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Daptomycin in bone and joint infections: a review of the literature

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Abstract
Introduction To review the pharmacology, pharmacokinetics, efficacy, and safety of daptomycin, a novel antibiotic for the treatment of bone and joint infections, a literature search of relevant articles was conducted.
Materials and methods A PubMed/MEDLINE search (1990–April 2008) to identify relevant English-language literature was conducted. Search terms included bone and joint infection, osteomyelitis, daptomycin, and methicillin-resistant Staphylococcus aureus (MRSA). Additional articles were identified by reviewing the bibliographies of articles cited. Programs and abstracts from infectious disease meetings were searched, and prescribing information of antibiotics indicated for bone and joint infections consulted. All articles identified from data sources published in English were evaluated.
Results Caused primarily by Gram-positive pathogens such as S. aureus and, to a lesser extent, Enterococcus faecalis, bone and joint infections are difficult to treat successfully. Surgical intervention and prolonged courses of antibiotics are frequently required, and failure of first-line antibiotic therapy is common. The emergence of S. aureus strains with reduced susceptibility to vancomycin, the long-standing gold standard for bone and joint infections, has complicated the clinical scenario. Few randomized trials comparing the efficacy of different antibiotics for bone and joint infections exist. Daptomycin, a novel intravenous lipopeptide antibiotic, has shown potent in vitro activity against a broad spectrum of Gram-positive bacteria, including many resistant pathogens commonly associated with bone and joint infections such as MRSA and vancomycin-resistant E. faecalis. Early clinical investigation of daptomycin in bone and joint infections unresponsive to antibiotics, such as vancomycin, has found a cure rate of approximately 80%, with a low incidence of adverse events and drug resistance.
Conclusion Further studies are warranted to determine if limited clinical evidence, described in individual case reports and a daptomycin-specific retrospective registry, suggests daptomycin is a promising option for patients with bone and joint infections such as MRSA osteomyelitis.

Keywords Bone · Daptomycin · Infection · Osteomyelitis · MRSA · VRE

Introduction

The treatment of bone and joint infections such as osteomyelitis, septic arthritis, and prosthetic joint infections can be difficult, requiring prolonged administration of antibiotics and extensive surgical procedures [1]. Most bone and joint infections are caused by Gram-positive cocci including Staphylococcus spp. and enterococci [1], increasingly resistant to commonly used antibiotics such as methicillin and other β-lactam agents [2, 3]. Vancomycin is often used to treat bone and joint infections caused by methicillin-resistant Staphylococcus aureus (MRSA), an organism seen with increasing frequency [4]. MRSA has recently emerged

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as an important cause of community-acquired infection in many parts of the United States [5], and recent surveys of *S. aureus* isolates report MRSA rates as high as 74% [6, 7]. Although vancomycin remains a first-line treatment for many bone and joint infections caused by typical organisms, its efficacy against MRSA infections in other settings is declining ominously [8]. This reduced susceptibility of *S. aureus* to vancomycin [3, 9] may be partially due to *S. aureus*-produced biofilms, which may facilitate resistance by promoting horizontal gene transfer [10–12]. The ability of pathogens to escape lysis and killing by vancomycin, termed "tolerance," represents an additional risk. Both genetic and physiologic factors can selectively suppress susceptibility to the killing action of antibiotics without a change in the minimum inhibitory concentration (MIC), i.e., can make bacteria antibiotic-tolerant and difficult to detect using standard susceptibility testing methods [13, 14].

Selection of antimicrobial therapy for bone and joint infections

Most cases of osteomyelitis require antimicrobial therapy, adequate drainage, thorough debridement, obliteration of dead space, and wound protection. Patients are initially treated empirically with broad-spectrum antimicrobials, changed to targeted antimicrobial therapy based on bone culture results of samples taken at debridement surgery or from deep bone biopsies. Septic arthritis, a medical emergency, requires prompt recognition and aggressive treatment for a good prognosis [15]. Delays in surgical drainage and antibiotic therapy may lead to progressive synovitis and irreversible destruction of cartilage and bone [16, 17]. Empirical antibiotic therapy directed against staphylococci, the most common causative organisms of septic arthritis in adults, should be given while awaiting culture results [15, 18]. If the Gram stain is negative in acute septic arthritis, empirical therapy should include an antimicrobial having activity against *S. aureus* and streptococci [15, 19]. Antibiotic therapy of prosthetic joint infections is based on a definitive microbiologic diagnosis, usually after the surgical removal of all bioprosthetic components [15].

Despite these general guidelines, high-quality evidence of the relative effectiveness of various regimens of antibiotic therapy, and their optimal duration, is scant [20]. A 2001 meta-analysis concluded that little high-quality evidence-based therapy for osteomyelitis and septic arthritis exists [21]. Increasing resistance to antibiotics has prompted the development of new drugs to treat Gram-positive infections, which may also be used in the treatment of bone and joint infections.

Current treatment options for *S. aureus* bone and joint infections

Staphylococcus aureus is the most common organism implicated in osteomyelitis and septic arthritis [1, 15]. Although the term MRSA denotes resistance to methicillin, it is synonymous with multidrug-resistant *S. aureus*, because many nosocomial MRSA strains are resistant to many other commonly used antibiotics. Approximately 20% of *S. aureus* isolates in Europe are reported as methicillin-resistant; the prevalence ranges from 33 to 55% in US hospitals. Since 1996, seven vancomycin-intermediate *S. aureus* (VISA) strains (i.e., vancomycin MIC = 8–16 mg/L) have been identified in Europe, Asia, and the United States, and VISA strains (vancomycin MIC $\geq$ 32 mg/L) were also reported in the United States between 2002 and 2005 [22].

Vancomycin was the last available drug to which *S. aureus* had remained uniformly sensitive, until recent reports of low-level glycopeptide resistance and the transfer of high-level vancomycin resistance from *Enterococcus* to *S. aureus* [23, 24]. A limited number of broad-spectrum antimicrobials are available to combat multidrug-resistant Gram-positive organisms.

Vancomycin

In 1997, the first clinical isolate of *S. aureus* having intermediate resistance to vancomycin was reported from Japan [25]. Since then, many *S. aureus* isolates with reduced susceptibility to glycopeptides have been reported from various locales [23, 26]. The first report of vancomycin-resistant *S. aureus* in the United States occurred in 2002. The patient had been treated with multiple antibiotics, including vancomycin. MRSA bacteremia later developed, and the patient was treated with vancomycin and rifampin. The Centers for Disease Control and Prevention confirmed that the *S. aureus* isolated was resistant to oxacillin, vancomycin, and teicoplanin [3].

Vancomycin itself has poor bone penetration and in some animal studies has shown an inability to sterilize bone [27, 28]. When bone and joint pathogens are susceptible, vancomycin concentrations in serum must be monitored, and vancomycin-associated adverse events (e.g., marrow suppression, ototoxicity, nephrotoxicity, and rash) may discourage its use [29]. Adverse effects, increasing MICs, and the increased prevalence of vancomycin-resistant enterococci (VRE), VISA, and vancomycin-resistant *S. aureus* (VRSA) are already limiting the use of vancomycin in the treatment of bone and joint infections [23, 26, 30, 31]. Vancomycin-susceptible clinical MRSA isolates demonstrate considerable heterogeneity in vitro with respect to vancomycin MIC and vancomycin killing, affecting the clinical

efficacy of the drug. A significant risk for vancomycin treatment failure in MRSA bacteremia has been demonstrated, with increasing vancomycin MICs still well within the susceptible range [32]. An increased risk of recurrence seen with vancomycin treatment of *S. aureus* osteomyelitis [33] further diminishes the clinical utility of this agent for the treatment of bone and joint infections.

Quinupristin/dalfopristin

Quinupristin/dalfopristin (Q–D), the first parenteral streptogramin, achieves a response in approximately two-thirds of patients with MRSA infections. This combination product also has efficacy in patients with Gram-positive complicated skin and skin structure infections (cSSIs) and nosocomial pneumonia [34, 35]. Rifampin plus either Q–D or vancomycin has been found significantly more effective than monotherapy in a preclinical trial of MRSA knee infection [36].

An evaluation of Q-D for the treatment of a variety of MRSA infections (44% bone and joint infections) in patients either intolerant of or failing prior therapy resulted in an overall success rate of 71.1% in the all-treated population ($n = 90$) and 66.7% in patients who were both clinically and bacteriologically evaluable ($n = 27$). The most common non-venous adverse events were arthralgias (10.8%), myalgias (8.6%), and nausea (8.6%) [37]. Q–D is not indicated for bone and joint infections, and little clinical data exist for the drug's use in that setting [34].

Linezolid

Linezolid is an oxazolidinone, a new class of antibacterial agents particularly effective against Gram-positive infections, including methicillin- and vancomycin-resistant strains [38]. It is available in oral and intravenous (IV) formulations and has been approved by the Food and Drug Administration for the treatment of numerous infections, including cSSIs or uncomplicated SSIs, without concomitant osteomyelitis, caused by *S. aureus* [39]. However, data on the effectiveness and tolerability of linezolid as prolonged therapy for bone and joint infections are lacking, and linezolid is not indicated for their treatment. No large, randomized trials have been published on the use of linezolid for orthopedic infections such as osteomyelitis and septic arthritis. Nevertheless, a recent retrospective study of linezolid for chronic osteomyelitis found that when used as monotherapy, or in combination with other antimicrobials and/or surgery, linezolid was associated with a cure rate of 85% at 12 weeks after the end of treatment and 78.8% at follow-up. Adverse events, including anemia and peripheral neuropathy, were reported in 51.5% of subjects, and 34.8% of subjects discontinued the study because of adverse events [40]. Peripheral and optic neuropathy have been reported in patients treated with linezolid, primarily in patients treated for longer than the maximum recommended duration of 28 days [39]. Early identification of linezolid-induced peripheral neuropathy is a particular concern, because this may be irreversible [41]. Resistance to linezolid has been reported among strains of both MRSA and *Enterococcus faecium* [37, 42, 43].

Tigecycline

Tigecycline, the first glycylcycline approved in the United States, is indicated for cSSIs and complicated intra-abdominal infections (cIAIs), not for bone and joint infections. Tigecycline has activity against both methicillin-susceptible *S. aureus* (MSSA) and MRSA. In four phase III trials in patients with cSSIs and cIAIs, tigecycline was noninferior to its comparators (vancomycin + aztreonam in two studies and imipenem/cilastatin in two studies), with clinical cure rates among clinically evaluable patients of >80% ($P < 0.001$ for noninferiority). Although there have been no human trials involving osteomyelitis, animal studies suggest tigecycline may have a role in treating bone infection. After 28 days of treatment of experimentally induced osteomyelitis, rabbits receiving tigecycline/oral rifampicin showed a 100% infection clearance [44]. Frequently reported adverse events include nausea and vomiting, diarrhea, local IV-site reaction, infection, and fever [45, 46]. Resistance to tigecycline has been reported among both Gram-positive and Gram-negative strains.

Daptomycin

This novel cyclic lipopeptide is bactericidal against Gram-positive bacteria, including MRSA and VRE. Daptomycin kills Gram-positive bacteria by disruption of multiple bacterial plasma membrane functions, without penetrating the cytoplasm [47]. Insertion of the lipophilic daptomycin tail into the bacterial cell membrane causes rapid membrane depolarization and a potassium ion efflux. Arrest of DNA, RNA, toxin production, and protein synthesis follows, resulting in bacterial cell death without lysis of the cell wall (Fig. 1) [48–50].

Microbiology

The in vitro potency of daptomycin has been demonstrated against a wide range of aerobic and anaerobic Gram-positive bacteria, including MRSA, glycopeptide-intermediate *S. aureus*, methicillin-resistant coagulase-negative staphylococci, and VRE [47]. The in vitro activity of daptomycin against three VISA isolates was compared with that of vancomycin, linezolid, and Q–D. Overall, daptomycin

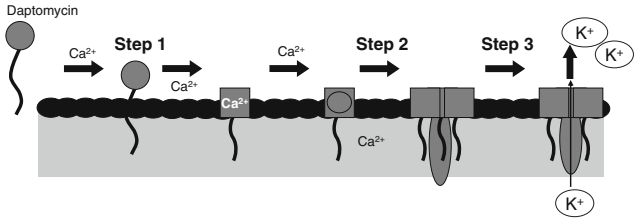

Fig. 1 Mechanism of action of daptomycin [48]. Reprinted with permission. *Step 1* calcium-dependent binding and insertion of the lipophilic tail into Gram-positive cytoplasmic membrane. *Step 2* oligomerization and channel formation occur. *Step 3* ion leakage and collapse of organism lead to cell death

was more active against all organisms tested, except *E. faecium* and VISA, against which its activity was similar to that of Q–D. In time-kill studies with MRSA, MRSE, VRE, and VISA, daptomycin demonstrated greater bactericidal activity than all others tested, killing ≥3 log CFU/mL within 8 h [51]. Daptomycin is also effective against a variety of streptococci, such as *β*-hemolytic streptococci and other *Streptococcus* spp. [52]. Susceptibility criteria are shown in Table 1. Synergy with daptomycin has been described in vitro with aminoglycosides, i.e., gentamicin, oxacillin, other *β*-lactams, and rifampicin [47, 53, 54]. Daptomycin exhibits a dose-dependent post-antibiotic effect lasting from 1 to 6 h against *E. faecalis* and *S. aureus* after exposure to concentrations ranging from 0.25 to 16 mg/L (i.e., between one- and eightfold the MIC) [55].

Pharmacology

With an 8-h half-life, once-daily dosing results in linear pharmacokinetics at doses up to 12 mg/kg, with minimal drug accumulation (Table 2) [47]. Daptomycin distributes primarily in the plasma, with penetration to vascularized tissues. The drug is highly protein-bound (92%); excretion occurs primarily via the kidneys. Approximately 80% of the total dose, of which two-thirds is intact drug, is recovered in the urine [47, 56]. In patients with severe renal impairment (creatinine clearance < 30 mL/min), the dosing interval is increased from once daily to every 48 h. Daptomycin's unique mechanism of action and its lack of metabolization by cytochrome P450 or other hepatic enzymes results in an absence of drug–drug interactions. Against 70 clinical isolates, interactions between daptomycin and 25 antimicrobials were additive or indifferent; antagonism was not observed. Synergistic interactions were observed between daptomycin and gentamicin against staphylococci and enterococci, including strains resistant to methicillin and vancomycin; in vitro synergistic interactions of daptomycin and rifampin have been shown against methicillin- and vancomycin-resistant staphylococci and enterococci [47, 56].

Skeletal muscle was the most sensitive tissue to the adverse effects of daptomycin in animal studies. Mild myopathy was easily predicted and monitored by measuring serum creatine phosphokinase concentrations; the effect was reversible upon the cessation of therapy [47, 56]. Dog studies demonstrated that adverse effects increased with fractionated compared with once-daily administration of the same total daily dose. Thus, once-daily dosing may increase the therapeutic-toxicity ratio by increasing efficacy and decreasing adverse effects [57].

Preclinical efficacy of daptomycin in bone and joint infection models

The efficacy of daptomycin against a range of infections has been demonstrated in animal studies. Using a variety of antibiotic-resistant and antibiotic-sensitive Gram-positive bacteria, daptomycin eradicated infections in the blood, muscle, kidney, heart, and bone tissues of animals [57–64]. In a rat model of chronic MSSA osteomyelitis, daptomycin 10 mg/kg subcutaneously every 12 h resulted in bacterial numbers similar to those of untreated animals, a finding

Table 1 Daptomycin susceptibility criteria [47]

Pathogen	Broth dilution MIC[a] (μg/mL)		
	S	I	R
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤1	[b]	[b]
Streptococcus pyogenes, *S. agalactiae*, and *S. dysgalactiae* sub-spp. *equisimilis*	≤1	[b]	[b]
Enterococcus faecalis (vancomycin-susceptible only)	≤4	[b]	[b]

I intermediate, *R* resistant, *S* susceptible

[a] The mean inhibitory concentration (MIC) interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth dilution using Mueller–Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth dilution using Mueller–Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2–5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20–24 h

[b] The current absence of data on daptomycin-resistant isolates precludes defining any categories other than "susceptible." Isolates yielding test results suggestive of a "non-susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing

Table 2 Pharmacokinetic parameters of daptomycin at steady-state in healthy subjects [47]

Dose (mg/kg)[a]	Pharmacokinetic parameters				
	AUC_{0-24} (μg h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (mL/h per kg)	C_{max} (μg/mL)
4 ($n = 6$)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 ($n = 6$)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 ($n = 6$)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 ($n = 9$)	1,039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 ($n = 9$)	1,277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; $t_{1/2}$, terminal elimination half-life; V_{ss}, volume of distribution at steady-state; CL_T, plasma clearance; C_{max}, maximum plasma concentration

[a] Doses of daptomycin > 6 mg/kg have not been approved

possibly related to underdosing [65]. Examination of several doses of daptomycin in an experimental murine *S. aureus* thigh infection model demonstrated concentration-dependent bactericidal activity. A mean peak/MIC ratio of 255 or a mean 24-h area under the concentration–time curve (AUC)/MIC ratio of 1,061 was needed to effect a 2 $\log_{10}$ reduction in vivo [66].

Daptomycin reduced bacterial cultures of bone infected with *S. aureus* in an experimental osteomyelitis rabbit model [63]. Daptomycin was as effective as vancomycin at comparable peak plasma levels of approximately 33 μg/mL for the two drugs [63]. High-dose daptomycin was compared with standard regimens of oxacillin and vancomycin in a difficult-to-treat rat tissue cage model of chronic *S. aureus* foreign body infection, so called as perforated Teflon cylinders are implanted subcutaneously in rats, and infected, in this case with MSSA strain I20, a clinical isolate from catheter-related sepsis. In vitro elimination of strain I20 was more rapid with 8 mg/L of daptomycin than with oxacillin or vancomycin at the same dose. After 7 days of therapy, the mean (±SEM) reduction in viable counts of MSSA I20 was 2.62 (±0.30) $\log_{10}$ CFU/mL in cages ($n = 18$) of daptomycin-treated rats, exceeding by more than twofold ($P < 0.01$) the viable count reductions in cages of oxacillin-treated and vancomycin-treated rats, respectively [67]. A comparative experiment of daptomycin and vancomycin in a rabbit model of MRSA osteomyelitis found that ten rabbits given daptomycin 25 mg/kg per day showed a 90% infection clearance, nine rabbits treated with daptomycin 15 mg/kg per day showed a 66.67% clearance, and eight rabbits treated with vancomycin showed a 33.3% clearance. Untreated controls ($n = 15$) demonstrated only a 13.3% clearance [68].

Daptomycin in bone and joint infections

Daptomycin was initially approved in 2003 for the treatment of cSSIs caused by *S. aureus* (including methicillin-resistant strains), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae* sub-spp. *equisimilis*, and *E. faecalis* (vancomycin-susceptible strains only) at a dose of 4 mg/kg per day administered IV. More than 90% of vancomycin-resistant *E. faecalis* isolates have demonstrated an in vitro MIC ≤ the susceptible breakpoint for daptomycin, but the efficacy of daptomycin in treating clinical infections caused by these microorganisms has not been established in clinical trials [47]. In 2006, daptomycin was approved as a once-daily therapy (6 mg/kg) for the treatment of *S. aureus* bloodstream infections (bacteremia), including right-sided endocarditis caused by MSSA and MRSA [47].

The use of daptomycin has been investigated in bone and joint infections. Case records of a prospective, randomized trial of daptomycin alone versus gentamicin plus either semisynthetic penicillin or vancomycin for *S. aureus* bacteremia and endocarditis [8] were retrospectively assessed to identify patients in the trial with concomitant complicated bone and joint infections (i.e., osteomyelitis or septic arthritis). Bone and joint infections were found in 21 of 120 patients treated with daptomycin (17.5%) and 11 of 115 control patients (9.6%). Treatment success was achieved in 16 patients treated with daptomycin by the end of therapy (76.2%) and was maintained in 14 patients (66.7%) 6 weeks after the end of therapy. Seven of 11 control patients achieved a successful outcome by the end of therapy (63.6%), with 6 patients (54.6%) maintaining success 6 weeks later [69].

A second retrospective chart review of patients with osteomyelitis treated with daptomycin was conducted at six sites in the United States. Anatomic sites of infection included the lower extremity (45%), upper extremity (24%), vertebrae (21%), and sternum/chest wall (10%); 41% of patients had prosthetic material present. The most common pathogen isolated was MRSA (64%). Fifty-two percent of patients received an antibiotic within 4 weeks of daptomycin treatment (vancomycin in 67% of cases). Forty-five percent of patients started daptomycin because previous therapy had failed. The median daptomycin dosage was 4.2 mg/kg (range 3.5–7.1 mg/kg), and the median

duration of therapy was 42 days (range 18–63 days). Forty-eight percent of patients received an antibiotic along with daptomycin, most commonly rifampin. Outcomes at end of therapy were cure (16/29, 55%), improved (10/29, 34%), and failure (3/29, 10%). Outcomes at follow-up were cure (19/29, 65%), improved (1/29, 3%), and failure (9/29, 31%). Clinical success (i.e., cure plus improved) was achieved with daptomycin in 90% of patients with osteomyelitis by the end of therapy, despite the large percentage who had failed treatment with prior antibiotics. Clinical success was maintained in 69% of patients at ≥6 months' follow-up. During the study period, there were six adverse events reported in six patients, all mild to moderate in severity [70].

Three case series on the use of daptomycin in bone and joint infections included 22 male and 31 female patients with a mean age of 65.8 years [33, 41, 71, 72]. Osteomyelitis was diagnosed in 43% of patients; other infections included total joint arthroplasty, laminectomy site infection, knee abscess, and bacteremia associated with septic arthritis. MRSA was isolated as the pathogen in 74% of patients, and more than one pathogen was isolated in 11% of cases. Daptomycin was given at a dosage of 4–6 mg/kg per day for a mean duration of 37.4 days. Patients were previously treated with antibiotics such as vancomycin, rifampicin, ciprofloxacin, linezolid, and Q–D. Cure of infection was achieved with daptomycin in 81% of cases, with a cure rate of 100% among patients with osteomyelitis and 60% of total joint arthroplasty infection cases. Development of non-susceptibility to daptomycin occurred in one case of MRSA infection of an epidural abscess [33]. A summary of ten patients from one case series who were treated with daptomycin for various bone and joint infections is shown in Table 3. Whether the effectiveness of treatment of bone and joint infection in each of these three case series can be solely attributed to daptomycin is uncertain, since other antibiotics were co-administered in most of the cases [41]; however, as previously stated, most of these patients had been treated with other antibiotics that did not result in a positive outcome, necessitating the change to daptomycin.

The outcomes of 25 patients with foot or ankle osteomyelitis who were treated with daptomycin at a median dose of 6 mg/kg (range 4–6.2 mg/kg) for a median duration of 38 days (range 6–59 days) were recently reported [73]. Twenty-three patients received daptomycin as secondary or tertiary therapy, primarily because they had not responded to prior antibiotic treatment ($n = 15$). Concomitant antibiotics were given to 11 patients, mostly for Gram-negative and/or anaerobic coverage. MRSA was the most common pathogen overall (15 of 25 patients). At the end of therapy, 16 patients' symptoms had resolved, eight patients improved, and one patient did not respond to therapy. At a median follow-up of 9 weeks, 19 patients' symptoms resolved, three patients improved, and three patients did not respond to therapy. Additional antibiotics were given to 52% of patients for a minimum of 8 days (median 30 days, range 8–232 days). Four patients with an implant (all removed) were successfully treated. Daptomycin appeared to be effective for previously treated foot and ankle osteomyelitis caused by Gram-positive bacteria in this trial, warranting additional controlled clinical studies of daptomycin as an alternative agent for patients with bone and joint

Table 3 Case summary of patients with bone and joint infections treated with daptomycin [33]

Patient number	Age/gender	Diagnosis	Pathogen	Prior antibiotic	DAP duration (days)	Resolution[a]
Rush Presbyterian St. Luke's Medical Center						
1	47/F	Osteo	MRSA	VAN	8	Yes
2	41/M	Septic joint, bact	MRSA	None	44	Yes
3	87/F	Septic arthritis, bact	MRSA	VAN, GEN	41	Relapse
4	67/F	Septic joint	Entero	VAN	4	Yes (w/amp)[b]
Fountain Valley Regional Hospital						
5	58/F	Septic arthritis, osteo, bact	MRSA	VAN, LIN, QUI	42	Yes
6	57/F	Osteo, wound infection	MRSA	VAN	35	Yes
7	83/F	Osteo	MRSA	VAN, QUI, LIN, MIN/RIF	28	Yes
8	72/M	Osteo	MRSA	VAN	21	Yes
9	67/F	Osteo, septic arthritis	MRSA	VAN, QUI, CEF, LIN	28	Yes
10	39/F	Osteo	Strep	CEF	42	Yes

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Osteo osteomyelitis, *bact* bacteremia, *MRSA* methicillin-resistant *Staphylococcus aureus*, *Entero Enterococcus faecalis*, *Strep* presumed streptococcus infection (no cultures available), *VAN* vancomycin, *GEN* gentamicin, *LIN* linezolid, *QUI* quinupristin/dalfopristin, *MIN/RIF* minocycline/rifampin, *CEF* cefepime, *DAP* daptomycin

[a] Resolution of signs and symptoms associated with the infection and discharge from the hospital

[b] Patient was switched to ampicillin once the pathogen was identified and was successfully treated

infections who are intolerant to other antibiotics or fail to improve. In a recent case report, continual daptomycin use for 18 months in a patient with MRSA osteomyelitis is noteworthy because of the extended duration of daptomycin use without significant toxicity and because of ultimate efficacy in treating the infection [74]. To date, no randomized, controlled trials comparing the effectiveness and safety of daptomycin with other antibiotics used to treat bone and joint infections have been completed [41].

The Cubicin Outcomes Registry and Experience (CORE) is a multicenter retrospective observational database containing information about patients treated with daptomycin in clinical practice. The characteristics and outcomes of patients with osteomyelitis who were treated with daptomycin were retrospectively evaluated from the CORE 2004 database [75]. Of the 67 patients with osteomyelitis who were clinically evaluable at the end of daptomycin therapy, 42 (63%) were cured, 13 (19%) were improved, 7 (10%) had failure, and 5 (7%) were nonevaluable. In about one half of the cases (48%), daptomycin was given concurrently with other antimicrobial agents; MRSA comprised 45% of the pathogens. Success occurred at a 94% rate when daptomycin was used alone, with no antimicrobial agents following it. These results indicate that daptomycin can be effectively used in clinical practice to treat osteomyelitis caused by a Gram-positive organism, including MRSA [75].

Antibiotic-loaded polymethlymethacrylate bone cement

Polymethlymethacrylate (PMMA) bone–cement spacers have been used in the revision of infected prosthetic joints and in the placement of orthopedic implants in patients at high risk for infection. The ability to deliver high local concentrations of antimicrobial agents with PMMA has made it a standard of care for patients with chronic infection at the site of a total joint replacement. The most commonly used antibiotics include tobramycin, gentamicin, vancomycin, and cephalosporins [76, 77].

A Mayo Clinic study recently evaluated the elution of daptomycin from PMMA in a continuous flow chamber designed to simulate in vivo conditions. Three-millimeter beads containing 2.5, 7.5, and 15.0% daptomycin (weight daptomycin per weight PMMA) were individually placed in a chamber with 1 mL Krebs Ringer buffer flowing at 1 mL/h. The majority of daptomycin was released in the first 24 h. When treating osteomyelitis, achieving the highest local concentration of antimicrobial is important. In this study, daptomycin eluted from 3-mm PMMA beads in a continuous flow chamber more completely than did vancomycin when tested at the same laboratory [78]. By doubling the amount of daptomycin in PMMA, local peak concentrations of drug were significantly increased [77]. In a recent study in which daptomycin was mixed with calcium sulfate hemihydrate to form a hardened pellet, daptomycin eluted from calcium sulfate for up to 28 days retained the ability to inhibit growth of *S. aureus* and *S. epidermidis* [79].

Resistance to daptomycin

As with all antibiotics, orthopedic cases of resistance to daptomycin have been reported, including patients with vertebral or sternal osteomyelitis, diskitis, and septic arthritis [80–82], all positive for MRSA. Interestingly, patients in all four reports had received previous vancomycin treatment. A positive correlation between reduced daptomycin susceptibility and vancomycin resistance in VISA has been reported. Similar to the mechanism of vancomycin resistance, the physical barrier of a thickened cell wall may contribute to *S. aureus* resistance to daptomycin [83]. However, a definitive mechanism of resistance to daptomycin has not yet been identified, and there are no known transferable elements conferring resistance to the drug. The isolation of glycopeptide-intermediate *S. aureus* (GISA) is rare (i.e., $\leq$0.3%) [84], and cross-resistance of daptomycin with vancomycin is seen in only a fraction of GISA isolates. Of 15 GISA isolates, 86.7% were susceptible to daptomycin, as reported in the US SENTRY Antimicrobial Surveillance Program [85]. Among almost 10,000 isolates tested, only four (0.04%) had a daptomycin MIC of 2 μg/mL (all were glycopeptide-susceptible *S. aureus*); only two (0.02%) GISA isolates were found (vancomycin MIC 4 μg/mL; daptomycin MIC 0.5–1.0 μg/mL) [86, 87].

To date, daptomycin has been largely used as salvage therapy following vancomycin failure [88, 89]. In the study by Fowler et al. [8], most patients had received vancomycin therapy for a mean of 2 days before starting either daptomycin or standard therapy. A post hoc analysis of MRSA-infected patients from this study reported that previous vancomycin therapy did not affect the clinical outcome of daptomycin-treated patients [90, 91]. Nonetheless, the activity of daptomycin against MRSA may be best exploited in patients who are treated with daptomycin early; heavy exposure to vancomycin prior to treatment with daptomycin may increase the likelihood of a suboptimal response [92].

Summary

Gram-positive organisms, particularly *S. aureus*, are responsible for the majority of bone and joint infections. The prevalence of increasingly resistant organisms is a major concern, both for achieving therapeutic success and