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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^2=0%);daptomycin versus vancomycin subgroup(OR=1.19,95%CI0.77-1.83,p=0.43,I^2=0%);overall microbiological success(OR=1.05,95%CI0.61-1.79,p=0.86,I^2=42%);microbiological success of daptomycin versus comparators for Staphylococcus Aureus (SA,OR=1.05,95%CI0.61-2.60,p=0.53,I^2=47%),for MRSA(OR=0.90,95%CI0.77-1.06,p=0.20,I^2=56%).And daptomycin tended to have a similar treatment-related adverse events(AEs) incidence in comparison with other antibiotics(OR=1.06,95%CI0.71-1.59,p=0.76,I^2=41%).There was a trend that daptomycin might cause less

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

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 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 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).

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 Fig.1. 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 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 to be eligible,with a Jadad score ≥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

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

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 with comparator drugs at TOC visit(6 RCTs,1674 patients, OR=1.05, 95% CI 0.84-1.31,p=0.65,I^2=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^2=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^2=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^2=47%;Fig.3. 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^2=11%;Fig.3. 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^2=56%;Fig.3. D).

Adverse events outcomes and mortality outcomes

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^2=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^2=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^2=11%;Fig.4. C).CPK elevations considered as adverse events were compared between daptomycin and comparator drugs.Significant more patients had CPK elevation in daptomyicn group than in comparator drugs group(5 RCTs,1521 patients,Odds Ratio=1.95,95%CI 1.04-3.65,p=0.04,I^2=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^2=0) and CE population(OR=0.99,95%CI0.73-1.35,p=0.97,I^2=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^2=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^2=47%).However,after we excluded Katz et al's study which used a different dosage,the heterogeneity declined,the result turned to favor daptomycin(OR=1.25,95%CI0.83-1.89,p=0.86,I^2=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^2=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

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^2=41%).But after we excluded Katz et al's study,daptomycin tended to have less treatment-related AEs(OR=0.85,95%CI0.68-1.07,p=0.86,p=0.17,I^2=0).Daptomycin tended to have less patients associated with discontinuation or death(OR=0.71,95%CI0.46-1.10,p=0.12,I^2=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^2=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 daptomycin group had anaphylactic shock,and resolved 4 days after 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^2=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^2=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

directly comparing linezolid with daptomycin for MRSA infections. What's more,cost-effcectiveness 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^2) 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 for 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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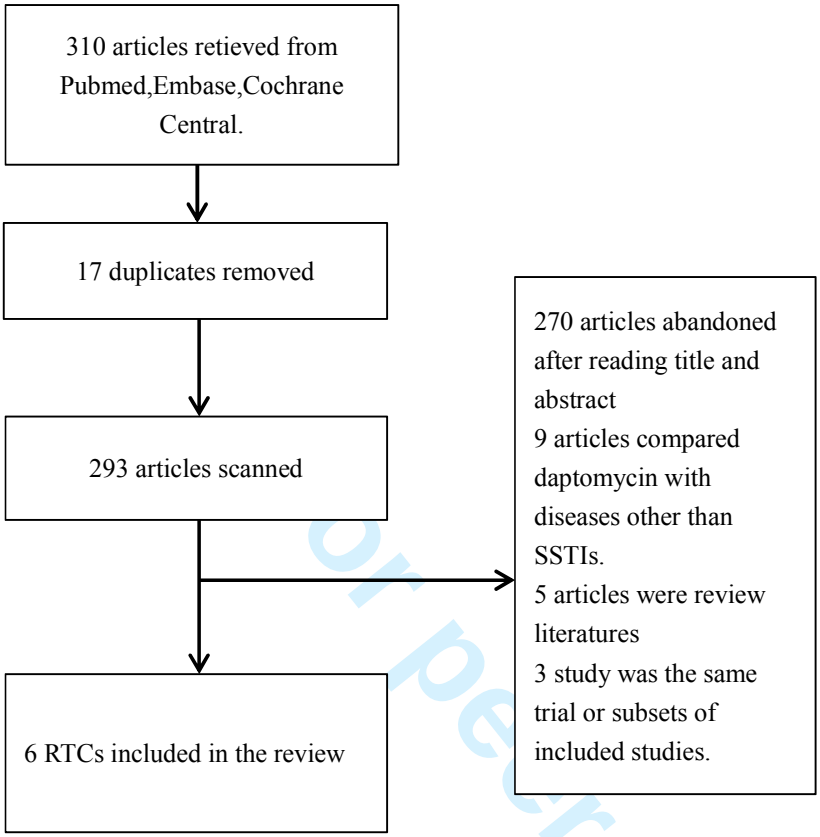


Fig.1. Study flow diagram for relevant randomized controlled trials.

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

Reference	Design	Jadad Score	Patients Characteristics	Group		Populaton	
				Daptomycin (dose,treatment duration)	Comparator (type,dose, treatment duraion)	ITT,n(Daptomycin vs comparator)	CE,n(daptomycin vs comparator)
Aikawa 2013	Multicenter Evaluator-Blinded RCT	2	N=101,PTs aged ≥20 years,SSTIs,MRSA 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)
Konychev 2013	Multi-center 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	Multicenter 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	Multicenter Evaluator-Blinded RCT	2	N=103,Patients ≥ 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	Multicenter 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	Multicenter Evaluator-Blinded RCT	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.

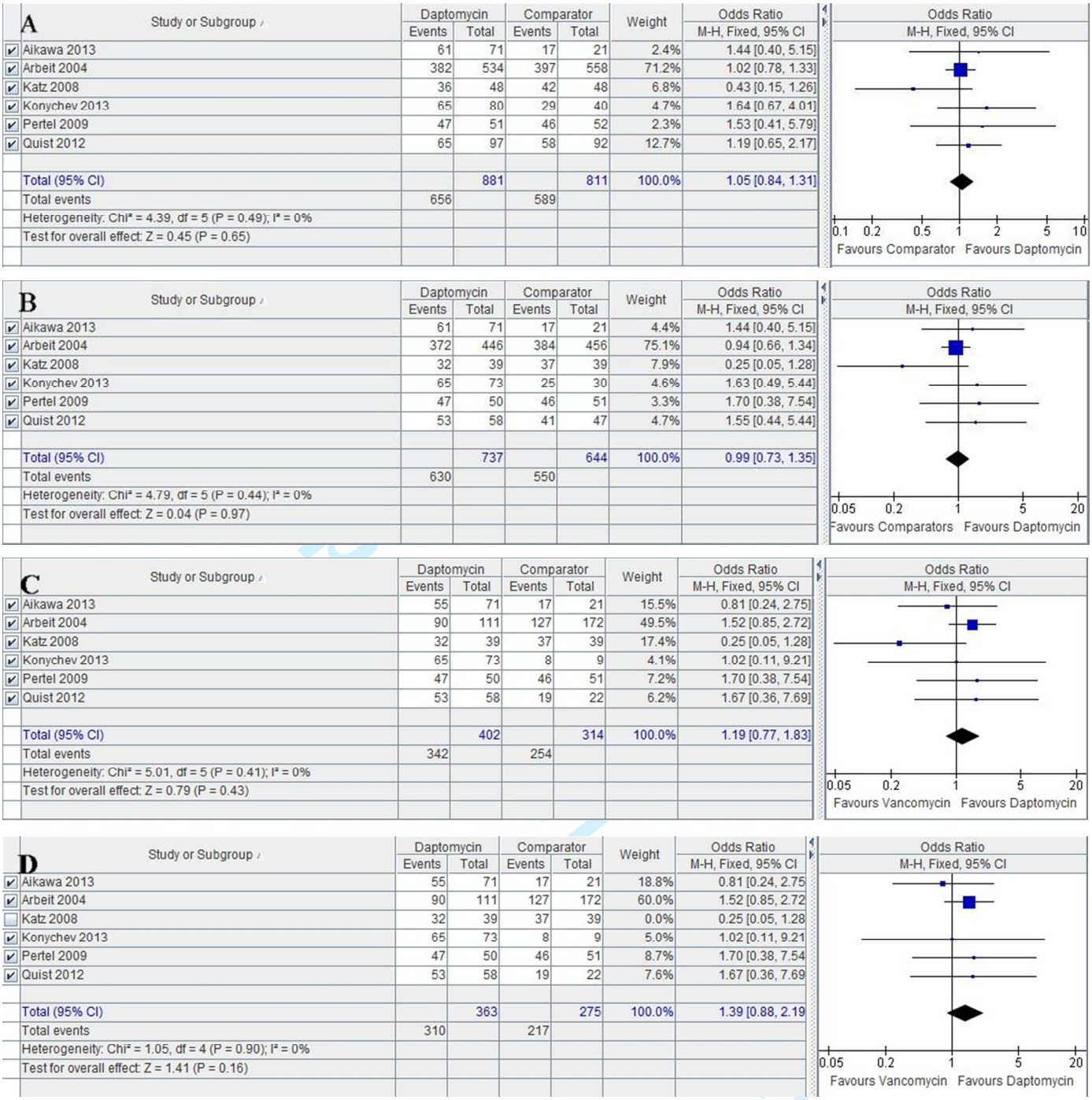
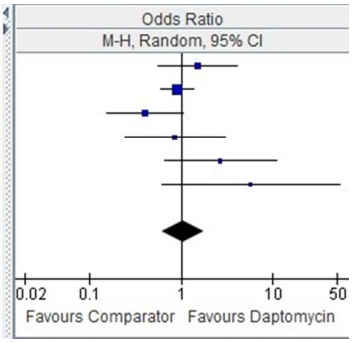


Fig.2. Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs): (A)Clinical success(ITT population) (B) Clinical success(CE population) (C) Daptomycin vs Vancomycin for clinical success(CE population). (D) Daptomycin vs Vancomycin for clinical success(CE population,excluded Katz et al.'s study). ITT,intention to treat;CE,clinically evaluable. 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.

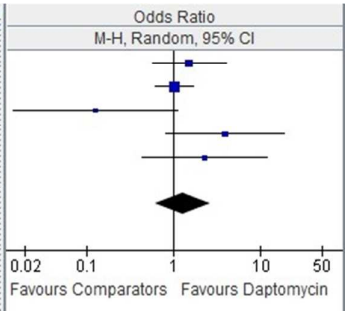
A

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
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		549	100.0%	1.05 [0.61, 1.79]
Total events	504		458			
Heterogeneity: Tau² = 0.17; Chi² = 8.61, df = 5 (P = 0.13); I² = 42%						
Test for overall effect: Z = 0.18 (P = 0.86)						



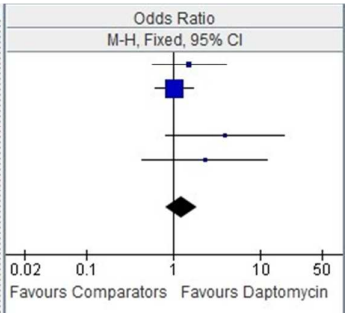
B

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
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]
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]
Total (95% CI)		382		316	100.0%	1.26 [0.61, 2.60]
Total events	302		257			
Heterogeneity: Tau² = 0.30; Chi² = 7.58, df = 4 (P = 0.11); I² = 47%						
Test for overall effect: Z = 0.63 (P = 0.53)						



C

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio 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]
Total (95% CI)		351		288	100.0%	1.25 [0.83, 1.89]
Total events	278		230			
Heterogeneity: Chi² = 3.36, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.05 (P = 0.29)						



D

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparators Events	Comparators Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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		65			
Heterogeneity: Chi² = 4.58, df = 2 (P = 0.10); I² = 56%						
Test for overall effect: Z = 1.27 (P = 0.20)						

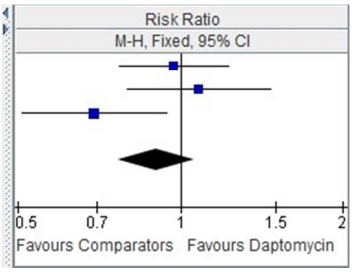


Fig.3. Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological success for Staphylococcus Aureus. (C)microbiological success for Staphylococcus Aureus(excluded Katz et al.'s study). (D) microbiological success for MRSA. 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.

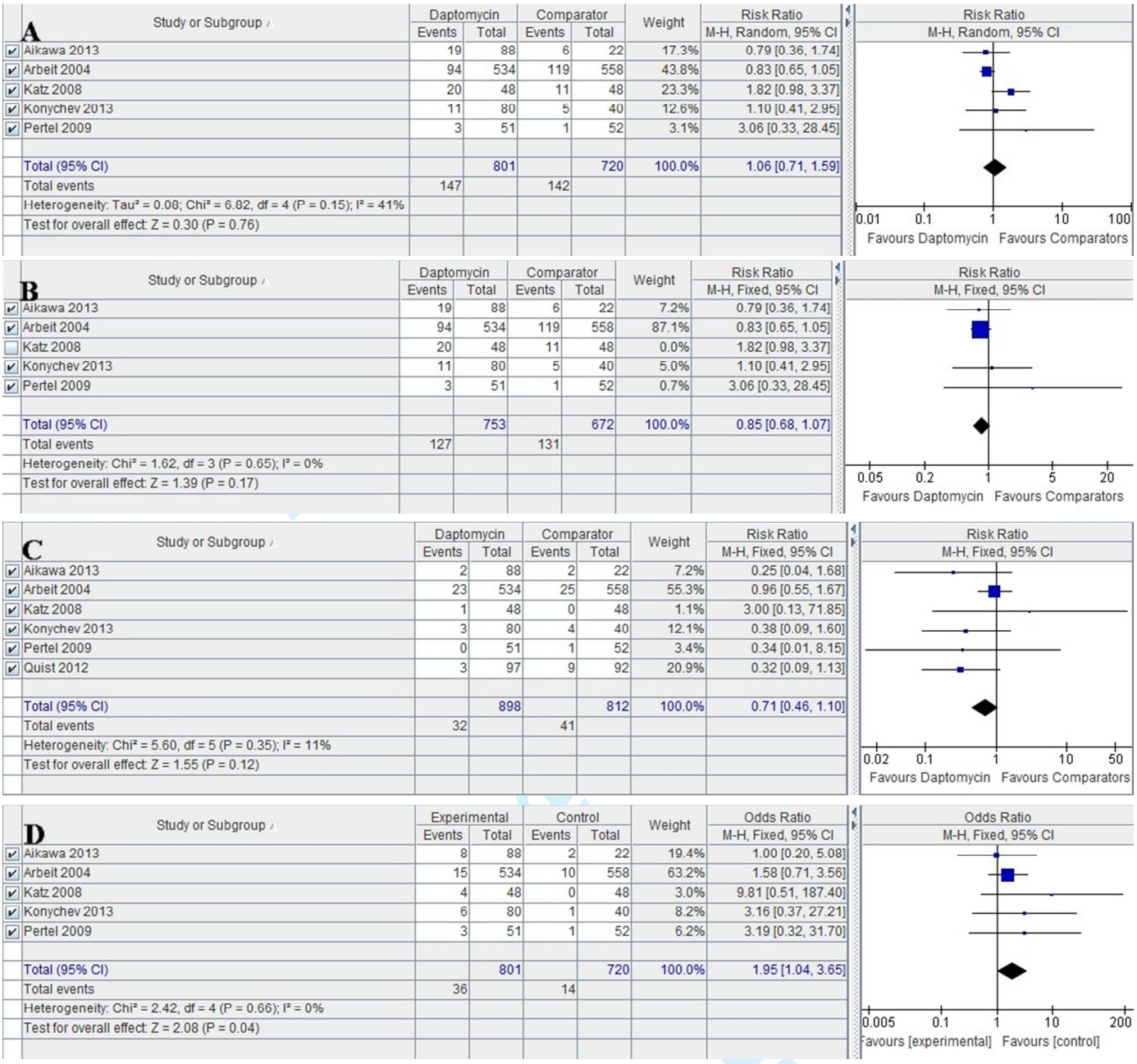


Fig.4.Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (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.

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^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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	20	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			
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.	

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

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BMJ Open

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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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < ANAESTHETICS, Infectious diseases & infestations < DERMATOLOGY, EPIDEMIOLOGY

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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Key words: Skin infections, Soft tissue infections, Daptomycin, Vancomycin, 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^2=0%); daptomycin versus vancomycin subgroup (OR=1.19,95% CI 0.77-1.83,p=0.43,I^2=0%);overall microbiological success(OR=1.05,95% CI 0.61-1.79, p=0.86,I^2=42%);microbiological success of daptomycin versus comparators for Staphylococcus Aureus (SA,OR=1.05,95% CI0.61-2.60,p=0.53,I^2=47%),for MRSA(OR=0.90,95% CI 0.77-1.06, p=0.20, I^2=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^2=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^2=11%). Significantly more patients in daptomyicn 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^2=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

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

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.

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^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 a fixed-effect model for meta-analysis was then used. Values of I^2 between 25 and 75 percent were considered to represent moderate levels of heterogeneity, and a random effects model was then utilized. Values of I^2 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.

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 ≥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

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.

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

Reference	Design	Jadad Score	Patients Characteristics	Group		Population	
				Daptomycin(dose, treatment duration)	Comparator (type, dose, treatment duration)	ITT,n(Daptomycin vs comparator)	CE,n(daptomycin vs comparator)
Konychev 2013[18]	Multicenter 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 q12h for 5–14 days or 10–28 days with bacteraemia	120(81 vs 39)	103(73 vs 30)
Aikawa 2013[19]	Multicenter Evaluator-Blinded RCT	2	N=101,PTs aged ≥20 years, SSTIs, MRSA 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)	74(55 vs 19)
Quist 2012[20]	Multicenter Evaluator-Blinded RCT	3	N=194, Adults requiring i.v. antimicrobial treatment for	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)

			cSSTIs				
Pertel 2009[21]	Multicenter Evaluator-Blinded RCT	2	N=103,Patients ≥ 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[22]	Multicenter 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[23]	Multicenter Evaluator-Blinded RCT	2	N=1092,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.

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^2=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^2=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. 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^2=0;Fig.2 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^2=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^2=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^2=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^2=56%;Fig.3. D).

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^2=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^2=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^2=11%;Fig.4 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^2=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^2=0) and CE population(OR=0.99,95% CI0.73-1.35,p=0.97,I^2=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^2=42%). Staphylococcus aureus(SA) was the main pathogen for SSTIs, the microbiological success rate for SA showed no significant difference

between the two groups(OR=1.26,95% CI 0.61-2.60,p=0.53,I^2=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^2=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^2=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^2=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^2=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^2=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

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^2=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^2=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

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^2) 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

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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Figure legends

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

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.

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.

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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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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Key words: Skin infections, Soft tissue infections, Daptomycin, Vancomycin, Staphylococcus aureus

Word count:3421 words

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 haves been repeatedly reported.

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- Daptomycin,a cyclic lipopeptide, was approved ten years ago in the USA and is now cleared in more than seventy countries~~approved~~ to treat gram-positive pathogens. ~~for about 10 years and~~ 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. Comparative ~~S~~subgroup analyses of daptomycin and vancomycin ~~clinical success~~ were conducted to determine the drug's rate of clinical success~~between daptomycin and vancomycin~~; ~~microbiological success~~the same was done for ~~of~~ daptomycin versus comparators, in relation to treating ~~for Staphylococcus~~ staphylococcus ~~Aureus~~ aureus, to determine their microbiological success~~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~~ has now, since 2003,been approved in more than ~~70~~ seventy countries and regions.~~Daptomycin was approved~~ to treat skin and soft tissue infections(SSTIs) ~~since 2003~~, ~~in~~ the purpose of this meta-analysis, ~~we try~~ 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 ~~were not inferior to~~was on a par with and maybe better than other first-line antibiotics for treating SSTIs ~~in the matter of~~as

shown by odds ratio(OR) for clinical success(OR=1.05,95% CI 0.84-1.31,p=0.65,I^2=0%); daptomycin versus vancomycin subgroup(OR=1.19,95% CI 0.77-1.83,p=0.43,I^2=0%);overall microbiological success(OR=1.05,95% CI0.61-1.79,p=0.86,I^2=42%);microbiological success of daptomycin versus comparators for Staphylococcus Aureus (SA,OR=1.05,95% CI0.61-2.60,p=0.53,I^2=47%),for MRSA(OR=0.90,95% CI 0.77-1.06,p=0.20,I^2=56%). ~~And~~ 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^2=41%). ~~There was a~~ 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^2=11%). Significantly more patients in daptomyicn group had CPK elevation ~~in daptomyicn group~~ 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^2=0).

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

INTRODUCTION

Skin and soft tissue infections (SSTIs) are among some of the most common infections, usually with mild to moderate severity, ~~however~~distressingly, the incidence of SSTIs has rapidly increased in US in the Community Acquired(CA)-MRSA era ~~and~~, which appears to disproportionately affect certain populations.[1]~~.~~ SSTIs ~~, was~~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

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infection which severe enough to cause disability of extremitiesy ~~disability~~ or even death. ~~According to~~ Because of their different clinical characteristics~~s~~, SSTIs were divided into uncomplicated SSTIs and complicated SSTIs(cSSTIs). cSSTIs were defined as specific source of infection or opportunistically pathogenic situations ~~like~~ 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 ~~7~~seven to ~~14~~fourteen days of therapy ~~was~~ are recommended.[4 5] ~~.~~The majority of community-acquired(CA) SSTIs in western countries were caused by ~~S~~staphylococcus aureus and beta-haemolytic streptococci.[2 6]~~.~~ Staphylococcus aureus ~~was~~is also the main pathogen of Hospital-Acquired SSTIs, where Methicillin-resistant Staphylococcus aureus(MRSA) ~~took~~exists in ~~a~~ high proportions.[3 7]~~.~~

Vancomycin ~~was~~ has been regarded as mainstay of parenteral therapy for MRSA infections for decades. ~~, but r~~Recently, however, ~~–~~its minimum inhibitory concentrations(MICs) in MRSA ~~–~~ ~~are elevating~~have been increasing, and linezolid resistance has been reported likewise.[8]~~.~~ In the fighting against MRSA, ~~D~~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~~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 ~~S~~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 ~~therapy~~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 ~~, which~~and this can be reversed when the therapy end~~s~~ed.[15] ~~.In an era~~With 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 therap~~y~~ies ~~w~~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.

~~In this~~ The purpose of this meta-analys~~e~~is~~,we try~~s to compare the safety and efficacy of daptomycin with other antibiotics to treat SSTIs, ~~especially with~~such 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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METHODS

Data sources~~.~~

~~We searched~~ 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, ~~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. ~~We~~Statistical 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 ~~that concerns~~related to daptomycin.

Study selection

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 impl~~y~~ied~~ing~~ 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, ~~we~~they were

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discussed thoroughly to reach consensus. Inclusion criteria:(i)~~A~~any randomized controlled trials that compare daptomycin with other antibiotics in treating SSTIs . (ii)~~I~~included patients were of any age, any gender ,had a SSSI requiring ~~i.v.~~ intravenous antibiotic treatment .(iii)~~D~~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.

Qualitative assessment

The ~~M~~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~~which evaluates randomization and blinding. If ~~elucidation of~~ 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 ~~as~~ a trial of high methodological quality.

Data extraction

Two review authors (WSZ and TZH) independently extracted data with a prespecified data extraction form specifically ~~tuned~~ designed for this review. The data extraction included the following detailed imformation:1.~~Y~~year of publication, clinical settings2.~~T~~the number of intention to treat(ITT) and clinically evaluable(CE) patients3.~~D~~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, the studies' corresponding authors were ~~we attempted to~~ contacted ~~the corresponding authors~~ to request these information. If this was not successful, ~~intention to treat (~~ITT~~)~~ analysis~~is~~ were conducted for all dichotomous outcomes (e.g. clinical success, microbiological success, treatment-related adverse events, all-cause mortality).

Analysed Outcomes

The ~~P~~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 ~~had resolution of signs and symptoms~~ 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 ~~pathogen~~but 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 ~~were~~ was assessed in population, methodology, and in the intervention and outcome measures of each study to ~~see~~ evaluate whether pooling of results was feasible. Heterogeneity assessment was performed using the

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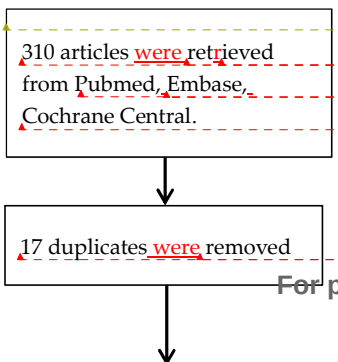
chi-squared test, where P value less than 0.1 was considered as significance set. A ~~F~~funnel plot was applied to check for publication bias ~~.Moreover,~~and I^2 was applied to estimate the total variation attribute to heterogeneity among studies.[17]~~.~~ Values of I^2 less than 25 percent were deemed to have low heterogeneity, and ~~we would then use~~ a fixed-effect model for meta-analysis was then used. Values of I^2 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^2 higher than 75 percent indicating high levels of heterogeneity, in which case ~~we did not perform~~ no meta-analysis was performed. 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 Fig.1~~.~~ shows the whole scanning and selection process. A total of 310 articles were retrieved by means of electronic databases searches ~~of the databases~~.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. ~~Meanwhile we wrote~~ Additionally, emails were sent to Aastrazeneca China which is in charge of ~~selling of~~marketing of daptomycin in China, we were informed that daptomycin for SSTIs phase-3 clinical trial was completed in China ~~has been finished,~~ yet so far no data published. Finally, ~~6~~ 6 out of the 23 articles reached the inclusion criteria.



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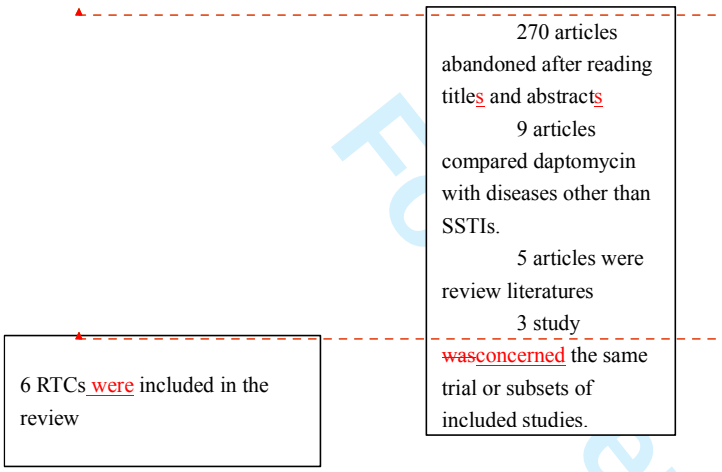

Fig. 1

~~Study characteristics~~

The main characteristics of the 6 RCTs(type of study design, Jadad score, characteristi~~ti~~cs 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 ~~to be~~ 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) .All the six studies were neither participants-blinded nor personnel-blinded. First, ~~O~~overall clinical success analysis were performed on both ITT and CE populations; ~~,~~second, ~~M~~microbiological success was analyzed on microbiologically evaluable population~~.~~; third, ~~A~~adverse events(AEs) were analyzed

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on ITT population. Note that, thirty-six patients with no MRSA identified as causative pathogen(of these, ~~33~~thirty-three ~~patients~~ were receiving daptomycin and ~~3~~three were ~~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,[18-20 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.~~Vancomycin was the only ~~C~~comparator drug~~s~~ used in ~~2~~two trials. ~~was vancomycin alone~~[19 21]. In one trial, ~~C~~comparator drugs were vancomycin and teicoplanin. ~~in one trial~~[20] . In two trials, ~~C~~comparaetor drugs were vancomycin and SSPs.~~semi-synthetic penicillins in two trials~~[18 23] . The ~~I~~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 ~~the patients~~ they already had at least 4 or 5 days of intravenous therapy and ~~had~~ demonstrated ~~a~~ clear~~ly~~ 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 ~~one~~another study.[22]. In all the six trials, ~~And~~ comparator 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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Reference	Design	Jadad Score	Patients Characteristics	Daptomycin(dose, treatment duration)	Comparator (type, dose, treatment duraion)	ITT,n(Daptomycin vs comparator)	CE,n(daptomycin vs comparator)
Konychev 2013[18]	Multicenter 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 q12h for 5–14 days or 10–28 days with bacteraemia	120(81 vs 39)	103(73 vs 30)
Arikawa 2013[19]	Multicenter Evaluator-Blinded RCT	2	N=101,PTs aged ≥20 years, SSTIs, MRSA 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)	74(55 vs 19)
Quist 2012[20]	Multicenter 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[21]	Multicenter Evaluator-Blinded RCT	2	N=103,Patients ≥ 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[22]	Multicenter 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[23]	Multicenter Evaluator-Blinded RCT	2	N=1092,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)

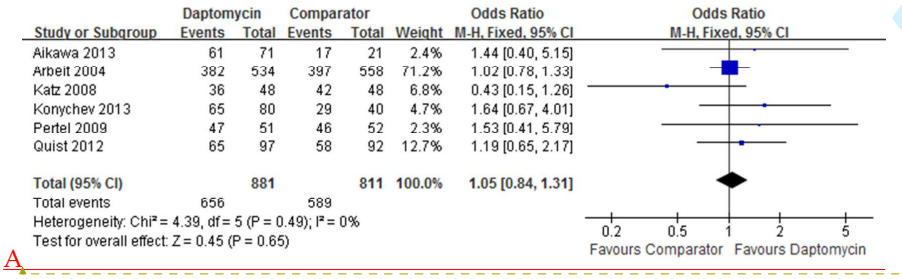
Jadad Score ranges from zero to five,score higher than two was considered as trial of high methodological quality. ITT, intention to treat; CE, clinically evaluable.

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 ~~with~~ 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^2=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^2=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. Since Katz et~~.~~ al's study used a higher dosage than the other included studies, after ~~we excluded Katz et.al's study~~its exclusion, the pooling result showed a trend favor~~s~~ing daptomycin(5 RCTs,638 patients, OR=1.39,95% CI 0.88-2.19,p=0.16,I^2=0;Fig.2~~.~~ D)



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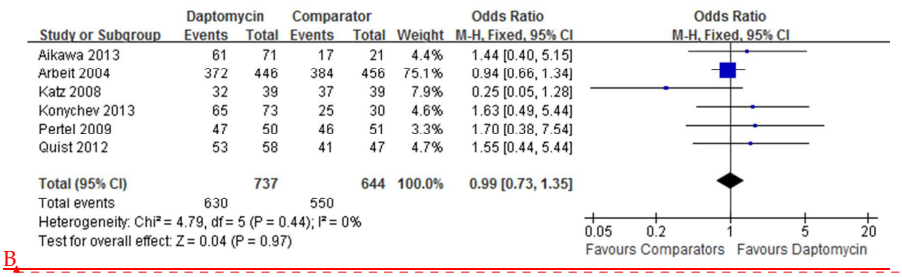

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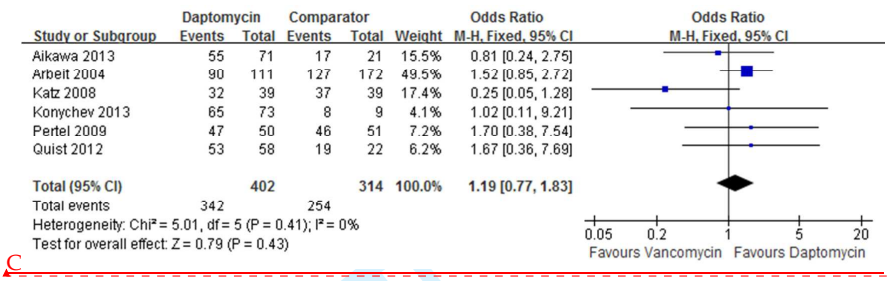

Fig.2

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~~(not significantly)~~ to that of comparator drugs(6 RCTs, 1173 patients, OR= 1.05,95% CI 0.61-1.79,p=0.86,I^2=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 ~~S~~staphylococcus ~~A~~aureus subgroup was not extractable in Quist et al.'s study[20]. In terms of microbiological success rate for ~~S~~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^2=47%;Fig.3, B). After ~~we excluded~~the exclusion of Katz

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et al.'s study, the overall heterogeneity dropped, ~~nevertheless,~~but the result remained unchanged(4 RCTs,639 patients, Odds Ratio=1.25,95%CI0.83-1.89,p=0.29,I^2=11%;Fig.3. C).For MRSA infections, ~~we successfully extracted~~ 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=0.9~~1~~0,95% CI 0.77-1.06,p=0.1~~2~~0,I^2=56%;Fig.3. D).

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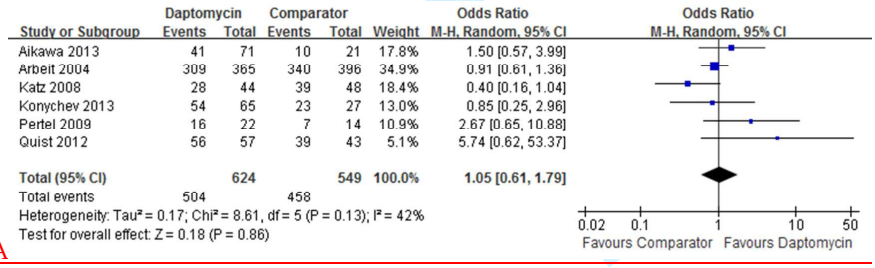

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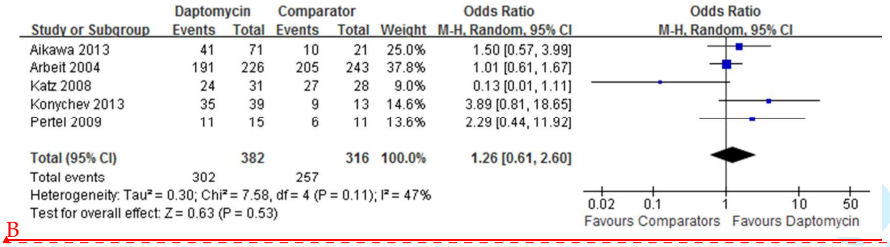

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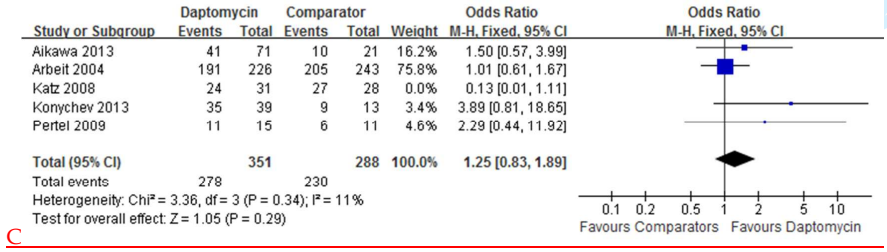

C

D

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. 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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Adverse events outcomes and mortality outcomes

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In terms of treatment-related adverse events(AEs),oneQuist et al's study was excluded from pooling result on behalf of thatbecause no information was given about whether adverse events were treatment-related or not.[20]. There was Nno 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^2=41%; Fig.4. A). After we excluded Katz et al.'s study was excluded, there was a dramatic decline in the heterogeneity declined dramatically, and the result turned changed to favor daptomycin(4 RCTs,1425 patients, Odds Ratio=0.85,95% CI 0.68-1.07, p=0.17, I^2=0;Fig.4. B).

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Discontinuation due to AEs and all-cause mortality during treatment were rare in the six included studies. No death reported in 3three studies,[18 21 22] ,while another study reported discontinuation due to AEs and death togethercombined.[20] .On account of the above reasons, we pooled discontinuation due to AEs and all-cause mortality were pooled together. With Aa 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^2=11%;Fig.4. C).A comparison of CPK elevations considered as adverse events were compared between daptomycin and comparator drugs. yielded that

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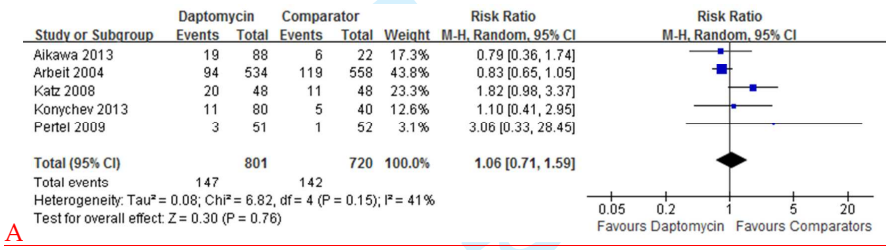
~~S~~significant~~ly~~ more patients had CPK elevation in the daptomyicn group than in the comparator drugs group(5 RCTs,1521 patients, Odds Ratio=1.95,95% CI 1.04-3.65,p=0.04,I^2=0;Fig.4. D).



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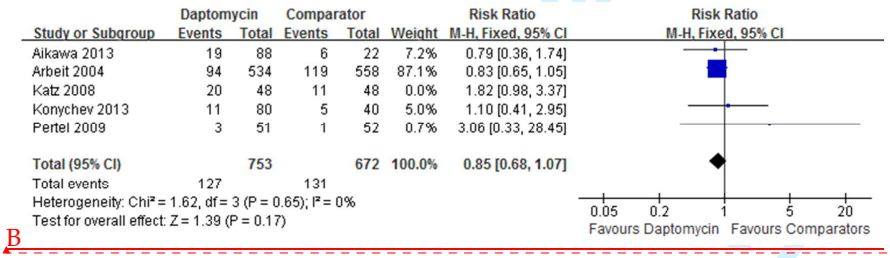

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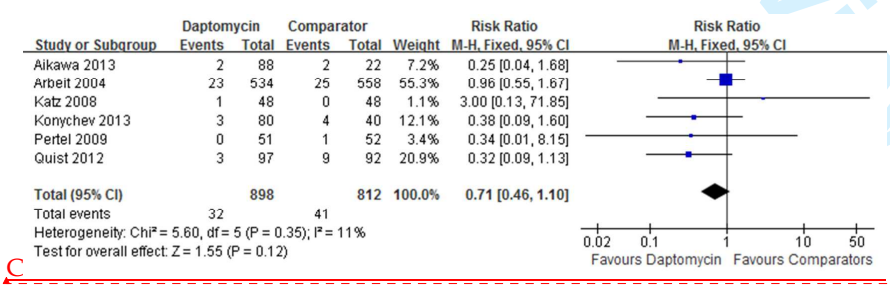

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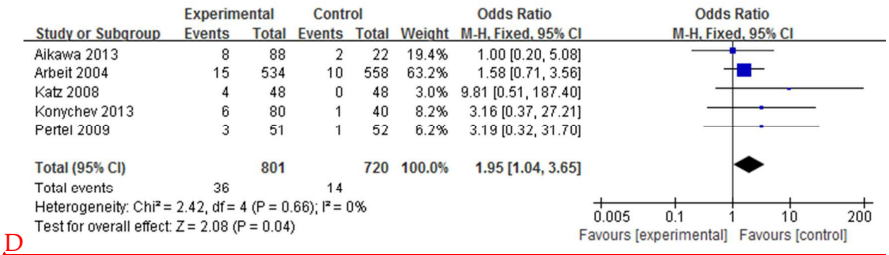

D

~~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~~

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~~phospholkinase(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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DISCUSION

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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 ~~shortages~~limitations found in the previous meta-analysis. First ~~of all~~, it enrolled only four trials, in which three ~~of them~~ 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. ~~ ;plus~~In addition, there was one historically controlled trial(not randomized) which was excluded in ~~our~~this review~~(not randomized)~~.[25] Besides the previous three RCTs ~~,we enrolled another~~ three more RCTs ~~which~~ 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, ~~ under the circumstance of~~because of the drug-resistant urgency. However, there were only a handful RCTs available, and a distinct lack of high quality meta-analysis ~~that 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^2=0) and CE population(OR=0.99,95% CI0.73-1.35,p=0.97,I^2=0) was equivalent to that of other drugs used to ~~for~~ treat~~ing~~ 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) ~~of daptomycin~~ led to ~~lower~~ reduced clinical ~~success rate~~ and ~~lower~~ reduced microbiological success rate in daptomycin, when compared with comparator drugs.[22] ~~.~~This ~~S~~shortened therapy duration could possibly have ~~had~~ undermined the efficacy of daptomycin and brought about some clinical heterogeneity, ~~which~~ result~~ed~~ing 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^2=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^2=47%). However, after ~~we excluded~~ the exclusion of Katz et al's study which used a different dosage, the heterogeneity declined, and the result ~~turned~~tended to favor daptomycin(OR=1.25,95% CI 0.83-1.89,p=0.86,I^2=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,I^2=56%).Only 203 patients were enrolled in the MRSA subgroup analysis, ~~meanwhile~~while simultaneously the heterogeneity was high; ~~,~~thus, ~~we should interpret~~ the result should be interpreted prudently. That ~~T~~the included studies were conducted in ~~different~~diverse countries ~~and~~ at different ~~years~~times, and that there was a lack of uniformity in~~as well as different~~ epidemiologic characteristics for ~~in~~ each trial, ~~also~~ should have some confounding impacts on the final results. Not all the included studies reported ~~D~~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] ~~.~~Furthermore, ~~T~~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^2=41%). ~~But~~However, 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^2=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^2=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^2=0),but on most occasions, ~~CPK level~~it declined to normal levels during or after the therapy ~~in most of the occasions~~. Therefore, one may conclude that ~~D~~daptomycin 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 ~~88~~eighty-eight patients in daptomycin group ~~had~~experienced 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 ~~on~~to 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 ~~S~~staphylococcus aureus and ~~E~~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 ~~give some evidence~~ provide helpful data to clinicians. The ~~D~~daptomycin vs. vancomycin subgroup analysis of our review found out that daptomycin tended to exhibit higher clinical success rate in comparison ~~with~~to vancomycin(OR=1.19,95% CI 0.77-1.83,p=0.43,I^2=0).And ~~after we~~ exclud~~ed~~ing Katz et al.' study, the pooling resulted ~~turned to~~ favored daptomycin even further(OR=1.39,95% CI 0.88-2.19,p=0.16,I^2=0)

Daptomycin ~~was~~is mainly metabolized by kidneys, Aikawa et al. demonstrated that patients with mild to moderate renal impairment ,when compared with patients ~~with~~having 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.[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] ~~,b~~But ~~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,v~~Vancomycin, however, has potential renal toxicity, which limit~~ed~~s it's usage with patients with renal impairment , ~~where~~and for whom daptomycin might be an eligible alternative agent. In recent years, vancomycin-resistant ~~S~~staphylococcus aureus (VRSA) infection cases have been~~were~~ 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^2) 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 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 ~~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 ~~lead~~led to insufficient credibility to draw couclusions for some potentially disputable issues.

Conclusions

~~However,through~~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. ~~In summary,b~~Based on the present evidence, daptomycin is a promising new agent for gram-positive infections like SSTIs, and ~~we expect~~ more high-quality RCTs are expected to explore it's potentiality.

Acknowledgements ~~We want to~~ All thanks to Professor Tomoko Yoshinari and ~~Professor~~ Ricardo Chaves,who were corresponding authors of two included studies. In the data extraction process, ~~we wrote~~ several emails were sent to them to ~~seek help for~~ deal~~ing~~ with problems ~~we had about~~involving some of the data. ~~They both~~Their patiently replie~~d~~s ~~us and~~ provided ~~us with~~ valuable help. ~~We also want to t~~Thanks, too, to Eileen Mcintyre ~~from~~ of Cubist Pharmaceutical, ~~we wrote email to him~~ to whom emails inquiries were sent regarding ~~ask about if there were~~ any ongoing clinical trials of daptomycin for skin and soft tissue infections. ~~He~~She wrote to Aastrazeneca China which is in charge of selling of daptomycin in China ~~about~~concerning our inquiry and the latter ~~contacted us and patiently answered our questions~~proved to be another helpful source of information. Finally, thanks to Helen Cadogan, English teacher and editor for the editorial assistance.

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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.

Conflict of interests ~~No conflict of interest~~ None declared.

Data sharing statement No additional data are available.

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

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.

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.

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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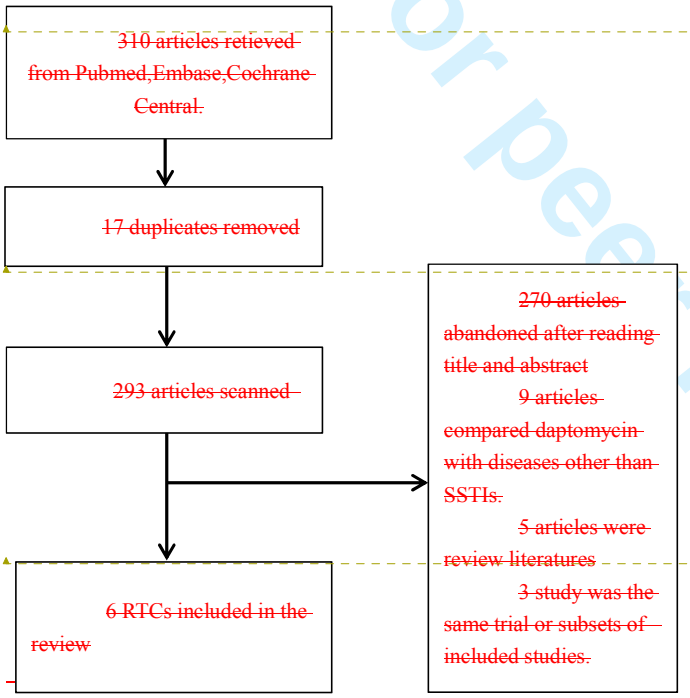

Fig.1. Study flow diagram for relevant randomized controlled trials.

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

				Group		Populaton	
Refere nce	Design	Jadad Score	Patients Characteristics	Daptomycin (dose,treatment duration)	Comparator (type,dose, treatment duraion)	ITT,n(Daptomycin vs comparator)	CE,n(daptomycin vs comparator)

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Aikaw a 2013	Multicenter Evaluator-Blinded RCT	2	N=101,PTs aged ⩾20 years,SSTIs,MRSA 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)
Jonyev 2013	Multi-center 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	Multicenter 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	Multicenter Evaluator-Blinded RCT	2	N=103,Patients ⩾ 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	Multicenter 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	Multicenter Evaluator-Blinded RCT	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.

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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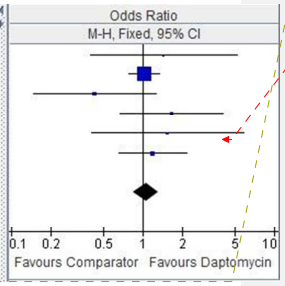
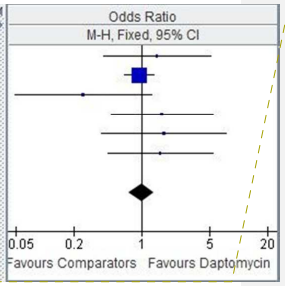
A

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio 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]
Total events	656		589			
Heterogeneity: Chi² = 4.39, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						



B

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
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	47	50	46	51	3.3%	1.70 [0.38, 7.54]
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: Chi² = 4.79, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						



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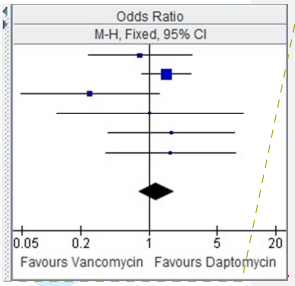
Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aikawa 2013	55	71	17	21	15.5%	0.81 [0.24, 2.75]
Arbeit 2004	90	111	127	172	49.5%	1.52 [0.85, 2.72]
Katz 2008	32	39	37	39	17.4%	0.25 [0.05, 1.28]
Konychev 2013	65	73	8	9	4.1%	1.02 [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		254			
Heterogeneity: Chi² = 5.01, df = 5 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						



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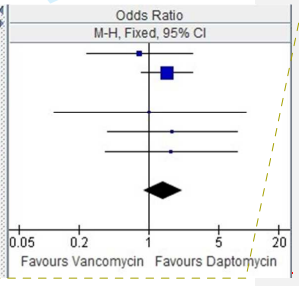
Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aikawa 2013	55	71	17	21	18.8%	0.81 [0.24, 2.75]
Arbeit 2004	90	111	127	172	60.0%	1.52 [0.85, 2.72]
Katz 2008	32	39	37	39	0.0%	0.25 [0.05, 1.28]
Konychev 2013	65	73	8	9	5.0%	1.02 [0.11, 9.21]
Pertel 2009	47	50	46	51	8.7%	1.70 [0.38, 7.54]
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: Chi² = 1.05, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						



~~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. 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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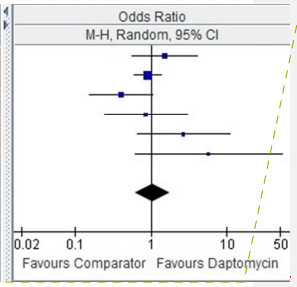
A	Daptomycin		Comparator		Weight	Odds Ratio
Study or Subgroup	Events	Total	Events	Total		M-H, Random, 95% CI
Aikawa 2013	41	71	10	21	17.8%	1.50 [0.57, 3.99]
Arbeit 2004	309	365	340	396	34.9%	0.91 [0.61, 1.36]
Katz 2008	28	44	39	48	18.4%	0.40 [0.16, 1.04]
Konychev 2013	54	65	23	27	13.0%	0.85 [0.25, 2.96]
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		549	100.0%	1.05 [0.61, 1.79]
Total events	504		458			
Heterogeneity: Tau² = 0.17; Chi² = 8.61, df = 5 (P = 0.13); I² = 42%						
Test for overall effect: Z = 0.18 (P = 0.86)						



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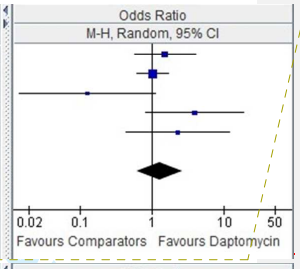
B	Daptomycin		Comparator		Weight	Odds Ratio
Study or Subgroup	Events	Total	Events	Total		M-H, Random, 95% CI
Aikawa 2013	41	71	10	21	25.0%	1.50 [0.57, 3.99]
Arbeit 2004	191	226	205	243	37.8%	1.01 [0.61, 1.67]
Katz 2008	24	31	27	28	9.0%	0.13 [0.01, 1.11]
Konychev 2013	35	39	9	13	14.6%	3.89 [0.81, 18.65]
Pertel 2009	11	15	6	11	13.6%	2.29 [0.44, 11.92]
Total (95% CI)		382		316	100.0%	1.26 [0.61, 2.60]
Total events	302		257			
Heterogeneity: Tau² = 0.30; Chi² = 7.58, df = 4 (P = 0.11); I² = 47%						
Test for overall effect: Z = 0.63 (P = 0.53)						



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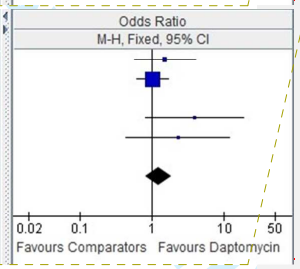
C	Daptomycin		Comparator		Weight	Odds Ratio
Study or Subgroup	Events	Total	Events	Total		M-H, Fixed, 95% CI
Aikawa 2013	41	71	10	21	16.2%	1.50 [0.57, 3.99]
Arbeit 2004	191	226	205	243	75.8%	1.01 [0.61, 1.67]
Katz 2008	24	31	27	28	0.0%	0.13 [0.01, 1.11]
Konychev 2013	35	39	9	13	3.4%	3.89 [0.81, 18.65]
Pertel 2009	11	15	6	11	4.6%	2.29 [0.44, 11.92]
Total (95% CI)		351		288	100.0%	1.25 [0.83, 1.89]
Total events	278		230			
Heterogeneity: Chi² = 3.36, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.05 (P = 0.29)						



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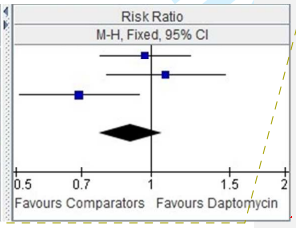
D	Daptomycin		Comparators		Weight	Risk Ratio
Study or Subgroup	Events	Total	Events	Total		M-H, Fixed, 95% CI
Aikawa 2013	45	55	16	19	32.6%	0.97 [0.77, 1.22]
Arbeit 2004	21	28	25	36	30.0%	1.08 [0.80, 1.46]
Katz 2008	22	37	24	28	37.4%	0.69 [0.51, 0.94]
Total (95% CI)		120		83	100.0%	0.90 [0.77, 1.06]
Total events	88		65			
Heterogeneity: Chi² = 4.58, df = 2 (P = 0.10); I² = 56%						
Test for overall effect: Z = 1.27 (P = 0.20)						



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~~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. Vertical line suggests no~~

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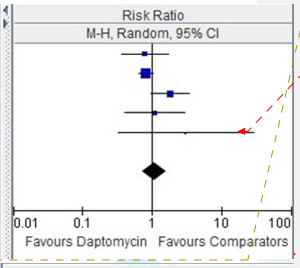
~~difference between daptomycin and comparator drugs. The size of each square represents the proportion of information given by each trial. CI,confidence interval.~~

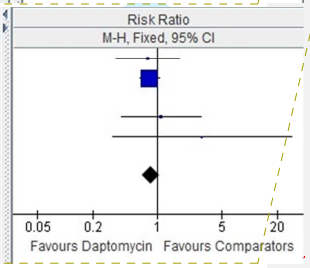
A

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Risk Ratio 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: Tau² = 0.08; Chi² = 6.82, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 0.30 (P = 0.76)						



B

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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: Chi² = 1.62, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.17)						



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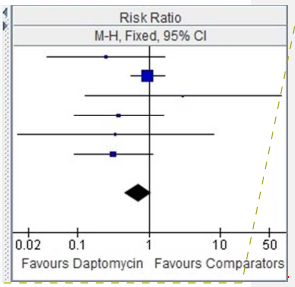
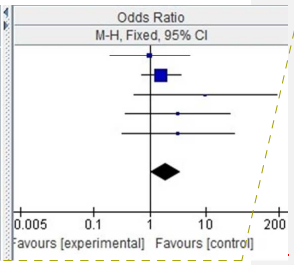
C

Study or Subgroup	Daptomycin Events	Daptomycin Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aikawa 2013	2	88	2	22	7.2%	0.25 [0.04, 1.68]
Arbeit 2004	23	534	25	558	55.3%	0.96 [0.55, 1.67]
Katz 2008	1	48	0	48	1.1%	3.00 [0.13, 71.85]
Konychev 2013	3	80	4	40	12.1%	0.38 [0.09, 1.60]
Pertel 2009	0	51	1	52	3.4%	0.34 [0.01, 8.15]
Quist 2012	3	97	9	92	20.9%	0.32 [0.09, 1.13]
Total (95% CI)		898		812	100.0%	0.71 [0.46, 1.10]
Total events	32		41			
Heterogeneity: Chi² = 5.60, df = 5 (P = 0.35); I² = 11%						
Test for overall effect: Z = 1.55 (P = 0.12)						



D

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aikawa 2013	8	88	2	22	19.4%	1.00 [0.20, 5.08]
Arbeit 2004	15	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]
Konychev 2013	6	80	1	40	8.2%	3.16 [0.37, 27.21]
Pertel 2009	3	51	1	52	6.2%	3.19 [0.32, 31.70]
Total (95% CI)		801		720	100.0%	1.95 [1.04, 3.65]
Total events	36		14			
Heterogeneity: Chi² = 2.42, df = 4 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						



~~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 phospholkinase(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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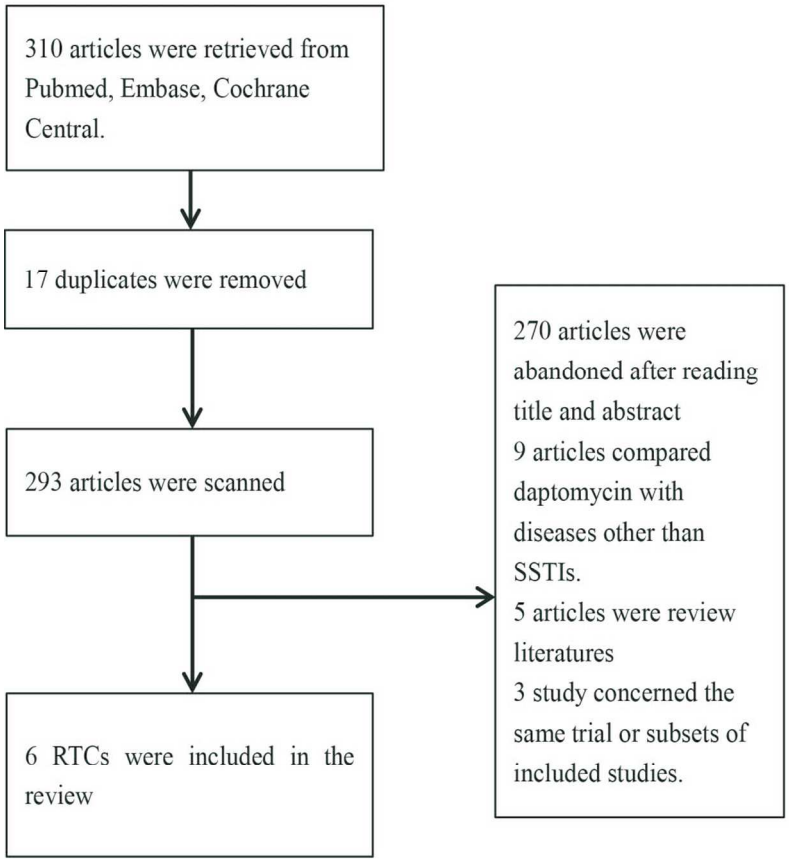

Fig. 1 Study flow diagram for relevant randomized controlled trials.
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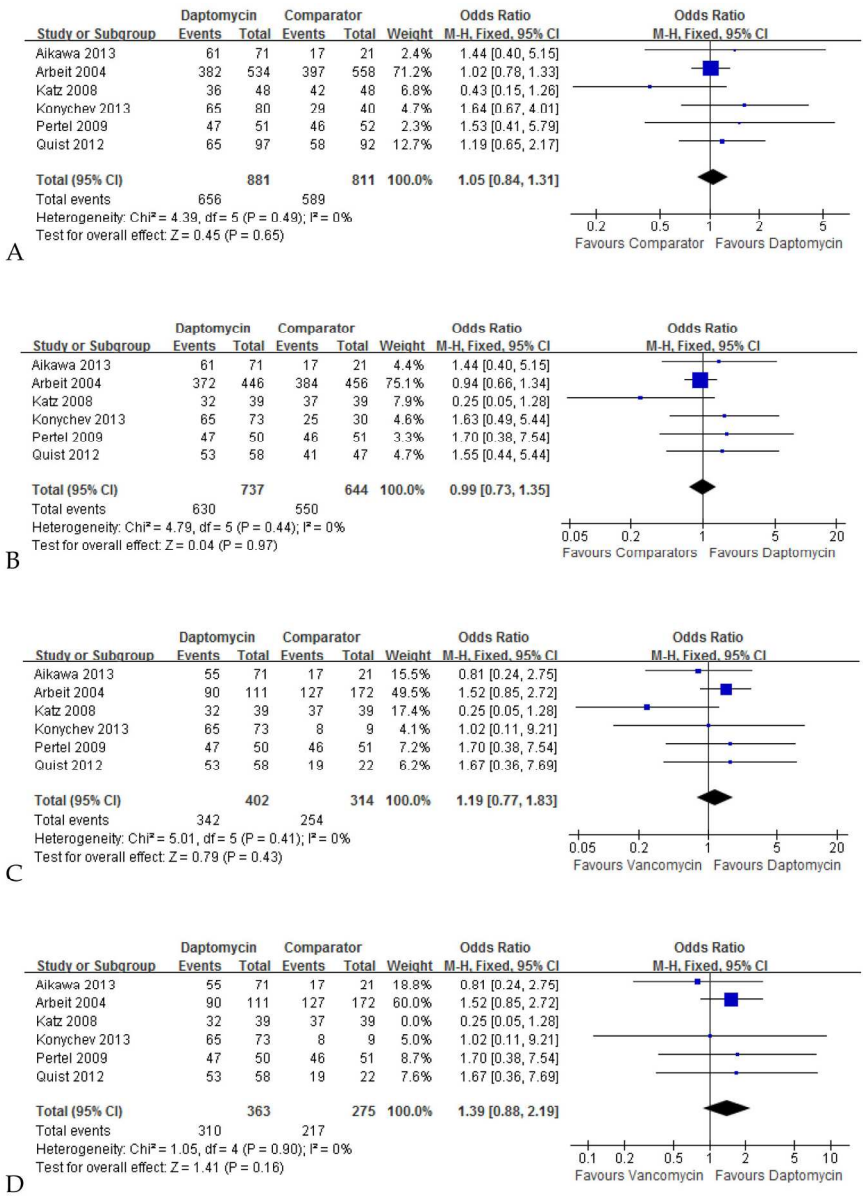

Fig.2 Meta-analysis of clinical success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs): (A)Clinical success(ITT population) (B) Clinical success(CE population) (C) Daptomycin vs. Vancomycin for clinical success(CE population). (D) Daptomycin vs. Vancomycin for clinical 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.
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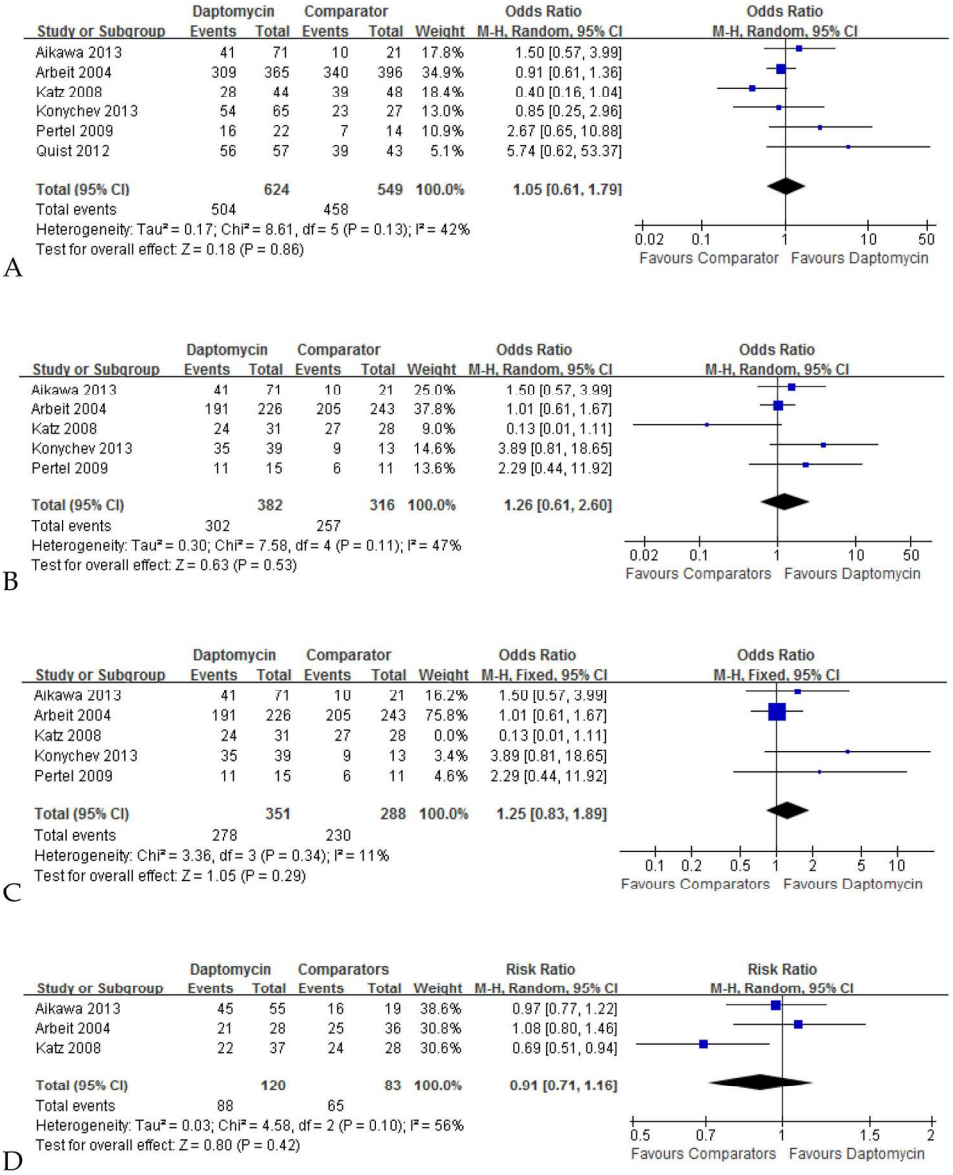

Fig.3. Meta-analysis of microbiological success compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on microbiologically evaluable population:(A)overall microbiological success (B) microbiological success for staphylococcus aureus. (C)microbiological success for 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.
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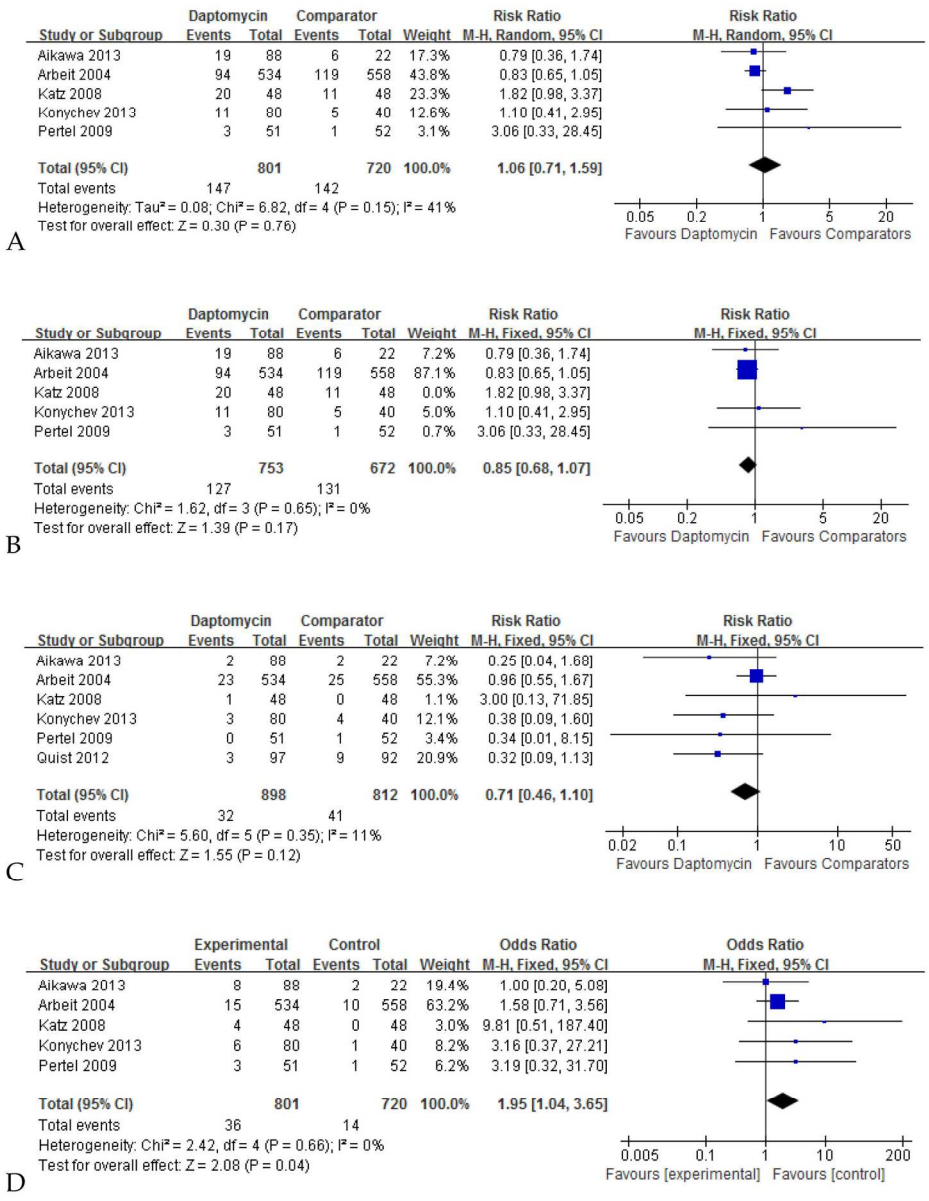

Fig.4.Meta-analysis of adverse events(AEs) compares daptomycin with comparator drugs for skin and soft tissue infections(SSTIs) based on ITT population:(A)Treatment-related adverse events (B)Treatment-related adverse events(excluded Katz et al's study) (C)Discontinuation due to AEs and all-cause mortality (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.
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PRISMA 2009 Checklist

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. **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.	
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 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.	
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. Co-interventions 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 trial[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^2 less than 25 percent were deemed to have low heterogeneity, and a fixed-effect model for meta-analysis was then used. Values of I^2 between 25 and 75 percent were considered to represent moderate levels of heterogeneity, and a random effects model was then utilized.	

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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^2 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,I^2=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, I^2=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,I^2=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,I^2=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,I^2=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,I^2=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, I^2=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	

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DISCUSSION			
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.	
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.	
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.	
FUNDING			
Funding	27	No funding.	

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

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