Daptomycin for the Treatment of Osteomyelitis and Prosthetic Joint Infection: Retrospective Analysis of Efficacy and Safety in an Outpatient Infusion Center

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Citation

Abstract
Data describing the use of daptomycin for osteoarticular infections are limited. We describe our experience with use of daptomycin for outpatient parenteral antimicrobial therapy (OPAT) of osteomyelitis and prosthetic joint infection (PJI). A retrospective analysis was done of patients who received ≥6 mg/kg of daptomycin for ≥2 weeks. All patients had a gram-positive pathogen and confirmed diagnosis of osteomyelitis or PJI. Outcomes were evaluated at end of therapy, test of cure (TOC, 6 months), and long-term follow-up (LTFU), if available. Seventy-three patients (59 osteomyelitis, 14 PJI) met inclusion criteria. The most common pathogens were methicillin-resistant Staphylococcus aureus (46.6%), methicillin-susceptible S. aureus (13.7%), and coagulase-negative staphylococci (21.9%). Daptomycin was administered for a median of 49 days (range, 21-183). At TOC, 93.2% and 100% of osteomyelitis and PJI patients, respectively, were either clinically cured or improved. LTFU data were available for 49 patients, with a median duration of follow-up of 15.5 months. Cure was achieved in 95.9% of these patients, with the remainder assessed as improved. Success occurred regardless of the presence of hardware or vertebral osteomyelitis or concomitant use of rifampin. Thirty-six patients received rifampin concomitantly, and 12 received short-term linezolid as step-down therapy (median 14 days). Only 5 adverse events were assessed as probably related to daptomycin, including 4 cases of asymptomatic elevation of creatine phosphokinase. At doses ≥6 mg/kg, daptomycin was well tolerated and effective as OPAT for osteomyelitis and PJI caused by gram-positive pathogens, with successful outcomes maintained at LTFU.

INTRODUCTION
Chronic osteomyelitis and prosthetic-joint infection (PJI) are challenging to treat, usually requiring a combination of surgical and medical management. For more than 30 years, vancomycin has been the drug of choice for treatment of osteoarticular infection (OAI) caused by methicillin-resistant strains of Staphylococcus aureus (MRSA) and coagulase-negative staphylococci (MRCNS), but vancomycin has several limitations. In particular, decreased susceptibility of S. aureus to vancomycin has been observed, reflected by increasing minimum inhibitory concentrations (MICs), known as “MIC creep,” and reduced efficacy against strains with MICs ≥2 µg/mL, despite an MIC of 2 µg/mL being defined as susceptible by the Clinical and Laboratory Standards Institute. Vancomycin is also associated with nephrotoxicity and ototoxicity, particularly when used at higher doses. Consequently, alternative therapies are needed for treatment of OAI caused by methicillin-resistant staphylococci.

Daptomycin is a cyclic lipopeptide with activity against a wide range of gram-positive pathogens. It is indicated for treatment of complicated skin and skin-structure infections and S. aureus bacteremia, including right-sided infective endocarditis. The once-daily administration of daptomycin makes it attractive for outpatient parenteral antimicrobial therapy (OPAT), but data supporting the efficacy of daptomycin for treatment of OAI are limited. In a rabbit model of osteomyelitis, daptomycin achieved concentrations in infected bone that were 1.3% of peak serum concentrations, and it has exhibited efficacy similar to vancomycin in animal models.

Based largely on registry data and small case series, daptomycin appears to be safe and effective for OAI. For example, efficacy of daptomycin was evaluated using a post hoc analysis of an open-label, randomized trial that
compared daptomycin with standard therapy for S. aureus bacteremia. Among 21 patients with OAI in the daptomycin group, 67% had a successful outcome at 6 weeks after end of therapy (EOT), compared with 55% of 11 patients who received standard therapy. Published literature describing the use of daptomycin for OAI has been further described in a recent review. At the Florida Infectious Diseases Group, daptomycin is used in a large percentage of patients who are treated in the outpatient infusion center for OAI. This provides a unique opportunity to describe the use of daptomycin, including effectiveness and safety, for the treatment of OAI in a real-world setting.

MATERIALS AND METHODS

STUDY DESIGN

A retrospective chart review was conducted at an outpatient infectious disease practice in Florida. Using ICD-9 codes and the office billing and clinical information systems, the investigators identified patients who had been treated with daptomycin for osteomyelitis or PJI caused by gram-positive organisms and who had ≥6 months of follow-up after the end of therapy. The minimum criteria required for a confirmed diagnosis were identification of a pathogenic gram-positive organism from a culture of the wound, needle aspirate, or surgical sample; clinical findings consistent with OAI (eg, drainage, erythema, pain, swelling); and consistent radiographic and/or histopathologic findings and/or inflammatory markers (latter for PJI only). Patients also had to have received daptomycin at a dose of ≥6 mg/kg for ≥2 weeks and been aged ≥18 years. However, patients who discontinued daptomycin earlier than 2 weeks due to an adverse event (AE) or clinical failure were included and categorized as clinical failures. Concomitant use of potentially synergistic antibiotics was allowed. Patients were excluded if they had mixed gram-positive and gram-negative infections, were receiving chemotherapy, or had been described in previous daptomycin studies.

STUDY PROCEDURES

Data were collected from clinic, hospital, and physician medical records. Information collected included patient demographics, including underlying medical conditions and risk factors for infection; characteristics of the infection, including site of infection, tests and procedures used to support the diagnosis, and prior use of antibiotics that had activity against gram-positive organisms; surgical procedures, antibiotics, post-treatment antibiotic suppression, and ancillary treatments used to manage the infection; clinical outcomes; and AEs.

Osteomyelitis was classified as contiguous or hematogenous in addition to whether the infection was hardware-associated. Because no standardized definitions are accepted, chronicity of infection was assessed by bone pathology results when available; this test provided an objective measurement that a clinical definition could not. Clinical outcomes were assessed at EOT, at the 6-month follow-up (test of cure [TOC]), and, if data were available, at a subsequent, final evaluation (long-term follow-up [LTFU]). The TOC evaluation was obtained by office visit, follow-up with the referring physician, or telephone call. Because definitions are not standardized for outcomes of OAI, the investigators, after much deliberation and based on prior trials, created definitions prior to the start of the trial. Cure at EOT was defined as resolution of signs and symptoms as determined by the treating physician plus improvement of inflammatory markers by ≥75% from baseline and/or bacteriologic eradication. At TOC and LTFU, assessment of cure was based solely on resolution of signs and symptoms. Patients who received oral antibiotics as step-down therapy could be considered cured if they otherwise met these criteria. Improvement was defined as partial resolution of signs and symptoms in the presence of continued positive cultures and/or requiring chronic suppressive therapy with oral antibiotics. Failure was defined as lack of improvement or worsening of signs and symptoms necessitating amputation or a change from daptomycin to an alternative antibiotic. This did not include oral suppressive or step-down therapies, which were classified as previously indicated. If daptomycin was discontinued due to an AE, this was recorded as a failure. Regardless of severity or causal relationship, AEs were recorded if the onset occurred from the first dose of daptomycin through 30 days after completion of daptomycin therapy. Descriptive statistics were calculated for collected data, but statistical hypothesis testing was not planned due to the relatively small numbers of patients in the subgroups analyzed. Although patients with PJI were presumed to have osteomyelitis of the contiguous bone, they were analyzed separately as the PJI group.

Once patient eligibility was confirmed, a 4-digit identification number was assigned. Precautions were taken to protect the personal information of each patient. The investigators requested and received a Waiver of Consent under the Common Rule and Waiver of Authorization under
HIPAA from a central Investigational Review Board.

RESULTS

PATIENT DEMOGRAPHICS AND CHARACTERISTICS OF INFECTION

Beginning in May 2008 and working backwards to January 2003, 1415 patients were screened for study inclusion. Seventy-three patients met all inclusion and exclusion criteria, including 59 with osteomyelitis and 14 with PJI. Basic demographic data are shown in Table 1. The most common underlying medical conditions included hypertension (50.7%), diabetes (28.8%), and heart disease (20.6%), with 21.6% of patients having no underlying illnesses. The most common risk factors for OAI were prior orthopedic procedure (74.0%), recent trauma (37.0%), and previous surgical site infection (15.1%).

In addition to the positive culture required for study eligibility, the diagnosis of infection was supported by surgical findings (69.9%), radiologic findings (58.9%), and histopathology (38.4%). Culture sources were deep wound (60.3%), bone (31.5%), surface drainage (5.5%), and needle aspirate (2.7%). The most common pathogens were MRSA (46.6%), methicillin-susceptible S. aureus (MSSA,13.7%), MRCNS (13.7%), and methicillin-susceptible coagulase-negative staphylococci (MSCNS, 8.2%). Other gram-positive organisms were isolated in 16.4% of patients, including Enterococcus faecalis (4 patients), Streptococcus agalactiae and Corynebacterium sp. (1 each), and gram-positive cocci not otherwise specified (5 patients).

The characteristics of the infections are described in Table 1. More than 90% of infections were classified as contiguous; of these cases, 8 were diabetic foot infections. Nearly two-thirds of the osteomyelitis cases were hardware-associated. The most common anatomic sites for osteomyelitis were the vertebra, tibia/fibula, or foot, whereas the majority of PJI were associated with the knee. Among the 35 patients who

During the 6 months prior to the current diagnosis, 29 patients (39.7%) had received antibiotics with activity against gram-positive organisms (Table 2). The most commonly used antibiotics during that time were vancomycin, daptomycin, and ceftriaxone, with some patients receiving multiple agents. The most common reason for failure of prior daptomycin therapy was retention of infection-associated hardware, whereas AEs were the most common cause of vancomycin failure, followed by hardware retention and clinical failure. No differences were observed in cure rates for patients who received or did not receive prior antibiotics (data not shown).

Table 2. Reasons For Failure in 29 Patients Who Received Prior Antibiotic Therapy
had bone pathology results, 62.9% had findings consistent with chronic osteomyelitis.

**MANAGEMENT OF INFECTION**

Sixty-eight patients (93.2%) had daptomycin initiated at a dose of 6 mg/kg, with the remainder (6.9%) receiving 8 mg/kg. Daptomycin was administered once daily to all patients but one, who was dosed every 72 h for a portion of the treatment course due to renal insufficiency. The median length of daptomycin therapy was 49 days (range, 21-183 days).

Thirty-eight patients (52.1%) received concomitant antibiotics with activity against the isolated pathogens for some period of time while on daptomycin, with some patients receiving >1 concomitant agent. Concomitant antibiotics were rifampin (36 patients), gentamicin (5), and oral linezolid, which was used in 1 patient in whom intravenous access was temporarily disrupted. In addition, 20 patients (27.4%) were treated with locally active antibiotics (eg, antibiotic-impregnated beads, bone cement), specifically an aminoglycoside (16 patients) or vancomycin (11 patients). After completing daptomycin therapy, 27 patients (37.0%) received ≥1 oral antibiotics for a median of 28 days (range, 2-371) as either step-down (24 patients) or suppressive therapy (3 patients). Thirteen patients (17.8%) received linezolid for a median duration of 14 days (range, 2-42). Nineteen patients (26.0%) received another oral antibiotic—a tetracycline (12.3%), clindamycin (5.5%), trimethoprim-sulfamethoxazole (4.1%), cefadroxil (4.1%), moxifloxacin (1.4%), or rifampin (1.4%)—for a median of 30 days (range, 7-371). Of the 3 patients who received chronic suppression, 2 patients, 1 each with vertebral and sternal osteomyelitis, received cefadroxil for about 6 months, and 1 patient with PJI who refused surgery received doxycycline for >12 months, remaining on suppression at this time. Management also included ≥1 surgical procedures in 66 patients (90.4%) and wound vacuum-assisted closure in 7 patients (9.6%).

**CLINICAL OUTCOMES**

At EOT, 100% of PJI patients and 98.3% of osteomyelitis patients were either cured or improved (Table 3). The one failure in the osteomyelitis group was a patient who discontinued daptomycin due to suspected allergy. A high success rate was maintained at TOC, with all PJI patients and 93.2% of osteomyelitis patients still assessed as cured or improved. An additional 3 osteomyelitis patients were considered failures at this evaluation. One patient had developed recurrent infection with Klebsiella pneumoniae and persistent MRSA, requiring addition of meropenem. The patient’s original MRSA isolate was susceptible to daptomycin, but testing was not performed on the recurrent isolate. A second patient with a significant history of psychiatric problems and noncompliance had return of osteomyelitis after repeatedly removing his own intravenous catheter. The third patient had return of osteomyelitis due to Staphylococcus epidermidis after initial cure in the presence of retained hardware. The recurrent organism retained its susceptibility to daptomycin, but therapy was changed to vancomycin plus rifampin.

**Figure 3**

Table 3. Clinical Outcomes After Treatment With Daptomycin

Data from LTFU were available for 49 patients (67.1%), with a median duration of follow-up for these patients of 15.5 months from EOT (range, 6.0-46.8). Thirty of these patients (41.1%) had durations of follow-up that exceeded 1 year. Cure was seen in 97.4% of patients at LTFU, with the remaining patient assessed as improved. No differences were observed in the cure rates for patients who were followed for 6-12 months compared to those who were followed for >12 months or among the 4 most common pathogens (data not shown).

When analyzed by the status of any infection-associated hardware (Table 4), the majority of patients responded to daptomycin therapy regardless of whether hardware was removed, replaced, or retained. Outcomes were similar in patients who did and did not receive concomitant rifampin.
Among osteomyelitis patients, 96.4% (27/28) of patients treated with rifampin were either cured or improved at TOC compared with 90.3% (28/31) of patients who did not receive rifampin. Among PJI patients, all patients were either cured or improved regardless of whether or not rifampin was co-administered. In addition, the subset of patients with vertebral osteomyelitis was analyzed separately, with 94.4%, 88.8%, and 100% of these patients either cured or improved at EOT, TOC, and LTFU, respectively (Figure 1).

**ADVERSE EVENTS**

Forty-five patients (61.6%) experienced 70 AEs (Table 5). The majority of AEs (78.6%) were considered by the investigators to be unrelated to daptomycin therapy. Daptomycin was discontinued in response to 3 AEs (4.3%)—rash and 2 instances of asymptomatic creatine phosphokinase (CPK) elevation. The drug was safely resumed in both patients with CPK elevation but was permanently discontinued in the patient with rash, who was consequently categorized as a treatment failure. An additional 7 AEs (10.0%) resulted in dose reductions: 2 instances each of renal insufficiency and CPK elevation (occurring in separate patients) and 1 instance each of myalgia, fatigue, and diarrhea. The cases of renal insufficiency were not felt to be related to daptomycin therapy, but doses were reduced per product labeling. The case of fatigue and 1 case of CPK elevation were ongoing at the time of study discontinuation, while the other 5 AEs resolved following dose reduction.

**DISCUSSION**

Osteomyelitis is one of the most common indications for OPAT. Although vancomycin remains the drug of choice for treatment of osteomyelitis due to methicillin-resistant staphylococci, alternatives are needed for patients in whom vancomycin is not an option due to intolerance, clinical...
failure, or resistance. Daptomycin possesses several characteristics that make it an attractive option for OPAT, including once-daily administration, short infusion time, and a low incidence of injection-site reactions.\textsuperscript{19} In addition, staphylococcal OAI may be associated with the production of biofilm, which can significantly hinder the activity of many antibiotics.\textsuperscript{32,33} Compared with vancomycin and linezolid, daptomycin has demonstrated greater activity against biofilm-associated S. aureus.\textsuperscript{32,33}

In this study, daptomycin was found to be effective when used as OPAT for the management of osteomyelitis or PJI. At the 6-month (TOC) evaluation, all 14 PJI patients and 55 of 59 osteomyelitis patients were considered to be cured or improved, although these patients represented a population that is difficult to treat. Many patients had chronic osteomyelitis on bone pathology and/or had received prior antibiotic therapy targeting gram-positive organisms. Nearly a third of the osteomyelitis cases involved the vertebrae, and nearly two-thirds were hardware-associated. In addition, LTFU data were available for 49 patients, representing two-thirds of all patients and with a median length of follow-up of approximately 16 months; among these patients, all were cured or improved. Satisfactory clinical success rates were achieved regardless of the status of associated hardware, use of concomitant rifampin, the presence of vertebral osteomyelitis, receipt of prior antibiotics, or duration of follow up.

Furthermore, despite median and maximum durations of therapy of 49 and 183 days, respectively, only 15 AEs occurred that were considered to be possibly or probably related to daptomycin. This included 4 instances of CPK elevation, including 2 in patients treated with the 8-mg/kg dose, reinforcing the need for CPK monitoring. Therapy was discontinued due to AEs in only 3 patients, 2 of whom had daptomycin safely resumed. Gram-negative bacteremia occurred in 8 patients (11.0%), but daptomycin would not be expected to have activity against this group of organisms.

A Phase 2 trial is currently underway to evaluate the efficacy of daptomycin for staphylococcal PJI.\textsuperscript{23} However, published clinical data regarding use of daptomycin for OAI have been limited to registry data,\textsuperscript{20-22} case series,\textsuperscript{23-28} and a post hoc analysis of patients with OAI in a randomized trial of S. aureus bacteremia.\textsuperscript{29} The majority of patients described in these publications had favorable clinical outcomes and generally tolerated daptomycin therapy.

The current study has several strengths compared with previous publications regarding the use of daptomycin for OAI. To the best of our knowledge, the 73 patients in this chart review constitute the single largest case series of daptomycin for OAI to be published to date. This is more than twice the size of the largest previous case series, which included 31 patients.\textsuperscript{23} A recent daptomycin registry study included 250 patients with osteomyelitis who were evaluable for efficacy and 327 who were evaluable for safety;\textsuperscript{22} however, outcomes could be assessed only through EOT.

The current study had a longer follow-up period than previous reports, requiring at least 6 months of follow-up for study inclusion. Additional long-term outcomes were available for 67% of patients, with a median duration of follow-up among these patients of nearly 16 months. Most previous case series evaluated outcomes at EOT or at some undefined follow-up period. Balter et al also required 26 months of follow-up for study inclusion, but their median duration of follow-up (9 months) was significantly shorter than the current study.\textsuperscript{27} In addition, all patients in this study were required to have positive cultures as well as other evidence supporting the diagnosis of OAI. Enrollment included many patients with infections that are particularly challenging to treat. Many had chronic osteomyelitis and/or had failed previous antibiotic regimens. Fourteen patients had PJI, and among osteomyelitis patients, nearly two-thirds had associated hardware. Eighteen patients had vertebral osteomyelitis.

However, as with previous reports, the current study is limited by the retrospective, noncomparative nature of the analysis, which prevented standardization of therapies. Concomitant systemic antibiotics with activity against gram-positive pathogens were received by 52% of patients, and 27% were treated with locally active therapy. Daptomycin was dosed at 6 mg/kg in 93% of patients, with the remainder receiving 8 mg/kg; these are the doses that are being evaluated in the prospective trial that is underway. Ancillary treatments and surgical interventions, which are a very important determinant of outcomes, were not controlled.

Although the development of nonsusceptibility to daptomycin was not seen, follow-up cultures were not available for 1 patient who failed therapy. Definitions of outcomes are not standardized and, although based on previous studies, were created by the investigators. Although the duration of follow up and size of the LTFU population were greater than previous studies of daptomycin, they
remain relatively small.

Outcomes by hardware status were described in Table 4, but placement of patients into these categories was challenging, as patients often had multiple surgical procedures at different times. Thus, patients were categorized according to the best possible description during that time period. Outcomes from different surgical modalities vary considerably depending on the publication, location, surgeon, etc. For example, a recent review suggests retention of hardware plus debridement for selected patients, but because our practice is a referral center, few patients would have met these criteria. In addition, there were no differences that we could detect based on hardware status.

CONCLUSION

At doses of ≥6 mg/kg in the current study, daptomycin was well tolerated and effective as OPAT for the treatment of osteomyelitis and PJI caused by MRSA and other gram-positive organisms. Clinical success was maintained in the majority of patients at both the 6-month and long-term follow-up evaluations, and success was achieved regardless of the presence of hardware or vertebral osteomyelitis or use of concomitant rifampin. This report represents the largest case series with the longest duration of follow-up to date. Patients treated with prolonged courses of daptomycin should have CPK levels monitored regularly and should be assessed for the development of daptomycin nonsusceptibility as clinically indicated. Until confirmatory data are available from an ongoing, prospective, randomized trial, data from case series such as this one provide support to clinicians who wish to use daptomycin for the management of OAIs.

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The investigators requested and received a Waiver of Consent under the Common Rule and Waiver of Authorization under HIPAA from a central Investigational Review Board.

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