Daptomycin for treatment of patients with bone and joint infections: a systematic review of the clinical evidence
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CRD summary
The authors concluded that daptomycin appears promising with regard to its effectiveness and safety for conventionally unresponsive bone and joint infections. Emergence of resistance is a potential drawback. In view of the lack of controlled studies, the frequent use of cointerventions, limitations in the search and the poor reporting of the review methods, these conclusions should be regarded with caution.

Authors' objectives
To evaluate the effectiveness and safety of daptomycin for the treatment of bone and joint infections.

Searching
PubMed and Scopus were searched to January 2007 without any language restrictions; the search terms were reported.

Study selection
Studies of the use of daptomycin were eligible for inclusion. In most of the included studies, 6 mg/kg daptomycin was given intravenously either daily or every 2 days for a mean duration of approximately 37 to 45 days. Doses in the lower range were used for patients with reduced renal function. In most cases daptomycin was given in combination with other antibiotics and/or (where reported) a surgical intervention such as prosthesis removal, debridement, incision and drainage or amputation. Participants in eligible studies were patients with bone and joint infections. The studies in the review included patients with a mean age of 60 to 66 years (range: 45 to 86 years, where reported) and a variety of bone and joint infections such as osteomyelitis, total joint arthroplasty infection, septic arthritis, discitis and infections of the hip and knee. Osteomyelitis was defined as the presence of positive imaging tests, with positive blood or tissue cultures and symptoms of infection. The most common pathogen was methicillin-resistant *Staphylococcus aureus* (MRSA), isolated either in the blood or from the infection site. More than one pathogen was detected in about 11% of cases. In most cases the indication for daptomycin was the failure of previous antibiotics (e.g. vancomycin, rifampicin, ciprofloxacin, levofloxacin), intolerable adverse effects, allergy or drug interactions. The outcomes of interest in the review were cure or failure. Cure was defined as complete symptom resolution and ongoing clinical improvement, verified by negative microbiological culture or imaging tests. Failure was defined as symptom persistence, ongoing positive cultures or imaging tests, or initial improvement verified by negative cultures but followed by relapse of the infection. The review also reported the development of daptomycin resistance. Follow-up for most patients ranged from 4 to 13 months. There were no specific inclusion criteria with respect to study design.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data describing the outcomes of each study (e.g. cure or failure) were tabulated.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The results of the studies were combined in narrative, grouped by study design. The percentage of cured patients was reported.
Results of the review
Thirteen studies were included: 2 retrospective (n=41) and 1 prospective (n=12) case series and 10 case studies (n=12).

Cure (3 case series, 10 case studies).
In the 3 case series, 81% (43 out of 53) patients were cured when daptomycin was administered, including all patients with osteomyelitis (n=23) and 60% of those with total joint arthroplasty infection (12 out of 20). The case studies reported that daptomycin as monotherapy cured 2 out of 8 patients; a further 2 patients were cured when vancomycin and rifampicin were added to daptomycin monotherapy. Daptomycin as part of combination therapy cured 3 out of 4 patients. Three of the 8 patients in whom treatment failed achieved full remission initially, but relapsed with MRSA after periods ranging from 12 days to 3 months.

Adverse events (3 case series, 10 case studies).
The case series reported little data on adverse events; nausea and elevated creatinine phosphokinase (CPK) levels were each reported in 1 patient in these studies. Seven case studies (n=7) reported this outcome. Four out of 7 patients reported adverse events associated with daptomycin, two of whom discontinued treatment. Adverse events included muscle pain and weakness, elevated CPK, elevated transaminases, acute renal failure (n=1) and creatinine disturbances.

Daptomycin resistance.
Daptomycin resistance was reported in only 1 patient in the 3 case series. Seven case studies assessed adverse events: 4 out of 7 patients with relevant reported data developed daptomycin resistance. This led to treatment failure in 3 patients and remission followed by relapse in one.

Authors' conclusions
Daptomycin appears promising with regard to its effectiveness and safety for conventionally unresponsive bone and joint infections, though evidence is limited. Emergence of resistance is a potential drawback.

CRD commentary
The study question and inclusion criteria were clear, but the search was limited to two databases which means that some studies might have been missed. It is unclear whether steps to minimise error and bias, such as having more than one independent reviewer make decisions, were taken in the study selection and data extraction processes. In addition, study validity does not appear to have been systematically assessed. It was difficult to evaluate the case series evidence because so few details were provided about these studies (e.g. whether the cases were consecutive presentations or selected; whether outcomes such as adverse effects were systematically assessed). The findings of the case studies differ markedly from the findings of the case series, but this was not discussed in the text. As the authors noted, it was unclear to what extent outcomes could be attributed to daptomycin given the high level of cointervention with other antibiotics and/or surgical procedures. They also noted that publication bias could not be excluded. In view of the lack of controlled studies, the frequent use of cointerventions, limitations in the search and the poor reporting of the review methods, the authors' conclusions should be regarded with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that randomised controlled trials comparing the effectiveness and safety of daptomycin with other antibiotics for bone and joint infections are needed.

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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.