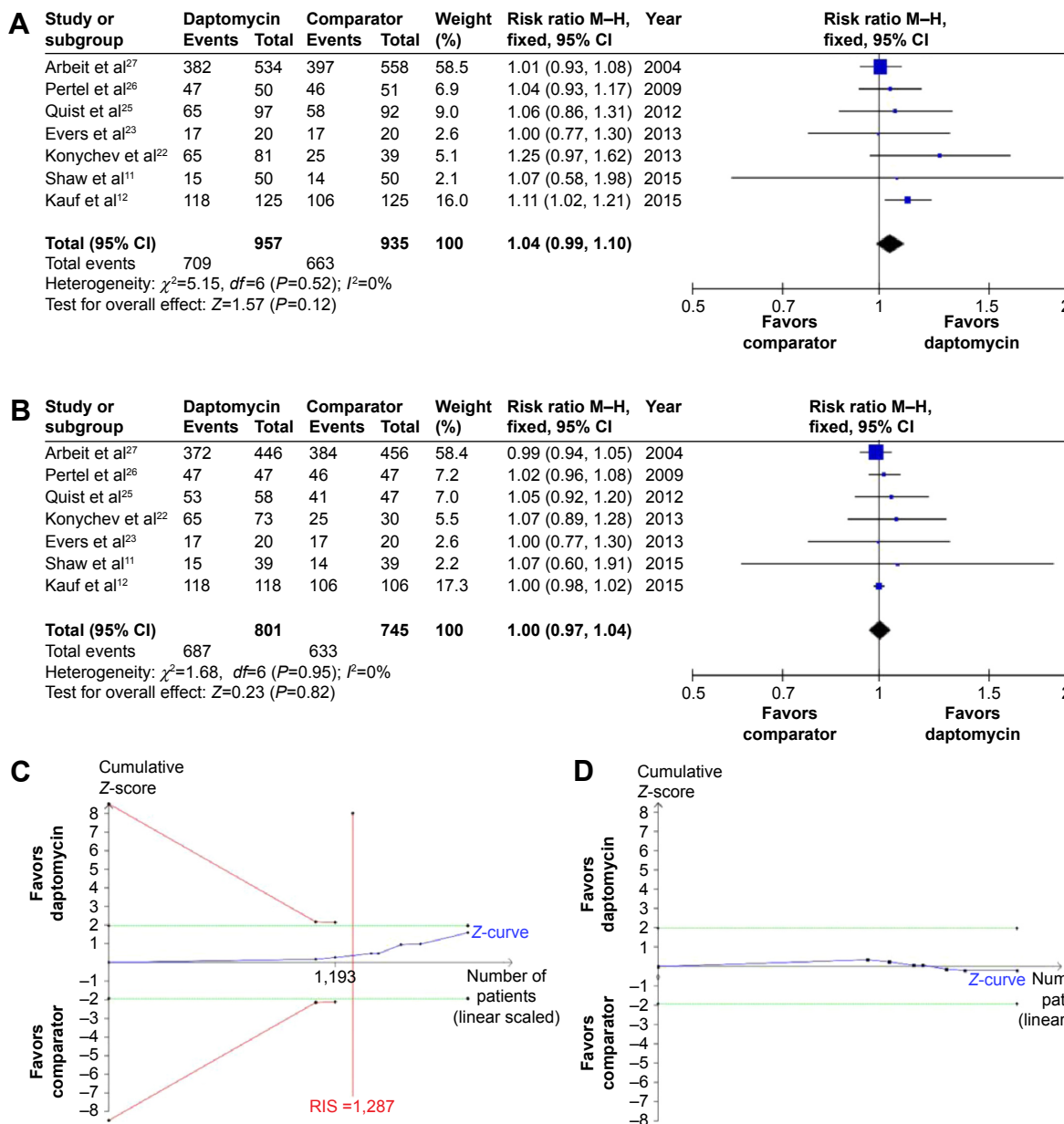


Figure 3 Effect of daptomycin versus other antibiotics on clinical success rate. **Notes:** (A) Forest plot of clinical success rate (ITT population). (B) Forest plot of clinical success rate (CE population). (C) Fixed effects model of TSA for clinical success rate (ITT population). A diversity-adjusted information size of 1,368 participants calculated on the basis of a clinical success rate of 71.0% in the comparator group, RRR =10%, $\alpha=5\%$ (two-sided), $\beta=20\%$, $I^2=0\%$. A full blue cumulative Z-curve did not cross the conventional boundary for benefit but did cross the RIS boundary. (D) The fixed effects model of TSA for the clinical success rate (CE population). Because the first information fraction exceeded 100% of RIS, the results were not renderable. **Abbreviations:** CE, clinically evaluable; CI, confidence interval; ITT, intention-to-treat; RIS, required information size; RRR, relative risk reduction; TSA, trial sequential analysis; df , degree of freedom; M-H, Mantel-Haenszel.

Secondary outcomes

Microbiological success rate

Five studies^{22,24–27} reported the microbiological success rate, and no statistically significant difference was found between the daptomycin and comparator groups (RR=1.00, 95% CI =0.95–1.06, $P=0.92$, $I^2=7\%$; Figure 5A). In order to calculate the between-trial variance, the DerSimonian and Laird method for random effects analysis was used to conduct TSA, and the cumulative Z-curve did not cross the

conventional boundary for benefit but did cross the RIS boundary (Figure 5B). Therefore, there was no statistically significant difference in the antimicrobial success rate between the two groups, indicating that sufficient evidence was established and that further trials were not required. In terms of the microbiological success rate for *S. aureus* infections, no significant difference was found between the two groups (RR =1.04, 95% CI =0.96–1.13, $P=0.30$, $I^2=9\%$; Figure 6). For methicillin-resistant *S. aureus* infections,

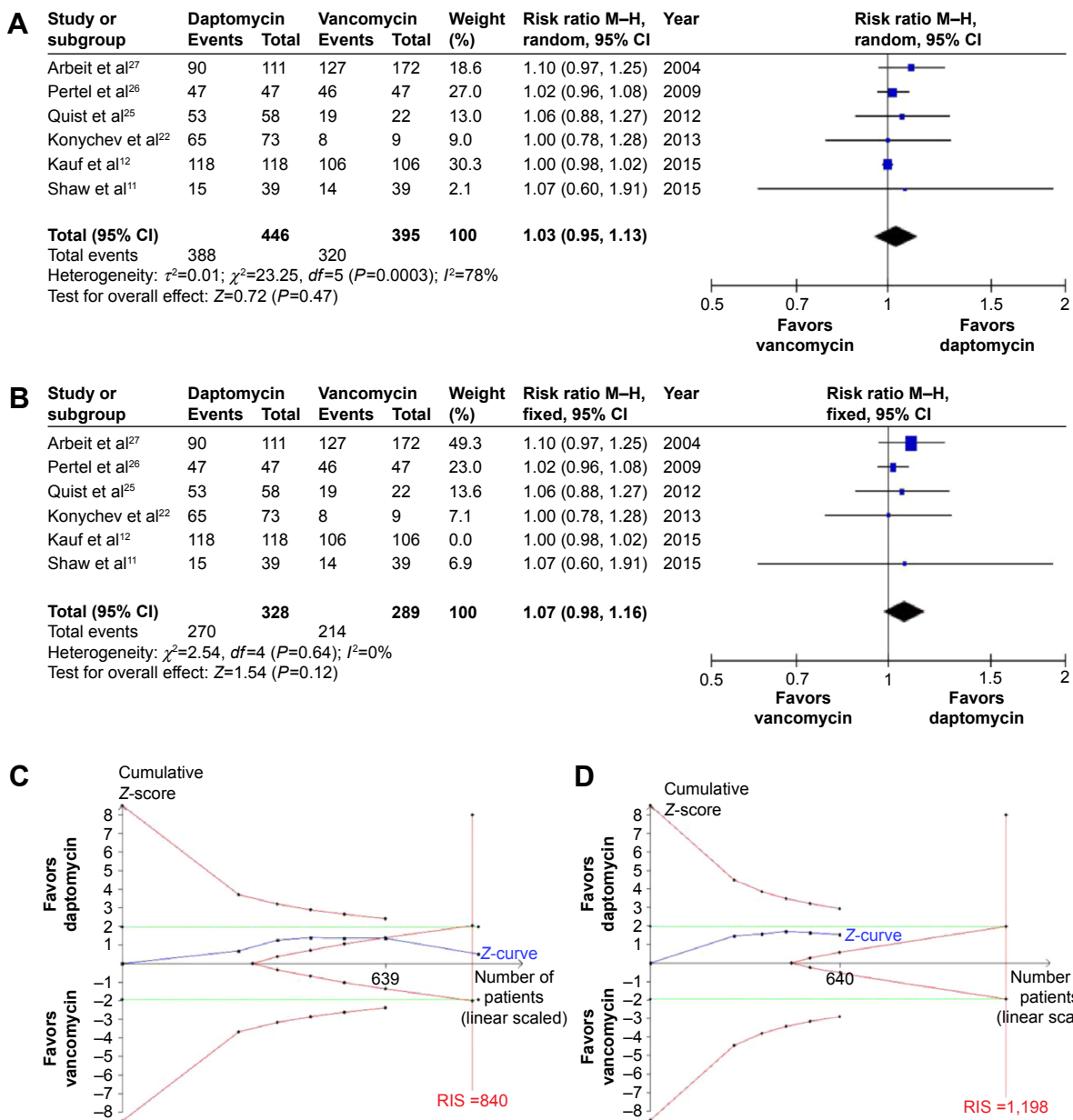


Figure 4 Effect of daptomycin versus vancomycin on clinical success rate.

Notes: (A) Forest plot of clinical success rate (CE population). (B) Forest plot of clinical success rate (CE population not including the study by Kauf et al). (C) Random effects model (DL method) of TSA for clinical success rate (CE population). A diversity-adjusted information size of 849 participants calculated on the basis of a clinical success rate of 81.0% in the vancomycin group, RRR = 10%, $\alpha=5\%$ (two-sided), $\beta=20\%$, $I^2=78\%$. A full blue cumulative Z-curve crossed the futility boundary and entered the futility area. (D) Fixed effects model of TSA for clinical success rate (CE population not including the study by Kauf et al). A diversity-adjusted information size of 1,198 participants calculated on the basis of a clinical success rate of 74.1% in the vancomycin group, RRR = 10%, $\alpha=5\%$ (two-sided), $\beta=20\%$, $I^2=0\%$. A full blue cumulative Z-curve did not cross the conventional boundary for benefit and did not enter the futility area.

Abbreviations: CE, clinically evaluable; CI, confidence interval; DL, DerSimonian and Laird; RIS, required information size; RRR, relative risk reduction; TSA, trial sequential analysis; df , degree of freedom; M-H, Mantel-Haenszel.

the microbiological success rate did not differ significantly between the two groups (RR = 1.12, 95% CI = 0.85–1.48, $P=0.42$, $I^2=0\%$; Figure 6). As only limited data were available, TSA was not conducted.

All-cause mortality and adverse events

All-cause mortality, overall treatment-related adverse events, and CPK events were similar between the daptomycin and

comparator groups (Figure 6). As only limited data were available, TSA was not conducted.

Publication bias

The Egger’s test provided no evidence of publication bias among the included trials for the clinical success rates ($P=0.205$ for the ITT population and $P=0.117$ for the CE population) and the microbiological success rate ($P=0.275$).

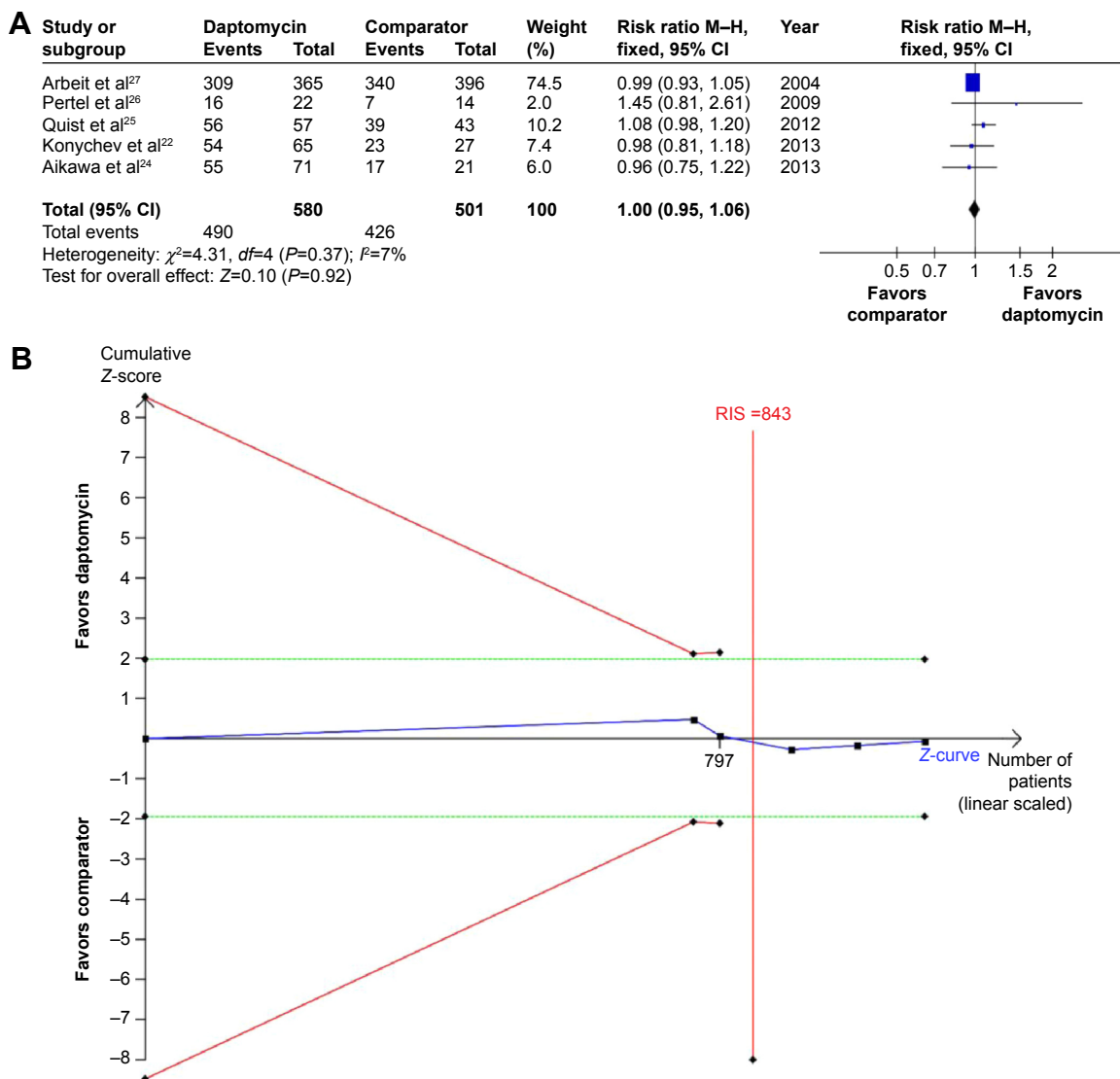


Figure 5 Effect of daptomycin versus other antibiotics on microbiological success rate based on the microbiologically evaluable population. **Notes:** (A) Forest plot of microbiological success rate. (B) Fixed effects model of TSA for microbiological success rate. A diversity-adjusted information size of 843 participants calculated on the basis of a microbiological success rate of 85.0% in the comparator group, RRR =10%, $\alpha=5\%$ (two-sided), $\beta=20\%$, $I^2=0\%$. A full blue cumulative Z-curve did not cross the conventional boundary for benefit but did cross the RIS boundary. **Abbreviations:** CI, confidence interval; RIS, required information size; RRR, relative risk reduction; TSA, trial sequential analysis; *df*, degree of freedom; M-H, Mantel-Haenszel.

Discussion

This systematic review of the currently available literature found that, (1) there were no significant differences in the clinical or microbiological success rate between the daptomycin and comparator groups, which was confirmed by TSA; (2) when compared with vancomycin, daptomycin did not have an advantage of improved clinical success, which was confirmed by TSA; (3) daptomycin and comparator drugs were equally efficacious in treating *S. aureus* or methicillin-resistant *S. aureus* infections, although TSA did not confirm these results; and (4) all-cause mortality, overall treatment-related adverse events, and CPK events were similar between the daptomycin group and the comparator or vancomycin group.

Some previous meta-analyses have been published on this topic,^{6,10} and the results have shown that the efficacy and safety of daptomycin in the treatment of SSTIs were similar to those of other antibiotics included in those meta-analyses. However, a conclusive result could not be found. Based on the cumulative evidence, the current meta-analysis was conducted by using TSA to provide more conservative estimates and to assess whether the available sample size has been large enough and is conclusive. In addition, GRADE Working Group criteria were used to assess the quality of evidence for outcomes, which helps physicians to make reliable clinical decisions.

The comparator group in this systematic review mainly included patients treated with vancomycin and those treated

with teicoplanin, semi-synthetic penicillin, and telavancin. Vancomycin and teicoplanin are glycopeptide antibiotics and have been widely prescribed for several decades to treat resistant gram-positive infections, particularly SSTIs. However, vancomycin requires serum concentration monitoring, and

some concerns regarding toxicity exist.²⁸ Telavancin has in vitro activity against gram-positive pathogens and has been licensed to be used in the treatment of complicated SSTIs. However, telavancin is accompanied by more adverse events (including QT prolongation, elevated serum creatinine, and

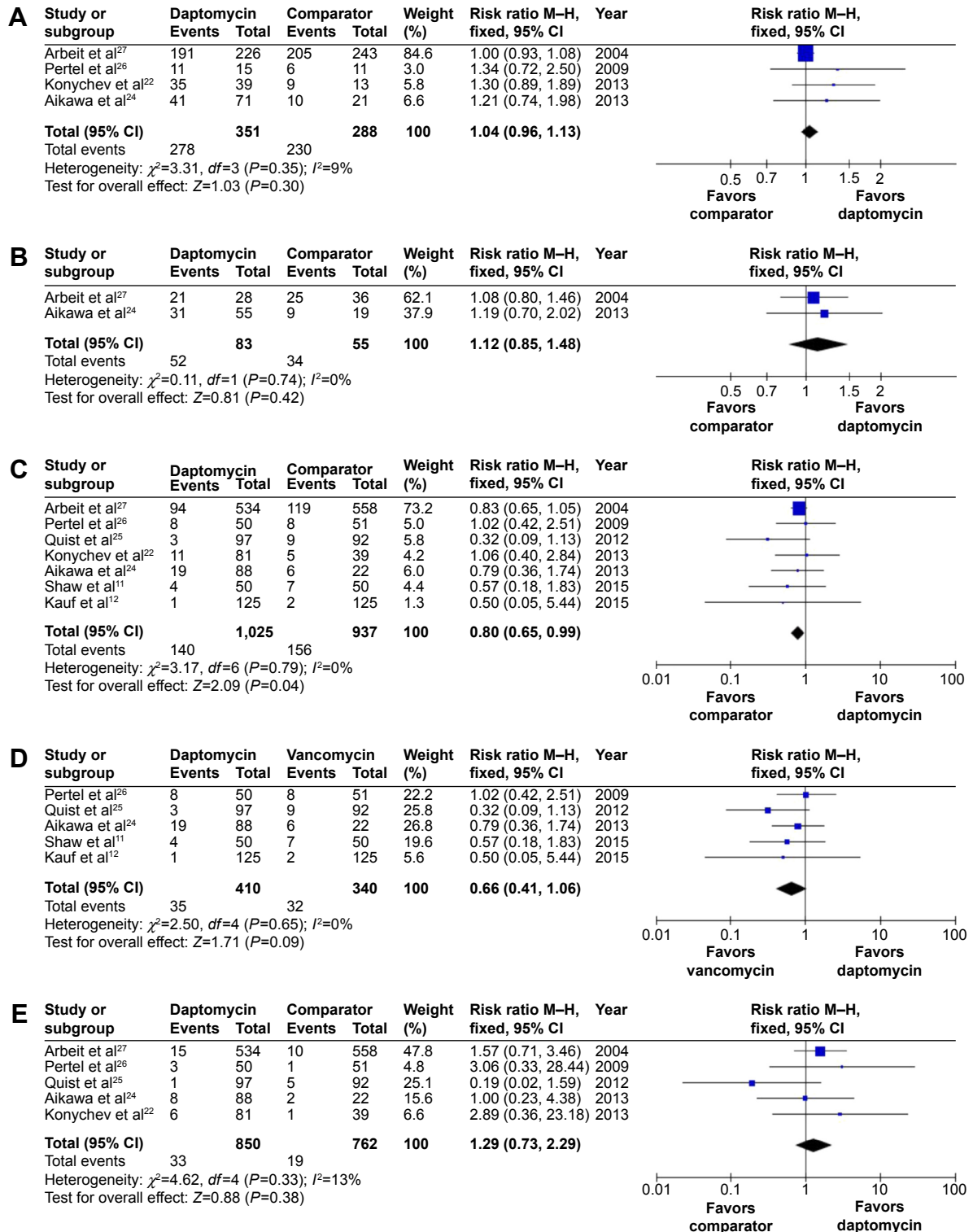


Figure 6 (Continued)

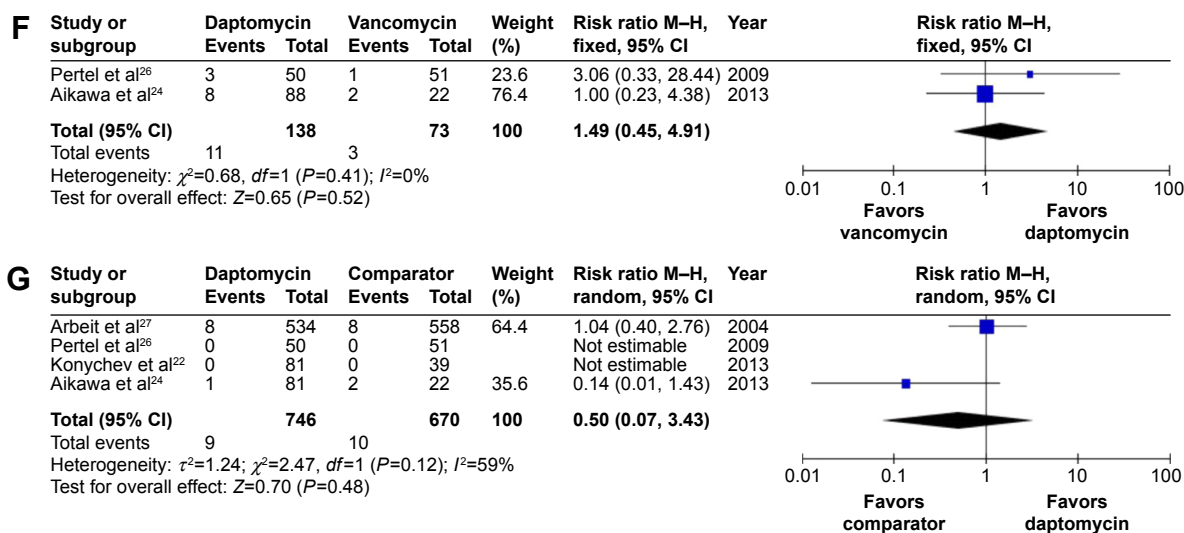


Figure 6 Forest plots of microbiological success rate (SA and MRSA), adverse events and all-cause mortality.

Notes: (A) Microbiological success rate for SA. (B) Microbiological success rate for MRSA. (C) Treatment-related adverse events (daptomycin vs comparator). The vertical line suggests no difference between daptomycin and the comparator drugs. (D) Treatment-related adverse events (daptomycin vs vancomycin). (E) Adverse events of CPK (daptomycin vs comparator). (F) Adverse events of CPK (daptomycin vs vancomycin). (G) All-cause mortality (daptomycin vs comparator).

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; MRSA, methicillin-resistant *Staphylococcus aureus*; SA, *Staphylococcus aureus*; df , degree of freedom; M-H, Mantel-Haenszel.

thrombocytopenia)^{29,30} than treatment with vancomycin, and the risk of death in patients with kidney problems or diabetes is substantially higher when treated with telavancin.³¹ Therefore, it should be used with caution. Daptomycin, which is a novel antibiotic for treating SSTIs, has bactericidal activity against *S. aureus* through the inhibition of DNA, RNA, and protein synthesis.³² However, because of an interaction between daptomycin and a pulmonary surfactant identified in vitro,³³ daptomycin is not prescribed for the treatment of pneumonia. In addition, if new pulmonary infiltrates are observed in patients treated with daptomycin,³⁴ these patients should be carefully watched for signs of daptomycin-induced acute eosinophilic pneumonia.

The present meta-analysis showed that the clinical and microbiological cure rates of daptomycin were not inferior to those of standard therapy for SSTIs, and this finding was confirmed by TSA. Therefore, daptomycin is a good alternative for patients with SSTIs when vancomycin is contraindicated. Further research should focus on other issues such as cost-efficiency, infection-related hospital length of stay, and whether the administration of daptomycin is convenient for outpatients.

Treatment-related adverse events were similar between both the groups. However, CPK is a special adverse event specific to daptomycin. Daptomycin binds to the skeletal muscle cell membranes, which can cause musculoskeletal injury and leakage of intracellular CPK from the myofibers through the modified membrane.³⁵ Therefore, the CPK

level should be closely monitored throughout the course of daptomycin therapy.

This systematic review has several limitations. First, due to the nature of the included studies, participant and personnel blinding was not performed, which may have resulted in performance and detection biases. Therefore, the GRADE approach was used to help physicians make reliable clinical decisions. Second, more than three classes of antibiotics were included in the comparator group; therefore, we compared daptomycin with vancomycin alone. Third, the study by Arbeit et al²⁷ had a high weight in this meta-analysis, which may also have influenced the overall results. Fourth, patients' habits and health history have important effects on drug metabolism and drug choice (eg, smoking, diet, other drug usage, and liver and kidney failure), which might have created potential biases in this meta-analysis.

Conclusion

No significant differences were found in the clinical or microbiological success rate between daptomycin and the comparator drugs, and no additional RCTs are required to analyze these two aspects. The overall treatment-related adverse events and all-cause mortality were similar between daptomycin and the comparator drugs, and further research should focus on other issues such as cost-effectiveness, infection-related hospital length of stay, and whether the administration of daptomycin is convenient for outpatients. Although daptomycin is a good alternative when other antibiotics are contraindicated for

patients with SSTIs and it can serve as a first-line treatment for SSTIs, clinicians should be aware of potential adverse events, such as daptomycin-induced acute eosinophilic pneumonia and CPK, when treating patients with daptomycin.

Disclosure

The authors report no conflicts of interest in this work.

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