

## The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections: a metaanalysis of randomized controlled trials.

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# The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections: a meta-analysis of randomized controlled trials.

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## Strengths and limitations of this study

- Skin and soft tissue infections (SSTIs) are most common infections, usually caused by gram-positive bacteria and are closely related to aging and obesity. Vancomycin and linezolid are the first-line antimicrobial agents for gram-positive infections, but recently cases of drug resistance has been repeatedly reported.
- Daptomycin, a cyclic lipopeptide, is now approved to treat gram-positive pathogens for about 10 years and drug resistance of daptomyin remains rare to date.
- This is the first meta-analysis of randomized controlled trials of daptomcyin for skin and soft tissue infectionsTo our knowledge, this is also the first time daptomycin's potential myotoxicity was confirmed by meta-analysisSubgroup analyses of clinical success were conducted between daptomycin and vancomycin; microbiological success of daptomycin versus comparators for Staphylococcus Aureus was also analyzed.

## ABSRACT

**Objective:** Daptomycin, a cyclic lipopeptide that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens is now approved in more than 70 countries and regions. Daptomycin was approved to treat skin and soft tissue infections(SSTIs) since 2003, in this meta-analysis, we try to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs.

Design: Meta-analysis of randomized controlled trials.

**Data sources:** We thoroughly searched PubMed,Embase,Cochrane Central to identify relevant RCTs.Six RCTs,a total of 1710 patients were included in this meta-analysis.

**Results:** The results demonstrated the efficacy of daptomycin were not inferior to other first-line antibiotics for **SSTIs** in the matter of odds ratio(OR) for clinical success(OR=1.05,95%CI0.84-1.31,p=0.65,I<sup>2</sup>=0%);daptomycin vancomycin versus subgroup(OR=1.19,95%CI0.77-1.83,p=0.43,I<sup>2</sup>=0%);overall microbiological success(OR=1.05,95%CI0.61-1.79,p=0.86,I<sup>2</sup>=42%);microbiological success of daptomycin versus (SA,OR=1.05,95%CI0.61-2.60,p=0.53,I<sup>2</sup>=47%),for comparators for Staphylococcus Aureus MRSA(OR=0.90,95%CI0.77-1.06,p=0.20,I<sup>2</sup>=56%).And similar daptomycin tended to have a treatment-related adverse events(AEs) incidence in comparison with other antibiotics(OR=1.06,95%CI0.71-1.59,p=0.76,I<sup>2</sup>=41%). There was a trend that daptomycin might cause less For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

discontinuation due to AEs and death compared with other first-line antibiotics  $(OR=0.71,95\%CI0.46-1.10,p=0.12,I^2=11\%)$ . Significant more patients had CPK elevation in daptomyicn group than in control group, however it could be reversed when the therapy ended  $(OR=1.95,95\%CI1.04-3.65,p=0.04,I^2=0)$ .

**Conclusion:** Our meta-analysis demonstrated the safety and efficacy of daptomycin was not inferior to other first-line drugs, and it had a tendency of exhibiting superior efficacy when compared with vancomycin or with comparators for SA infections, but more high-quality RCTs needed to draw a credible conclusion.

## Introduction

Skin and soft tissue infections (SSTIs) are most common infections, usually with mild to moderate severity, however, the incidence of SSTIs has rapidly increased in US in the Community Acquired(CA)-MRSA era and appears to disproportionately affect certain populations[1].SSTIs was usually caused by purulent pathogenic bacteria which invade epidermis, dermis and subcutaneous tissue[2].SSTIs has a wide-spread range, from superficially localized skin infection to deep inside necrotizing soft tissue infection which severe enough to cause extremity disability or even death. According to different clinical charateristics,SSTIs were divided into uncomplicated SSTIs and complicated SSTIs(cSSTIs).cSSTIs were defined as specific source of infection or opportunistically pathogenic situation like trauma, cancer, chemotherapy which accompanied by impairment of skin barrier function or decreased immune function[3].

For hospitalized patients with complicated SSTI(cSSTI), besides surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered. Antibiotic options include vancomycin, linezolid, daptomycin, telavancin and clindamycin. 7 to 14 days of therapy was recommended [4 5]. The majority of community-acquired(CA) SSTIs in western countries were caused by Staphylococcus aureus and beta-haemolytic streptococci[2 6]. Staphylococcus aureus was also the main pathogen of Hospital-Acquired SSTIs, where Methicillin-resistant Staphylococcus aureus(MRSA) took a high proportion [3 7].

Vancomycin was regarded as mainstay of parenteral therapy for MRSA infections for decades,but recently its minimum inhibitory concentrations(MICs) in MRSA are elevating,and linezolid resistance has been reported likewise[8].Daptomycin,a cyclic lipopeptide, that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens is now approved in more than 70 countries and regions[9 10]. Analyses of daptomycin treatment outcomes showed that treatment with daptomycin has resulted in high clinical success rate for a wide range of gram-positive infections, such as complicated skin and soft tissue infections(cSSTIs) at the dosage of 4 mg/kg/day[11], Staphylococcus aureus bacteraemia(SAB),right-sided infective endocarditis at the dosage of 6 mg/kg/day[12].

Linezolid can cause anemia, thrombocytopenia, and gastrointestinal side effects, especially in prolonged therapy[13]. The main side effect of vancomycin is nephrotoxicity, and teicoplanin can cause fever[14]. Daptomycin is a comparably safer antibiotic, with myotoxicity being the most relevant side effect which can be reversed when the therapy ended[15]. In an era drug resistance becomes an urgent problem, we need new antibiotics which can treat infectious diseases, daptomycin might become an alternative agent, especially when standard therapy won't work.

## Aims

In this meta-analysis, we try to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs. The safety endpoints, were treatment-related adverse events (AEs), discontinuation due to AEs and all-cause For peer review only - http://bmjopen.bmj.com/ste/about/guidelines.xhtml

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mortality, and creatine phosphokinase(CPK) elevation. The efficacy endpoints were clinical success and microbiological success at the test of cure(TOC) visit.

## **Methods**

Data sources.

We searched Pubmed(up to September 2013), Embase(up to September 2013) and Cochrane Central(Issue 9 of 12, Sept 2013) to find relevant clinical trials with a prespecified search strategy, and revised appropriately through databases. Trials other than RCT were eliminated from consideration. Search terms included 'daptomycin', 'cubicin', 'lipopeptide', 'skin and soft tissue infections', 'cellulitis', 'wounds infection', 'abscess' and 'erysipelas', and they were combined by PICOs principle. No language restriction settled in the searching process. We consulted statistical experts to make search strategy and wrote emails to relevant corresponding authors and pharmaceutical companies to get information about any ongoing RCTs that concerns daptomycin.

## Study selection

Two authors(WSZ and TZH) independently searched and scanned relevant literatures, after reading the title and abstract of every retrieved literature to determine which literatures requiring further assessment. Full articles were obtained when the information given in the titles, abstracts implying that: the study was a prospective design research, comparing daptomycin with vancomycin or other antibiotics (with or without co-interventions). When disagreement existed, we discussed thoroughly to reach consensus. Inclusion criteria:(i)Any randomized controlled trials that compare daptomycin with other antibiotics in treating SSTIs . (ii)Included patients were of any age, any gender ,had a SSSI requiring i.v. antibiotic treatment .(iii)Daptomycin intravenous infusion with any dosage, comparator antibiotics intravenous infusion with any dosage. Co-interventions that target confirmed or probable infections with gram-negative aerobic and anaerobic pathogens were permitted.

## Qualitative assessment

Methodological quality of the RCTs included in this review was independently evaluated by two authors(WSZ and TZH), using the Jadad scale[16]. Jadad scale evaluates randomization and blinding. If elucidation of methodology revealed that the study applied appropriate randomization and blinding procedures, two scores given to randomization and two scores to blinding. If only mentioned about randomization or blinding but no detail elucidated, one score deducted accordingly. If information about attrition was thoroughly elucidated, one score given. Thus, the score ranges from zero to five, score higher than two was considered as trial of high methodological quality.

## Data extraction

Two review authors (WSZ and TZH) independently extracted data with a prespecified data extraction form specifically tuned for this review. The data extraction included the following detailed imformation: 1. Year of publication, clinical settings 2. The number of intention to treat(ITT) and clinically evaluable(CE) patients3.Descriptions of dose, route, and timing of daptomycin and other antibiotics.4.Clinical success, microbiological success,treatment-related adverse events(AEs), discontinuation due to adverse events(AEs) and all-cause mortality, and creatine phosphokinase(CPK) elevation cases. If missing data detected from the trial reports, we attempted to contact the corresponding authors to request these information. If this was not successful, intention-to-treat (ITT) analysis were conducted for all dichotomous outcomes (e.g. clinical success, microbiological success, treatment-related adverse events,all-cause mortality). For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

## Analysed Outcomes

Primary outcomes of this review were clinical success and microbiological success. Outcomes were judged by clinical and microbiologic evaluations performed at baseline (within 72 h before receipt of the first dose of study drug) and test-of-cure(TOC) visit(6–20 days after receipt of the last dose). Clinical success defined as had resolution of signs and symptoms such that no further antibiotic therapy was required at TOC visit. Microbiological success defined as eradication of pathogen (admission pathogen absent in culture) or presumed eradication of the pathogen (no material available for culture but patient was deemed as cured or improved by the study investigator at TOC visit.Secondary outcomes were proportions of patients with treatment-related adverse events, discontinuation due to adverse events and all-cause mortality,and CPK elevation cases.

Data analysis and statistical methods

Data analyses of this review were performed by Review Manager 5.2(Version: 5.2.6,Cochrane Collabration,UK).Clinical heterogeneity were assessed in population, methodology, intervention and outcome measures of each study to see whether pooling of results was feasible.Heterogeneity assessment was performed using the chi-squared test, where P value less than 0.1 was considered as significance set. Funnel plot was applied to check for publication bias.Moreover,  $I^2$  was applied to estimate the total variation attribute to heterogeneity among studies[17]. Values of  $I^2$  less than 25 percent were deemed to have low heterogeneity, and we would then use a fixed-effect model for meta-analysis. Values of  $I^2$  between 25 and 75 percent were considered to represent moderate levels of heterogeneity, therefore, we then utilized a random effects model. Values of  $I^2$  higher than 75 percent indicating high levels of heterogeneity, in which case we did not perform meta-analysis. All statistical tests were two-sided and a *p* value less than 0.05 was considered statistically significant.

## Results

Study selection process

Flow diagram in <u>Fig.1.</u> shows the whole scanning and selection process. A total of 310 articles were retrieved by means of electronic search of the databases. After deleting duplicates, 293 articles retained to read title and abstract. Full text of 23 articles were obtained for further review after the scanning. Meanwhile we wrote email to Aastrazeneca China which is in charge of selling of daptomycin in China, we were informed that daptomycin for SSTIs phase-3 clinical trial in China has been finished, yet so far no data published. Finally 6 out of the 23 articles reached the inclusion criteria.

## Study characteristics

The main characteristics of the 6 RCTs(type of study design,Jadad score,characteritics of patients,dose and treatment duration of studied drugs,ITT population,CE population) included in this meta-analysis were presented in <u>Table 1</u>.All of the 6 studies were multi-center trials[18-23].The total number of patients of included trials were 1710.Only adults were enrolled in the included trials,and one trial only aimed at elder patients aged at least 65 years[18]. In terms of methodology,all the six enrolled trials were deemed to be eligible,with a Jadad score  $\geq$ 2.Allocation concealment was not thoroughly stated in all the 6 included trials.Funnel plot were performed to check publication bias(standard error of logOR plotted against OR).All the six studies were neither participants-blinded nor personnel-blinded.Overall clinical success analysis were performed on both ITT and CE population. Microbiological success was analyzed on microbiologically **For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml** 



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evaluable population.Adverse events(AEs) were analyzed on ITT population.Note that,thirty-six patients with no MRSA identified as causative pathogen(33 patients receiving daptomycin and 3 patients receiving vancomycin) were excluded from the efficacy analysis of MITT-MRSA population in one study[19].

Four out the six included studies were phase-3 trials[19-21 23],one study was phase-2 trial[22] and one study was phase-4 trial[21].Comparator drugs in this review refers to vancomycin(mainly),semi-synthetic penicillins(SSPs) and teicoplanin,which were used as counterpart for daptomycin in control group in included studies.Comparator drugs used in 2 trials was vancomycin alone[19 21].Comparator drugs were vancomycin and teicoplanin in one trial[20].Comparetor drugs were vancomycin and semi-synthetic penicillins in two trials[18 23]. Infecting organism was confirmed not MRSA in patients randomized to vancomycin(control),investigators were permitted to switch therapy to a SSP in one study[18].ITT patients of all the six studies were designated to receive intravenous therapy,but patients could be switched to oral treatment in three trials if the patients already had at least 4 or 5 days of intravenous therapy and had a clearly clinical improvement[18 22 23].Daptomycin with a dosage of 4 mg/kg/day were administered in five trials,while daptomycin with a dosage of 10 mg/kg/day were administered in one study[22].And comparator drugs in all the six trials were administered according to the standard of care.The efficacy endpoints and safety endpoints were similar across the six included studies.

Clinical success rate analysis was performed on ITT population(all randomized patients with a SSSI who received  $\geq 1$  dose of study medication) and CE population(all patients in the ITT population who met protocol-specified inclusion or exclusion criteria relating to the prespecified assessments and to the absence of confounding factors, including completion of the required visits) as well. The pooling result of ITT population showed clinical success rate of daptomycin was similar with comparator drugs at TOC visit(6 RCTs, 1674 patients, OR=1.05, 95% CI 0.84-1.31, p=0.65, I<sup>2</sup>=0; Fig.2. A). Pooling result of CE population also demonstrated no difference existed in clinical success rate between daptomycin and other antibiotics for treating SSTIs (6 RCTs, 1381 patients, OR=0.99, 95% CI 0.73-1.35, p=0.97, I<sup>2</sup>=0; Fig.2. B).

In terms of daptomycin vs vancomycin subgroup, clinical success rate of daptomycin was higher(not significantly) than that of vancomycin(6 RCTs,716 patients,  $OR=1.19,95\%CI 0.77-1.83,p=0.43,I^2=0;Fig.2.$  C).Briefly, 342 out of 402 patients in daptomycin group and 254 out of 314 patients in vancomycin group achieved clinical success at TOC visit.Katz et.al's study used a higher dosage than the other included studies,after we excluded Katz et.al's study,the pooling result showed a trend favors daptomycin(5 RCTs,638 patients, $OR=1.39,95\%CI0.88-2.19,p=0.16,I^2=0;Fig.2.$  D)

Microbiological success

Microbiological success was performed on microbiologically evaluable patients(all patients in the clinically evaluable population who had an causative gram-positive organism isolated at baseline),the pooling result showed the microbiological success rate of daptomycin was similar(not significantly) to that of comparator drugs(6 RCTs, 1173 patients,OR= 1.05,95% CI 0.61-1.79,p=0.86,I<sup>2</sup>=42%;Fig.3. A).In brief,504 out of 624 patients in daptomycin group and 458 out of 549 patients in control group achieved microbiological success.

The data of Staphylococcus Aureus subgroup was not extractable in Quist et al.'s study[20]. In terms of microbiological success rate for Staphylococcus aureus(Methicillin-susceptible and Methicillin-resistant),the pooling result demonstrated no significant difference existed between daptomycin and comparator drugs(5 RCTs,698 patients,Odds Ratio=1.59,95%CI 0.61-2.60,p=0.53,I<sup>2</sup>=47%;<u>Fig.3.</u> B).After we excluded Katz et al.'s study,the overall heterogeneity dropped,nevertheless,the result remained unchanged(4 RCTs,639 patients,Odds Ratio=1.25,95%CI0.83-1.89,p=0.29,I<sup>2</sup>=11%;<u>Fig.3.</u> C).For MRSA infections,we successfully extracted data from 3 studies,the overall heterogeneity was expectedly high,under which circumstance random model was applied,and the result showed the success rate of daptomycin was slightly lower than that of comparator drugs(3 RCTs,203 patients,OR=0.90,95%CI 0.77-1.06,p=0.20,I<sup>2</sup>=56%;<u>Fig.3.</u> D).

Adverse events outcomes and mortality outcomes

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In terms of treatment-related adverse events(AEs), one study was excluded from pooling result on behalf of that no information was given about whether adverse events were treatment-related or not[20]. No significant difference detected between daptomycin and comparator drugs(5 studies,1521 patients,Odds Ratio=1.06,95%CI0.71-1.59,p=0.76,I<sup>2</sup>=41%;Fig.4. A). After we excluded Katz et al.'s study,the heterogeneity declined dramatically, and the result turned to favor daptomycin(4 RCTs,1425 patients,Odds Ratio=0.85,95%CI 0.68-1.07,p=0.17,I<sup>2</sup>=0;Fig.4. B).

Discontinuation due to AEs and all-cause mortality during treatment were rare in the six included studies. No death reported in 3 studies[18 21 22], while another study reported discontinuation due to AEs and death together[20]. On account of the above reasons, we pooled discontinuation due to AEs and all-cause mortality together. A total of 1710 patients enrolled in the analysis, the pooling result suggested no significant difference existed between daptomycin and comparator drugs(6 RCTs,1710 patients,Odds Ratio=0.76,95%CI 0.46-1.10,p=0.12,I<sup>2</sup>=11%;Fig.4. C). CPK elevations considered as adverse events were compared between daptomycin and comparator drugs. Significant more patients had CPK elevation in daptomycin group than in comparator drugs group(5 RCTs,1521 patients,Odds Ratio=1.95,95%CI 1.04-3.65,p=0.04,I<sup>2</sup>=0;Fig.4. D).

## Discusion

This is an up-dated meta-analysis compares efficacy and safety of daptomycin with vancomycin and other antibiotics for treating SSTIs[24]. There were some clear shortages found in the previous meta-analysis. First of all, it enrolled only four trials, three of them were RCTs, including one RCT which found to have considerable heterogeneity in our analyses due to a high dose of daptomycin with a short duration ;plus one historically controlld trial which was excluded in our review(not randomized). Besides the previous three RCTs , we enrolled another three RCTs which considered to be eligible in terms of clinical homogeneity. Daptomycin was approved by FDA September 2003 for treatment of complicated skin and soft tissue infections under the circumstance of drug-resistant urgency. However, there were only a handful RCTs available, and lack of high quality meta-analysis that provides us with high-level clinical evidence.

The results of our review indicate daptomycin was as effective and safe as other drugs in treating SSTIs.The clinical success rate of daptomycin in both ITT population(OR=1.05,95%CI0.84-1.31,p=0.65,I<sup>2</sup>=0) and CE population(OR=0.99,95%CI0.73-1.35,p=0.97,I<sup>2</sup>=0) was equivalent to other drugs for treating SSTIs.Of note, in Katz et al's study, high dose(10 mg/kg/day) with a short treatment duration (4 days) of daptomycin led to lower clinical success rate and lower microbiological success rate in daptomycin compared with comparator drugs[22]. Shortened therapy duration could possibly have had undermined the efficacy of daptomycin and brought about some clinical heterogeneity which resulted in statistical heterogeneity in our data analyses. The microbiological success rate of daptomycin was also similar to other first-line drugs(OR=1.05,95%CI0.61-1.79,p=0.86,I<sup>2</sup>=42%). Staphylococcus aureus(SA) was the main pathogen for SSTIs, the microbiological success rate for SA has no significant difference between the two groups(OR=1.26,95%CI0.61-2.60,p=0.53,I<sup>2</sup>=47%).However,after we excluded Katz et al's study which different dosage,the heterogeneity declined,the result turned used а to favor daptomycin(OR=1.25,95%CI0.83-1.89,p=0.86,I<sup>2</sup>=11%).MRSA was the most common drug-resistant pathogen in SSTIs, the pooling result of success rate of daptomycin versus comparators showed no significant difference existed between the groups(OR=0.90,95%CI 0.77-1.06,p=0.20,I<sup>2</sup>=56%).Only 203 patients enrolled in the MRSA subgroup analysis, meanwhile the heterogeneity was high, thus we should interpret the result prudently. The included studies were conducted in different countries and different

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years, as well as different epidemiologic characteristics in each trial also should have some confounding impacts on the final results.Duration of treatment were not reported by all the included studies, however, Arbeit et al's study found out that significant more patients in daptomycin group than patients in comparator drugs group needed only 4 to 7 days of treatment[23], while two other included studies found no significant difference existed between the two groups in terms of duration of treatment [18 21]. There were no significant difference between daptomycin and comparator drugs in terms of treatment-related AEs(OR=1.06,95%CI0.71-1.59,p=0.76,I<sup>2</sup>=41%).But after we excluded Katz et al's to less study,daptomycin tended have treatment-related AEs(OR=0.85,95%CI0.68-1.07,p=0.86,p=0.17,I<sup>2</sup>=0).Daptomycin tended to have less patients associated with discontinuation or death(OR=0.71,95%CI0.46-1.10,p=0.12,I<sup>2</sup>=11%). Daptomycin was reported to have potential muscle toxicity[15], as a result, CPK were closely monitored in the included studies during the treatment process.CPK elevation occurred more frequently in daptomycin-treated patients(OR=1.95,95%CI1.04-3.65,p=0.04,I<sup>2</sup>=0),but CPK level declined to normal level during or after the therapy in most of the occasions. Daptomycin exhibited a tendency it might have superior efficacy and better safety in comparison with other comparator drugs in the matter of microbiological success, treatment-related AEs, discontinuation or death. Of note, in Aikawa et al's study, one patient out of the 88 patients in group had anaphylactic shock, and resolved 4 days after daptomycin drug treatment discontinuation[19]. Therefore, despite the safety of daptomycin is satisfying, clinicians should be cautious about administering it on patients of hypersensitivity.

Infectious Diseases of America recommended that vancomycin was to be used for empirical therapy in clinical settings with an increased prevalence of MRSA; for institutions with preponderant MRSA isolates that have vancomycin MIC values >2 mg/mL, alternative agents, such as daptomycin, should be used[25]. An antimicrobial resistance surveillance in China also had documented Staphylococcus aureus and Escherichia coli were the most common multidrug-resistant pathogens, for which linezolid, tigecycline, daptomycin, and vancomycin provided best antimicrobial coverage[26]. Vancomycin was also the first-line drug to treat MRSA infections for hospitalized children. So comparing the efficacy of daptomycin with vancomycin is necessary and could give some evidence to clinicians. Daptomycin vs vancomycin subgroup analysis of our review found daptomycin tended to exhibit higher clinical success rate in comparison with vancomycin(OR=1.19,95%CI0.77-1.83,p=0.43,I<sup>2</sup>=0). And after we excluded Katz et al.' study, the pooling resulted turned to favor daptomycin further(OR=1.39,95%CI0.88-2.19,p=0.16,I<sup>2</sup>=0)

Daptomycin was mainly metabolized by kidneys, Aikawa et al. demonstrated that compared with patients with normal renal function clearance of daptomycin was not markedly different in patients with mild to moderate renal impairment. Furthermore, 6 mg/kg of daptomycin once daily was found to be safe for extended dialysis patients, which simultaneously could lower the substantial risk of under dosing of daptomycin[27].In hospitalized children with cSSTIs,vancomycin,clindamycin and linezolid were recommended for treatment, whereas daptomycin was not mentioned [4]. Nevertheless, daptomycin therapy demonstrated clinical improvement for invasive gram-positive bacterial infections in children[28], but of which clearance in infants and 2-6 years children were higher than that of adolescents and adults, as a result daptomycin might need a higher dosage than adults to achieve efficacious exposures infants and 2-6 children[29]. On the contrary vancomycin has potential renal toxicity, which limited it's usage with patients with renal impairment, where daptomycin might be an eligible alternative agent. In recent years, vancomycin-resistant Staphylococcus aureus (VRSA) infection cases were repeatedly reported in the United States[30].daptomycin with an equivalent efficacy to vancomycin could be used as an eligible alternative treatment.Of note, Aikawa et al. found a trend that along with the increment of MICs of daptomycin, the clinical success rate declined gradually[19]. In spite of that, till now nonsusceptibility to daptomycin remains rare[31].Recently,one meta-analysis demonstrated that compared with vancomycin,linezolid had superior efficacy for MRSA infections[32]. To our knowledge, there was no RCT For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

directly comparing linezolid with daptomycin for MRSA infections. What's more,cost-effectiveness analysis studies of daptomycin,vancomycin and linezolid for MRSA-related cSSTIs found out that daptomycin and linezolid were potentially more cost-effective than vancomycin,however, daptomycin had no advantage when compared with linezolid[33 34].RCTs about daptomycin aimed for other diseases also proved daptomycin was safe and effective in treating diseases like prosthetic joint infection[35],or Staphylococcus aureus bacteraemia and infective endocarditis (SAB/IE) at a dosage of 6 mg/kg/day[12].Note that, age was a risk factor for SSTIs since the average ages of patients all exceeded 40 years in included studies.The mean or median body weight index in four trials(all exceeded 25 kg/m<sup>2</sup>) also revealed that obesity was a risk factor[18 19 21 22].Additionally,diabetes mellitus, peripheral vascular disease and immunocompromise were also the usual comorbid conditions for SSTI[21-23].Wounds infections were common in surgical departments and surgical ICU,and it accounted for nearly 41% of the total patients in four included studies,though the efficacy and safety data were not charted for specific type of SSTI in every included trial,the high proportion of wounds infections in included studies are adequate to exhibit the safety and efficacy of daptomycin of wounds infections.

There are several limitations exist in our meta-analysis.First of all,all the six RCTs we included were not participants-blinded or personnel-blinded,thus,performance bias was unpredictable.Furthermore,Arbeit et al's study had dominant influence on overall clinical success rate analysis both on ITT population and CE population,as it weighed more than 70% in the two analyses.Addtionally,too few of our data analyses reached statistical significance,which lead to insufficient credibility to draw couclusions for some potentially disputable issues.However,through our analyses,suffice it to say daptomycin have a not inferior efficacy and equivalent safety to comparator drugs,especially when compared with vancomycin which has been considered as the standard therapy for cSSTIs.In summary,based on the present evidence,daptomycin is a promising new agent for gram-positive infections like SSTIs,and we expect more high-quality RCTs to explore it's potentiality.

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## Conflict of interests No conflict of interest declared

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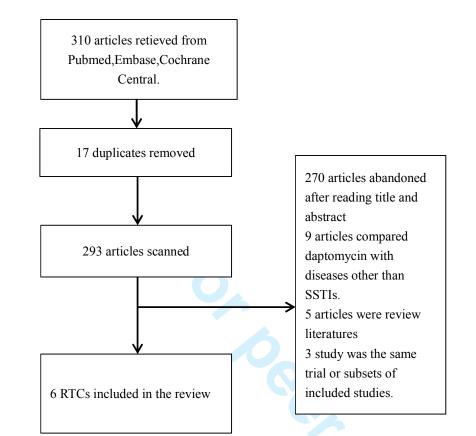


Fig.1. Study flow diagram for relevant randomized controlled trials.

<u>Table 1</u> Main Characteristics of the Studies Included in the Meta-Analysis

				Gro	oup	Populat	on
Refere nce	Design	Jadad Score	Patients Characteristics	Daptomycin (dose,treatment duration)	Comparator (type,dose, treatment duraion)	ITT,n(Daptomyci n vs comparator)	CE,n(daptom ycin vs comparator)
Aikaw a 2013	Multicenter Evaluator- Blinded RCT	2	N=101,PTs aged ≥20 years,SSTIs,M RSA confirmed within 3 days	4 mg/kg over 30 min once daily,for 7–14 days	Vancomycin 1 g over at least 60 min,twice daily,7–14 days	111(88 vs 22)	92(71 vs 21)
Konyc hev 2013	Multi-cent er Evaluator- Blinded RCT	3	N=120, patients aged ≥65 years with cSSTIs	4 mg/kg or 6 mg/kg over 30 min once daily for 5–14 days or 10–28 days with bacteraemia	SSP 2 g every 6 h or every 4 h for PTs with bacteraemia; vancomycin 1 g every 12 h for 5–14 days or 10–28 days with bacteraemia	120(81 vs 39)	103(73 vs 30)
Quist 2012	Multicente r Evaluator- Blinded RCT	3	N=194, Adults requiring i.v. antimicrobial treatment for cSSTIs	Daptomycin 4 mg/kg i.v. once daily	vancomycin 1 g i.v. twice daily; teicoplanin 400 mg i.v. once daily	189(97 vs 92)	108(58 vs 47)
Pertel 2009		2	N=103,Patients $\geq$ 18 years, cellulitis or erysipelas i.v. antibiotic therapy	Daptomycin 4 mg/kg i.v. once daily for 7–14 days	vancomycin was administered i.v. according to standard of care for 7–14 days	103(51 vs 52)	101(50 vs 51)
Katz 2008	Multicente r Evaluator- Blinded RCT	3	N=100, PTs ≥ 18 years with cSSSI requiring i.v. antibiotic treatment	daptomycin 10 mg∕ kg i.v. q24h for 4 days	vancomycin 1 g i.v. q12h for up to 14 days	96(48 vs 48)	79(39 vs 39)
Arbeit 2004		2	N=patients were aged 18– 85 years	Daptomycin 4 mg/kg i.v. once daily for 7–14 days	penicillinase-resistant penicillin 4–12 g iv q.d. or vancomycin,1 g iv q12h by 60-min infusion	1092(534 vs 558)	1002(446 vs 456)

Jadad Score ranges from zero to five, score higher than two was considered as trial of high methodological quality. ITT, intention to treat; CE, clinically evaluable.

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	Study or Subgroup /	Dapto	mycin	Comp	arator	Weight	Odds Ratio	Odds Ratio
A	Study of Subgroup /	Events	Total	Events	Total	weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Aikawa 2013		61	71	17	21	2.4%	1.44 [0.40, 5.15]	
Arbeit 2004		382	534	397	558	71.2%	1.02 [0.78, 1.33]	l - <u>+</u> -
Katz 2008		36	48	42	48	6.8%	0.43 [0.15, 1.26]	<u>_</u>
Konychev 2013		65	80	29	40	4.7%	1.64 [0.67, 4.01]	
Pertel 2009		47	51	46	52	2.3%	1.53 [0.41, 5.79]	
Quist 2012		65	97	58	92	12.7%	1.19 [0.65, 2.17]	
Total (95% CI)			881		811	100.0%	1.05 [0.84, 1.31]	•
Total events		656		589				1
Heterogeneity: Chi*	<sup>a</sup> = 4.39, df = 5 (P = 0.49); l <sup>a</sup> = 0%							
Test for overall effe	ct: Z = 0.45 (P = 0.65)							0.1 0.2 0.5 1 2 5 10 Favours Comparator Favours Daptomycin
								ravours comparator ravours Daptomych
D	Study or Subgroup	Dapto	mycin	Comp	arator	Weight	Odds Ratio	Odds Ratio

	R Study or Subgroup	Dapio	Daptomycin			Weight	Ouus Ralio	Ouus Raiio		
	B Study of Subgroup /	Events	Total	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
r	Aikawa 2013	61	71	17	21	4.4%	1.44 [0.40, 5.15]			
r	Arbeit 2004	372	446	384	456	75.1%	0.94 [0.66, 1.34]			
r	Katz 2008	32	39	37	39	7.9%	0.25 [0.05, 1.28]	I		
r	Konychev 2013	65	73	25	30	4.6%	1.63 [0.49, 5.44]	· · · · · · · · · · · · · · · · · · ·		
r	Pertel 2009	47	50	46	51	3.3%	1.70 [0.38, 7.54]			
V	Quist 2012	53	58	41	47	4.7%	1.55 [0.44, 5.44]			
~	Total (95% CI)		737		644	100.0%	0.99 [0.73, 1.35]	▲		
	Total events	630		550						
	Heterogeneity: Chi <sup>a</sup> = 4.79, df = 5 (P = 0.44); l <sup>a</sup> = 0%									
8	Test for overall effect: Z = 0.04 (P = 0.97)							0.05 0.2 1 5 20		
1		2						Favours Comparators Favours Daptomycin		

	C Study or Subgroup	Dapto	mycin	Comp	arator	Weight	Odds Ratio	2 Odds Ratio
	C Study of Subgroup /	Events	Total	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
V	Aikawa 2013	55	71	17	21	15.5%	0.81 [0.24, 2.75]	1
r	Arbeit 2004	90	111	127	172	49.5%	1.52 [0.85, 2.72]	
r	Katz 2008	32	39	37	39	17.4%	0.25 [0.05, 1.28]	ī
V	Konychev 2013	65	73	8	9	4.1%	1.02 [0.11, 9.21]	ī
V	Pertel 2009	47	50	46	51	7.2%	1.70 [0.38, 7.54]	ī
۲	Quist 2012	53	58	19	22	6.2%	1.67 [0.36, 7.69]	I
	Total (95% CI)		402		314	100.0%	1.19 [0.77, 1.83]	
	Total events	342		254				
	Heterogeneity: Chi <sup>2</sup> = 5.01, df = 5 (P = 0.41); l <sup>2</sup> = 0%							
	Test for overall effect: Z = 0.79 (P = 0.43)		1					0.05 0.2 1 5
			1					Favours Vancomycin Favours Daptomyci

	Study or Subgroup /		mycin	Comparator		Weight	Odds Ratio	Odd	ds Ratio	
D	Study of Subgroup /	Events	Total	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fi	xed, 95% CI	
Aikawa 2013		55	71	17	21	18.8%	0.81 [0.24, 2.75		•	
Arbeit 2004		90	111	127	172	60.0%	1.52 [0.85, 2.72		+	
Katz 2008		32	39	37	39	0.0%	0.25 [0.05, 1.28			
Konychev 2013		65	73	8	9	5.0%	1.02 [0.11, 9.21			
Pertel 2009		47	50	46	51	8.7%	1.70 [0.38, 7.54	·	<b></b>	-
Quist 2012		53	58	<mark>1</mark> 9	22	7.6%	1.67 [0.36, 7.69		+ · · ·	_
Total (95% CI)			363		275	100.0%	1.39 [0.88, 2.19		•	
Total events		310		217					1.00	
Heterogeneity: Chi <sup>2</sup>	= 1.05, df = 4 (P = 0.90); I <sup>2</sup> = 0%							+ +	+	
Test for overall effect	t Z = 1.41 (P = 0.16)							0.05 0.2	1 5	2
								Favours Vancomyci	n Favours Dapt	tomycin

Fig.2. Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs): (A )Clinical success(ITT population) (B) Clinical success(CE population) (C) Daptomycin vs Vancomycin for clinical success(CE population). (D) Daptomycin vs Vancomycin for clinical success(CE population). (D) Daptomycin vs Vancomycin for clinical success(CE population, excluded Katz et al.'s study). ITT,intention to treat;CE,clinically evaluable. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI,confidence interval.

▲ Study or Subgroup /	Dapto	mycin		parator	Weight	Odds Ratio	Odds Ratio
A	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Aikawa 2013	41	71			17.8%		
Arbeit 2004	309	365			34.9%		
🖌 Katz 2008	28	44	39	48	18.4%	0.40 [0.16, 1.04]	
Konychev 2013	54	65	23	27	13.0%	0.85 [0.25, 2.96]	
Pertel 2009	16	22	2 7	14	10.9%	2.67 [0.65, 10.88]	· · · · · · · · · · · · · · · · · · ·
Quist 2012	56	57	39	43	5.1%	5.74 [0.62, 53.37]	· · ·
Total (95% CI)		624		549	100.0%	1.05 [0.61, 1.79]	•
Total events	504		458				T
Heterogeneity: Tau <sup>2</sup> = 0.17; Chi <sup>2</sup> = 8.61, df = 5 (P = 0.13); I <sup>2</sup> = 42%							
Test for overall effect: Z = 0.18 (P = 0.86)							0.02 0.1 1 10 Favours Comparator Favours Dapto
	Daptor	nycin	Compa	arator		Odds Ratio	Odds Ratio
B Study or Subgroup A	Events	Total	Events	Total	Weight -	I-H, Random, 95% CI	M-H, Random, 95% Cl
Aikawa 2013	41	71	10	21	25.0%	1.50 [0.57, 3.99]	
Arbeit 2004	191	226	205	243	37.8%	1.01 [0.61, 1.67]	
Katz 2008	24	31	27	28	9.0%	0.13 [0.01, 1.11]	T
Konychev 2013	35	39	9	13	14.6%	3.89 [0.81, 18.65]	
Pertel 2009	11	15	6	11	13.6%	2.29 [0.44, 11.92]	
		15	0		13.076	2.23 [0.44, 11.52]	
Total (95% CI)		382		316	100.0%	1.26 [0.61, 2.60]	•
Total events	302		257				
Heterogeneity: Tau <sup>2</sup> = 0.30; Chi <sup>2</sup> = 7.58, df = 4 (P = 0.11); l <sup>2</sup> = 47% Test for overall effect: Z = 0.63 (P = 0.53)							0.02 0.1 1 10 Favours Comparators Favours Daptor
	Daptomycin		Comparator		10000	Odds Ratio	Odds Ratio
C Study or Subgroup A	Events	Total	Events	Total	Weight -	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Aikawa 2013	41	71	10	21	16.2%	1.50 [0.57, 3.99]	
Arbeit 2004	191	226	205	243	75.8%	1.01 [0.61, 1.67]	
Katz 2008	24	31	27	28	0.0%	0.13 [0.01, 1.11]	
Konychev 2013	35	39	9	13	3.4%	3.89 [0.81, 18.65]	
Pertel 2009	11	15	6	11	4.6%	2.29 [0.44, 11.92]	
		254		000	100.00/	4 05 10 02 4 001	
Total (95% CI) Total events	278	351	230	288	100.0%	1.25 [0.83, 1.89]	
Heterogeneity: Chi <sup>2</sup> = 3.36, df = 3 (P = 0.34); l <sup>2</sup> = 11%	2.0		200				
Test for overall effect: Z = 1.05 (P = 0.29)							0.02 0.1 1 10
							Favours Comparators Favours Daptor
Chudu or Culturaroun	Dapto	mycin	Compa	arators	Woight	Risk Ratio	Risk Ratio
D Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Aikawa 2013	45	55	16	19	32.6%	0.97 [0.77, 1.22]	
Arbeit 2004	21	28	25	36	30.0%	1.08 [0.80, 1.46]	
Katz 2008	22	37	24	28	37.4%	0.69 [0.51, 0.94]	
Total (95% CI)		120		83	100.0%	0.90 [0.77, 1.06]	
Total events	88	120	65	00		0.00 [0.11, 1.00]	
Heterogeneity: Chi <sup>*</sup> = 4.58, df = 2 (P = 0.10); l <sup>*</sup> = 56%	00		00				
Test for overall effect: $Z = 1.27$ (P = 0.10), P = 55%							0.5 0.7 1 1.5

<u>Fig.3.</u> Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological success for Staphylococcus Aureus. (C)microbiological success for Staphylococcus Aureus(excluded Katz et al.'s study). (D) microbiological success for MRSA. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI,confidence interval.

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	Study or Subgroup	Dapto Events	mycin Total	Comp Events	arator Total	Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
	Aikawa 2013	19	88	Events 6	22	17.3%	0.79 [0.36, 1.74]	
_	Arbeit 2004	94	534	119	558	43.8%	0.83 [0.65, 1.05]	
	Katz 2008	20	48	11	48	23.3%	1.82 [0.98, 3.37]	
	Konychev 2013	11	80	5	40	12.6%	1.10 [0.41, 2.95]	
_	Pertel 2009	3	51	1	52	3.1%	3.06 [0.33, 28.45]	
	61612005		51		JZ	5.170	5.00 [0.55, 20.45]	
-	Total (95% CI)		801		720	100.0%	1.06 [0.71, 1.59]	
-	Total events	147	001	142	120	100.0%	1.00 [0.71, 1.53]	
-	Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 6.82, df = 4 (P = 0.15); l <sup>2</sup> = 41%	147		142				
-	Test for overall effect: Z = 0.30 (P = 0.76)							0.01 0.1 1 10
-	rest for overall effect. Z = 0.50 (P = 0.70)					-		Favours Daptomycin Favours Compara
		Dentem	wain	Compo	rotor		Risk Ratio	Biok Datio
	Study or Subgroup	Daptorr vents		Compai Events	Total	Weight -	M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
	Aikawa 2013	19	88	6	22	7.2%	0.79 [0.36, 1.74]	M-H, Fixed, 95% CI
_	Arbeit 2004	94	534	119	558	87.1%	0.83 [0.65, 1.05]	
_	(atz 2008	20	48	11	48	0.0%	1.82 [0.98, 3.37]	-
_	Konychev 2013	11	48 80	5	48	5.0%	1.10 [0.41, 2.95]	
	Pertel 2009	3	51	5 1		0.7%		•
	-eitei 2003	3	51	1	52	0.7%	3.06 [0.33, 28.45]	
1	Fotal (95% CI)		753		672	100.0%	0.85 [0.68, 1.07]	•
1	Fotal events	127		131				
H	Heterogeneity: Chi <sup>2</sup> = 1.62, df = 3 (P = 0.65); l <sup>2</sup> = 0%							
1	Fest for overall effect: Z = 1.39 (P = 0.17)							0.05 0.2 1 5 3
								Favours Daptomycin Favours Compara
		Dant	omycin	Com	parator		Risk Ratio	1 Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
V	Aikawa 2013	2			2 22	7.2%	0.25 [0.04, 1.68]	
	Arbeit 2004	23						
_	Katz 2008	1						
_	Konychev 2013	3				12.1%		
_	Pertel 2009	0						
_	Quist 2012	3	1					
-	Total (95% CI)		898		812	2 100.0%	0.71 [0.46, 1.10]	▲
1	Total events	32	2	41				
-	Heterogeneity: Chi <sup>2</sup> = 5.60, df = 5 (P = 0.35); l <sup>2</sup> = 11%							
1	Test for overall effect: Z = 1.55 (P = 0.12)							Favours Daptomycin Favours Compar
	Study or Subgroup	Exper	imental	Co	ntrol	Weight	Odds Ratio	Odds Ratio
		Events	Total	Events	Total	Treight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
_	Aikawa 2013	8		2	2 22			
V	Arbeit 2004	15	5 534	10	558	63.2%	1.58 [0.71, 3.56]	
~	Katz 2008	4	48	0	48	3.0%	9.81 [0.51, 187.40]	
r	Konychev 2013	6	6 80	1	4(	8.2%	3.16 [0.37, 27.21]	
r	Pertel 2009	3	3 51	1	52	2 6.2%	3.19 [0.32, 31.70]	· · · · · · · · · · · · · · · · · · ·
_			004		70/	100.00	1.05 (1.04.2.65)	
-	Total (95% CI)	~	801	-	720	100.0%	1.95 [1.04, 3.65]	
- 11	Total events	36		14	•			
-	Heterogeneity: Chi <sup>2</sup> = 2.42, df = 4 (P = 0.66); l <sup>2</sup> = 0%							
ł	Test for overall effect: $Z = 2.08$ (P = 0.04)		-					0.005 0.1 1 10

Fig.4. Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (D)creatine phosphokinase(CPK) elevations regarded as adverse events. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI,confidence interval.

## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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## PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page a
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.		
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
) Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING	<u> </u>		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. 43 doi:10.1371/journal.pmed1000097

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# **BMJ Open**

## The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections: a metaanalysis of randomized controlled trials.

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SCHOLARONE<sup>™</sup> Manuscripts

## The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections: a meta-analysis of randomized controlled trials.

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Staphylococcus aureus

Word count: 3421 words

## ABSRACT

**Objective:** Daptomycin, a cyclic lipopeptide that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens, has now, since 2003,been approved in more than seventy countries and regions to treat skin and soft tissue infections(SSTIs),the purpose of this meta-analysis, is to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs.

Design: Meta-analysis of randomized controlled trials.

**Data sources:** We thoroughly searched PubMed, Embase, Cochrane Central to identify relevant RCTs. Six RCTs, with a total of 1710 patients were included in this meta-analysis.

**Results:** The results demonstrated the efficacy of daptomycin was on a par with and maybe better than other first-line antibiotics for treating SSTIs as shown by odds ratio(OR) for clinical success(OR=1.05,95% CI 0.84-1.31,p=0.65,I<sup>2</sup>=0%); daptomycin versus vancomycin subgroup (OR=1.19,95% CI 0.77-1.83,p=0.43,I<sup>2</sup>=0%);overall microbiological success(OR=1.05,95% CI 0.61-1.79, p=0.86,I<sup>2</sup>=42%);microbiological success of daptomycin versus comparators for Staphylococcus Aureus (SA,OR=1.05,95% CI 0.61-2.60,p=0.53,I<sup>2</sup>=47%),for MRSA(OR=0.90,95% CI 0.77-1.06, p=0.20, I<sup>2</sup>=56%). However, daptomycin tended to have a similar treatment-related adverse events(AEs) incidence in comparison with other antibiotics(OR=1.06,95% CI 0.71-1.59,p=0.76,I<sup>2</sup>=41%). The trend showed that daptomycin might cause less discontinuation due to AEs and death compared with other first-line antibiotics (OR=0.71,95% CI 0.46-1.10,p=0.12,I<sup>2</sup>=11%). Significantly more patients in daptomycin group had CPK elevation than those in control group; however it could be reversed when the therapy ended (OR=1.95,95% CI 1.04-3.65,p=0.04,I<sup>2</sup>=0).

**Conclusion:** This meta-analysis demonstrated the safety and efficacy of daptomycin was not inferior to that of other first-line drugs, and daptomycin tended to exhibit superior efficacy **For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml** 

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when compared with vancomycin or with comparators for SA infections; nevertheless, more high-quality RCTs are needed to draw a more credible conclusion.

## Strengths and limitations of this study

- Skin and soft tissue infections (SSTIs) are some of the most common infections, usually caused by gram-positive bacteria and are closely related to aging and obesity. Vancomycin and linezolid are the first-line antimicrobial agents for gram-positive infections, but recently cases of drug resistance have been repeatedly reported.
- Daptomycin, a cyclic lipopeptide, was approved ten years ago in the USA and is now cleared in more than seventy countries to treat gram-positive pathogens. To date, drug resistance of daptomycin remains rare.
- This is the first meta-analysis of randomized controlled trials of daptomcyin for skin and soft tissue infections. To our knowledge, this is also the first time daptomycin's potential myotoxicity was confirmed by meta-analysis. Comparative subgroup analyses of daptomycin and vancomycin were conducted to determine the drug's rate of clinical success; the same was done for daptomycin versus comparators, in relation to treating staphylococcus aureus, to determine their microbiological success.

## **INTRODUCTION**

Skin and soft tissue infections (SSTIs) are among some of the most common infections, usually with mild to moderate severity, distressingly, the incidence of SSTIs has rapidly increased in US in the Community Acquired(CA)-MRSA era, which appears to disproportionately affect certain populations.[1] SSTIs are usually caused by purulent pathogenic bacteria which invade epidermis, dermis and subcutaneous tissue.[2] SSTIs has a wide-spread range, from superficially localized skin infection to deep inside necrotizing soft tissue infection which severe enough to cause disability of extremities or even death. Because of their different clinical characteristics, SSTIs were divided into uncomplicated SSTIs and complicated SSTIs(cSSTIs). cSSTIs were defined as specific source of infection or opportunistically pathogenic situations such as trauma, cancer, chemotherapy which were accompanied by impairment of skin barrier function or decreased immune function.[3]

For hospitalized patients with complicated SSTI(cSSTI), besides surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered. Antibiotic options include vancomycin, linezolid, daptomycin, telavancin and clindamycin and seven to fourteen days of therapy are recommended.[4 5] The majority of community-acquired(CA) SSTIs in western countries were caused by staphylococcus aureus and beta-haemolytic streptococci.[2 6] Staphylococcus aureus is also the main pathogen of Hospital-Acquired SSTIs, where Methicillin-resistant Staphylococcus aureus(MRSA)exists in high proportions.[3 7]

Vancomycin has been regarded as mainstay of parenteral therapy for MRSA infections for decades. Recently, however, its minimum inhibitory concentrations(MICs) in MRSA have been increasing, and linezolid resistance has been reported likewise.[8] In the fighting against MRSA, daptomycin, a cyclic lipopeptide, that exhibits rapid, concentration-dependent bactericidal activity **For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml** 

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in vitro against a broad spectrum of gram-positive pathogens is now approved in more than seventy countries and regions.[9 10] Analyses of daptomycin treatment outcomes showed that treatment with daptomycin has resulted in high clinical success rate for a wide range of gram-positive infections, such as complicated skin and soft tissue infections(cSSTIs) at the dosage of 4 mg/kg/day[11] or for staphylococcus aureus bacteraemia(SAB)and right-sided infective endocarditis at the dosage of 6 mg/kg/day.[12]

Linezolid can cause anemia, thrombocytopenia, and gastrointestinal side effects, especially in prolonged therapeutical usage.[13] The main side effect of vancomycin is nephrotoxicity, and teicoplanin can cause fever.[14] Daptomycin is a comparably safer antibiotic, with myotoxicity being the most relevant side effect and this can be reversed when the therapy ends.[15] With drug resistance an urgent problem, new antibiotics are needed treat infectious diseases, and daptomycin might become such an alternative agent, especially when standard therapies don't work. Comparator drugs in this review refers to vancomycin(mainly),semi-synthetic penicillins(SSPs) and teicoplanin, which were used as counterpart for daptomycin in control group in included studies.

The purpose of this meta-analyses to compare the safety and efficacy of daptomycin with other antibiotics to treat SSTIs, such as vancomycin or semi-synthetic penicillins. The safety endpoints were treatment-related adverse events(AEs), discontinuation due to AEs and all-cause mortality, and creatine phosphokinase(CPK) elevation. The efficacy endpoints were clinical success and microbiological success at the test of cure(TOC) visit.

## **METHODS**

#### Data sources

Pubmed(up to September 2013), Embase(up to September 2013) and Cochrane Central(Issue 9 of 12, Sept 2013) were searched to find relevant clinical trials with a prespecified search strategy, which was revised appropriately through databases. Trials other than RCT were eliminated from consideration. Search terms included 'daptomycin', 'cubicin', 'lipopeptide', 'skin and soft tissue infections', 'cellulitis', 'wounds infection', 'abscess' and 'erysipelas', and they were combined by PICOs principle. No language restriction settled in the searching process. Statistical experts were consulted to make search strategy and emails were sent to corresponding authors of relevant studies and pharmaceutical companies resulted in information about any ongoing RCTs related to daptomycin.

## Study selection

Two authors(WSZ and TZH) independently searched and examined the relevant literatures, scanned the title and abstract of every retrieved literature to determine which required further assessment. Full articles were obtained when the information given in the titles, abstracts implied that the study included a prospective design research for the purpose of comparing daptomycin with vancomycin or other antibiotics(with or without co-interventions). When disagreement existed, they were discussed thoroughly to reach consensus. Inclusion criteria:(i)any randomized controlled trials that compare daptomycin with other antibiotics in treating SSTIs . (ii)included patients were of any age, any gender ,had a SSSI requiring intravenous antibiotic treatment .(iii)daptomycin intravenous infusion with any dosage, comparator antibiotics intravenous infusion with any dosage. Co-interventions that targeted confirmed or probable infections with gram-negative aerobic and anaerobic pathogens were permitted, status

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## Qualitative assessment

The methodological quality of the RCTs included in this review was independently evaluated by two authors(WSZ and TZH), using the Jadad scale,[16] which evaluates randomization and blinding. If the methodology revealed that the study applied appropriate randomization and blinding procedures, two scores were given to randomization and two scores to blinding. If only mentioned about randomization or blinding but no detail elucidated, one score deducted accordingly. If information about attrition was thoroughly elucidated, one score was given. Thus, the score ranges from zero to five, and a score higher than two was considered a trial of high methodological quality.

## Data extraction

Two review authors (WSZ and TZH) independently extracted data with a prespecified data extraction form specifically designed for this review. The data extraction included the following detailed imformation:1.year of publication, clinical settings2.the number of intention to treat(ITT) and clinically evaluable(CE) patients3.descriptions of dose, route, and timing of daptomycin and other antibiotics.4.clinical success, microbiological success, treatment-related adverse events(AEs), discontinuation due to adverse events(AEs) and all-cause mortality, and CPK elevation cases. If missing data detected from the trial reports, the studies' corresponding authors were contacted to request these information. If this was not successful, ITT analyses were conducted for all dichotomous outcomes (e.g. clinical success, microbiological success, treatment-related adverse events, all-cause mortality).

## Analysed Outcomes

The primary outcomes of this review were clinical success and microbiological success . Outcomes were judged by clinical and microbiologic evaluations performed at the baseline (within 72 hours before receipt of the first dose of study drug) and test-of-cure(TOC) visit(6–20 days after receipt of the last dose). Clinical success was defined as the test subjects exhibiting biological indicators that no further antibiotic therapy was required at TOC visit. Microbiological success was defined as eradication of pathogen (present at admission but absent from culture at TOC visit) or presumed eradication of the pathogen (no material available for culture but patient was deemed as cured or improved by the study investigator at TOC visit. Secondary outcomes were proportions of patients with treatment-related adverse events, discontinuation due to adverse events and all-cause mortality, and cases of CPK elevation.

Data analysis and statistical methods

Data analyses of this review were performed by Review Manager 5.2(Version: 5.2.6,Cochrane Collabration, UK).Clinical heterogeneity was assessed in population, methodology, and in the intervention and outcome measures of each study to evaluate whether pooling of results was feasible. Heterogeneity assessment was performed using the chi-squared test, where P value less than 0.1 was considered as significance set. A funnel plot was applied to check for publication bias and I<sup>2</sup> was applied to estimate the total variation attribute to heterogeneity among studies.[17] Values of I<sup>2</sup> less than 25 percent were deemed to have low heterogeneity, and a fixed-effect model for meta-analysis was then used. Values of I<sup>2</sup> between 25 and 75 percent were considered to represent moderate levels of heterogeneity, and a random effects model was then utilized. Values of I<sup>2</sup> higher than 75 percent indicating high levels of heterogeneity, in which case no meta-analysis was performed. All statistical tests were two-sided and a p value less than 0.05 was considered statistically significant.

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## RESULTS

## Study selection process

Flow diagram in Fig.1 shows the whole scanning and selection process. A total of 310 articles were retrieved by means of electronic databases searches .After deleting duplicates, 293 articles were retained to read the title and abstract. Full text of 23 articles were then obtained for further review after the scanning. Additionally, emails were sent to Aastrazeneca China which is in charge of marketing of daptomycin in China, we were informed that daptomycin for SSTIs phase-3 clinical trial was completed in China, yet so far no data published. Finally,6 out of the 23 articles reached the inclusion criteria.

The main characteristics of the 6 RCTs(type of study design, Jadad score, characteristics of patients, dose and treatment duration of studied drugs, ITT population, CE population) included in this meta-analysis were presented in Table 1 All of the 6 studies were multi-center trials.[18-23] The total number of patients of included trials were 1710. Only adults were enrolled in the included trials, and one trial only aimed at elder patients aged at least 65 years [18]. In terms of methodology, all the six enrolled trials were deemed eligible, with a Jadad score  $\geq$ 2.Allocation concealment was not thoroughly stated in all the 6 included trials. Funnel plots were performed to check publication bias(standard error of logOR plotted against OR). All the six studies were neither participants-blinded nor personnel-blinded. First, overall clinical success analysis were performed on both ITT and CE populations; second, microbiological success was analyzed on microbiologically evaluable population; third, adverse events(AEs) were analyzed on ITT population. Note that, thirty-six patients with no MRSA identified as causative pathogen(of these, thirty-three were receiving daptomycin and three were receiving vancomycin) were excluded from the efficacy analysis of MITT-MRSA population in one study.[19]Four out the six included For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

studies were phase-3 trials,[18-20 23] one was phase-2 trial [22] and one was phase-4.[21] Vancomycin was the only comparator drug used in two trials.[19 21]In one trial, comparator drugs were vancomycin and teicoplanin.[20] In two trials, comparator drugs were vancomycin and SSPs.[18 23] The infecting organism was confirmed as not MRSA in patients randomized to vancomycin(control), investigators were permitted to switch therapy to a SSP in one study.[18]ITT patients of all the six studies were designated to receive intravenous therapy, but patients could be switched to oral treatment in three trials if they already had at least 4 or 5 days of intravenous therapy and demonstrated clear clinical improvement.[18 22 23] Daptomycin, at a dosage of 4 mg/kg/day was administered in five trials; at the same drug at a dosage of 10 mg/kg/day was administered in another study.[22] In all the six trials, comparator drugs were administered according to the standard of care. The efficacy and safety endpoints were similar across the six included studies.

				Group		Population	
Reference	Design	Jadad	Patients	Daptomycin(dose,	Comparator	ITT,n(Daptom	CE,n(daptom
		Score	Characteristics	treatment duration)	(type, dose,	ycin vs	ycin vs
					treatment duration)	comparator)	comparator)
Konychev	Multicenter	3	N=120, patients	4 mg/kg or 6 mg/kg	SSP 2 g every 6 h or	120(81 vs 39)	103(73 vs 30)
2013[18]	Evaluator-		aged ≥65 years	over 30 min once	every 4 h for PTs		
	Blinded RCT		with cSSTIs	daily for 5–14 days	with bacteraemia;		
				or 10–28 days with	vancomycin 1 g		
				bacteraemia	q12h for 5–14 days		
					or 10–28 days with		
					bacteraemia		
Aikawa	Multicenter	2	N=101,PTs aged	4 mg/kg over 30	Vancomycin 1 g	111(88 vs 22)	74(55 vs 19)
2013[19]	Evaluator-		≥20 years, SSTIs,	min once daily,for	over at least 60		
	Blinded RCT		MRSA confirmed	7–14 days	min,twice daily,7–14		
			within 3 days		days		
Quist	Multicenter	3	N=194, Adults	Daptomycin 4	vancomycin 1 g i.v.	189(97 vs 92)	108(58 vs 47
2012[20]	Evaluator-		requiring i.v.	mg/kg i.v. once	twice daily;		
	Blinded RCT		antimicrobial	daily	teicoplanin 400 mg		
			treatment for	n	i.v. once daily		

Table 1 Main Characteristics of the Studies Included in the Meta-Analysis

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2				cSSTIs				
5	Pertel	Multicenter	2	N=103,Patients ≥	Daptomycin 4	vancomycin was	103(51 vs 52)	101(50 vs 51)
	2009[21]	Evaluator-		18 years, cellulitis	mg/kg i.v. once	administered i.v.		
)		Blinded RCT		or erysipelas i.v.	daily for 7–14 days	according to		
,				antibiotic therapy		standard of care for		
5						7–14 days		
0 1	Katz	Multicenter	3	N=100, PTs ≥ 18	daptomycin 10 mg⁄	vancomycin 1 g i.v.	96(48 vs 48)	79(39 vs 39)
	2008[22]	Evaluator-		years with cSSSI	kg i.v. q24h for 4	q12h for up to 14		
2		Blinded RCT		requiring i.v.	days	days		
3				antibiotic				
4				treatment				
5 6	Arbeit	Multicenter	2	N=1092,patients	Daptomycin 4	penicillinase-resista	1092(534 vs	1002(446 vs
7	2004[23]	Evaluator-		were aged 18–85	mg/kg i.v. once	nt penicillin 4–12 g	558)	456)
8		Blinded RCT		years	daily for 7–14 days	iv q.d. or		
9 20						vancomycin,1 g iv		
.0 21						q12h by 60-min		
22						infusion		

Jadad Score ranges from zero to five, score higher than two was considered as trial of high methodological quality. ITT, intention to treat; CE, clinically evaluable.

## Clinical success

Clinical success rate analysis was performed on ITT population(all randomized patients with a SSSI who received≥1 dose of study medication) and CE population(all patients in the ITT population who met protocol-specified inclusion or exclusion criteria relating to the prespecified assessments and to the absence of confounding factors, including completion of the required visits)as well. The pooling result of ITT population showed clinical success rate of daptomycin was similar to that of comparator drugs at TOC visit(6 RCTs,1674 patients, OR=1.05, 95% CI 0.84-1.31,p=0.65,I<sup>2</sup>=0;Fig.2 A). Pooling the result of CE population also demonstrated no difference existed in clinical success rate between daptomycin and other antibiotics for treating SSTIs (6 RCTs,1381 patients, OR=0.99,95% CI 0.73-1.35,p=0.97,I<sup>2</sup>=0;Fig.2 B).

In terms of daptomycin vs vancomycin subgroup, clinical success rate of daptomycin was higher(not significantly) than that of vancomycin(6 RCTs,716 patients, OR=1.19,95% CI 0.77-1.83,p=0.43,I<sup>2</sup>=0;<u>Fig.2</u> C).Briefly, 342 out of 402 patients in daptomycin group and 254 out of 314 patients in vancomycin group achieved clinical success at TOC visit. Since Katz et al's study

used a higher dosage than the other included studies, after its exclusion, the pooling result showed a trend favoring daptomycin(5 RCTs,638 patients, OR=1.39,95% CI

0.88-2.19,p=0.16,I<sup>2</sup>=0;<u>Fig.2</u>D)

## Microbiological success

Microbiological success rate analysis was performed on microbiologically evaluable patients (all patients in the clinically evaluable population who had an causative gram-positive organism isolated at baseline); the pooling result showed the microbiological success rate of daptomycin was similar to that of comparator drugs (6 RCTs, 1173 patients, OR= 1.05,95% CI 0.61-1.79, p=0.86, I<sup>2</sup>=42%; Fig.3. A). In brief, 504 out of 624 patients in daptomycin group and 458 out of 549 patients in control group achieved microbiological success.

The data of staphylococcus aureus subgroup was not extractable in Quist et al.'s study[20]. In terms of microbiological success rate for staphylococcus aureus(Methicillin-susceptible and Methicillin-resistant),the pooling result demonstrated no significant difference existed between daptomycin and comparator drugs(5 RCTs,698 patients, Odds Ratio=1.59,95% CI 0.61-2.60,p=0.53,I<sup>2</sup>=47%;Fig.3, B). After the exclusion of Katz et al.'s study, the overall heterogeneity dropped, but the result remained unchanged(4 RCTs,639 patients, Odds Ratio=1.25,95%CI0.83-1.89,p=0.29,I<sup>2</sup>=11%;Fig.3. C).For MRSA infections, data was successfully extracted from 3 studies, the overall heterogeneity was expectedly high, under which circumstance random model was applied, and the result showed the success rate of daptomycin was slightly lower than that of comparator drugs(3 RCTs,203 patients, OR=0.91,95% CI 0.77-1.06,p=0.10,I<sup>2</sup>=56%;Fig.3, D).

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Adverse events outcomes and mortality outcomes

In terms of treatment-related adverse events(AEs),Quist et al's study was excluded from pooling result because no information was given about whether adverse events were treatment-related or not.[20] There was no significant difference detected between daptomycin and comparator drugs(5 studies,1521 patients, Odds Ratio=1.06,95% CI 0.71-1.59, p=0.76, I<sup>2</sup>=41%; Fig.4 A). After Katz et al.'s study was excluded, there was a dramatic decline in heterogeneity, and the result changed to favor daptomycin(4 RCTs,1425 patients, Odds Ratio=0.85,95% CI 0.68-1.07, p=0.17, I<sup>2</sup>=0;Fig.4 B).

Discontinuation due to AEs and all-cause mortality during treatment were rare in the six included studies. No death reported in three studies,[18 21 22] while another study reported discontinuation due to AEs and death combined.[20] On account of the above reasons, discontinuation due to AEs and all-cause mortality were pooled together. With a total of 1710 patients enrolled in the analysis, the pooling result suggested there was no significant difference existed between daptomycin and comparator drugs(6 RCTs,1710 patients, Odds Ratio=0.76,95% CI 0.46-1.10,p=0.12,I<sup>2</sup>=11%;<u>Fig.4</u> C).A comparison of CPK elevations considered as adverse events between daptomycin and comparator drugs yielded that significantly more patients had CPK elevation in the daptomycin group than in the comparator drugs group(5 RCTs,1521 patients, Odds Ratio=1.95,95% CI 1.04-3.65,p=0.04,I<sup>2</sup>=0;Fig.4 D).

## DISCUSION

This is an up-dated meta-analysis based on Bliziotis et al's study, which compares efficacy and safety of daptomycin with vancomycin and other antibiotics for treating SSTIs.[24] There were some clear limitations found in the previous meta-analysis. First, it enrolled only four trials, in which three were RCTs, including one RCT which was found to have considerable heterogeneity in our analyses due to a high dose of daptomycin with a short duration. In addition, there was one historically controlled trial(not randomized) which was excluded in this review.[25] Besides the previous three RCTs three more RCTs were considered to be eligible in terms of clinical homogeneity. Daptomycin was approved by FDA September,2003,for treatment of complicated skin and soft tissue infections, because of the drug-resistant urgency. However, there were only a handful RCTs available, and a distinct lack of high quality meta-analysis yielding high-level clinical evidence.

The results of this review indicate daptomycin was as effective and safe as other drugs in treating SSTIs. The clinical success rate of daptomycin in both ITT population(OR=1.05,95% CI 0.84-1.31,p=0.65,I<sup>2</sup>=0) and CE population(OR=0.99,95% CI0.73-1.35,p=0.97,I<sup>2</sup>=0) was equivalent to that of other drugs used to treat SSTIs. Of note, in Katz et al's study, a high dose(10 mg/kg/day) intake of daptomycin with a short treatment duration (4 days) led to reduced clinical and reduced microbiological success rate in daptomycin, when compared with comparator drugs.[22] This shortened therapy duration could possibly have undermined the efficacy of daptomycin and brought about some clinical heterogeneity, resulting in statistical heterogeneity in our data analyses. The microbiological success rate of daptomycin was also similar to that of other first-line drugs(OR=1.05,95% CI 0.61-1.79,p=0.86,I<sup>2</sup>=42%). Staphylococcus aureus(SA) was the main pathogen for SSTIs, the microbiological success rate for SA showed no significant difference For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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between the two groups(OR=1.26,95% CI 0.61-2.60,p=0.53,I<sup>2</sup>=47%). However, after the exclusion of Katz et al's study which used a different dosage, the heterogeneity declined, and the result tended to favor daptomycin(OR=1.25,95% CI 0.83-1.89,p=0.86,I<sup>2</sup>=11%).With MRSA as the most common drug-resistant pathogen in SSTIs, the pooling result of the success rate of daptomycin versus comparators indicated no significant difference existed between the groups(OR=0.90,95% CI 0.77-1.06,p=0.20,I<sup>2</sup>=56%). Only 203 patients were enrolled in the MRSA subgroup analysis, while simultaneously the heterogeneity was high; thus, the result should be interpreted prudently. That the included studies were conducted in diverse countries at different times, and that there was a lack of uniformity in epidemiologic characteristics for each trial, should have some confounding impacts on the final results. Not all the included studies reported duration of treatment; however, Arbeit et al's study found out that significant more patients in daptomycin group than patients in comparator drugs group needed only 4 to 7 days of treatment; [23] two other included studies found no significant difference existed between the two groups in terms of duration of treatment.[18 21] Furthermore, there were no significant difference between daptomycin and comparator drugs in terms of treatment-related AEs(OR=1.06,95% CI 0.71-1.59,p=0.76,I<sup>2</sup>=41%). However, after Katz et al's study was excluded, daptomycin tended to have less treatment-related AEs(OR=0.85,95% CI  $0.68-1.07,p=0.86,p=0.17,I^2=0$ ), to have less patients associated with discontinuation or death(OR=0.71,95% CI 0.46-1.10,p=0.12,I<sup>2</sup>=11%). Daptomycin was reported to have potential muscle toxicity, [15] as a result, CPK were closely monitored in the included studies during the treatment process. This close monitoring revealed that CPK elevation occurred more frequently in daptomycin-treated patients(OR=1.95,95% CI1.04-3.65,p=0.04,I<sup>2</sup>=0),but on most occasions, it declined to normal levels during or after the therapy. Therefore, one may conclude that daptomycin might be a safer and more efficacious drug to use, in comparison with other comparator drugs, in the matter of microbiological success, treatment-related AEs, discontinuation

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or death. Of note, in Aikawa et al's study, one patient out of the eighty-eight patients in daptomycin group experienced anaphylactic shock, which was resolved 4 days after discontinuation of drug treatment.[19] Therefore, despite the safety of daptomycin is satisfying, clinicians should be cautious about administering it to patients of hypersensitivity.

Infectious Diseases of America recommended that vancomycin be used for empirical therapy in clinical settings with an increased prevalence of MRSA; for institutions with preponderant MRSA isolates that have vancomycin MIC values >2 mg/mL, alternative agents, such as daptomycin, should be used.[26] An antimicrobial resistance surveillance in China also had documented staphylococcus aureus and escherichia coli were the most common multi-drug-resistant pathogens, for which linezolid, tigecycline, daptomycin, and vancomycin provided best antimicrobial coverage.[27] Vancomycin was also the first-line drug to treat MRSA infections for hospitalized children. So comparing the efficacy of daptomycin with vancomycin is necessary and useful since it could provide helpful data to clinicians. The daptomycin vs. vancomycin subgroup analysis of our review found out that daptomycin tended to exhibit higher clinical success rate in comparison to vancomycin(OR=1.19,95% CI 0.77-1.83,p=0.43,I<sup>2</sup>=0).And excluding Katz et al' study, the pooling resulted favored daptomycin even further(OR=1.39,95% CI 0.88-2.19,p=0.16,I<sup>2</sup>=0)

Daptomycin is mainly metabolized by kidneys, Aikawa et al demonstrated that patients with mild to moderate renal impairment ,when compared with patients having normal renal function, clearance of daptomycin was not markedly different. Furthermore,6 mg/kg of daptomycin once daily was found to be safe for extended dialysis patients, which simultaneously could lower the substantial risk of under dosing of daptomycin.[28] In hospitalized children with cSSTIs, vancomycin, clindamycin and linezolid were recommended for treatment, whereas **For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml**  Page 17 of 71

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daptomycin was not mentioned.[4] Nevertheless, daptomycin therapy demonstrated clinical improvement for invasive gram-positive bacterial infections in children.[29] But the clearance of daptomycin in infants and 2-6 years children were higher than that of adolescents and adults, as a result in order to achieve efficacious exposures, this younger group might need a higher dosage of daptomycin. [30] Vancomycin, however, has potential renal toxicity, which limits it's usage with patients with renal impairment, and for whom daptomycin might be an eligible alternative agent. In recent years, vancomycin-resistant staphylococcus aureus (VRSA) infection cases have been repeatedly reported in the United States, [31] for these, daptomycin with an equivalent efficacy to vancomycin could be used as an eligible alternative treatment. Of note, Aikawa et al found a trend that along with the increment of MICs of daptomycin, the clinical success rate declined gradually.[19]In spite of that, up till now, nonsusceptibility to daptomycin remains rare.[32] Recently, one meta-analysis demonstrated that compared with vancomycin, linezolid had superior efficacy for MRSA infections.[33]To our knowledge, there was no RCT directly comparing linezolid with daptomycin for MRSA infections. What's more, cost-effectiveness analysis studies of daptomycin, vancomycin and linezolid for MRSA-related cSSTIs found out that daptomycin and linezolid were potentially more cost-effective than vancomycin; however, daptomycin had no advantage when compared with linezolid.[34 35] RCTs about daptomycin aimed at other diseases also proved daptomycin was safe and effective in treating issues like prosthetic joint infection,[36]or staphylococcus aureus bacteraemia and infective endocarditis (SAB/IE) at a dosage of 6 mg/kg/day.[12] Note that age was a risk factor for SSTIs since the average ages of patients all exceeded 40 years old in included studies. The mean or median body weight index in four trials(all exceeded 25 kg/m<sup>2</sup>) also revealed that obesity is also a risk factor.[18 19 21 22] Additionally, diabetes mellitus, peripheral vascular disease and immunocompromise present the usual comorbid conditions for SSTI.[21-23] Wounds infections were common in

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surgical departments and surgical ICU, and it accounted for nearly 41% of the total patients in four included studies. Though the efficacy and safety data were not charted for specific type of SSTI in every included trial, the high proportion of wounds infections in included studies are adequate to exhibit the safety and efficacy of daptomycin for these.

There are several limitations exist in our meta-analysis. First of all, none of the six included RCTs were participants-blinded or personnel-blinded, thus, performance bias was unpredictable. Furthermore, Arbeit et al's study had dominant influence on overall clinical success rate analysis both on ITT and CE populations, as it weighed more than 70% in these two analyses. Additionally, too few of our data analyses reached statistical significance, which led to insufficient credibility to draw conclusions for some potentially disputable issues.

#### Conclusions

By our analyses, suffice it to say daptomycin have a not inferior efficacy and equivalent safety to comparator drugs, especially when compared with vancomycin which has been considered as the standard therapy for cSSTIs. Based on the present evidence, daptomycin is a promising new agent for gram-positive infections like SSTIs, and more high-quality RCTs are expected to explore it's potentiality.

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**Contributors** WSZ and TZH conceived this study, identified studies for inclusion, and extracted data together. The English manuscript was written and revised by WSZ. Other authors made supportive contributions. All the authors read and approved the final manuscript.

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**Data sharing statement** No additional data are available.

# **Figure legends**

Fig. 1 Study flow diagram for relevant randomized controlled trials.

<u>Fig.2</u> Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs): (A )Clinical success(ITT population) (B) Clinical success(CE population) (C) Daptomycin vs. Vancomycin for clinical success(CE population). (D) Daptomycin vs. Vancomycin for clinical success(CE population, excluded Katz et al's study). ITT, intention to treat; CE, clinically evaluable. The vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval.

<u>Fig.3.</u> Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological success for staphylococcus aureus. (C)microbiological success for staphylococcus aureus(excluded Katz et al's study). (D) microbiological success for MRSA. The vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval.

Fig.4.Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (D)creatine phosphokinase(CPK) elevations regarded as adverse events. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval.

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Daptomycin,a cyclic lipopeptide<u>, was approved ten years ago in the USA and</u> is now <u>cleared</u> in more than seventy countries approved to treat gram-positive pathogens<u></u> for about 10 yearsand-To date, drug resistance of daptomyin remains rare to date.

This is the first meta-analysis of randomized controlled trials of daptomcyin for skin and soft tissue infections. To our knowledge, this is also the first time daptomycin's potential myotoxicity was confirmed by meta-analysis. <u>Comparative Ss</u>ubgroup analyses of <u>daptomycin and vancomycin elinical success</u> were conducted <u>to determine the drug's rate of</u> <u>clinical success</u>between daptomycin and vancomycin; microbiological successthe same was <u>done for of</u>-daptomycin versus comparators, <u>in relation to treating for Staphylococcus</u>-<u>staphylococcus Aureus aureus, to determine their microbiological successwas also analyzed</u>.

#### ABSRACT

**Objective:** Daptomycin, a cyclic lipopeptide that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens, <u>-is-has</u> now, <u>since 2003, been</u> approved in more than <u>-70-seventy</u> countries and regions. Daptomycin wasapproved to treat skin and soft tissue infections(SSTIs)-<u>since 2003, in-the purpose of</u> this meta-analysis, <u>we try-is</u> to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs.

**Design:** Meta-analysis of randomized controlled trials.

**Data sources:** We thoroughly searched PubMed, Embase, Cochrane Central to identify relevant RCTs. Six RCTs, with a total of 1710 patients were included in this meta-analysis.

**Results:** The results demonstrated the efficacy of daptomycin were not inferior towas on a par with and maybe better than other first-line antibiotics for treating SSTIs in the matter of as

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> shown by odds ratio(OR) for clinical success(OR=1.05,95%\_CI\_0.84-1.31,p=0.65,P=0%); daptomycin versus vancomycin subgroup(OR=1.19,95%\_CI\_0.77-1.83,p=0.43,P=0%); overall microbiological success(OR=1.05,95%\_CI\_0.61-1.79,p=0.86,P=42%); microbiological success of daptomycin versus comparators for Staphylococcus Aureus (SA,OR=1.05,95%\_CI\_0.61-2.60,p=0.53,P=47%), for MRSA(OR=0.90,95%\_CI\_0.77-1.06,p=0.20,P=56%), <u>And-However</u>, daptomycin tended to have a similar treatment-related adverse events(AEs) incidence in comparison with other antibiotics(OR=1.06,95%\_CI\_0.71-1.59,p=0.76,P=41%), <u>There was a The</u> trend <u>showed</u> that daptomycin might cause less discontinuation due to AEs and death compared with other first-line antibiotics (OR=0.71,95%\_CI\_0.46-1.10,p=0.12,P=11%). Significantly more patients <u>in daptomycin</u> group had CPK elevation <u>in daptomycin group</u> than those in control group; however it could be reversed when the therapy ended (OR=1.95,95%\_CI\_1.04-3.65,p=0.04,P=0). **Conclusion:** Our This meta-analysis demonstrated the safety and efficacy of daptomycin was not inferior to <u>that of</u> other first-line drugs, and <u>--itdaptomycin had a tendency of tended to</u> exhibiting superior efficacy when compared with vancomycin or with comparators for SA infections; <u>butnevertheless</u>, \_-more high-quality RCTs <u>are</u> needed to draw a <u>more</u> credible

conclusion.

#### INTRODUCTION

Skin and soft tissue infections (SSTIs) are <u>among some of the</u> most common infections,\_ usually with mild to moderate severity,<u>howeverdistressingly</u>, the incidence of SSTIs has rapidly increased in US in the Community Acquired(CA)-MRSA era-<u>and</u>, <u>which</u> appears to disproportionately affect certain populations.[1]-\_SSTIs\_<u>wasare</u> usually caused by purulent pathogenic bacteria which invade epidermis, dermis and subcutaneous tissue.[2]\_-SSTIs has a wide-spread range,\_from superficially localized skin infection to deep inside necrotizing soft tissue Formatted: Indent: First line: 3 ch

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infection which severe enough to cause <u>disability of</u> extremit<u>iesy</u> <u>disability</u> or even death. According to <u>Because of their</u> different clinical characteristics, SSTIs were divided into uncomplicated SSTIs and complicated SSTIs(cSSTIs).\_cSSTIs were defined as specific source of infection or opportunistically pathogenic situations <u>like such as</u> trauma,\_cancer,\_chemotherapy which<u>were</u> accompanied by impairment of skin barrier function or decreased immune function\_[3].

For hospitalized patients with complicated SSTI(cSSTI),besides surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered. Antibiotic options include vancomycin, linezolid, daptomycin, telavancin and clindamycin- and 7seven to 14fourteen days of therapy-was\_are recommended [4 5]. The majority of community-acquired (CA) SSTIs in western countries were caused by Sstaphylococcus aureus and beta-haemolytic streptococci. [2 6]. Staphylococcus aureus \_\_wasis also the main pathogen of Hospital-Acquired SSTIs, where Methicillin-resistant Staphylococcus aureus (MRSA) tookexists in a-high proportions. [3 7].

Vancomycin was has been regarded as mainstay of parenteral therapy for MRSA infections for decades\_\_but +Recently\_however,\_-its minimum inhibitory concentrations(MICs) in MRSA\_are elevatinghave been increasing\_ and linezolid resistance has been reported likewise\_[8]-In the fighting against MRSA, Ddaptomycin, a cyclic lipopeptide, that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens is now approved in more than 70seventy countries and regions\_[9 10]- Analyses of daptomycin treatment outcomes showed that treatment with daptomycin has resulted in high clinical success rate for a wide range of gram-positive infections, such as complicated skin and soft tissue infections(cSSTIs) at the dosage of 4 mg/kg/day[11]\_or\_\_\_for\_Sstaphylococcus aureus bacteraemia(SAB),and\_right-sided infective endocarditis at the dosage of 6 mg/kg/day\_[12]-

Linezolid can cause anemia, thrombocytopenia, and gastrointestinal side effects, especially in prolonged therapytherapeutical usage.[13]: The main side effect of vancomycin is nephrotoxicity, and teicoplanin can cause fever.[14]: Daptomycin is a comparably safer antibiotic, with myotoxicity being the most relevant side effect\_-whichand this can be reversed when the therapy endsed.[15].In an eraWith drug resistance an urgent problem, becomes an urgent problem, we need new antibiotics are needed which can treat infectious diseases, and daptomycin might become such an alternative agent, especially when standard therapyies wdon't work.. Comparator drugs in this review refers to vancomycin(mainly).semi-synthetic penicillins(SSPs). and teicoplanin, which were used as counterpart for daptomycin in control group in included studies.

In this The purpose of this meta-analyseis, we trys to compare the safety and efficacy of daptomycin with other antibiotics to treat SSTIs, especially withsuch as vancomycin or semi-synthetic penicillins, which has long been considered the stand therapy for complicated SSTIs\_The safety endpoints were treatment-related adverse events(AEs), discontinuation due to AEs and all-cause mortality, and creatine phosphokinase(CPK) elevation. The efficacy endpoints

were clinical success and microbiological success at the test of cure(TOC) visit.

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# Formatted: Indent: First line: 3 ch **METHODS** Formatted: First line: 3 ch Data sources. Formatted: Indent: First line: 3 ch We searched Pubmed (up to September 2013), Embase (up to September 2013) and Cochrane Formatted: Font: Not Bold Central (Issue 9 of 12, Sept 2013) were searched to find relevant clinical trials with a prespecified search strategy, and which was revised appropriately through databases. Trials other than RCT were eliminated from consideration. Search terms included 'daptomycin',-\_\_\_\_\_' cubicin',\_\_\_\_ 'lipopeptide', 'skin and soft tissue infections', 'cellulitis', 'wounds infection', 'abscess' and 'erysipelas', and they were combined by PICOs principle. No language restriction settled in the searching process. WeStatistical experts were consulted statistical experts to make search strategy and-wrote emails were sent to relevant corresponding authors of relevant studies and pharmaceutical companies to get resulted in information about any ongoing RCTs\_-thatconcernsrelated to daptomycin. Formatted: First line: 3 ch Study selection Formatted: Indent: First line: 3 ch Two authors(WSZ and TZH) independently searched and scanned examined the relevant literatures, after reading scanned the title and abstract of every retrieved literature to determine which literatures requiring required further assessment. Full articles were obtained when the information given in the titles, abstracts implyieding that: the study was included a prospective design research for the purpose of comparing daptomycin with vancomycin or other antibiotics(with or without co-interventions).When disagreement existed, wethey were

discussed thoroughly to reach consensus. Inclusion criteria:(i)Aany randomized controlled trials that compare daptomycin with other antibiotics in treating SSTIs . (ii)Iincluded patients were of any age, any gender ,had a SSSI requiring i.v.-intravenous antibiotic treatment .(iii)Ddaptomycin intravenous infusion with any dosage, comparator antibiotics intravenous infusion with any dosage.\_Co-interventions that targeted confirmed or probable infections with gram-negative aerobic and anaerobic pathogens were permitted.

Qualitative assessment

<u>The Mm</u>ethodological quality of the RCTs included in this review was independently evaluated by two authors(WSZ and TZH), using the Jadad scale,[16]\_-Jadad scalewhich evaluates randomization and blinding. If elucidation of <u>the</u> methodology revealed that the study applied appropriate randomization and blinding procedures,\_two scores <u>were</u> given to randomization and two scores to blinding. If only mentioned about randomization or blinding but no detail elucidated,\_one score deducted accordingly.\_If information about attrition was thoroughly elucidated,\_one score <u>was</u> given.\_Thus,\_the score ranges from zero to five, <u>and a</u> score higher than two was considered-<u>as a</u> trial of high methodological quality.

Data extraction

Two review authors (WSZ and TZH) independently extracted data with a prespecified data extraction form specifically <u>tuned\_designed</u> for this review. The data extraction included the following detailed imformation:1.¥year of publication,\_clinical settings2.**F**the number of intention to treat(ITT) and clinically evaluable(CE) patients3.**P**descriptions of dose, route, and timing of daptomycin and other antibiotics.4.**C**clinical success, microbiological success,\_treatment-related adverse events(AEs), discontinuation due to adverse events(AEs) and all-cause mortality, and

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creatine phosphokinase(CPK) elevation cases. If missing data detected from the trial reports, <u>the</u> <u>studies' corresponding authors were</u> we attempted to contact<u>ed</u> the corresponding authors to request these information. If this was not successful,\_<u>intention to treat (ITT)</u> analys<u>es</u> were conducted for all dichotomous outcomes (e.g. clinical success, microbiological success,\_ treatment-related adverse events,\_all-cause mortality).

Analysed Outcomes

The Pprimary outcomes of this review were clinical success and microbiological success . Outcomes were judged by clinical and microbiologic evaluations performed at the baseline (within 72 hours before receipt of the first dose of study drug) and test-of-cure(TOC) visit(6–20 days after receipt of the last dose). Clinical success was defined as had resolution of signs andsymptoms the test subjects exhibiting biological indicators such that no further antibiotic therapy was required at TOC visit. Microbiological success was defined as eradication of pathogen (present at admission\_-pathogenbut absent in from culture at TOC visit) or presumed eradication of the pathogen (no material available for culture but patient was deemed as cured or improved by the study investigator at TOC visit. Secondary outcomes were proportions of patients with treatment-related adverse events, discontinuation due to adverse events and all-cause mortality, and cases of CPK elevation-cases.

Data analysis and statistical methods

Data analyses of this review were performed by Review Manager 5.2(Version: 5.2.6,Cochrane Collabration,\_UK).Clinical heterogeneity <u>were was</u> assessed in population, methodology, <u>and in the</u> intervention and outcome measures of each study to <u>see evaluate</u> whether pooling of results was feasible.\_Heterogeneity assessment was performed using the

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chi-squared test, where P value less than 0.1 was considered as significance set. <u>A Ff</u>unnel plot was applied to check for publication bias\_<u>Moreover,and</u> I<sup>2</sup> was applied to estimate the total variation attribute to heterogeneity among studies\_[17]. Values of I<sup>2</sup> less than 25 percent were deemed to have low heterogeneity, and <u>we would then use</u> a fixed-effect model for meta-analysis<u>was then</u> used. Values of I<sup>2</sup> between 25 and 75 percent were considered to represent moderate levels of heterogeneity, therefore, we then utilized and a random effects model was then utilized. Values of I<sup>2</sup> higher than 75 percent indicating high levels of heterogeneity, in which case we did not perform no meta-analysis<u>was performed</u>. All statistical tests were two-sided and a <u>p</u> value less than 0.05 was considered statistically significant.

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#### RESULTS

17 duplicates were removed

Study selection process

Flow diagram in Fig.1, shows the whole scanning and selection process. A total of 310	•	1	F (1
articles were retrieved by means of electronic <u>databases</u> search <u>es</u> of the databases. After deleting			F
			F
duplicates, 293 articles <u>were</u> retained to read <u>the</u> title and abstract. Full text of 23 articles were <u>then</u>	•		F
obtained for further review after the scanning. <u>Meanwhile we wrote Additionally</u> , emails were		$-\frac{\eta}{\eta}$	F
sent to Aastrazeneca China which is in charge of <u>selling of marketing of</u> daptomycin in China, we			F
were informed that daptomycin for SSTIs phase-3 clinical trial was completed in China-has been-			F
finished,, yet so far no data published. Finally6 out of the 23 articles reached the inclusion	l		F
criteria.			F
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310 articles <u>were retr</u> ieved		444	F
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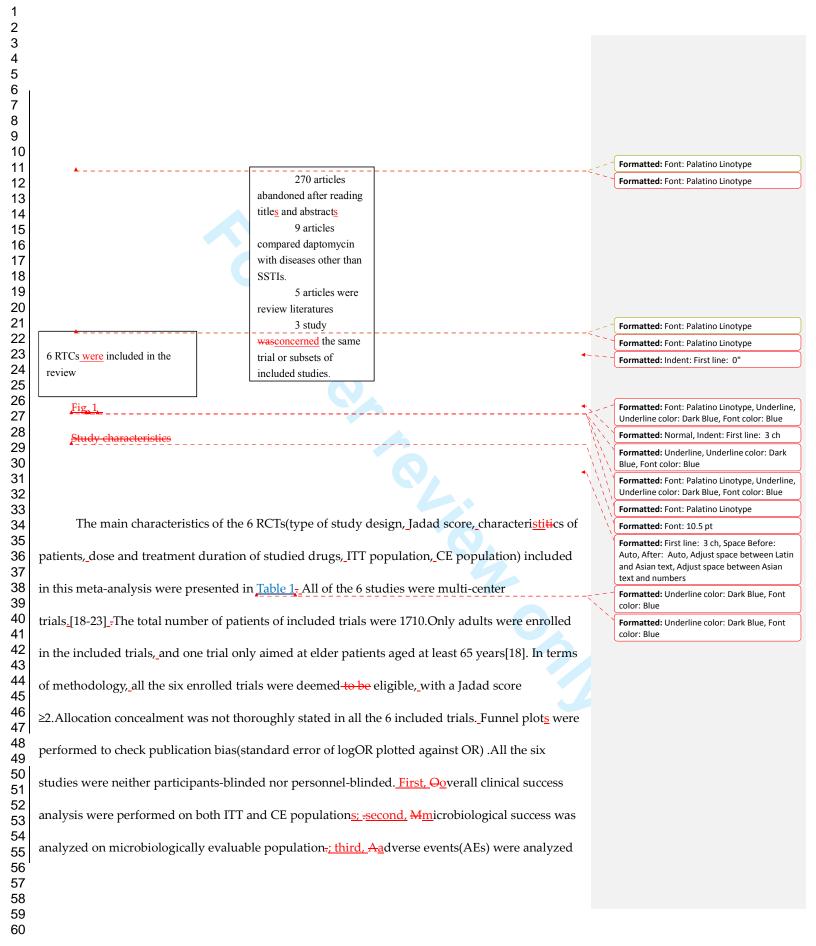
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on ITT population.\_Note that,\_thirty-six patients with no MRSA identified as causative pathogen(<u>of these, 33thirty-three patients-were</u> receiving daptomycin and <u>3three were patients-</u>receiving vancomycin) were excluded from the efficacy analysis of MITT-MRSA population in one study.[19]<del>.</del>

Four out the six included studies were phase-3 trials [18-20 23] one study was phase-2 trial [22] and one-study was phase-4\_trial[21]-Comparator drugs in this review refers tovancomycin(mainly),semi-synthetic penicillins(SSPs) and teicoplanin,which were used ascounterpart for daptomycin in control group in included studies. Vancomycin was the only Comparator drugs used in 2<u>two</u> trials\_was vancomycin alone[19 21]-In one trial, Ccomparator drugs were vancomycin and teicoplanin<u>, in one trial</u>[20] -<u>In two trials, Cc</u>ompar<u>ae</u>tor drugs were vancomycin and SSPs.semi synthetic penicillins in two trials[18 23].The linfecting organism was confirmed as not MRSA in patients randomized to vancomycin(control), investigators were permitted to switch therapy to a SSP in one study.[18]-ITT patients of all the six studies were designated to receive intravenous therapy, but patients could be switched to oral treatment in three trials if the patients they already had at least 4 or 5 days of intravenous therapy and -haddemonstrated a clearly clinical improvement.[18 22 23]. Daptomycin, at with a dosage of 4 mg/kg/day were was administered in five trials, while daptomycin with at the same drug at a dosage of 10 mg/kg/day were was administered in oneanother study.[22]- In all the six trials, Andcomparator drugs in all the six trials were administered according to the standard of care. The efficacy and safety endpoints were similar across the six included studies.

 Table 1 Main Characteristics of the Studies Included in the Meta-Analysis

 Group
 Population

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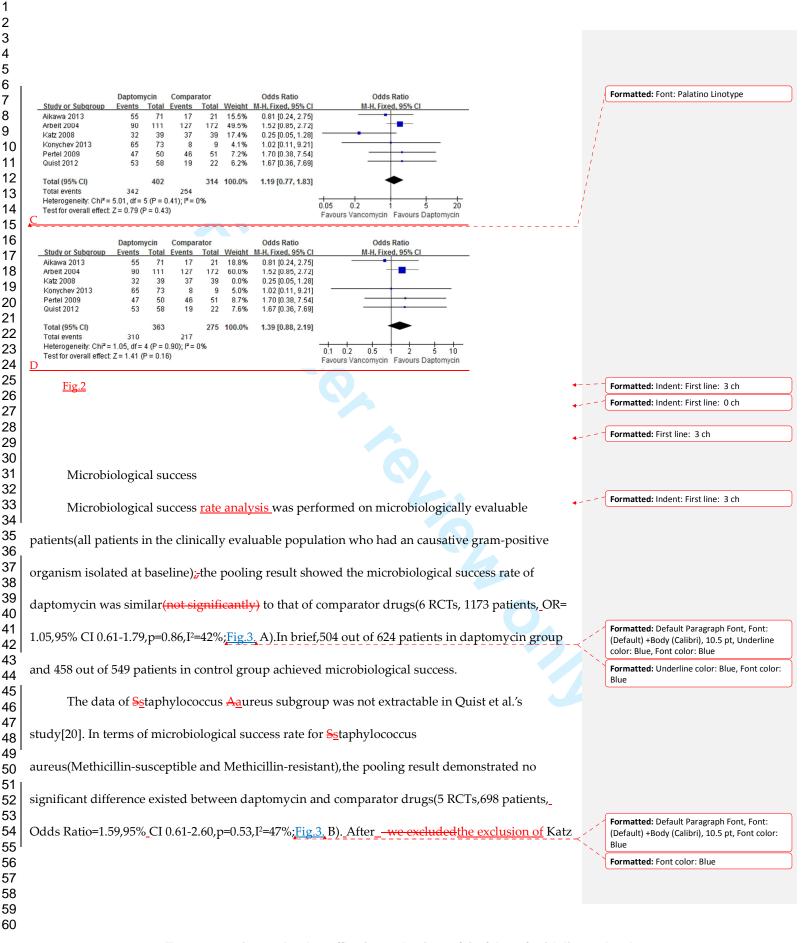
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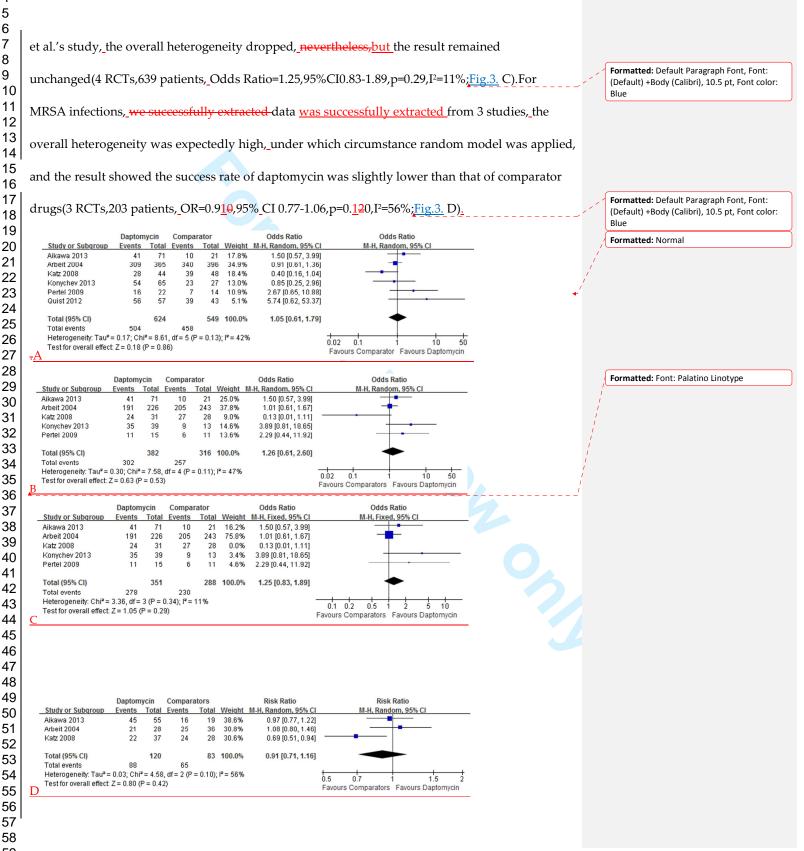
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ference	Design	Jadad	Patients	Daptomycin(dose,	<u>Comparator</u>	ITT,n(Daptom	CE,n(daptom	Formatt
• -		Score	Characteristics	treatment duration)	<u>(type, dose,</u>	<u>ycin vs</u>	<u>ycin vs</u>	Formatt
					treatment duraion)	<u>comparator)</u>	comparator)	Formatt
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nychev	Multicenter	<u>3</u>	N=120, patients	<u>4 mg/kg or 6 mg/kg</u>	<u>SSP 2 g every 6 h or</u>	<u>120(81 vs 39)</u>	<u>103(73 vs 30)</u>	Formatt
<u>13</u> [18]	Evaluator-		<u>aged ≥65 years</u>	<u>over 30 min once</u>	<u>every 4 h for PTs</u>		,%	Formatt
	Blinded RCT		with cSSTIs	daily for 5–14 days	with bacteraemia;			Formatt
				or 10–28 days with	vancomycin 1 g			Formatt
				bacteraemia	<u>q12h for 5–14 days</u> or 10, 28 days with		\ <sup>\$</sup>	Formatt
					<u>or 10–28 days with</u> bacteraemia		1	Formatt
kawa	<u>Multicenter</u>	2	N=101,PTs aged	4 mg/kg over 30_	Vancomycin 1 g	111(88 vs 22)	74(55 vs 19)	Formatt
<u>(3</u> [19]	Evaluator-	4	$\geq 20$ years, SSTIs,	<u>min once daily,for</u>	<u>over at least 60</u>	<u></u>	7 7 105 VS 17	Formatt
<u></u> [+/]	Blinded RCT		MRSA confirmed	7–14 davs	min,twice daily,7–14		an the	Formatt
			within 3 days		<u>days</u>			Formatt
ist_	Multicenter	3	<u>N=194, Adults</u>	Daptomycin 4	vancomycin 1 g i.v.	<u>189(97 vs 92)</u>	108(58 vs 47)	Formatt
<u>2</u> [20]	Evaluator-		requiring i.v.	mg/kg i.v. once	twice daily;		T.	Formatt
	Blinded RCT		antimicrobial	daily	teicoplanin 400 mg			Formatt
			treatment for		i.v. once daily		W	Formatt
			<u>cSSTIs</u>					Formatt
<u>tel</u>	Multicenter	2	<u>N=103,Patients ≥</u>	Daptomycin 4	vancomycin was	<u>103(51 vs 52)</u>	<u>101(50 vs 51)</u>	Formatt
<u>9</u> [21]	Evaluator-		<u>18 years, cellulitis</u>	<u>mg/kg i.v. once</u>	administered i.v.			Formatt
	Blinded RCT		or erysipelas i.v.	<u>daily for 7–14 days</u>	according to		\\\\	Formatt
			antibiotic therapy		standard of care for			Formatt
					<u>7–14 days</u>			Formatt
<u>tz</u>	<u>Multicenter</u>	3	<u>N=100, PTs ≥ 18</u>	_daptomycin 10 mg/		<u>96(48 vs 48)</u>	<u>79(39 vs 39)</u>	Formatt
<u>)8</u> [22]	Evaluator-		years with cSSSI	<u>kg i.v. q24h for 4</u>	<u>g12h for up to 14</u>			Formatt
	Blinded RCT		requiring i.v.	_ <u>days</u>	_ <u>days</u>			Formatt
			antibiotic				W4	Formatt
<u>beit</u>	Multicontor	2	<u>treatment</u>	Daptomycin 4	popicillipaso resista	1092(534 yrs	1002(446 ver	Formatt
<u>)4</u> [23]	<u>Multicenter</u> Evaluator-	<u>2</u>	<u>N=1092,patients</u> were aged 18–85	<u>Daptomycin 4</u> mg/kg i.v. once_	<u>penicillinase-resista</u> nt penicillin 4–12 g	<u>1092(534 vs</u> <u>558)</u>	<u>1002(446 vs</u> <u>456)</u>	Formatt
<u> </u>	Blinded RCT		vears	daily for 7–14 days	<u>iv q.d. or</u>	<u> </u>		Formatt
	<u> </u>		<u>,</u>	<u></u>	vancomycin,1 g iv			Formatt
					q12h by 60-min			Formatt
					infusion			Formatt
	Jadad Score r	<u>ange</u> s fr	om zero to five,sco	ore higher than two	was considered as t	<u>rial of hig</u> h		Formatt
				CE, clinically evalua			<u> </u>	Formatt
								Formatt
							18	Formatt
	Clinical suc	COSE					-11	Formatt
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	Clinical suc	cess ra	te analysis was r	performed on ITT	population(all ra	ndomized pat	tients	Formatt
	emilear sue		te unuryous wus p		population(un ta	naonnizea pa	lientes	Formatt
with a	SSSI who re	eceived	≥1 dose of study	medication) and	CE population(al	ll patients in t	he ITT	Formatt
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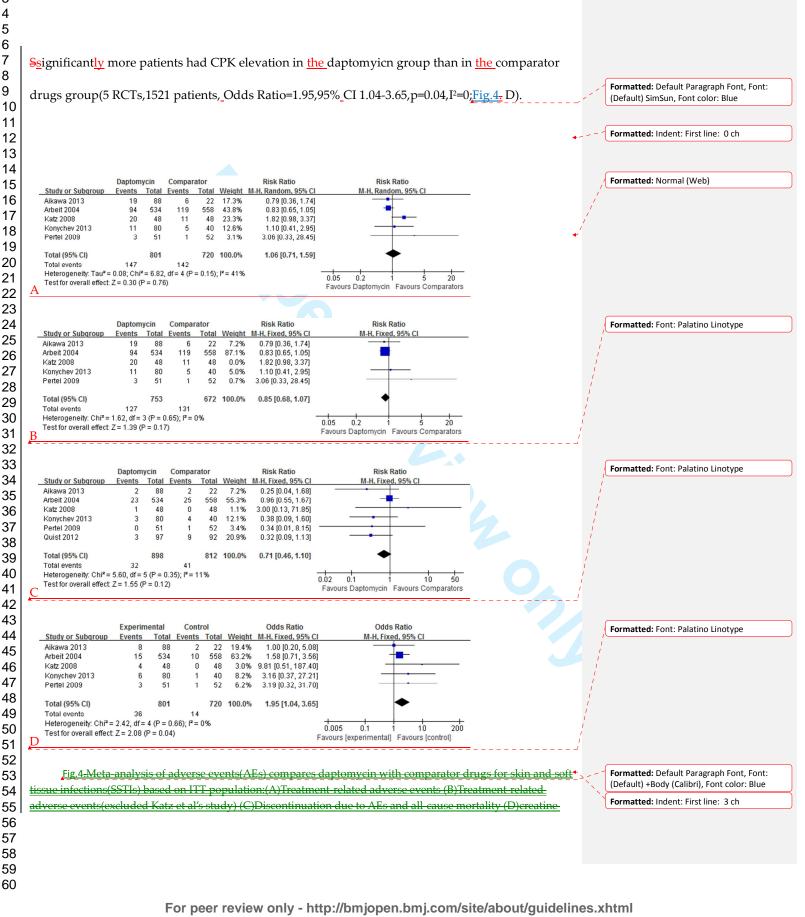
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6 7	population who met protocol-specified inclusion or exclusion criteria relating to the prespecified		
8 9	economic and to the choice of conform ding factors in the ding completion of the required		
10	assessments and to the absence of confounding factors, including completion of the required		
11 12	visits)as well. The pooling result of ITT population showed clinical success rate of daptomycin was		
13 14	similar with to that of comparator drugs at TOC visit(6 RCTs,1674 patients, OR=1.05, 95% CI		
15 16	0.84-1.31,p=0.65,I <sup>2</sup> =0; <u>Fig.2-</u> A). Pooling the result of CE population also demonstrated no difference	1	Formatted: Default Paragraph Font, Font: (Default) +Body (Calibri), 10.5 pt, Underline color: Dark Blue, Font color: Blue
17 18	existed in clinical success rate between daptomycin and other antibiotics for treating SSTIs (6		
19 20	RCTs,1381 patients, OR=0.99,95% CI 0.73-1.35,p=0.97,I <sup>2</sup> =0; <u>Fig.2-</u> B).	1	Formatted: Default Paragraph Font, Font: (Default) +Body (Calibri), 10.5 pt, Underline color: Dark Blue, Font color: Blue
21 22	In terms of daptomycin vs vancomycin subgroup, clinical success rate of daptomycin was		
23 24	higher(not significantly) than that of vancomycin(6 RCTs,716 patients, OR=1.19,95%_CI		
25 26 27	0.77-1.83,p=0.43,I <sup>2</sup> =0;Fig.2-C).Briefly, 342 out of 402 patients in daptomycin group and 254 out of		Formatted: Default Paragraph Font, Font: (Default) +Body (Calibri), 10.5 pt, Underline color: Dark Blue, Font color: Blue
28 29	314 patients in vancomycin group achieved clinical success at TOC visit. <u>Since Katz et-</u> al's study		Formatted: Underline color: Dark Blue, Font color: Blue
30	used a higher dosage than the other included studies, after <u>we excluded Katz et.al's studyits</u>		
31 32 33	exclusion, the pooling result showed a trend favorsing daptomycin(5 RCTs,638 patients,		
34 35	OR=1.39,95%_CI_0.88-2.19,p=0.16,I <sup>2</sup> =0; <u>Fig.2</u> ,D)	1	Formatted: Default Paragraph Font, Font: (Default) +Body (Calibri), 10.5 pt, Underline color: Dark Blue, Font color: Blue
36 37			Formatted: Font color: Dark Blue
38	Daptomycin Comparator Odds Ratio Odds Ratio	i	Formatted: Font: (Default) Times New Roman
39	Study or Subgroup         Events         Total         Weight         M-H, Fixed, 95% Cl         M-H, Fixed, 95% Cl           Aikawa 2013         61         71         7         21         2.4%         1.44 [0.40, 5.15]           Arbeit 2004         382         534         397         558         71.2%         1.02 [0.78, 1.33]	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Formatted: Normal
40 41	Katz 2008 36 48 42 48 6.8% 0.43 [0.15, 1.26]	Ä.	
42	Perfel 2009 47 51 46 52 2.3% 1.53 (0.41, 5.79)	/	
43	Quist 2012 65 97 58 92 12.7% 1.19 [0.65, 2.17]	; ;	
44	Total (95% CI) 881 811 100.0% 1.05 [0.84, 1.31] Total events 656 589		
45	Heterogeneity: Chi <sup>2</sup> = 4.39, df = 5 (P = 0.49); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) Favours Comparator Favours Daptomycin		
46	<u>A</u>		
47 48	Daptomycin Comparator Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl	i	Formatted: Font: Palatino Linotype
49	Aikawa 2013 61 71 17 21 4.4% 1.44 [0.40, 5.15]	- /	
50	Katz 2008 32 39 37 39 7.9% 0.25 (0.05, 1.28)	1	
51	Konychev 2013 65 73 25 30 4.6% 1.63 [0.49, 5.44] Pertel 2009 47 50 46 51 3.3% 1.70 [0.38, 7.54]	1	
52	Quist 2012 53 58 41 47 4.7% 1.55 [0.44, 5.44]	;	
53	Total (95% CI) 737 644 100.0% 0.99 [0.73, 1.35] Total events 630 550		
54 55	Heterogeneity: Chi <sup>2</sup> = 4.79, df = 5 (P = 0.44); l <sup>2</sup> = 0%         0.05         0.2         1         5         20         /           Test for overall effect Z = 0.04 (P = 0.97)         Favours Comparators         Favours Daptomycin         /		
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7	Fig.3. Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue		Formatted: Default Paragraph Font, Font:
8	infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological	1	(Default) +Body (Calibri), Underline color: Blue, Font color: Blue
9	success for <u>Staphylococcus Aureus. (C)microbiological success for Staphylococcus Aureus(excluded Katz et al.'s</u> study). (D) microbiological success for MRSA. Vertical line suggests no difference between daptomycin and		<b>Formatted:</b> Default Paragraph Font, Font:
10 11	comparator drugs. The size of each square represents the proportion of information given by each trial.		(Default) +Body (Calibri) Formatted: Indent: First line: 3 ch
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21	Adverse events outcomes and mortality outcomes		
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23 24	In terms of treatment-related adverse events(AEs), <del>oneQuist et al's</del> study was excluded from		Formatted: Indent: First line: 0 ch
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26	pooling result_ <del>on behalf of that<u>because</u> no information was given about whether adverse events</del>		
27	were treatment-related or not <u>.[20]- There was Nn</u> o significant difference detected between		
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30	daptomycin and comparator drugs(5 studies,1521 patients,_Odds Ratio=1.06,95%_CI_0.71-1.59,_		
31	p=0.76, I <sup>2</sup> =41%; Fig.4. A). After we excluded Katz et al.'s study was excluded, there was a dramatic	1	Formatted: Default Paragraph Font, Font:
32 33	p=0.70, 1=4170, 112.4 A). Alter we excluded Raz et al. 5 study was excluded, diele was a dramate	_	(Default) SimSun, Font color: Blue
34	decline in the heterogeneity declined dramatically, and the result turned changed to favor		
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36 37	daptomycin(4 RCTs,1425 patients,_Odds Ratio=0.85,95%_CI 0.68-1.07,_p=0.17,_I <sup>2</sup> =0; <u>Fig.4-</u> B).		(Default) SimSun, Font color: Blue
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39	Discontinuation due to AEs and all-cause mortality during treatment were rare in the six		
40 41	included studies. No death reported in 3three studies. [18 21 22], while another study reported		
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43	discontinuation due to AEs and death togethercombined.[20]_On account of the above reasons,		
44 45	we pooled discontinuation due to AEs and all-cause mortality were pooled together. With Aa total		
46	we pooled discontinuation due to AEs and an-cause mortanty were pooled together. with Aa total		
47	of 1710 patients enrolled in the analysis <u>, the pooling result sugg</u> ested <u>there was</u> no significant		
48 49			
50	difference existed between daptomycin and comparator drugs(6 RCTs,1710 patients,_Odds		
51	Ratio=0.76,95%_CI 0.46-1.10,p=0.12,I <sup>2</sup> =11%;Fig.4-C).A comparison of CPK elevations considered as	1	Formatted: Default Paragraph Font, Font: (Default) SimSun, Font color: Blue
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54	adverse events <del>were compared</del> between daptomycin and comparator drugs <del>, <u>yielded that</u></del>		
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phosphokinase(CPK) elevations regarded as adverse events. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CL confidence interval.

## DISCUSION

This is an up-dated meta-analysis <u>based on Bliziotis et al's study, which</u> compares efficacy and safety of daptomycin with vancomycin and other antibiotics for treating SSTIs\_[24]\_-There were some clear <del>shortages]imitations</del> found in the previous meta-analysis.\_First-<del>of all</del>, it enrolled only four trials, <u>in which</u> three-<u>of them</u> were RCTs, including one RCT which <u>was</u> found to have considerable heterogeneity in our analyses due to a high dose of daptomycin with a short duration\_\_\_<del>;plus</del>In <u>addition</u>, there <u>was</u> one historically controlled trial(<u>not randomized</u>) which was excluded in <del>ourthis</del> review(<del>not randomized</del>).[25]\_Besides the previous three RCTs <del>;we enrolled</del> another three <u>more</u> RCTs <u>which-were</u> considered to be eligible in terms of clinical homogeneity.\_ Daptomycin was approved by FDA September<sub>z</sub>-2003<sub>z</sub> for treatment of complicated skin and soft tissue infections<sub>z</sub>\_<u>under the circumstance of because of the</u> drug-resistant urgency. However,<u></u> there were only a handful RCTs available,<u>and a distinct</u> lack of high quality meta-analysis <del>that</del>provides us with yielding high-level clinical evidence.

The results of our-this review indicate daptomycin was as effective and safe as other drugs in treating SSTIs.\_The clinical success rate of daptomycin in both ITT population(OR=1.05,95%\_CI\_ 0.84-1.31,p=0.65,I<sup>2</sup>=0) and CE population(OR=0.99,95%\_CI0.73-1.35,p=0.97,I<sup>2</sup>=0) was equivalent to that of other drugs used to for-treating SSTIs.\_Of note,\_in Katz et al's study, <u>a</u> high dose(10 Formatted: Indent: First line: 3 ch

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mg/kg/day) intake of daptomycin with a short treatment duration (4 days) of daptomycin led to lower reduced clinical success rate and lower reduced microbiological success rate in daptomycin\_ when compared with comparator drugs.[22] -This Sehortened therapy duration could possibly have had undermined the efficacy of daptomycin and brought about some clinical heterogeneity, which resulteding in statistical heterogeneity in our data analyses. The microbiological success rate of daptomycin was also similar to that of other first-line drugs(OR=1.05,95%\_CI\_ 0.61-1.79,p=0.86,I<sup>2</sup>=42%). Staphylococcus aureus(SA) was the main pathogen for SSTIs, the microbiological success rate for SA has showed no significant difference between the two groups(OR=1.26,95%\_CI\_0.61-2.60,p=0.53,I<sup>2</sup>=47%). However, after we excluded the exclusion of Katz et al's study which used a different dosage, the heterogeneity declined, and the result turnedtended to favor daptomycin(OR=1.25,95% CI\_0.83-1.89,p=0.86,I<sup>2</sup>=11%). With MRSA was-as\_ the most common drug-resistant pathogen in SSTIs, the pooling result of the success rate of daptomycin versus comparators showed-indicated no significant difference existed between the groups(OR=0.90,95%\_CI 0.77-1.06,p=0.20,I2=56%).Only 203 patients were enrolled in the MRSA subgroup analysis, meanwhile while simultaneously the heterogeneity was high<sub>t</sub>-thus, we should interpret the result should be interpreted prudently. That Fthe included studies were conducted in differentdiverse countries and at different vearstimes, and that there was a lack of uniformity in<del>as well as different</del> epidemiologic characteristics for in each trial, also should have some confounding impacts on the final results. Not all the included studies reported Dduration of treatment; were not reported by all the included studies, however, Arbeit et al's study found out that significant more patients in daptomycin –group than patients in comparator drugs group needed only 4 to 7 days of treatment<sub>[</sub>[23], while two other included studies found no significant difference existed between the two groups in terms of duration of treatment.[18 21] -Furthermore, Fthere were no significant difference between daptomycin and comparator drugs in terms of

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treatment-related AEs(OR=1.06,95% CI 0.71-1.59,p=0.76,I<sup>2</sup>=41%). ButHowever, after we excluded Katz et al's study was excluded, daptomycin tended to have less treatment-related AEs(OR=0.85,95%\_CI\_0.68-1.07,p=0.86,p=0.17,I<sup>2</sup>=0).Daptomycin tended, to have less patients associated with discontinuation or death(OR=0.71,95% CI 0.46-1.10,p=0.12,I<sup>2</sup>=11%). Daptomycin was reported to have potential muscle toxicity.[15], as a result, CPK were closely monitored in the included studies during the treatment process. This close monitoring revealed that CPK elevation occurred more frequently in daptomycin-treated patients(OR=1.95,95%\_CI1.04-3.65,p=0.04,I<sup>2</sup>=0),but on most occasions, CPK levelit declined to normal levels during or after the therapy in most of the occasions. Therefore, one may conclude that Ddaptomycin might be a safer and more efficacious drug to use, exhibited a tendency it might have superior efficacy and better safety in comparison with other comparator drugs, in the matter of microbiological success, treatment-related AEs, discontinuation or death. Of note, in Aikawa et al's study, one patient out of the 88eighty-eight patients in daptomycin group hadexperienced anaphylactic shock, and which was resolved 4 days after-drug treatment discontinuation of drug treatment.[19]-Therefore, despite the safety of daptomycin is satisfying, clinicians should be cautious about administering it onto patients of hypersensitivity. Infectious Diseases of America recommended that vancomycin-was to be used for empirical therapy in clinical settings with an increased prevalence of MRSA; for institutions with preponderant MRSA isolates that have vancomycin MIC values >2 mg/mL,\_alternative agents, such as daptomycin, should be used. [26]. An antimicrobial resistance surveillance in China also had documented Sstaphylococcus aureus and Eescherichia coli were the most common multi\_drug-resistant pathogens, for which linezolid, tigecycline, daptomycin, and vancomycin provided best antimicrobial coverage.[27]-Vancomycin was also the first-line drug to treat MRSA 

infections for hospitalized children. So comparing the efficacy of daptomycin with vancomycin is necessary and <u>useful since it</u> could <u>give some evidence provide helpful data</u> to clinicians. <u>The</u> <u>Dd</u>aptomycin vs\_ vancomycin subgroup analysis of our review found<u>out that</u> daptomycin tended to exhibit higher clinical success rate in comparison <u>withto</u> vancomycin(OR=1.19,95%\_CI\_ 0.77-1.83,p=0.43,I<sup>2</sup>=0).And<u>after we</u> excluded<u>ing</u> Katz et al-' study, the pooling resulted<u>turned to</u> favor<u>ed</u> daptomycin<u>even</u> further(OR=1.39,95%\_CI\_0.88-2.19,p=0.16,I<sup>2</sup>=0)

Daptomycin wasis mainly metabolized by kidneys, Aikawa et al- demonstrated that patients with mild to moderate renal impairment, when compared with patients with normal renal function, clearance of daptomycin was not markedly different in patients with mildto moderate renal impairment. Furthermore,6 mg/kg of daptomycin once daily was found to be safe for extended dialysis patients, which simultaneously could lower the substantial risk of under dosing of daptomycin.[28].-In hospitalized children with cSSTIs, vancomycin, clindamycin and linezolid were recommended for treatment, whereas daptomycin was not mentioned.[4]-Nevertheless, daptomycin therapy demonstrated clinical improvement for invasive gram-positive bacterial infections in children.[29] .-bBut-of which the clearance of daptomycin in infants and 2-6 years children were higher than that of adolescents and adults, as a result in order to achieve efficacious exposures, this younger group daptomycin might need a higher dosage of daptomycin. than adults to achieve efficacious exposures infants and 2-6 children[30]. On the contrary, vVancomycin, however, has potential renal toxicity, which limiteds it's usage with patients with renal impairment, where and for whom daptomycin might be an eligible alternative agent. In recent years, vancomycin-resistant Sstaphylococcus aureus (VRSA) infection cases have beenwere repeatedly reported in the United States,[31],for these, daptomycin with an equivalent efficacy to vancomycin could be used as an eligible alternative treatment. Of note, Aikawa et al-

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found a trend that along with the increment of MICs of daptomycin, the clinical success rate declined gradually.[19]-In spite of that, up till now, -nonsusceptibility to daptomycin remains rare.[32]\_-Recently, one meta-analysis demonstrated that compared with vancomycin, linezolid had superior efficacy for MRSA infections.[33]-To our knowledge, there was no RCT directly comparing linezolid with daptomycin for MRSA infections. What's more, cost-effectiveness analysis studies of daptomycin, vancomycin and linezolid for MRSA-related cSSTIs found out that daptomycin and linezolid were potentially more cost-effective than vancomycin, however, daptomycin had no advantage when compared with linezolid. [34 35] -RCTs about daptomycin aimed forat other diseases also proved daptomycin was safe and effective in treating diseasesissues like prosthetic joint infection.[36]ror Sstaphylococcus aureus bacteraemia and infective endocarditis (SAB/IE) at a dosage of 6 mg/kg/day.[12]-.Note that, age was a risk factor for SSTIs since the average ages of patients all exceeded 40 years old in included studies. The mean or median body weight index in four trials(all exceeded 25 kg/m<sup>2</sup>) also revealed that obesity was is also a risk factor. [18 19 21 22]-Additionally, diabetes mellitus, peripheral vascular disease and immunocompromise were also present the usual comorbid conditions for SSTI\_[21-23]-Wounds infections were common in surgical departments and surgical ICU, and it accounted for nearly 41% of the total patients in four included studies.<u>\_+tT</u>hough the efficacy and safety data were not charted for specific type of SSTI in every included trial, the high proportion of wounds infections in included studies are adequate to exhibit the -safety and efficacy of daptomycin for woundsinfectionsthese.

There are several limitations exist in our meta-analysis. First of all, allnone of the six included RCTs we included were not participants-blinded or personnel-blinded, thus, performance bias was unpredictable. Furthermore, Arbeit et al's study had dominant influence on overall clinical success rate analysis both on ITT population and CE populations, as it weighed more than 70% in these two analyses. Additionally, too few of our data analyses reached statistical significance, which leadled to insufficient credibility to draw couclusions for some potentially disputable issues.

#### **Conclusions**

However,throughBy our analyses,\_suffice it to say daptomycin have a not inferior efficacy and equivalent safety to comparator drugs,\_especially when compared with vancomycin which has been considered as the standard therapy for cSSTIs.\_In summary,bBased on the present evidence,\_daptomycin is a promising new agent for gram-positive infections like SSTIs,\_and-weexpect\_\_more high-quality RCTs are expected to explore it's potentiality.

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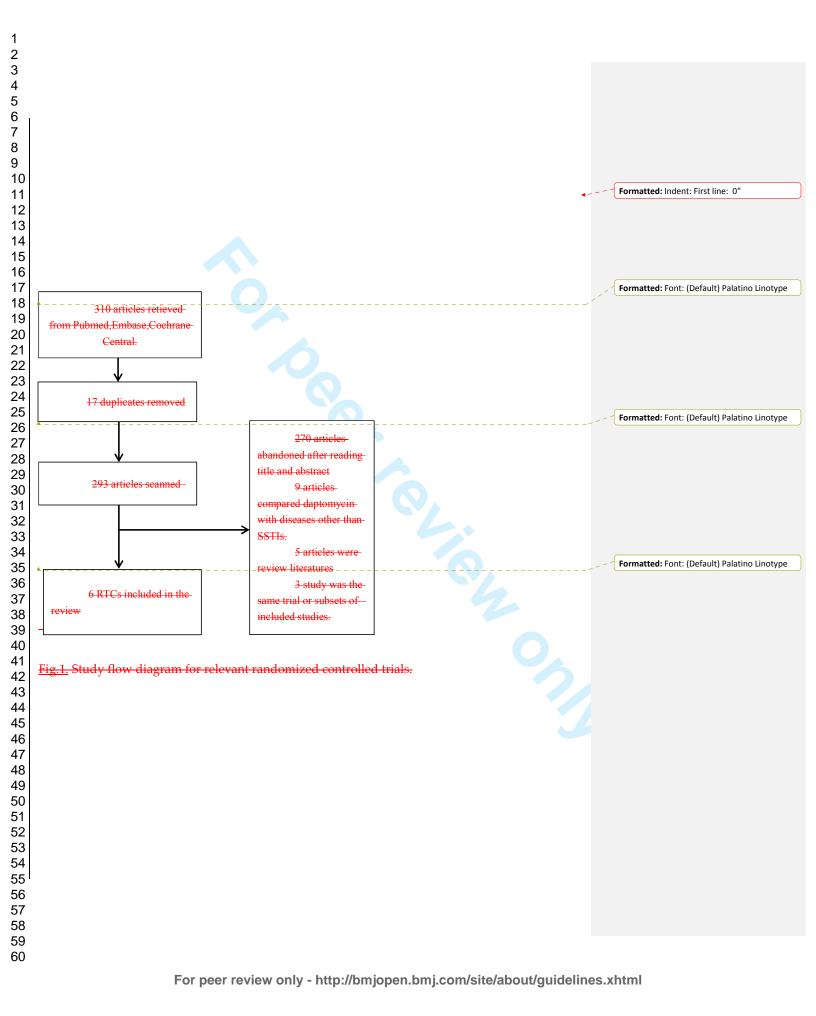
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7 8	<b>Contributors</b> WSZ and TZH conceived this study, identified studies for inclusion, and		
9	extracted data together. The English manuscript was written and revised by WSZ. Other authors		
10	<u>extracted data together. The English manuscript was written and revised by WSZ. Other authors</u>		
11	made supportive contributions. All the authors read and approved the final manuscript.		
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17	Conflict of interests No conflict of interest _ None declared.		Formatted: Indent: First line: 3 ch
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23	Fig. 1 Study flow diagram for relevant randomized controlled trials.		Formatted: Indent: First line: 3 ch
24	Fig.2 Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft		
25 26	tissue infections(SSTIs): (A)Clinical success(ITT population) (B) Clinical success(CE population) (C)		
27	Daptomycin vs. Vancomycin for clinical success(CE population). (D) Daptomycin vs. Vancomycin for clinical success(CE population, excluded Katz et al's study). ITT, intention to treat; CE, clinically evaluable. The		
28	vertical line suggests no difference between daptomycin and comparator drugs. The size of each square		
29	represents the proportion of information given by each trial. CI, confidence interval.		
30 21	Fig.3. Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and		
31 32	soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success		
33	(B) microbiological success for staphylococcus aureus. (C)microbiological success for staphylococcus		
34	aureus(excluded Katz et al's study). (D) microbiological success for MRSA. The vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of		
35	information given by each trial. CL, confidence interval.		
36 37	Fig.4.Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and		
38	soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related		
39	adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (D)creatine		
40	phosphokinase(CPK) elevations regarded as adverse events. Vertical line suggests no difference between		
41	daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CL, confidence interval.		
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51			_ <del>Group</del>		<u>Populaton</u>	****	Formatted: Font: Times New Roman Formatted: Indent: First line: 0 ch
52 53	efere	ad Patients		Comparator	_ITT,n(Daptomyci _	<u>CE,n(daptom</u>	Formatted: Indent: First line: 0 ch
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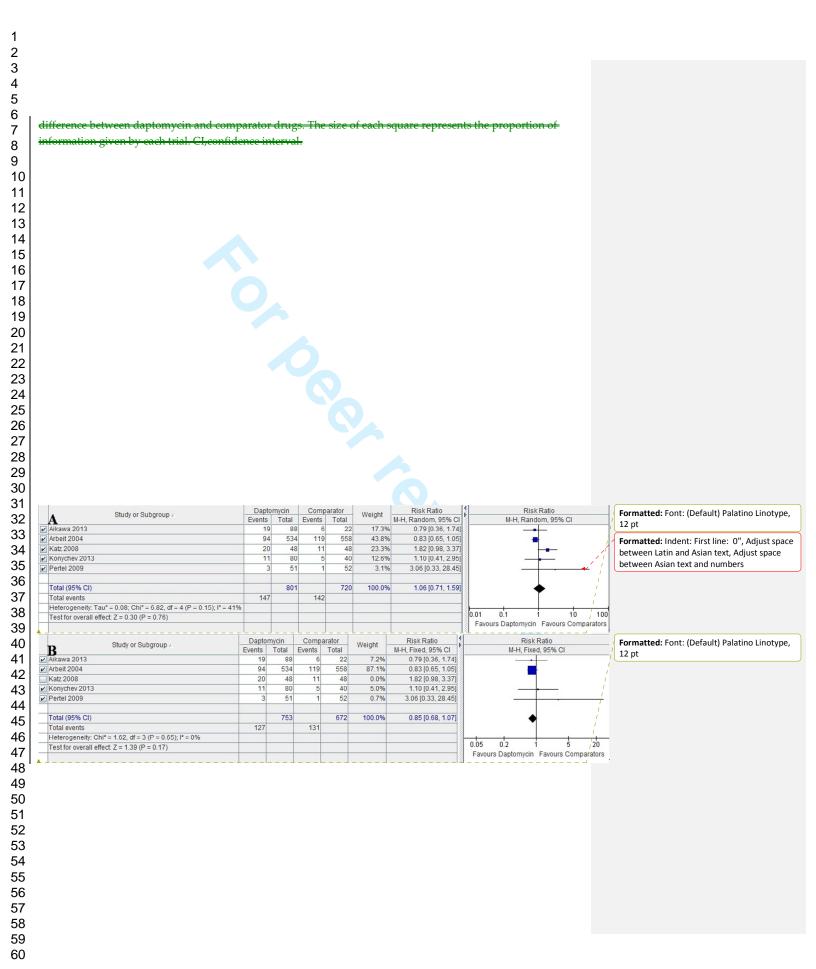
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4	£	were aged 18-	_mg/kg i.v. once_	penicillin 4–12 g iv		456)	Formatted	[90]
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A F N= N=00000000000000000000000000000000	013       Evaluator- Blinded       aged ≥20       30 min once daily;for 7-14       at least 60 min,twice daily;7-14 days         RCT       RSA confirmed within 3 days       days       alily;7-14 days         nye       Multi-cent       3       N=120; patients aged       mg/kg over 30       every 4 h for PTs with bacteraemia; Plinded         3-       Evaluator- Property RCT       >65 years with min once daily       bacteraemia; patients aged       vancomycin 1 g every to r10-28 days         8CT       or 10-28 days       vancomycin 1 g every to r28 days with bacteraemia       vancomycin 1 g every to r28 days with bacteraemia         st       Multicente       3       N=194, Adults       Daptomycin 4       vancomycin 1 g i.v. to -28 days with bacteraemia         st       Multicente       3       N=194, Adults       Daptomycin 4       vancomycin 1 g i.v. to once daily         RCT       r       requiring i.v. mg/kg i.v. once       twice daily; to once daily       twice daily; to once daily         Binded       treatment for esSTHs       mg/kg i.v. once       administered i.v. ecollulits or daily for 7.14       vancomycin 1 g i.v. days         90-       r       > 18 years, mg/kg i.v. once       administered i.v. days       gl for up to 14 days         8CT       antibiotic therapy       therapy       days       f care for 7.14 days	H3       Evaluator- Binded       ged-≥20       30 min once daily,for 7-14       daily,7-14 days         RCT       RSA confirmed within 3 days       days       dily,7-14 days         NCT       RSA confirmed within 3 days       mg/kg or 6       SSP 2 g every 6 h or patients aged       120(81 v+ 39)         eff       patients aged       mg/kg over 30       every 4 h for PTs with         Binded       oSSTIs- set or 128 days       for 5-14 days       vancomycin 1 g every         RCT       or 10-28 days with bacteraemia       for 5-14 days or with bacteraemia       for 5-14 days or with bacteraemia       for 5-14 days or with bacteraemia         RCT       r       requiring i.v. mg/kg i.v. once with bacteraemia       for 5-14 days or with bacteraemia       for 5-14 days or with bacteraemia         Binded       requiring i.v. mg/kg i.v. once set       twice daily: teicoplanin 400 mg to vance daily       for 5-14 days         P1       f       requiring i.v. mg/kg i.v. once set i.v. once daily       for 5-14 days         RCT       estimation       daily for 7-14       according to standard         Binded       reatiment for revealuator       daily for 7-14       according to standard         Binded       reatiment for revealuator       daily for 7-14       according to standard         Binded       N=100, PTs >	013       Evaluator- Binded       aged ⇒20       30 min once daily,7-14       at + east 60 min,twice- daily,7-14         RCF       RSA-confirmed- within 3 days       daily,67-714       daily,7-14       daily,7-14         NCF       RSA-confirmed- within 3 days       mg/k govr 30       every 1 h for PTs with       103(73 vs 30)         -       ef       patients aged- mg/k govr 30       every 1 h for PTs with       103(73 vs 30)         31       Evaluator- et or 10-28 days       into noce daily to 51-14 days or with       10-32 days with bacternemia       103(73 vs 30)         RCT       of 10-28 days       into noce daily to 32 days with bacternemia       10-32 days with bacternemia       10-32 days with bacternemia         ist       Multicente       3       N=194, Adults       Deptomycin 4       vancomycin 1 g i.v.       199(07 vs 92)       108(58 vs 47)         ist       Multicente       3       N=194, Adults       Deptomycin 4       vancomycin 1 g i.v.       199(07 vs 92)       108(58 vs 47)         ist       Multicente       3       N=104, Adults       Deptomycin 4       vancomycin 1 g i.v.       199(07 vs 92)       108(58 vs 47)         ist       Multicente       3       N=104, Adults       Deptomycin 4       vancomycin 1 g i.v.       199(07 vs 92)       101(50 vs 51)       100(50	013 Evaluate- Bilindel years,SSTR,M diabyfor 7-14 days RCT RSA confirmed days within 3 days ary Multi-ent 3 N-120, 4 mg/kg or 6 SSP 2 givery 6 h or 120(61 vs 39) 103(73 vs 307 Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted Formatted

A Study or Subgroup /	Events	mycin Total 7	Events		Weight	Odds Ratio M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	Formatted: Font: (Default) Palatino Linotype 12 pt
2 Aikawa 2013 2 Arbeit 2004	61	534	4 397	558	2.4% 71.2%	1.02 [0.78, 1.33]		Formatted: Indent: First line: 0", Adjust space
[Katz 2008 [Konychev 2013	36				6.8% 4.7%			between Latin and Asian text, Adjust space between Asian text and numbers
Pertel 2009	47	51	46	52	2.3%	1.53 [0.41, 5.79]		between Asian text and numbers
Quist 2012	65	97	58	92	12.7%	1.19 [0.65, 2.17]	· · · ·	
Total (95% CI)		881	1	811	100.0%	1.05 [0.84, 1.31]	▲ /	
Total events	656		589					
Heterogeneity: Chl* = 4.39, df = 5 (P = 0.49); l* = 0% Test for overall effect: Z = 0.45 (P = 0.65)				-			0.1 0.2 0.5 1 2 5 10	
							Favours Comparator Favours Daptomycin	
B Study or Subgroup /	Dapto			arator	Weight	Odds Ratio	Odds Ratio	Formatted: Font: (Default) Palatino Linotype
Aikawa 2013	Events 61	Total 71	Events 17	Total 21	4.4%	M-H, Fixed, 95% CI 1.44 [0.40, 5.15]	M-H, Fixed, 95% Cl	12 pt
Arbeit 2004	372				75.1%			
Katz 2008	32				7.9%		· · · · · · · · · · · · · · · · · · ·	
Konychev 2013	65				4.6%		i i i	
Quist 2012	53				4.7%			
Total (95% CI) Total events	630	737	550	644	100.0%	0.99 [0.73, 1.35]	┥	
Heterogeneity: Chi <sup>a</sup> = 4.79, df = 5 (P = 0.44); l <sup>a</sup> = 0%	000	4	550					
Test for overall effect: Z = 0.04 (P = 0.97)							0.05 0.2 1 5 20 Favours Comparators Favours Daptomycin	
C Study or Subgroup	Dapto Events	mycin Total	Comp: Events	arator Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl	Formatted: Font: (Default) Palatino Linotype
Aikawa 2013	55	71		21	15.5%	0.81 [0.24, 2.75]	M=H, FIXED, 55% CI	12 pt
Arbeit 2004	90	111	127	172	49.5%	1.52 [0.85, 2.72]	+ /	
Katz 2008 Konychev 2013	32	39 73		39 9	17.4% 4.1%	0.25 [0.05, 1.28] 1.02 [0.11, 9.21]	· · · · · · /	
Pertel 2009	47	50		51	7.2%	1.70 [0.38, 7.54]		
Quist 2012	53	58	19	22	6.2%	1.67 [0.36, 7.69]	/	
Total (95% CI)		402		314	100.0%	1.19 [0.77, 1.83]		
Total events	342	402	254	514	100.070	1.15 [0.77, 1.00]		
Heterogeneity: Chi <sup>2</sup> = 5.01, df = 5 (P = 0.41); l <sup>2</sup> = 0%								
Test for overall effect: Z = 0.79 (P = 0.43)							Favours Vancomycin Favours Daptomycin	
							8	
D Study or Subgroup /	Daptor Events	nycin Total	Compa Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl	Formatted: Font: (Default) Palatino Linotype 12 pt
Aikawa 2013	55	71	17	21	18.8%	0.81 [0.24, 2.75		12 pt
Arbeit 2004 Katz 2008	90 32	111 39	127 37	172 39	60.0% 0.0%	1.52 [0.85, 2.72 0.25 [0.05, 1.28	<b>+</b> ∎− /	
Konychev 2013	65	73		9	5.0%	1.02 [0.11, 9.21	<i>i</i>	
Pertel 2009	47	50	46	51	8.7%	1.70 [0.38, 7.54	<i>i</i>	
Quist 2012	53	58	19	22	7.6%	1.67 [0.36, 7.69	· · · · · /	
Total (95% CI)		363		275	100.0%	1.39 [0.88, 2.19		
Total events	310		217				j j	
Heterogeneity: Chi <sup>2</sup> = 1.05, df = 4 (P = 0.90); i <sup>2</sup> = 0% Test for overall effect: Z = 1.41 (P = 0.16)	_						0.05 0.2 1 5 20	
restion overall effect. 2 = 1.41 (F = 0.10)							Favours Vancomycin Favours Daptomycin	
			''					
2. O M. (	apares (	<del>dapte</del>	mycir	<del>ı with</del>	compai			Formatted: Font: 10.5 pt
<u>ig.2. Meta analysis of clinical success con</u>								
<u>19.2. Meta analysis of clinical success con</u> nfections(SSTIs): (A )Clinical success(ITT		tion)	(B) C	linica	l <del> succes</del>	s(CE populatic	<del>n) (C) Daptomycin vs</del>	Formatted: Font: 10.5 pt

information given by each trial. CI, confidence interval.

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A	udy or Subgroup 🗚	Events		Events		Weight	Odds Ratio M-H, Random, 95% CI		<b>Formatted:</b> Font: (Default) Palatino Linoty
Aikawa 2013     Arbeit 2004     Katz 2008		41 309	9 365	5 340	0 396	34.9%	6 0.91 [0.61, 1.36]	N	
Katz 2008     Konychev 2013     Redel 2000		28	4 65	5 23	3 27	13.0%	6 0.85 [0.25, 2.96]	N	
Pertel 2009     Quist 2012		16 56							-
Total (95% CI)			624		549	100.0%	6 1.05 [0.61, 1.79]		
	7; Chi² = 8.61, df = 5 (P = 0.13); l² = 42%	504		458					±
Test for overall effect: Z = 0	J.18 (P = 0.86)							0.02 0.1 1 10 / 5 Favours Comparator Favours Daptomycin	50 1
B Stud	dy or Subgroup 🕗	Daptor		Compa		Weight	Odds Ratio	Odds Ratio M-H, Random, 95% Cl	Formatted: Font: (Default) Palatino Linoty
Aikawa 2013		Events 41	71	10	21	25.0%			
Arbeit 2004     Katz 2008		191 24			28	37.8% 9.0%	0.13 [0.01, 1.11]	· · · · · · · · · · · · · · · · · · ·	/
Konychev 2013     Pertel 2009		35 11				14.6% 13.6%	3.89 [0.81, 18.65] 2.29 [0.44, 11.92]		
Total (95% CI)			382		316	100.0%		/ · · · · · · · · · · · · · · · · · · ·	
Total events	0; Chi² = 7.58, df = 4 (P = 0.11); l² = 47%	302		257					
Test for overall effect: Z = 0								0.02 0.1 1 10 / 50 Favours Comparators Favours Daptomycin	
C Stur	dy or Subgroup A	Daptor		Compa		Weight	Odds Ratio	Odds Ratio	Formatted: Font: (Default) Palatino Linoty
Aikawa 2013		Events 41	71	10	21	16.2%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99]		
<ul> <li>✓ Arbeit 2004</li> <li>✓ Katz 2008</li> </ul>		191 24	31	205 27	28	75.8% 0.0%	1.01 [0.61, 1.67] 0.13 [0.01, 1.11]	Т	1
Konychev 2013     Pertel 2009		35 11				3.4% 4.6%	3.89 [0.81, 18.65] 2.29 [0.44, 11.92]		
Total (95% CI)			351		288	100.0%	1.25 [0.83, 1.89]	į į	
Total events	5, df = 3 (P = 0.34); I <sup>2</sup> = 11%	278		230					
Test for overall effect: Z = 1		=	_		_			0.02 0.1 1 10 / 50 Favours Comparators Favours Daptomycin	
stu			omycin		parators	Weight	Risk Ratio	Risk Ratio	Formatted: Font: (Default) Palatino Linoty
Aikawa 2013		Events 45	5 55		6 19	32.6%			_//
Arbeit 2004 Katz 2008		21							
Total (95% CI)			120	F	83	100.0%	0.90 [0.77, 1.06]		
Total events Heterogeneity: Chi* = 4.58,	df = 2 (P = 0.10): I* = 56%	88		65					
Test for overall effect: Z = 1								0.5 0.7 1 1.5 Favours Comparators Favours Daptomycin	2
⊥ Fig. <del>3. Meta-analys</del>	sis of microbiological suc		ompar	ros da		cin wit	h comparator (		Field Code Changed
	STIC) based on microbiol								Formatted: Font: 10.5 pt
	iccess for Staphylococcus								
	Katz et al.'s study). (D) m							ne suggests no-	
	-		~						



Ob days Outbarray		mycin	Compa	rator	State of the second	Risk Ratio	1 Risk Ratio	Formatted: Font: (Default) Palatino Linotyp
C Study or Subgroup /		mycin Total		Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	12 pt
Aikawa 2013	2	88	2	22	7.2%	0.25 [0.04, 1.68]		1 12 pt
rbeit 2004	23	534	25	558	55.3%	0.96 [0.55, 1.67]		1
atz 2008	1	48	0	48	1.1%	3.00 [0.13, 71.85]	Ţ	1
onychev 2013	3	80	4	40	12.1%	0.38 [0.09, 1.60]		
ertel 2009	0	51	1	52	3.4%	0.34 [0.01, 8.15]	· · · · · · · · · · · · · · · · · · ·	
uist 2012	3	97	9	92	20.9%	0.32 [0.09, 1.13]		
otal (95% CI)		898		812	100.0%	0.71 [0.46, 1.10]	▲ /	
otal events	32		41				i i	
eterogeneity: Chi <sup>2</sup> = 5.60, df = 5 (P = 0.35); l <sup>2</sup> = 11%								-
est for overall effect: Z = 1.55 (P = 0.12)							0.02 0.1 1 10 / 50	
							Favours Daptomycin Favours Comparato	rs
						1996 - 19 19 19		
Study or Subgroup	Experim		Contr		Weight	Odds Ratio	Odds Ratio	Formatted: Font: (Default) Palatino Linotyp
kawa 2013	Events 8	Total 88		Total 22	19.4%	M-H, Fixed, 95% Cl 1.00 [0.20, 5.08]	M-H, Fixed, 95% Cl	—/ 12 pt
awa 2013 peit 2004	15	534	2	558	63.2%			i
tz 2008		48	0	48	3.0%			1
	4			48	3.0%	9.81 [0.51, 187.40]		-1
nychev 2013	6	80	1			3.16 [0.37, 27.21]		
rtel 2009	3	51	1	52	6.2%	3.19 [0.32, 31.70]	· · · · · · · · · · · · · · · · · · ·	
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al (95% CI)		801		720	100.0%	1.95 [1.04, 3.65]	● /	
al events	36		14				/	
erogeneity: Chi <sup>2</sup> = 2.42, df = 4 (P = 0.66); l <sup>2</sup> = 0%							0.005 0.1 1 10 / 2	+- )0
t for overall effect: Z = 2.08 (P = 0.04)								
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n <del>ts(excluded Katz et al's study) (C)D</del>	HISCONTINUE	ation	<del>due to</del>	AEs	<del>and all-</del>	<del>cause mortalit</del>	<del>y (D)creatine</del>	
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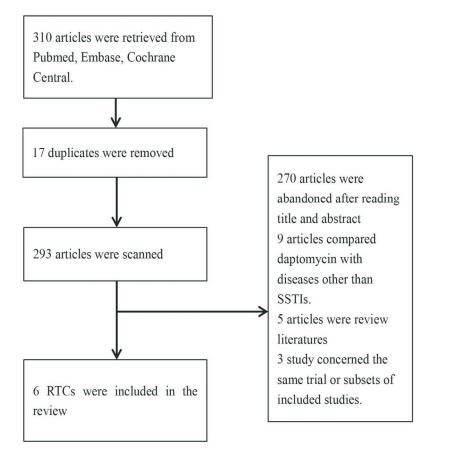


Fig. 1 Study flow diagram for relevant randomized controlled trials. 136x121mm (300 x 300 DPI)

		Daptom	vcin	Compa	rator		Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total			Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
	Aikawa 2013	61	71	17	21	2.4%	1.44 [0.40, 5.15]	
	Arbeit 2004	382	534	397	558	71.2%	1.02 [0.78, 1.33]	
	Katz 2008	36	48	42	48	6.8%	0.43 [0.15, 1.26]	
	Konychev 2013	65	80	29	40	4.7%	1.64 [0.67, 4.01]	
	Pertel 2009	47	51	46	52	2.3%	1.53 [0.41, 5.79]	· · · · · · · · · · · · · · · · · · ·
	Quist 2012	65	97	58	92	12.7%	1.19 [0.65, 2.17]	
	Total (95% CI)		881		811	100.0%	1.05 [0.84, 1.31]	<b>•</b>
	Total events	656		589				
	Heterogeneity: Chi <sup>2</sup> =				0%			0.2 0.5 1 2 5
۸	Test for overall effect	: Z = 0.45 (	P = 0.6	5)				Favours Comparator Favours Daptomycin
A								
		Daptomy		Compara			Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events			M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	Aikawa 2013	61	71	17	21	4.4%	1.44 [0.40, 5.15]	
	Arbeit 2004	372	446	384	456	75.1%	0.94 [0.66, 1.34]	
	Katz 2008	32	39	37	39	7.9%	0.25 [0.05, 1.28]	
	Konychev 2013	65	73	25	30	4.6%	1.63 [0.49, 5.44]	
	Pertel 2009 Quist 2012	47 53	50 58	46 41	51 47	3.3% 4.7%	1.70 [0.38, 7.54]	
	QUIST 2012	55	00	41	47	4.7 70	1.55 [0.44, 5.44]	
	Total (95% CI)		737		644	100.0%	0.99 [0.73, 1.35]	<b>•</b>
	Total events	630		550				
	Heterogeneity: Chi <sup>2</sup> =				1%		-	0.05 0.2 1 5 20
В	Test for overall effect:	Z = 0.04 (F	P = 0.97	)				Favours Comparators Favours Daptomycin
D								
		Daptom	ycin	Compa	rator		Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
	Aikawa 2013	55	71	17	21	15.5%	0.81 [0.24, 2.75]	
	Arbeit 2004	90	111	127	172	49.5%	1.52 [0.85, 2.72]	+ <b>-</b> -
	Katz 2008	32	39	37	39	17.4%	0.25 [0.05, 1.28]	
	Konychev 2013	65	73	8	9	4.1%	1.02 [0.11, 9.21]	
	Pertel 2009	47	50	46	51	7.2%	1.70 [0.38, 7.54]	
	Quist 2012	53	58	19	22	6.2%	1.67 [0.36, 7.69]	
	Total (95% CI)		402		314	100.0%	1.19 [0.77, 1.83]	*
	Total events	342	5 (D - 1	254	000			
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect:				0%0			0.05 0.2 1 5 20
С	restior overall ellect.	2=0.79 (	r = 0.4	5)				Favours Vancomycin Favours Daptomycin
C								
		Daptom		Compa			Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total				M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
	Aikawa 2013	55	71	17	21	18.8%	0.81 [0.24, 2.75]	
	Arbeit 2004	90	111	127	172	60.0%	1.52 [0.85, 2.72]	
	Katz 2008	32	39	37	39	0.0%	0.25 [0.05, 1.28]	
	Konychev 2013	65	73	8	9	5.0%	1.02 [0.11, 9.21]	
	Pertel 2009 Outlet 2012	47	50	46	51	8.7%	1.70 [0.38, 7.54]	
	Quist 2012	53	58	19	22	7.6%	1.67 [0.36, 7.69]	
	Total (95% CI)		363		275	100.0%	1.39 [0.88, 2.19]	-
	Total events	310		217	-			
	Heterogeneity: Chi <sup>2</sup> =				0%			0.1 0.2 0.5 1 2 5 10
-	Test for overall effect	Z=1.41 (	P = 0.1	6)				Favours Vancomycin Favours Daptomycin
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Fig.2 Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs): (A )Clinical success(ITT population) (B) Clinical success(CE population) (C) Daptomycin vs. Vancomycin for clinical success(CE population). (D) Daptomycin vs. Vancomycin for clinical success(CE population, excluded Katz et al's study). ITT, intention to treat; CE, clinically evaluable. The vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval. 158x210mm (300 x 300 DPI)

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		Daptom	iycin	Compar			Odds Ratio	Odds Ratio
-	Study or Subgroup	Events	Total	Events			M-H, Random, 95% Cl	
	Aikawa 2013	41	71	10	21	17.8%	1.50 [0.57, 3.99]	
	Arbeit 2004	309	365	340	396	34.9%	0.91 [0.61, 1.36]	
	Katz 2008	28	44	39	48	18.4%	0.40 [0.16, 1.04]	
	Konychev 2013	54	65	23	27	13.0%	0.85 [0.25, 2.96]	
	Pertel 2009	16	22	7	14	10.9%	2.67 [0.65, 10.88]	
	Quist 2012	56	57	39	43	5.1%	5.74 [0.62, 53.37]	
	Total (95% CI)		624	458	549	100.0%	1.05 [0.61, 1.79]	•
	Total events Heterogeneity: Tau <sup>2</sup> =	504 - 0.17: Chi	Z - 0 61		- 0.12)	18 - 4000		
	Test for overall effect:				- 0.13)	1,1 - 42.70		0.02 0.1 1 10
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		Daptomy		Compara			Odds Ratio	Odds Ratio
_	Study or Subgroup	Events		Events			M-H, Random, 95% Cl	M-H, Random, 95% Cl
	Aikawa 2013 Arboit 2004	41	71	10	21	25.0%	1.50 [0.57, 3.99]	
	Arbeit 2004 Katz 2008	191 24	226 31	205 27	243 28	37.8% 9.0%	1.01 [0.61, 1.67] 0.13 [0.01, 1.11]	
	Kalz 2008 Konvchev 2013	24 35	39	27	28 13	9.0%	3.89 [0.81, 18.65]	
	Pertel 2009	11	15	9	11	13.6%	2.29 [0.44, 11.92]	
	Total (95% CI)		382		316	100.0%	1.26 [0.61, 2.60]	•
							1120 [010 1] 2100]	-
		302		257				
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: :				= 0.11);	I² = 47%		0.02 0.1 1 10 Favours Comparators Favours Daptomy
	Total events Heterogeneity: Tau <sup>2</sup> =	0.30; Chi² Z = 0.63 (F	? = 0.53	df= 4 (P = )		I²= 47%		Favours Comparators Favours Daptomy
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect :	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptor	P = 0.53	df= 4 (P = ) Compa	rator		Odds Ratio	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Study or Subgroup	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom Events	P = 0.53	df = 4 (P = ) Compa Events	rator Total	Weight	M-H, Fixed, 95% Cl	Favours Comparators Favours Daptomy
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : <u>Study or Subgroup</u> Aikawa 2013	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom <u>Events</u> 41	P = 0.53 Nycin <u>Total</u> 71	df = 4 (P = ) Compa <u>Events</u> 10	rator <u>Total</u> 21	Weight 16.2%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Study or Subgroup Alkawa 2013 Arbeit 2004	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom <u>Events</u> 41 191	P = 0.53	df = 4 (P = ) Compa <u>Events</u> 10 205	rator Total 21 243	Weight 16.2% 75.8%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Study or Subgroup Alkawa 2013 Arbeit 2004 Katz 2008	0.30; Chi <sup>2</sup> Z = 0.63 (F Dapton Events 41 191 24	P = 0.53 Nycin Total 71 226 31	df = 4 (P = ) Compa <u>Events</u> 10 205 27	rator Total 21 243 28	Weight 16.2% 75.8% 0.0%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Study or Subgroup Alkawa 2013 Arbeit 2004	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom <u>Events</u> 41 191	P = 0.53	df = 4 (P = ) Compa <u>Events</u> 10 205	rator Total 21 243	Weight 16.2% 75.8% 0.0% 3.4%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Atkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009	0.30; Chi <sup>2</sup> Z = 0.63 (F <u>Daptor</u> <u>Events</u> 41 191 24 35	P = 0.53 Nycin <u>Total</u> 71 226 31 39 15	df = 4 (P = ) Compa Events 10 205 27 9	rator <u>Total</u> 243 28 13 11	Weight 16.2% 75.8% 0.0% 3.4% 4.6%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Study or Subgroup Alkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI)	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom <u>Events</u> 41 191 24 35 11	9 = 0.53 <b>iycin</b> <u>Total</u> 71 226 31 39	df = 4 (P = ) Compa Events 10 205 27 9	rator <u>Total</u> 243 28 13 11	Weight 16.2% 75.8% 0.0% 3.4%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92]	Favours Comparators Favours Daptomy Odds Ratio
	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 <b>Total (95% CI)</b> Total events	0.30; Chi <sup>2</sup> Z = 0.63 (F <u>Events</u> 41 191 24 35 11 278	e = 0.53 nycin <u>Total</u> 71 226 31 39 15 351	df = 4 (P = ) Compa <u>Events</u> 10 205 27 9 6 230	rator Total 243 28 13 11 288	Weight 16.2% 75.8% 0.0% 3.4% 4.6%	M-H, Fixed, 95% Cl 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Study or Subgroup Alkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI)	0.30; Chi <sup>2</sup> Z = 0.63 (F <u>Daptorr</u> <u>Events</u> 41 191 24 35 11 278 3.36, df=	P = 0.53 Total 71 226 31 39 15 351 3 (P = 1	df = 4 (P = ) Compa Events 10 205 27 9 6 230 0.34); P =	rator Total 243 28 13 11 288	Weight 16.2% 75.8% 0.0% 3.4% 4.6%	<u>M.H. Fixed, 95% Cl</u> 1.50 [U.57, 3.99] 1.01 [U.61, 1.67] 0.13 [U.01, 1.11] 3.89 [U.81, 18.65] 2.29 [U.44, 11.92] 1.25 [U.83, 1.89]	Pavours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% Cl
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3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Aikawa 2013 Arbeit 2004 Katy 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptorr Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptorr Events 45	P = 0.53 <u>Total</u> 71 226 31 39 15 <b>351</b> 3 (P = 1 P = 0.2 ycin <u>Total</u> 55	df = 4 (P = ) Compa 205 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 16	rator <u>Total</u> 21 243 28 13 11 <b>288</b> 11% <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>1</b>	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6%	<u>M.H. Fixed, 95% C1</u> 1.60 [0.67, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> Risk Ratio <u>M.H. Random, 95% C1</u> 0.97 [0.77, 1.22]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Atkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptorr Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptorr Events 45 21	P = 0.53 nycin <u>Total</u> 71 226 31 39 15 351 351 3 (P = 0.2 ycin <u>Total</u> 55 28	df = 4 (P = ) Compa 205 205 207 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 10 230 230 0.34); I <sup>2</sup> =	rator 21 243 28 13 11 288 11% 11% 11% 11% 11% 11% 13 13 13 13 14 15 16 17 17 18 18 19 19 19 19 19 19 19 19 19 19	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6% 30.8%	<u>M-H, Fixed, 95% C1</u> 1.50 [U.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> <b>Risk Ratio</b> <u>M-H, Random, 95% C1</u> 0.97 [0.77, 1.22] 1.08 [0.80, 1.46]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Aikawa 2013 Arbeit 2004 Katy 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptorr Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptorr Events 45	P = 0.53 <u>Total</u> 71 226 31 39 15 <b>351</b> 3 (P = 1 P = 0.2 ycin <u>Total</u> 55	df = 4 (P = ) Compa 205 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 16	rator <u>Total</u> 21 243 28 13 11 <b>288</b> 11% <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>11%</b> <b>1</b>	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6%	<u>M.H. Fixed, 95% C1</u> 1.60 [0.67, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> Risk Ratio <u>M.H. Random, 95% C1</u> 0.97 [0.77, 1.22]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Atkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptorr Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptorr Events 45 21	P = 0.53 nycin <u>Total</u> 71 226 31 39 15 351 351 3 (P = 0.2 ycin <u>Total</u> 55 28	df = 4 (P = ) Compa 205 205 207 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 10 230 230 0.34); I <sup>2</sup> =	rator <u>Total</u> 243 288 111 288 111% 111% total 19 36 28	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6% 30.8%	<u>M-H, Fixed, 95% C1</u> 1.50 [U.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> <b>Risk Ratio</b> <u>M-H, Random, 95% C1</u> 0.97 [0.77, 1.22] 1.08 [0.80, 1.46]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Total (95% CI) Total events	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptom Events 45 21 22 88	P = 0.53 nycin Total 71 226 31 39 15 351 351 3 (P = 1 P = 0.2 ycin Total 55 28 37 120	df = 4 (P = ) Compa Events 10 205 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 16 25 24 85	rator <u>Total</u> 243 283 13 11 288 11% 11% tors <u>Total</u> 19 36 28 83	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6% 30.8% 30.6%	<u>M.H. Fixed, 95% C1</u> 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> <b>Risk Ratio</b> <u>M.H. Random, 95% C1</u> 0.97 [0.77, 1.22] 1.08 [0.80, 1.46] 0.69 [0.51, 0.94]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Atkawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Atkawa 2013 Arbeit 2004 Katz 2008 Total (95% CI)	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom Events 41 191 24 35 11 278 3.36, df = Z = 1.05 ( Daptom Events 45 21 22 88	P = 0.53 nycin Total 71 226 31 39 15 351 351 3 (P = 1 P = 0.2 ycin Total 55 28 37 120	df = 4 (P = ) Compa Events 10 205 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara Events 16 25 24 85	rator <u>Total</u> 243 283 13 11 288 11% 11% tors <u>Total</u> 19 36 28 83	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6% 30.8% 30.6%	<u>M.H. Fixed, 95% C1</u> 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> <b>Risk Ratio</b> <u>M.H. Random, 95% C1</u> 0.97 [0.77, 1.22] 1.08 [0.80, 1.46] 0.69 [0.51, 0.94]	Pavours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI 0.1 0.2 0.5 1 2 5 11 Favours Comparators Favours Daptomy Risk Ratio M-H, Random, 95% CI
3	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Total (95% CI) Total events	0.30; Chi <sup>2</sup> Z = 0.63 (F Daptom Events 41 191 24 35 11 278 3.36, df Z = 1.05 ( Daptom Events 45 21 22 88 0.03; Chi <sup>2</sup>	P = 0.53 Nycin <u>Total</u> 71 2266 31 39 15 <b>351</b> 351 361 70 28 37 <b>120</b> 24 4.58,	df = 4 (P = Compa <u>Events</u> 100 205 27 9 6 230 0.34); I <sup>2</sup> = 9) Compara <u>Events</u> 16 25 24 65 df = 2 (P	rator <u>Total</u> 243 283 13 11 288 11% 11% tors <u>Total</u> 19 36 28 83	Weight 16.2% 75.8% 0.0% 3.4% 4.6% 100.0% Weight 38.6% 30.8% 30.6%	<u>M.H. Fixed, 95% C1</u> 1.50 [0.57, 3.99] 1.01 [0.61, 1.67] 0.13 [0.01, 1.11] 3.89 [0.81, 18.65] 2.29 [0.44, 11.92] <b>1.25 [0.83, 1.89]</b> <b>Risk Ratio</b> <u>M.H. Random, 95% C1</u> 0.97 [0.77, 1.22] 1.08 [0.80, 1.46] 0.69 [0.51, 0.94]	Favours Comparators Favours Daptomy Odds Ratio M-H, Fixed, 95% CI

Fig.3. Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological success for staphylococcus aureus. (C)microbiological success for staphylococcus aureus(excluded Katz et al's study). (D) microbiological success for MRSA. The vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval. 158x187mm (300 x 300 DPI)

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		Daptom	ycin	Compara	tor		Risk Ratio	Risk Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
	Aikawa 2013	19	88	6	22	17.3%	0.79 [0.36, 1.74]	
	Arbeit 2004	94	534	119	558	43.8%	0.83 [0.65, 1.05]	-
	Katz 2008	20	48	11	48	23.3%	1.82 [0.98, 3.37]	
	Konychev 2013	11	80	5	40	12.6%	1.10 [0.41, 2.95]	
	Pertel 2009	3	51	1	52	3.1%	3.06 [0.33, 28.45]	
	Total (95% CI)		801		720	100.0%	1.06 [0.71, 1.59]	+
	Total events	147		142	-			
	Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				0.15);	1*= 41%		0.05 0.2 1 5 20
A	Testior overall ellect.	Z = 0.30 (i	0.70	)				Favours Daptomycin Favours Comparate
		Daptom	ycin	Compara	tor		Risk Ratio	Risk Ratio
1	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
	Aikawa 2013	19	88	6	22	7.2%	0.79 [0.36, 1.74]	
	Arbeit 2004	94	534	119	558	87.1%	0.83 [0.65, 1.05]	<b></b>
	Katz 2008	20	48	11	48	0.0%	1.82 [0.98, 3.37]	
	Konychev 2013	11	80	5	40	5.0%	1.10 [0.41, 2.95]	
	Pertel 2009	3	51	1	52	0.7%	3.06 [0.33, 28.45]	
	Total (95% CI)		753		672	100.0%	0.85 [0.68, 1.07]	•
	Total events	127		131				
	Heterogeneity: Chi <sup>2</sup> =	1.62 df=	3 (P = 0	.65); I <sup>2</sup> = 0	%		-	
В	Test for overall effect:	Z = 1.39 (I	P = 0.17					0.05 0.2 1 5 20 Favours Daptomycin Favours Comparato
B _	Test for overall effect: Study or Subgroup	Z = 1.39 (I Daptom Events	P = 0.17 Nycin Total	Compara	Total		Risk Ratio M-H, Fixed, 95% Cl	
B _	Test for overall effect: Study or Subgroup Aikawa 2013	Z = 1.39 ( Daptom Events 2	P = 0.17 Nycin <u>Total</u> 88	Compara Events 2	Total 22	7.2%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68]	Favours Daptomycin Favours Comparato Risk Ratio
B -	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004	Z = 1.39 ( Daptom Events 2 23	P = 0.17 <b>Iycin</b> <u>Total</u> 88 534	Compara Events 2 25	Total 22 558	7.2% 55.3%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67]	Favours Daptomycin Favours Comparato Risk Ratio
B -	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008	Z = 1.39 ( Daptom Events 2 23 1	P = 0.17 Nycin <u>Total</u> 88 534 48	Compara Events 2 25 0	Total 22 558 48	7.2% 55.3% 1.1%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67] 3.00 [0.13, 71.85]	Favours Daptomycin Favours Comparato Risk Ratio
B -	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013	Z = 1.39 () Daptom Events 2 23 1 3	P = 0.17 <b>Total</b> 88 534 48 80	Compars Events 2 25 0 4	Total 22 558 48 40	7.2% 55.3% 1.1% 12.1%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67] 3.00 [0.13, 71.85] 0.38 [0.09, 1.60]	Favours Daptomycin Favours Comparato Risk Ratio
B 	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009	Z = 1.39 () Daptom Events 2 23 1 3 0	P = 0.17 Nycin <u>Total</u> 88 534 48 80 51	Compara Events 2 25 0 4 1	Total 22 558 48 40 52	7.2% 55.3% 1.1% 12.1% 3.4%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67] 3.00 [0.13, 71.85] 0.38 [0.09, 1.60] 0.34 [0.01, 8.15]	Favours Daptomycin Favours Comparato Risk Ratio
B _	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012	Z = 1.39 () Daptom Events 2 23 1 3	P = 0.17 <b>Total</b> 88 534 48 80 51 97	Compars Events 2 25 0 4	Total 22 558 48 40 52 92	7.2% 55.3% 1.1% 12.1% 3.4% 20.9%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67] 3.00 [0.13, 71.85] 0.38 [0.09, 1.60] 0.34 [0.01, 8.15] 0.32 [0.09, 1.13]	Favours Daptomycin Favours Comparato Risk Ratio
B _	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI)	Z = 1.39 () Daptom <u>Events</u> 2 23 1 3 0 3	P = 0.17 Nycin <u>Total</u> 88 534 48 80 51	Compara Events 2 25 0 4 1 9	Total 22 558 48 40 52 92	7.2% 55.3% 1.1% 12.1% 3.4%	M-H, Fixed, 95% Cl 0.25 [0.04, 1.68] 0.96 [0.55, 1.67] 3.00 [0.13, 71.85] 0.38 [0.09, 1.60] 0.34 [0.01, 8.15]	Favours Daptomycin Favours Comparato Risk Ratio
B 	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI) Total events	Z = 1.39 () Daptom <u>Events</u> 2 23 1 3 0 3 3 3	P = 0.17 Total 88 534 48 80 51 97 898	Compara 2 25 0 4 1 9	Total 22 558 48 40 52 92 812	7.2% 55.3% 1.1% 12.1% 3.4% 20.9%	M.H, Fixed, 95% Cl 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 [0.13, 71.85] 0.38 (0.09, 1.60] 0.34 (0.01, 8.15] 0.32 (0.09, 1.13] 0.71 [0.46, 1.10]	Favours Daptomycin Favours Comparato
B -	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI)	Z = 1.39 () Daptom <u>Events</u> 2 23 1 3 0 3 3 2 5.60, df=	P = 0.17 Total 88 534 48 80 51 97 898 5 (P = 0	Compara Events 2 25 0 4 1 9 41 1.35);   <sup>2</sup> = 1	Total 22 558 48 40 52 92 812	7.2% 55.3% 1.1% 12.1% 3.4% 20.9%	M.H, Fixed, 95% Cl 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 [0.13, 71.85] 0.38 (0.09, 1.60] 0.34 (0.01, 8.15] 0.32 (0.09, 1.13] 0.71 [0.46, 1.10]	Favours Daptomycin Favours Comparato Risk Ratio
_	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI) Total events Heterogeneity: Chi <sup>≠</sup> =	Z = 1.39 () Daptom <u>Events</u> 2 23 1 3 0 3 32 5.60, df= Z = 1.55 ()	P = 0.17 <b>Total</b> 88 534 48 80 51 97 <b>898</b> 5 (P = 0 P = 0.12	Compars <u>Events</u> 2 25 0 4 1 9 41 0.35);   <sup>2</sup> = 1 2)	Total 22 558 48 40 52 92 812 1%	7.2% 55.3% 1.1% 12.1% 3.4% 20.9%	M-H, Fixed, 95% Cl 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 [0.13, 71.85] 0.38 (0.09, 1.60] 0.34 (0.01, 8.15] 0.32 (0.09, 1.13] 0.71 [0.46, 1.10]	Risk Ratio M-H, Fixed, 95% Cl
_	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI) Total events Heterogeneity: Chi <sup>™</sup> = Test for overall effect:	Z = 1.39 () Daptom Events 2 23 1 3 0 3 3 2 5.60, df = Z = 1.55 () Experii	P = 0.17 Total 88 534 48 80 51 97 898 5 (P = 0 P = 0.12 mental	Compars Events 2 25 0 4 1 9 41 .35);   <sup>2</sup> = 1 2) Com	Total 22 558 48 40 52 92 812 1%	7.2% 55.3% 1.1% 12.1% 3.4% 20.9%	M-H, Fixed, 95% Cl 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 (0.13, 71.85) 0.38 (0.09, 1.60) 0.34 (0.01, 8.15) 0.32 (0.09, 1.13] 0.71 [0.46, 1.10]	Favours Daptomycin Favours Comparato
_	Test for overall effect: <u>Study or Subgroup</u> Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: <u>Study or Subgroup</u>	Z = 1.39 () Daptom <u>Events</u> 2 2 2 3 0 3 3 2 5.60, df= Z = 1.55 () <u>Experin</u>	P = 0.17 Total 88 534 48 80 51 97 898 5 (P = 0.12 mental Tota	Compara <u>Events</u> 2 25 0 4 1 9 41 1.35);   <sup>2</sup> = 1 2) Comi	Total 22 558 48 40 52 92 812 1% trol Tota	7.2% 55.3% 1.1% 12.1% 3.4% 20.9% 100.0%	M-H, Fixed, 95% Cl 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 (0.13, 71.85) 0.38 (0.09, 1.60) 0.34 (0.01, 8.15) 0.32 (0.09, 1.13] 0.71 (0.46, 1.10) Odds Ratio nt M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
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_	Test for overall effect: Study or Subgroup Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009 Quist 2012 Total (95% CI) Total events Heterogeneity: Chi <sup>₽</sup> = Test for overall effect: Study or Subgroup Aikawa 2013 Arbeit 2004 Katz 2008 Konychev 2013 Pertel 2009	Z = 1.39 () Daptom Events 2 2 2 2 3 0 3 3 2 5.60, df= Z = 1.55 () Experin Events 8 15 4	P = 0.17 <u>Total</u> 88 534 48 80 51 97 898 5 (P = 0.12 mental <u>Tota</u> 8 5 3 4 8 5 3 4 8 5 3 4 8 5 3 4 8 5 3 4 8 5 4 8 8 5 4 8 8 5 1 97 8 8 8 8 8 8 8 8 8 8 8 8 8	Compars Events 2 25 0 4 1 9 41 .35);   <sup>2</sup> = 1 2) Coni al Events 8 2 4 1 1 1 1 1 1 1 1 1 1 1 1 1	Total 22 558 48 40 52 92 812 1% trol Tota 2 55 4 4 5	7.2% 55.3% 1.1% 12.1% 3.4% 20.9% 100.0% 100.0%	M.H. Fixed, 95% CI 0.25 (0.04, 1.68) 0.96 (0.55, 1.67) 3.00 (0.13, 71.85) 0.38 (0.09, 1.60) 0.34 (0.01, 8.15) 0.32 (0.09, 1.13] 0.71 [0.46, 1.10] Odds Ratio t M.H. Fixed, 95% CI % 1.00 (0.20, 5.08) % 1.58 (0.71, 3.56) % 9.81 [0.51, 187.40] % 3.16 [0.37, 27.21] % 3.19 [0.32, 31.70]	Favours Daptomycin Favours Comparato
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Fig.4.Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (D)creatine phosphokinase(CPK) elevations regarded as adverse events. Vertical line suggests no difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI, confidence interval. 158x195mm (300 x 300 DPI)



Section/topic	#	Checklist item	Reported on page #	
TITLE				
Title	1	The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections: a meta-analysis of randomized controlled trials		
ABSTRACT				
Structured summary	2	Daptomycin, a cyclic lipopeptide that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens, has now, since 2003,been approved in more than seventy countries and regions to treat skin and soft tissue infections(SSTIs),the purpose of this meta-analysis, is to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs. <b>Design:</b> Meta-analysis of randomized controlled trials. <b>Data sources:</b> We thoroughly searched PubMed, Embase, Cochrane Central to identify relevant RCTs. Six RCTs, with a total of 1710 patients were included in this meta-analysis.		
INTRODUCTION         Rationale       3       Skin and soft tissue infections (SSTIs) are some of the most common infections, usually caused by gram-positive bacteria and are closely related to aging and obesity. Vancomycin and linezolid are the first-line.				
Rationale	3	Skin and soft tissue infections (SSTIs) are some of the most common infections, usually caused by gram-positive bacteria and are closely related to aging and obesity. Vancomycin and linezolid are the first-line antimicrobial agents for gram-positive infections, but recently cases of drug resistance have been repeatedly reported. Daptomycin, a cyclic lipopeptide, was approved ten years ago in the USA and is now cleared in more than seventy countries to treat gram-positive pathogens. To date, drug resistance of daptomycin remains rare. This is the first meta-analysis of randomized controlled trials of daptomcyin for skin and soft tissue infections. To our knowledge, this is also the first time daptomycin's potential myotoxicity was confirmed by meta-analysis. Comparative subgroup analyses of daptomycin versus comparators, in relation to treating staphylococcus aureus, to determine their microbiological success.		
Objectives	4	the purpose of this meta-analysis, is to compare the safety and efficacy of daptomycin with other antibiotics, especially with vancomycin which has long been considered the stand therapy for complicated SSTIs.		
METHODS				
Protocol and registration	5	Not registered		
Eligibility criteria	6	Inclusion criteria:(i)any randomized controlled trials that compare daptomycin with other antibiotics in treating SSTIs . (ii)included patients were of any age, any gender ,had a SSSI requiring intravenous antibiotic treatment .(iii)daptomycin intravenous infusion with any dosage, comparator antibiotics intravenous infusion with any dosage. Configure the second streatment dosage. Configure that targeted confirmed or probable infections with gram-negative aerobic and anaerobic		

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		pathogens were permitted.	
Information sources	7	Trials other than RCT were eliminated from consideration. Search terms included 'daptomycin', 'cubicin', 'lipopeptide', 'skin and soft tissue infections', 'cellulitis', 'wounds infection', 'abscess' and 'erysipelas', and they were combined by PICOs principle. No language restriction settled in the searching process. Statistical experts were consulted to make search strategy and emails were sent to corresponding authors of relevant studies and pharmaceutical companies resulted in information about any ongoing RCTs related to daptomycin.	
Search	8	Pubmed(up to September 2013), Embase(up to September 2013) and Cochrane Central(Issue 9 of 12, Sept 2013) were searched to find relevant clinical trials with a prespecified search strategy, which was revised appropriately through databases. Strategy for Pubmed: (((((daptomycin[Title/Abstract]) OR cubicin[Title/Abstract]) OR lipopeptide[Title/Abstract]) AND ((((((skin and soft tissue infections[Title/Abstract])) OR cellulitis[Title/Abstract]) OR wounds infection[Title/Abstract]) OR abscess[Title/Abstract]) OR erysipelas[Title/Abstract])) AND (((((randomized controlled trials[Title/Abstract]) OR randomized[Title/Abstract]) OR trial[Title/Abstract]) OR controlled[Title/Abstract]) OR clinical trials[Title/Abstract]) OR controlled[Title/Abstract])	
Study selection	9	A total of 310 articles were retrieved by means of electronic databases searches .After deleting duplicates, 293 articles were retained to read the title and abstract. Full text of 23 articles were then obtained for further review after the scanning. Additionally, emails were sent to Aastrazeneca China which is in charge of marketing of daptomycin in China, we were informed that daptomycin for SSTIs phase-3 clinical trial was completed in China, yet so far no data published. Finally,6 out of the 23 articles reached the inclusion criteria.	
Data collection process	10	Two review authors (WSZ and TZH) independently extracted data with a prespecified data extraction form specifically designed for this review. The data extraction included the following detailed imformation:1.year of publication, clinical settings2.the number of intention to treat(ITT) and clinically evaluable(CE) patients3.descriptions of dose, route, and timing of daptomycin and other antibiotics.	
Data items	11	Clinical success was defined as the test subjects exhibiting biological indicators that no further antibiotic therapy was required at TOC visit. Microbiological success was defined as eradication of pathogen (present at admission but absent from culture at TOC visit) or presumed eradication of the pathogen (no material available for culture but patient was deemed as cured or improved by the study investigator at TOC visit. Secondary outcomes were proportions of patients with treatment-related adverse events, discontinuation due to adverse events and all-cause mortality, and cases of CPK elevation.	
Risk of bias in individual studies	12	In terms of methodology, all the six enrolled trials were deemed eligible, with a Jadad score ≥2.Allocation concealment was not thoroughly stated in all the 6 included trials. Funnel plots were performed to check publication bias(standard error of logOR plotted against OR).	
Summary measures	13	Compare the odds ratio between the two groups.	
Synthesis of results	14	Values of I <sup>2</sup> less than 25 percent were deemed to have low heterogeneity, and a fixed-effect model for meta-analysis was then used. Values of I <sup>2</sup> between 25 and 75 percent were considered to represent moderate levels of heterogeneity, and a random effects model was then utilized.	



Section/topic	#	Checklist item	Reported on page #	
Risk of bias across studies	15	Heterogeneity assessment was performed using the chi-squared test, where P value less than 0.1 was considered as significance set. A funnel plot was applied to check for publication bias and I <sup>2</sup> was applied to estimate the total variation attribute to heterogeneity among studies.		
Additional analyses	16	No additional analyses		
RESULTS				
Study selection	17	A total of 310 articles were retrieved by means of electronic databases searches .After deleting duplicates, 293 articles were retained to read the title and abstract. Full text of 23 articles were then obtained for further review after the scanning. Additionally, emails were sent to Aastrazeneca China which is in charge of marketing of daptomycin in China, we were informed that daptomycin for SSTIs phase-3 clinical trial was completed in China, yet so far no data published. Finally,6 out of the 23 articles reached the inclusion criteria.		
Study characteristics	18	All of the 6 studies were multi-center trials.[18-23] The total number of patients of included trials were 1710.Only adults were enrolled in the included trials, and one trial only aimed at elder patients aged at least 65 years[18]. In terms of methodology, all the six enrolled trials were deemed eligible, with a Jadad score ≥2.Allocation concealment was not thoroughly stated in all the 6 included trials.		
Risk of bias within studies	19	Daptomycin, at a dosage of 4 mg/kg/day was administered in five trials; at the same drug at a dosage of 10 mg/kg/day was administered in another study		
Results of individual studies	20	The pooling result of ITT population showed clinical success rate of daptomycin was similar to that of comparator drugs at TOC visit(6 RCTs, 1674 patients, OR=1.05, 95% CI 0.84-1.31, p=0.65, l <sup>2</sup> =0)Pooling the result of CE population also demonstrated no difference existed in clinical success rate between daptomycin and other antibiotics for treating SSTIs (6 RCTs, 1381 patients, OR=0.99,95% CI 0.73-1.35, p=0.97, l <sup>2</sup> =0). In terms of daptomycin vs vancomycin subgroup, clinical success rate of daptomycin was higher(not significantly) than that of vancomycin(6 RCTs, 716 patients, OR=1.19,95% CI 0.77-1.83, p=0.43, l <sup>2</sup> =0). the pooling result showed the microbiological success rate of daptomycin was similar to that of comparator drugs(6 RCTs, 1173 patients, OR= 1.05,95% CI 0.61-1.79, p=0.86, l <sup>2</sup> =42%). In terms of microbiological success rate for staphylococcus aureus(Methicillin-susceptible and Methicillin-resistant), the pooling result demonstrated no significant difference existed between daptomycin and comparator drugs(5 RCTs, 698 patients, Odds Ratio=1.59,95% CI 0.61-2.60, p=0.53, l <sup>2</sup> =47%). For MRSA infections, data was successfully extracted from 3 studies, the overall heterogeneity was expectedly high, under which circumstance random model was applied, and the result showed the success rate of daptomycin was slightly lower than that of comparator drugs(3 RCTs, 203 patients, OR=0.91,95% CI 0.77-1.06, p=0.10, l <sup>2</sup> =56%). In terms of treatment-related adverse events(AEs), daptomycin and comparator drugs(5 studies, 1521 patients, Odds Ratio=1.06,95% CI 0.71-1.59, p=0.76, l <sup>2</sup> =41%)		
Synthesis of results	21	Z=0.45,i^2=0		
Risk of bias across studies	22	Katz et al's study was found to have considerable heterogeneity in our analyses due to a high dose of daptomycin with a short duration		
Additional analysis	23	No additional analysis only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

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4	DISCUSSION					
5 6 7	Summary of evidence	24	By our analyses, suffice it to say daptomycin have a not inferior efficacy and equivalent safety to comparator drugs, especially when compared with vancomycin which has been considered as the standard therapy for cSSTIs.			
8 9 1( 12 13 14 14	Limitations	25	There are several limitations exist in our meta-analysis. First of all, none of the six included RCTs were participants-blinded or personnel-blinded, thus, performance bias was unpredictable. Furthermore, Arbeit et al's study had dominant influence on overall clinical success rate analysis both on ITT and CE populations, as it weighed more than 70% in these two analyses. Additionally, too few of our data analyses reached statistical significance, which led to insufficient credibility to draw conclusions for some potentially disputable issues.			
16	Conclusions	26	Based on the present evidence, daptomycin is a promising new agent for gram-positive infections like SSTIs, and more high-quality RCTs are expected to explore it's potentiality.			
19	FUNDING					
20 21	Funding	27	No funding.			
200 27 28 30 31 32 30 31 32 30 31 32 30 31 32 30 37 38 39 40 41 42 42 42 42 42	From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org. Page 2 of 2					
46 47 48 48	3		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			