Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis
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CRD summary
The authors concluded that daptomycin was effective and safe for treatment of skin and soft tissue infections. The evidence appeared to support the authors’ conclusions, but the small number of studies and the differences between them should be taken into account when interpreting the findings.

Authors’ objectives
To evaluate the efficacy and safety of daptomycin compared to other antibacterials for skin and soft tissue infections (SSTIs).

Searching
PubMed, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published up to March 2009. Search terms were reported. Abstracts from the 10th to 18th European Conferences for Clinical Microbiology and Infection and Interscience Conferences on Antimicrobial Agents and Chemotherapy and reference lists of relevant articles were screened.

Study selection
Randomised controlled trials (RCTs) and comparative studies that compared the efficacy and toxicity of daptomycin with any other comparator antimicrobial regimen for SSTIs were eligible for inclusion. In vitro studies and studies that evaluated only pharmacokinetic and/or pharmacodynamic outcomes were excluded.

The primary review outcome was clinical success defined as complete or almost complete resolution of local and systemic signs or symptoms of infection without the need to continue or restart antimicrobial treatment. Secondary outcomes included clinical success in patients with complicated SSTIs, microbiological success, clinical success in patients with methicillin-resistant Staphylococcus aureus (MRSA) infections, clinical success of daptomycin versus vancomycin, time to clinical improvement or clinical cure, treatment-related adverse events, treatment withdrawals due to possible or probable treatment-related toxicity, all-cause mortality and development of resistance.

Studies compared daptomycin regimens (doses generally 4mg/kg or 10 mg/kg intravenously daily for between three and 14 days) with vancomycin, semisynthetic penicillin or penicillinase-resistant penicillin (generally for between seven and 14 days). All studies except one were in patients with complicated SSTIs; one was in patients with superficial mostly non-complicated SSTIs (cellulitis or erysipelas). Some studies were in patients at risk of MRSA. All studies were in adults (aged≥18 years). Studies were published between 2004 and 2009.

Two reviewers independently selected studies.

Assessment of study quality
Two reviewers independently assessed validity using Jadad criteria of randomisation, blinding and withdrawals. Studies that scored more than 2 out of the maximum possible 5 points were considered to be good quality.

Data extraction
Two reviewers independently extracted outcome data for clinical evaluable and intention-to-treat (ITT) populations. Disagreements were resolved by consensus among all reviewers.

Methods of synthesis
Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using fixed-effect Mantel-Haenszel and random-effects DerSimonian and Laird models. Heterogeneity was assessed using $\chi^2$ and $I^2$ statistics. Results for fixed-effect models were presented in the absence of significant heterogeneity ($I^2 \leq 50\%$, $p>0.1$); otherwise results from
random-effects models were presented. Odds ratios for outcomes with a small number of events were calculated using the Peto fixed-effect model. For the main outcome, RCTs were analysed alone and combined with the non-randomised study. Potential for publication bias was assessed using a funnel plot and Egger's test.

**Results of the review**

Four comparative studies were included (n=1,557 patients who received at least one dose of the allocated regimen). These included three randomised controlled trials (RCTs, n=1,295) and one non-randomised study with a historical control group (n=56 in the daptomycin group and 212 in the control group). Sample size ranged from 100 to 1,092. The authors stated that the three RCTs were single-blinded and had a satisfactory Jadad score (2 or more): two trials scored 2 points and one scored 3 points. One RCT reported a sample size calculation.

**Efficacy** For RCTs, there was no statistically significant difference between daptomycin and comparator regimens in clinical success rates in either the clinically evaluable or ITT populations. No significant heterogeneity was found. Results were similar (but with statistical heterogeneity, $I^2=85\%$) when the non-randomised study was included and when only studies with complicated SSTIs were analysed (three studies). No evidence of significant publication bias was found.

There was no statistically significant difference between daptomycin and comparator regimens in microbiological success (two studies, fixed-effect model), patients with MRSA infections (two studies, random-effects model) and for daptomycin versus vancomycin (three studies, random-effects model).

**Toxicity, mortality and resistance:** Studies reported a variety of potentially treatment-related adverse events (rates ranged from zero to 42\%). The most common adverse events in treatment groups were nausea, vomiting and dizziness. Frequently reported adverse events were increased blood creatine kinase, rash and dizziness in daptomycin groups and erythema and pruritus in comparator groups.

There was no statistically significant difference between daptomycin and comparator regimens in withdrawals due to toxicity (four studies, Mantel-Haenszel and Peto fixed-effect models). Two studies reported higher rates of treatment-related adverse events in daptomycin groups. Three studies reported no deaths; the other reported equal numbers of deaths in both treatment groups (eight). Two of two studies reported no development of resistance with daptomycin.

**Cost information**

One study (non-randomised) reported that the daptomycin group had a shorter hospital stay and lower overall costs than the historical control group.

**Authors' conclusions**

Daptomycin was effective and safe for treatment of SSTIs

**CRD commentary**

The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched and some attempts were made to minimise publication bias. Potential for publication bias was assessed, but this was of limited value due to the small number of studies. It was unclear whether attempts were made to minimise language bias. The validity of RCTs was assessed and results were reported; the validity of the non-randomised study was not assessed. Methods were used to minimise reviewer errors and bias in the review process.

In the main analysis, RCTs were analysed separately. For many of the other outcomes, data from the RCTs and the non-randomised study were combined; this may not have been appropriate. There appeared to be some clinical differences between studies. Statistical heterogeneity was assessed and although potential sources were not investigated statistically, some reasons were discussed.

The evidence appeared to support the authors' conclusions, but the small number of studies and the differences between them should be taken into account when interpreting the findings.
Implications of the review for practice and research

Practice: The authors stated that the review supported suggestions on treatment from the Infectious Diseases Society of America.

Research: The authors stated that further well-designed research was needed (particularly in patients with MRSA) to identify the optimal dose and duration of daptomycin treatment and compare daptomycin with vancomycin, linezolid and tigecycline.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.