Daptomycin for the Treatment of Osteomyelitis Associated With a Diabetic Foot Ulcer

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Abstract: This report describes a case of Staphylococcus aureus osteomyelitis associated with a chronic foot ulcer that was successfully treated with surgical debridement and 6 weeks of daptomycin therapy. Daptomycin was chosen because of its excellent activity against the causative organism and the patient’s history of penicillin allergy. Its tolerability and ease of administration also facilitated long-term outpatient management. The present case provides further evidence that supports consideration of daptomycin as a treatment for S aureus osteomyelitis, especially in light of reports of methicillin-sensitive S aureus (MSSA) infection recurrence after vancomycin use and safety issues surrounding long-term use of linezolid.

Osteomyelitis is a common complication associated with diabetic foot infection. Thirty-three to 68% of patients with diabetic foot infections are found to have underlying osteomyelitis. Staphylococcus aureus is the most commonly isolated pathogen in diabetic foot osteomyelitis, although other gram-positive cocci or gram-negative bacilli may be isolated and polymicrobial infection including anaerobic organisms can also be seen.

A complicated infection, osteomyelitis can be difficult to treat and generally requires surgical intervention combined with at least 4 to 6 weeks of antimicrobial therapy for maximal response. Intravenous therapy is generally preferred; however, information regarding optimal antimicrobial therapy is lacking. Few large, well-designed comparative trials have been performed, and meta-analyses of these trials have been unable to determine the best type, route, or duration of antimicrobial therapy. Therefore, therapy is usually guided by bone culture results and patient-specific factors.

Daptomycin is a cyclic glycopeptide that kills gram-positive bacteria by disrupting multiple bacterial plasma membrane functions. As such, daptomycin possesses bactericidal activity against both methicillin-susceptible S aureus (MSSA) and methicillin-resistant S aureus (MRSA), as well as other gram-positive cocci including vancomycin-susceptible and vancomycin-resistant enterococci. It has been shown to be effective in the treatment of complicated skin and skin structure infections including diabetic foot ulcers. Though limited, retrospective analyses and case reports published thus far support the efficacy and safety of daptomycin in the treatment of osteomyelitis. This report describes a case of S aureus diabetic foot osteomyelitis that was successfully treated with daptomycin.
Case Report

A 66-year-old man presented with a history of diabetes mellitus, hypertension, chronic lymphocytic leukemia (CLL), and penicillin allergy. His surgical history included right trans-metatarsal amputation (TMA) in 1994 with revision TMA in 2002. The patient had been managed previously for several episodes of minimal lower extremity breakdown, which were treated with numerous antibiotic agents including levofloxacin, ciprofloxacin, and clindamycin.

The patient presented in May 2006 with a right planatar ulcer secondary to bony prominence that required hospital admission and was treated at that time with intravenous vancomycin and cefepime. Incision and drainage of the wound was performed. Wound cultures revealed *S. aureus* resistant only to tetracycline. Bone cul-
tures were negative. Vancomycin was later discontinued and the patient continued on cefepime for a total of 6 weeks. Treatment resulted in complete ulcer healing.

In September 2006, the patient again presented with re-breakdown of the ulcer. This was initially treated on an outpatient basis with oral levofloxacin 750 mg/daily and was later changed to oral ciprofloxacin 500 mg/twice daily for 14 days. The ulcer continued to progress and by November 2006, the patient was admitted to the hospital for management of a limb-threatening infection (Figure 1).

Upon admission the patient presented with normal vital signs except for a temperature of 100.4°F. The physical examination revealed an infected right plantar ulcer at the medial aspect of the TMA site. The ulcer was surrounded by a 4-cm area of erythema and was draining purulent fluid. Pertinent laboratory data included a white blood cell count of 28.1 × 109/L with 16% segmented neutrophils and 78% lymphocytes. This was consistent with the patient’s baseline complete blood count due to CLL. The erythrocyte sedimentation rate was also elevated at 43 mm/h. Initial radiographs of the right foot showed erosive changes of the bone underlying the ulcer. Superficial wound culture indicated *S. aureus*.

TREATMENT was initiated with intravenous daptomycin 500 mg/day (4 mg/kg/day). Two days after admission, the patient underwent incision and drainage with debridement of infected soft tissue and bone (Figure 2). Bone cultures obtained during debridement also grew *S. aureus* that was susceptible to all agents tested except penicillin and tetracycline. The wound was closed 5 days after surgery was performed and the patient responded well to therapy (Figure 3). There were no further fevers and the wound began to heal with reduced signs of infection. During hospitalization, negative pressure wound therapy via a vacuum-assisted closure device was used daily until the wound was healed.

A peripherally inserted central catheter was placed, and the patient was discharged to continue treatment on an outpatient basis for a total of 6 weeks of daptomycin therapy. Regular evaluations were performed during the entire course of outpatient treatment (Figure 4). Creatine phosphokinase levels were monitored routinely and no elevations were noted. Daptomycin-related adverse effects were not seen. A superficial dehiscence, which initially required debridement, developed while the patient was still on therapy, but was closed completely within 2 months (Figure 5). Upon final evaluation in June 2007, almost 6 months after completing daptomycin therapy, the ulcer was healed and there was no indication of recurrence of the osteomyelitis. Radiographic evaluation of the foot at this time revealed no erosive changes or hypertrophic bone formation at the distal edges of the remaining metatarsals.

**Discussion**

This report describes a successful outcome associated with the use of daptomycin for diabetic foot osteomyelitis. Although there have been several previously published reports and retrospective analyses of daptomycin’s efficacy in the management of bone and joint infections, these reports have included small numbers of patients. A review of the post-marketing experience with daptomycin for the treatment of osteomyelitis included the largest group of patients to date. In this study, 67 patients from the 2004 database had a diagnosis of osteomyelitis, were evaluable at the end of therapy, and had at least one post-treatment assessment. *S. aureus* was the most common pathogen reported and most isolates were methicillin-resistant. Overall, success (cured + improved) was achieved in 82% of patients after a median follow-up period of 76 days.

Daptomycin was initially chosen for this patient based upon his history of penicillin allergy and concern that the infection might be caused by MRSA, given his significant prior use of antibiotics. Vancomycin was not chosen as empiric therapy because of the increasing prevalence of MRSA strains with reduced susceptibility to vancomycin and recent reports of clinical failures associated with vancomycin among patients with bacteremia caused by MRSA strains with minimum inhibitory concentrations (MICs) > 1.0–1.5 mcg/mL. Although culture results revealed the osteomyelitis was caused by MSSA, daptomycin was continued for the entire course of treatment because of the drug’s bactericidal activity against MSSA and concerns regarding the higher risk of recurrence with vancomycin when compared to treatment with beta-lactams in the management of MSSA osteomyelitis. Moreover, daptomycin’s tolerability and once-daily regimen facilitated outpatient management. Use of oral quinolone therapy was not considered due to failure with levofloxacin and ciprofloxacin prior to admission.

Linezolid was considered as a potential treatment option in this case, given the patient’s penicillin allergy and the drug’s availability in an oral dosage form that produces serum concentrations equivalent to those achieved with intravenous dosing. Linezolid has been...
used successfully in the management of osteomyelitis caused by gram-positive cocci; however, long-term use (>28 days) is complicated by the occurrence of significant and sometimes irreversible adverse effects, including bone marrow suppression, peripheral and optic neuropathies, and lactic acidosis.17–19 Daptomycin has been associated with infrequent and mild adverse effects in previous reports and reviews of daptomycin therapy for osteomyelitis.5,8–12 In this case, daptomycin was well tolerated over the 6-week therapy period. Although elevated creatine phosphokinase levels have been noted to occur with daptomycin, this potential side effect was not observed in this patient, and he did not experience any myalgias or muscle weakness.5

Conclusion

Daptomycin’s activity versus both MSSA and MRSA, as well as its once-daily dosing regimen and tolerability, make it an appealing alternative to vancomycin or linezolid for patients requiring long-term treatment for gram-positive infections. The presented case provides further evidence in support of daptomycin’s efficacy as a treatment for S. aureus osteomyelitis. Prospective comparative trials are needed to confirm the results reported here.

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References