Efficacy and safety of daptomycin: systematic review and meta-analysis

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Abstract

Background: The aim of this study was to assess whether daptomycin is safer and more efficacious than comparators for the treatment of serious infection caused by gram-positive microorganisms.

Methods: Electronic databases (Medline, EMBASE, the Cochrane Central Register of Controlled Trials and clinical registered trials) were searched to identify randomized controlled trials (RCTs) that assessed the efficacy and safety of daptomycin *versus* therapy with any other antibiotic comparator. Two reviewers independently applied selection criteria, performed a quality assessment and extracted the data. Heterogeneity was assessed, and a random-effects or fixed-effects model, when appropriate, was used for estimates of risk ratio (RR). The primary outcome assessed was the risk of clinical treatment failure among the intention-to-treat population and the presence of any treatment related adverse event (AEs).

Results: A total of seven trials fulfilled the inclusion criteria. Daptomycin treatment failure rates were no different to comparator regimens (RR = 0.96; CI 95% 0.86–1.06). No significantly different treatment related AEs were identified when comparing groups (RR = 0.91; CI 95% 0.83–1.01).

Conclusions: No significant differences in treatment failure rates and safety were found using daptomycin or any of the comparators treatment.

Keywords: daptomycin, skin infections, systematic review

Introduction

Antibiotic resistance is steadily increasing, creating a growing worldwide health problem. Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a common cause of complicated skin infections, bacteremia, endocarditis, and pneumonia.[1]

Vancomycin remains the first treatment option in patients with invasive MRSA infections, but its renal toxicities, narrow spectrum, and low concentration in some tissues has led to the need for new treatment alternatives.[1,2] In addition, the emergence of vancomycin-resistant enterococci (VRE) as a cause of nosocomial infections is a current concern, raising the need for new antibiotic options.

Daptomycin is a lipopeptide antibiotic with a broad spectrum of activity against clinically relevant gram-positive bacteria, including *S. aureus* regardless of methicillin susceptibility. In addition, it demonstrates significant activity against VRE. Given the possibility of once-a-day administration and its safety profile, daptomycin is considered a good option to complete treatment in the ambulatory setting.[3]

Daptomycin is approved by the Food and Drug Administration in adults for skin and soft tissues complicated infections (cSSI) and infectious right-side endocarditis. This drug is not indicated for the treatment of pneumonia because it binds to the pulmonary surfactant and loses activity[3–5]

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Detailed descriptions of its use remain limited particularly in children.[2]

Taking into account the previous statements, the following clinical question can be raised: Is daptomycin an effective and safe option for gram-positive infections?

To answer this question the authors developed the present systematic review and meta-analysis to evaluate daptomycin's risk of treatment failure and treatment related adverse events (AEs) compared with the standard of care (SOC).

Material and methods

A literature search was conducted in EMBASE, Medline, and the Cochrane Central Register of Controlled Trials and clinical registered trials databases using the search terms 'daptomycin' with the following filters: clinical trial, review, comparative study, systematic reviews, randomized controlled trial (RCT), controlled clinical trial, practice guideline, meta-analysis and guidelines, and use in human studies. Articles published in English, Spanish, or French until September 2018 were reviewed. The reference lists in the reviewed articles were manually examined for additional relevant studies (Table 1). The efficacy end-point was treatment failure. We used this criterion because it is the main concern at the moment for antibiotics prescription. The safety end-point was any AE that was treatment related.

Study selection

Data extraction and qualitative assessment were performed by two reviewers (MTR and DB) who independently appraised the literature and considered only RCTs for further assessment. In case of disagreement, a third reviewer (RL) analyzed the data and managed the scientific discussion until consensus was reached.

A study qualified if it was a RCT, and it compared the efficacy and safety of daptomycin with other antibacterial agents or placebo. Trials were included regardless of being blinded or open-label. The methodological quality of the included studies was assessed with the Jadad scale.[13] Trials scoring ⩾2 were considered for evaluation.

Data analysis and statistical methods

The risk of therapeutic failure end points was based on intention-to-treat or modified intention-to-treat (MITT), that included only patients with documented *S. aureus* infection or other selected specifications by authors and we determine relative risk based on this appropriate measure. In order to be more conservative pooled risk ratio (RR) and 95% confidence intervals (CIs) were calculated for failure and safety outcomes using the random-effects model (DerSimonian-Laird), calculations were carried out using the meta-analysis calculator by EpiData software version 3.1, Geneva, Switzerland (WHO). Heterogeneity bias was estimated using the Q test. Potential publication bias was estimated using Egger's test. The null hypothesis was rejected if $p < 0.05$. The systematic review was carried out using the Preferred Reporting Items for Systematic Reviews Statement.[14]

Results

The literature search identified a total of 566 potentially relevant articles, a total of 64 were RCTs and were initially evaluated by screening of the title and abstract. A total of 57 RCT studies were excluded because they did not meet the inclusion criteria, were duplications, or new analysis of previously published studies. (Figure 1)

Included studies and main characteristics

Finally, 7 full-text articles including 1798 patients under analysis for therapeutic failure rates were selected to be included in this systematic review and fully analyzed.[6–12] Two out of the seven studies included were carried out in a pediatric population[9,11] (one for treatment of bacteremia[11] and one for microbiologically documented skin infections[9]), five were carried out in adult patients (four for skin infections) and one for the treatment of bacteremia and endocarditis. Table 1 summarizes the main characteristics of included articles.

Comments about included studies

Arbeit and colleagues[6] studied the safety and efficacy of daptomycin *versus* the standard of care (SOC) for treatment of microbiologically documented cSSI and concluded that daptomycin was similar and comparable with conventional therapy. Frequency and severity of AEs were similar in both groups, with gastrointestinal disorders being the most commonly reported AEs.

**Table 1.** Included studies' main characteristics.

Authors	Conflict of interest	Study design	Patients (*n*)	Intervention	End points	Jadad score
Arbeit et al.[6]	The study was supported by and conducted under the auspices of Cubist Pharmaceuticals	multicenter, randomized 1:1, controlled, evaluator-blinded trials	Eligible patients were aged 18–85 years (in South Africa, they were aged ≤65 years). Primary inclusion criterion was a cSSI that was due, at least in part, to gram-positive organisms and that required hospitalization and parenteral antimicrobial iv therapy for ≥96 h	1092 patients were enrolled and received ≥1 dose of daptomycin (4 mg/kg/day iv q.d.) or a penicillinase-resistant penicillin or vancomycin medication	Efficacy defined as TOC evaluation for resolution of signs and symptoms in patients with positive cultures meaning no further antibiotic therapy was required and evaluation for clinical relapse or new infection at 20–28 days completion of therapy visit. Safety ≥1 AE considered to be related to study treatment	2
Fowler Jr et al.[7]	Study was designed and supported by Cubist Pharmaceuticals Data were held and analyzed by the sponsor. However, the authors had complete and unfettered access to the data and vouch for the veracity and completeness of the data and analyses used in this article	intention-to-treat open-label, randomized 1:1, multicenter clinical trial,	Eligible patients were 18 years of age or older and had one or more blood cultures that were positive for *S. aureus*	124 patients were randomly assigned to daptomycin (6 mg/kg/day iv) (MIT = 120, PP = 79) and 122 to receive initial low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin (MIT = 115, PP = 60) Population included all patients in the MITT group with documented adherence to the protocol	The primary outcome was the clinical success rate in each of the two treatment groups in the MITT population at the visit 42 days after the end of therapy	3
Pertel et al.[8]	Financial support was provided by Cubist Pharmaceuticals	prospective, randomized, Evaluator-blinded, multicenter trial	Patients ≥18 years of age who had a primary diagnosis of cellulitis or erysipelas requiring hospitalization and iv antibiotic therapy	A total of 103 patients were randomized. Patients in the daptomycin group received 4 mg/kg/day iv. One patient in each group did not receive study drug; 50 were treated with daptomycin and 51 with vancomycin	An exploratory clinical trial was conducted to evaluate whether the treatment of cellulitis or erysipelas with daptomycin would result in faster resolution of symptoms and signs compared with treatment with vancomycin among hospitalized patients. Clinical success was defined as a patient cured or improved	3

(Continued)

Table 1. (Continued)

Authors	Conflict of interest	Study design	Patients (n)	Intervention	End points	Jadad score
Aikawa et al.[9]	Some of the authors are employees of MSD KK, a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA	Open-label, randomized, active-comparator controlled parallel-group, multicenter, phase III study. Allocation system was not reported	111 male and female Japanese patients aged >20 years who required hospitalization and treatment with systemic antibacterial agents with SSTIs caused MRSA. Of the 111 patients who were randomized, 88 received daptomycin and 22 received vancomycin	Patients were randomized 4:1 to receive intravenous daptomycin (4 mg/kg over 30 min) once daily or vancomycin (1 g over at least 60 min) twice daily for 7–14 days	Clinical and microbiological response at TOC was used as the primary end-point for efficacy evaluation in this study. Clinical responses at TOC were evaluated by study investigators within 7–14 days of the last dose of study medication	3
Konychev et al.[10]	Sponsored by Novartis Pharma AG	intention-to-treat population, open-label, multicenter, randomized 2:1 phase IIIb study	Eligible patients were aged ≥65 years with SSTI with or without bacteremia	In total, 120 patients were randomized (81 to daptomycin; 39 to the comparator). Daptomycin was administered every 24 h at a dose of 4 mg/kg (in the absence of bacteremia) or 6 mg/kg (with bacteremia);	Primary objective was descriptive comparison of clinical success (blinded sponsor assessment) in clinically evaluable patients at TOC at 7–14 days post treatment. Secondary objectives were microbiological outcome and duration of treatment and safety	3
Bradley et al.[11]	Merck & Co, Inc. provided financial support for the study	intent-to-treat, randomized 2:1, evaluator-blinded Multicenter clinical trial	Patients between 1 and 17 years old with cSSI known or suspected to be caused by gram-positive bacteria and thought to require iv antibacterial therapy	257 patients randomized to daptomycin (MITT = 207; ME = 167) and 132 randomized to SOC (MITT = 105 = ME = 78) ME caused by culture gram-positive pathogens. Daptomycin was administered once daily with dosing by patient age: 12–17 years, 5 mg/kg; 7–11 years, 7 mg/kg; 2–6 years, 9 mg/kg; 12–23 months, 10 mg/kg	The primary objective was to evaluate daptomycin safety. The secondary objective was to assess the efficacy of daptomycin compared with SOC at TOC in patients with positive cultures	4
Arrieta et al.[12]	Merck & Co, Inc. provided financial support for the study	Randomized (2:1), evaluator-blinded, multicenter, phase IV clinical trial	Patients between 1 and 17 years old with proven/probable *S. aureus* bacteremia	55 children were randomized to daptomycin (40 were clinically evaluable) at once daily age-dependent dosages and 27 to SOC (12 were clinically evaluable). Daptomycin was dosed once daily iv by patient age: 12–17 years, 7 mg/kg; 7–11 years, 9 mg/kg; 1–6 years, 12 mg/kg	Primary objective was to evaluate daptomycin safety in children who received ≥1 dose; secondary objectives included comparing daptomycin efficacy with SOC	3

AE, adverse event; cSSI, complicated skin, and skin-structure infection. iv, intravenous; MITT, modified intention-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; PP, per protocol; SOC, standard of care; TOC, test of cure ; ME, microbiologically evaluable.
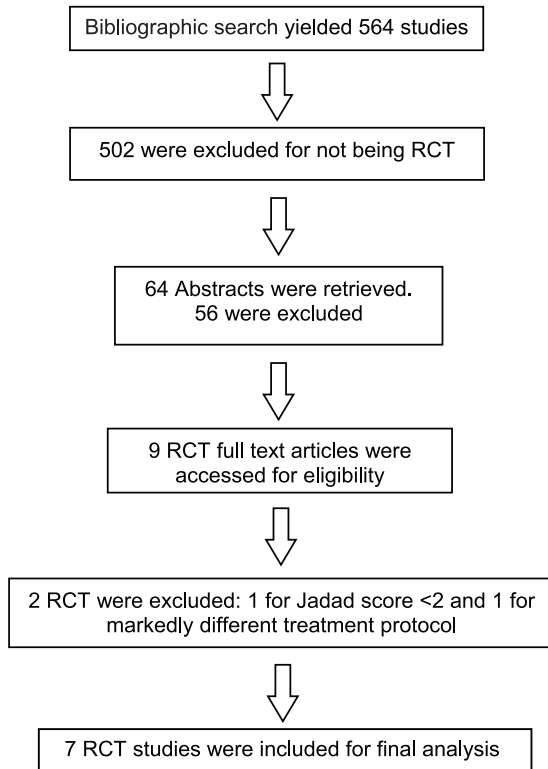
Figure 1. Flow diagram of the identification process and selection of the included articles.

The trial carried out by Fowler and colleagues[7] supported the efficacy of daptomycin in adults with bacteremia and endocarditis caused by *S. aureus*. This study was not able to identify a statistically significant difference when compared with standard treatment. Rates of AEs were similar between daptomycin and standard therapy. Renal impairment was more common in patients who received standard therapy and creatine kinase elevation was significantly more common in the daptomycin group.

Pertel and colleagues[8] reported a similar clinical response and AEs rates between daptomycin *versus* vancomycin comparator in adults with cSSI mainly in erysipelas and cellulitis.

Kornychev and colleagues[10] analyzed the efficacy and safety of daptomycin in adult patients with cSSIs reporting no significant clinical failures in the daptomycin group. Incidence rates of AEs were similar in both groups.

Aikawa and colleagues[9] studied the efficacy and safety of daptomycin *versus* comparators in Japanese patients with MRSA cSSI infections and concluded that daptomycin was clinically and microbiologically effective. AEs occurred with similar frequency in patients treated with daptomycin or vancomycin.

Pediatric patient trials carried out by Bradley and colleagues[11] and Arrieta and colleagues[12] were also included (one in patients with bacteremia and one in patients with microbiologically documented cSSI). Daptomycin performance in both trials was no different from comparators and the rate of any reported AEs were not statistically significant different between groups (Tables 1–3).

Therapeutic failures rate, no heterogeneity in trials 'results for therapeutic failure were detected' (heterogeneity bias: DerSimonian-Laird's test: Q: 1.12; df: 5; $p = 0.95$). Typical RR for therapeutic failure was RR 0.96; CI 95% 0.86–1.06 (Figure 2). The cumulative meta-analysis shows a persistent but nonsignificant direction and magnitude of the therapeutic failure rate. Consistency is according with the homogeneity of included trials results (Figure 3). Sensitivity analysis did not demonstrate any relevant result modification [withdrawal of Arbeit's study reduced risk by 3.94% (the highest) and Aikawa's study 0.02% (the least)]. Egger's test yielded a significant probability of publication bias for treatment failure: $t = 5.11$; $df = 5$; $p = 0.003$ (Figure 5).

Treatment related AEs rate: Rates of treatment related AEs were not different between daptomycin and comparators (typical RR 0.91; CI 95% 0.83–1.01) (Figure 4). No heterogeneity was detected (heterogeneity bias: DerSimonian-Laird's test: $Q = 3.90$; $df = 6$; $p = 0.67$).

The most frequently reported AEs were gastrointestinal disturbances in all groups. It is well known that a creatine phosphokinase (CPK) level increase is considered a subrogate index of muscle toxicity[7] All of the trials included paid special attention to this topic, in a very heterogeneous way, making its synthesis not advisable by means of a meta-analysis. We present these observations in Table 4.

Sensitivity analysis did not highlight any relevant result modification (withdrawing Arbeit's paper reduced risk by 2.27% (the highest) and withdrawing Pertel's paper reduced risk by −1.38%).

Table 2. Studies' efficacy end-point: therapeutic failure.

Author	Daptomycin *n*/N (%)	Comparator *n*/N (%)	RR (CI 95%)
Arbeit et al.[6]	110/428 (26.31)	120/471 (25.47)	1.00 (0.86–1.17)
Fowler Jr. et al.[7]	67/120 (55.83)	67/115 (58.26)	0.95 (0.74–1.22)
Pertel et al.[8]	3/50 (6.00)	5/51 (9.81)	0.74 (0.29–1.85)
Konychev et al.[10]	8/73 (10.95)	5/30 (16.66)	0.85 (0.54–1.33)
Aikawa et al.[9]	45/55 (81.8)	16/19 (84.2)	0.9590 (0.68–1.33)
Bradley et al.[11]	15/209 (7.17)	10/104 (9.61)	0.89 (0.64–1.23)
Arrieta et al.[12]	10/51 (19.60)	5/22 (9.09)	0.94 (0.63–1.39)
TOTAL	258/986 (26.16)	228/812 (28.07)	0.96 (0.86–1.06)

Table 3. Studies' safety (at least one adverse event).

Author	Daptomycin *n*/N (%)	Comparator *n*/N (%)	RR (CI 95%)
Arbeit et al.[6]	94/534 (17.60)	119/558 (21.32)	0.88 (0.74–1.03)
Fowler Jr. et al.[7]	42/120 (35.00)	49/116 (42.24)	0.85 (0.65–1.12)
Pertel et al.[8]	3/50 (6.00)	1/51 (1.96)	3.06 (0.32–28.43)
Konychev et al.[10]	11/80 (13.75)	5/40 (12.5)	1.23 (0.45–3.33)
Aikawa et al.[9]	62/88 (70.5)	19/22 (86.4)	0,90 (0.72–1.14)
Bradley et al.[11]	35/256 (13.67)	22/133 (16.54)	0.82 (0.50–1.34)
Arrieta et al.[12]	8/55 (14.54)	4/26 (15.38)	0,97 (0.68–1.50)
TOTAL	255/1183 (21.55)	219/946 (23.15)	0.91 (0.83–1.01)

Egger's test yielded a significant probability of publication bias: $t = 3.23$; $df = 5$; $p = 0.02$. (Figure 5)

Discussion

We conducted this systematic review to evaluate the performance of daptomycin, in terms of safety and risk of therapeutic failure, when it was prescribed for the treatment of all types of infections (except pneumonia) in children and adults, against the usual therapy antibiotic comparators.

A nonsignificant trend for less risk of therapeutic failures of daptomycin in patients with cSSI, endocarditis, or bacteremia was demonstrated in the clinical trials included in this meta-analysis,

especially for those caused by *S. aureus*. All RCTs included in this systematic review suggested this trend, both in adults and children suffering complicated skin infections, bacteremia, or endocarditis. This meta-analysis achieved the same conclusion.

With regard to AEs, daptomycin had been reported to have the potential to cause muscle toxicity, therefore, CPK levels were measured in all included studies.

Some studies showed that high doses of daptomycin may elevate CPK levels, however, in healthy volunteers doses up to 12 mg/kg/day were not associated with muscle toxicity and in one study carried out on patients treated with high doses
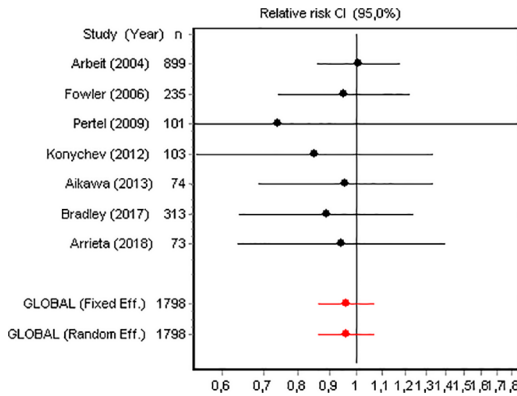
Figure 2. Forest plot about probability of therapeutic failure.
Typical RR for therapeutic failure: RR 0.96; CI 95% 0.86–1.06.
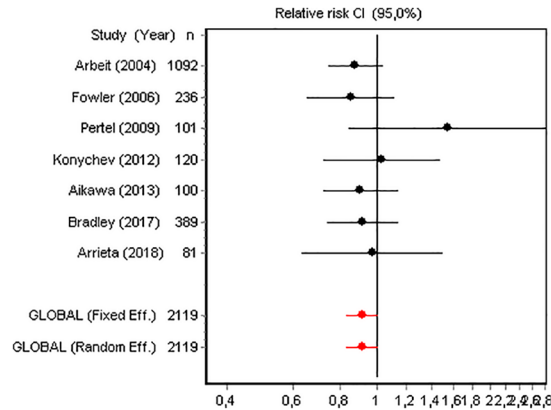
Figure 4. Forest plot about the probability of adverse events.
Rates of treatment related AEs were not different between daptomycin and comparators (typical RR 0.91; CI 95% 0.83–1.01).
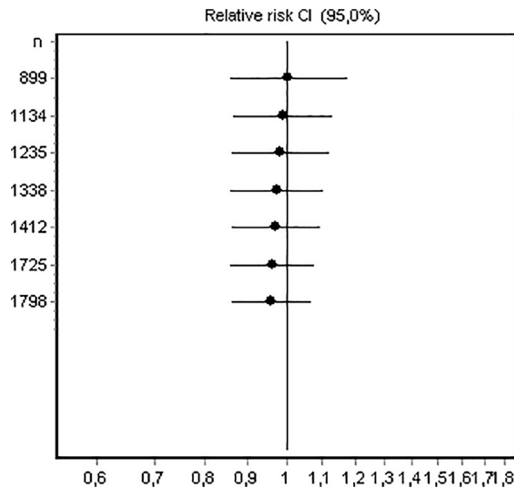
Figure 3. Cumulative probability of therapeutic failure.
Cummulative meta-analysis showed a persistent but nonsignificant trend toward less therapeutic failures using daptomycin.
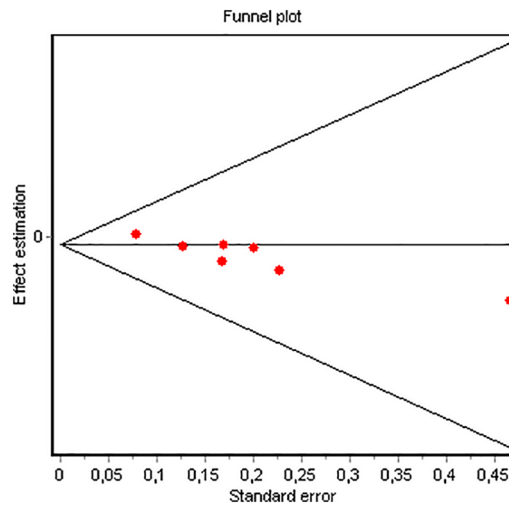
Figure 5. Publication bias in therapeutic failure assessment.
Egger's test yielded a significant probability of publication bias assessing therapeutic failure rate ($t = -5.11$; $df = 5$; $p = 0.003$).

(>6 mg/kg/day) of daptomycin, the rate of CPK elevations were low.[1,15]

Our meta-analysis showed that elevated CPK levels were more frequent in the daptomycin group, but discontinuation of the drug was seldom required due to this AE. In addition, in these patients, the elevated CPK levels dropped rapidly. No data is available about the long-term AEs related to its potential muscle toxicity because this follow-up was not carried out.

Given the similar risk of therapeutic failure of daptomycin, its low incidence of any AEs, and the potential to be used as monotherapy, there is support for its use as an alternative strategy to reduce the use of broad spectrum antibiotics. In addition, daptomycin administration once-a-day is an important therapy for use in ambulatory treatment in selected patients to reduce health care associated infection risk.

Emergence of antibiotic resistance is a major problem in health care and it is, therefore, very important to control the use of antibiotics. It is

Table 4. Drug-related CPK elevations.

Author	CPK level	Observations
Arbeit et al.[6]	15 patients in the daptomycin group (2.8%) and 10 in the comparator group (1.8%) presented CPK level elevation	Daptomycin was discontinued in one patient with mild–moderate weakness and upper extremity muscle pain
Fowler et al.[7]	CPK elevations were most common in the daptomycin group than in the comparator group (6.7% *versus* 0.9%). Among patients with CPK normal baseline levels elevations were in 23/92 in dapto *versus* 12/96 comparator (25 *versus* 12.5%) More than 500 U/l was seen in 11/116 (9.5%) in the daptomycin group *versus* 2/11 (1.5%) comparator group	Daptomycin was discontinued in three patients
Pertel et al.[8]	None	
Konychev et al.[10]	Six patients (7.5%) in the daptomycin group presented CPK levels above 500 U/l and 1 (2.5%) in the comparator group	Daptomycin was discontinued in one patient
Aikawa et al.[9]	One patient in each group presented CPK >500 U/l. Otherwise, CPK levels above 200 U/l were seen in 9.1% in both groups	No CPK elevations led to discontinuation of treatment
Bradley et al.[11]	14/256 patients (5.5%) in the daptomycin group presented CPK level above 500 U/l and 7/133 (5.3%) in the comparator group	No CPK elevations led to discontinuation of treatment
Arrieta et al.[12]	8/55 daptomycin treated (15%) *versus* 3/26 SOC (12%) had values 1–2.5 greater above the upper limit of CPK normal values and in 2/55 daptomycin group was higher	Daptomycin was discontinued in one patient

CPK, creatine phosphokinase; SOC, standard of care.

remarkable that daptomycin resistance is uncommon. In our setting, the daptomycin price per 500 mg is 10 times higher than the price of 500 mg of vancomycin. If the need of vancomycin and the potential risk of renal failure is considered, economical concerns should be balanced against the benefits in selected cases, especially in an endovascular setting. A study, using a Monte Carlo simulation, shows that daptomycin was the most cost-effective treatment in 100% of the 10,000 simulations, with a willingness to pay €12,000 per additional cure (the approximate cost of treatment for an MRSA bacteremia episode). This study concluded that daptomycin is more cost-effective than vancomycin when treating MRSA bacteremia and that the higher cost of daptomycin does not imply a higher cost of treatment for this infection.[16]

Daptomycin should potentially be reserved for intolerance, or when the narrower spectrum antibiotics fail, especially when targeted against MRSA and VRE in selected infections.

A limitation of the present meta-analysis is that all of the RCTs included in this systematic review were funded by the pharmaceutical industry, resulting in a considerable risk of bias. Concerns arose when it was discovered that all of the funded RCT studies were only conducted in patients with cSSI infections, only a few were in patients with bacteremia or endocarditis, with different doses and follow-ups. For these reasons, we applied strict selection criteria in an effort to standardize our study, but this strategy does not allow for publication bias. Other limitation are that the microbiologically documented infections were caused in the majority of cases by *S. aureus*, and we cannot extrapolate the results to other gram-positive bacteria.

The authors concluded that to answer the initial clinical question further studies are required on other types of infections, comparing daptomycin with new antigram-positive pathogens and other gram-positive microorganisms, and with studies of cost *versus* efficacy.

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final drafting and all have approved the final version to be published.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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References
1. González-Ruiz A, Gargalianos-Kakolyris P, Timerman A, *et al.* Daptomycin in the clinical setting: 8-year experience with gram-positive bacterial infections from the EU-CORESM registry. *Adv Ther* 2015; 32: 496–509.

2. Seaton A, Gonzalez Ruiz A, Cleveland K, *et al.* Real world daptomycin use across wide geographical regions: results from a pooled analysis of CORE and EU-CORE. *Ann Clin Microbiol Antimicrob* 2016; 15: 18.

3. Heidary M, Khosravi AD, Khoshnood S, *et al.* Daptomycin. *J Antimicrob Chemother* 2018; 73: 1–11.

4. Garazzino S, Castagnola E, Di Gangi M, *et al.* Daptomycin for children in clinical practice experience. *Pediatr Infect Dis J* 2016; 35: 639–644.

5. Garau J. Management of cSSTIs: the role of daptomycin. *Curr Med Res Opin* 2006; 22: 2079–2087.

6. Arbeit RD, Maki D, Tally FP, *et al.* The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004; 38: 1673–1681.

7. Fowler VG Jr, Boucher HW, Corey GR, *et al.* Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006; 355: 653–665.

8. Pertel PE, Eisenstein BI, Link AS, *et al.* The efficacy and safety of daptomycin vs. vancomycin for the treatment of cellulitis and erysipelas. *Int J Clin Pract* 2009; 63: 368–375.

9. Aikawa N, Kusachi S, Mikamo H, *et al.* Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. *J Infect Chemother* 2013; 19: 447–455.

10. Konychev A, Heep M, Moritz RK, *et al.* Safety and efficacy of daptomycin as first-line treatment for complicated skin and soft tissue infections in elderly patients: an open-label, multicentre, randomized phase IIIb trial. *Drugs Aging* 2013; 30: 829–836.

11. Bradley J, Glasser C, Patino H, *et al.* Daptomycin for complicated skin infections: a randomized trial. *Pediatrics* 2017; 139. pii: e20162477.

12. Arrieta AC, Bradley JS, Popejoy MW, *et al.* Randomized multicenter study comparing safety and efficacy of daptomycin versus standard-of-care in pediatric patients with staphylococcal bacteremia. *Pediatr Infect Dis J* 2018; 37: 893–900.

13. Jadad AR, Moore RA, Carrol D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.

14. Higgins JPT and Green S GS. Cochrane handbook for systematic reviews of interventions, Version 5.1.0. *The Cochrane Collaboration*, https://handbook-5-1.cochrane.org/

15. González Ruiz A, Seaton A and Hamed K. Daptomycin: an evidence –based review of its role in the treatment of gram- positive infections. *Infect Drug Resist* 2016; 9: 47–58.

16. Rubio-Terrés C, Rubio-Rodriguez D, Majos N, *et al.* Análisis farmacoeconómicos del tratamiento de la bacteremia por *Staphylococcus aureus* resistente a meticilina com daptomicina y vancomicina. *Rev Esp Quimioter* 2012; 25: 283–292.