Daptomycin

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Daptomycin, the first in a class of agents known as lipopeptides, is a novel antimicrobial agent used for the treatment of gram-positive infections. The compound has a distinctive mechanism of action that exerts its bactericidal activity by disrupting plasma membrane function without penetrating into the cytoplasm. The agent has received much interest because of its activity against multidrug-resistant, gram-positive bacteria such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and glycopeptide-intermediate and -resistant S. aureus. Daptomycin demonstrates concentration-dependent killing and is eliminated primarily by glomerular filtration. It was approved in September 2003 for the treatment of complicated skin and soft tissue infections. It has a safety profile similar to other agents commonly administered to treat gram-positive infections. Daptomycin is a welcome addition to the antimicrobial armamentarium for the treatment of bacterial infections. Further clinical experience with this compound will help define its role in the treatment of resistant gram-positive organisms.

Key Words: daptomycin, methicillin-resistant Staphylococcus aureus, multidrug resistant, lipopeptide, concentration-dependent activity, bactericidal, gram positive, resistance, GISA, VRSA.

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The past 10 years have seen a nearly 25% increase in resistance among gram-positive pathogens in the United States, most notably, staphylococci, enterococci, and streptococci. These isolates are increasingly widespread and pose an immense challenge to health care. Presently, 95% of clinical Staphylococcus aureus isolates in the United States are penicillin resistant and more than 50% are methicillin resistant.1, 2 The most frightening trend is the appearance of vancomycin-resistant S. aureus (VRSA) and Enterococcus species (VRE) in the United States.3–5 The Centers for Disease Control and Prevention report that more than 70% of bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly given to treat those organisms.6

Common infections of skin and soft tissue, pneumonia, and osteomyelitis, and more severe infections such as endocarditis and meningitis are frequently caused by gram-positive organisms.5, 7–11 Despite continued advances in medical practice, vaccinations, and stringent isolation policies, multidrug-resistant bacteria continue to infect worldwide at alarming rates. Effective treatment options are limited, finding appropriate cures is an immense challenge, and unfortunately, since 1980, few new classes of antimicrobial agents have been introduced to combat these infections. This warrants development of effective therapies to treat these ever-changing multidrug-resistant gram-positive bacteria.

Daptomycin (LY-146032, Cubicin; Cubist Pharmaceuticals, Lexington, MA) is a lipopeptide antimicrobial agent that was approved in September 2003 for treatment of complicated skin and soft tissue infections.12 It has received much attention because of its rapid in vitro bactericidal activity against a broad range of multidrug-resistant gram-positive pathogens including methicillin-resistant S. aureus (MRSA), glycopeptide-intermediate S. aureus (GISA), VRSA, VRE, and penicillin-resistant Streptococcus pneumoniae.13

Originally discovered and developed in the early 1980s by Eli Lilly and Company (Indianapolis, IN), daptomycin showed great promise in treating serious gram-positive infections. Trials conducted into the early 1990s involved several hundred subjects. Eli Lilly reported promising efficacy when the compound was administered for blood stream infections, endocarditis, and complicated skin and soft tissue infections; however, dosages of 4 mg/kg every 12 hours caused effects such as forearm weakness, myalgias, and elevated creatine kinase levels in some subjects. Although these effects were entirely reversible with no longstanding damage upon discontinuation of the drug, in 1991 Eli Lilly, without publicly explaining the decision, put clinical investigations on hold. In 1997, Cubist Pharmaceuticals licensed the worldwide rights to the agent with the intent of developing it for treatment of serious gram-positive infections. Clinical trials began in the United States and Europe in 1999.

Chemistry and Structure

Daptomycin is a 13-member amino acid cyclic lipopeptide compound that contains a water-soluble hydrophilic core with a lipophilic tail (Figure 1).14 The N-terminal is a 13-member amino acid peptide linked to a decanoyl side chain; the C-terminal residue is linked to the molecule by an ester bond on the hydroxyl side.
DAPTOMYCIN  Tedesco and Rybak

Mechanism of Action

Daptomycin exerts its mechanism of action on the cell membrane of gram-positive bacteria. Several in vitro studies showed that its effects on the cell membrane are concentration dependent, rapid, and unlike that of any other antibiotic. Early studies suggested that lipoteichoic acid biosynthesis was the target site for daptomycin’s mechanism of action; however, more recent publications reported bactericidal activity against Staphylococcus and Enterococcus isolates even without the presence of lipoteichoic acid synthesis.

A multistep model for daptomycin’s mechanism of action was proposed (Figure 2). It is believed that the agent exerts its bactericidal activity by disrupting plasma membrane function without penetrating into the cytoplasm. The acyl tail portion of the compound binds and inserts itself into the cytoplasmic membrane and forms a channel that causes depolarization of the membrane. This depolarization is correlated with daptomycin’s bactericidal activity. In particular, attachment to the cytoplasmic membrane forms ion-conducting structures that allow efflux of potassium (and possibly other) cytoplasmic ions, thus inhibiting macromolecular synthesis and leading to cell death. Although this action is lethal, it does not rupture the cell wall but leaves an intact ghost cell behind.

Perhaps this mechanism may lessen the immune response from sudden release of exotoxin proteins.

The specific nature of the conducting structure is under investigation, but larger molecules (molecular weight > 600 daltons) are not released from cytoplasm of daptomycin-treated cells, suggesting that the antibiotic forms a nonspecific pore. This mechanism was shown by investigators who compared two levels of depolarization against various levels of viability. The findings of this analysis were 2-fold. First, the study supported the role of the membrane potential in daptomycin’s mechanism of action, and second, it indicated that the depolarization is dose dependent. The drug’s mode of action is dependent on physiologic levels of free calcium ions, shown by virtually nonexistent activity without the presence of this ion.

The morphostructural mechanism of daptomycin’s killing originally was evaluated by atomic force microscopy (AFM). This technique allows for high-resolution visualization and digital image manipulation of cell surface structures in three dimensions. Experiments conducted against Bacillus cereus over 8 hours using AFM revealed that the organism displays uncharacteristic bacterial surface formations, including flattening and shrinking of cells when it comes in contact with daptomycin.

Spectrum of Activity

Gram-Positive Activity

In vitro studies confirmed the activity of daptomycin in several thousand clinical strains of multidrug-resistant and -susceptible gram-positive bacteria.

Figure 2. Daptomycin’s mechanism of action. Step 1: Calcium-dependent binding and insertion of the lipophilic tail into gram-positive cytoplasmic membrane. Step 2: Oligomerization and channel formation occurs. Step 3: Ion leakage and collapse of organism lead to cell death.
positive organisms (Table 1). \textsuperscript{18–31} Most promising is daptomycin’s potency against organisms that are resistant to first-line therapeutic options. Organisms such as MRSA and coagulase-negative staphylococci consistently have shown minimum inhibitory concentrations where 90% are susceptible (MIC\textsubscript{90}) at 0.5 \( \mu \)g/ml. \textsuperscript{18, 19, 32, 33} In addition to the several hundred MRSA isolates tested, numerous GISA isolates and Michigan and Pennsylvania VRSA isolates were susceptible to daptomycin, with MICs of 0.13–1.0 \( \mu \)g/ml. \textsuperscript{18, 20–22, 33, 34} Reported MICs are consistently below or at a tentative breakpoint of 1 \( \mu \)g/ml or less for this species. \textsuperscript{23}

Daptomycin also has activity against most \textit{Enterococcus} sp, including VRE, with reported MIC\textsubscript{90}s of 0.5–1.0 \( \mu \)g/ml. \textsuperscript{19, 20, 22, 24, 25} Susceptibility interpretative breakpoints approved by the United States Food and Drug Administration are listed in Table 2.\textsuperscript{14}

### Table 1. In Vitro Susceptibility Testing of Several Multidrug-Resistant and -Susceptible Gram-Positive Organisms Against Daptomycin

| Organism                      | No. of Isolates | MIC\textsubscript{90} | MIC Range (\( \mu \)g/ml) |
|-------------------------------|-----------------|------------------------|-----------------------------|
| \textit{Enterococcus faecalis} |                 |                        |                             |
| Vancomycin susceptible\textsuperscript{19, 20, 24} | 2200            | 1.0–2.0                | 0.015–4.0                   |
| Vancomycin resistant\textsuperscript{19, 22, 28} | 231             | 0.5–4.0                | 0.25–8.0                    |
| \textit{Enterococcus faecium}  |                 |                        |                             |
| Vancomycin susceptible\textsuperscript{20, 24} | 358             | 1.0–4.0                | 0.5–8.0                     |
| Vancomycin resistant\textsuperscript{19, 20, 22, 24, 25} | 249             | 1.0–4.0                | 0.25–4.0                    |
| \textit{Listeria monocygnogenes} \textsuperscript{23} | 25              | 4.0                    | 2.0–8.0                     |
| \textit{Staphylococcus aureus} |                 |                        |                             |
| Glycopeptide intermediate\textsuperscript{21, 25, 29} | 22              | 4.0                    | 0.5–16                      |
| Methicillin resistant\textsuperscript{19, 20, 22, 25, 27, 29, 30} | 711             | 0.25–1.0               | 0.06–2.0                    |
| Methicillin susceptible\textsuperscript{19, 20, 22, 25, 27, 29, 30} | 1473          | 0.5–1.0                | 0.015–2.0                   |
| Vancomycin intermediate\textsuperscript{20, 21} | 47              | 1.0                    | 0.0625–2.0                  |
| Vancomycin resistant\textsuperscript{23, 2} | 2              | NA                     | 0.25–1                      |
| \textit{Staphylococcus coagulase negative} \textsuperscript{19, 23–25} |                 |                        |                             |
| Methicillin resistant\textsuperscript{19, 20, 22, 24, 25} | 954             | 0.5–1.0                | 0.004–1.0                   |
| Methicillin susceptible\textsuperscript{19, 20, 24, 25} | 728             | 0.25–2.0               | 0.03–0.5                    |
| \textit{Staphylococcus epidermidis} \textsuperscript{25} |                 |                        |                             |
| Methicillin resistant\textsuperscript{20, 25} | 65              | 0.25–0.5               | 0.12–1.0                    |
| Methicillin susceptible\textsuperscript{20, 25} | 66              | 0.25                    | 0.06–1.0                    |
| \textit{Staphylococcus sp} |                 |                        |                             |
| \textit{S. haemolyticus}\textsuperscript{22, 23, 25, 30} | 56              | 0.25–0.5               | 0.03–1.0                    |
| \textit{S. saprophyticus}\textsuperscript{17} | 30              | 0.5                    | 0.25–1.0                    |
| \textit{Streptococcus sp} |                 |                        |                             |
| Group G\textsuperscript{27} | 10             | 0.06                    | 0.015–0.06                  |
| \textit{S. milleri} \textsuperscript{27} | 30              | 1.0                     | 0.25–1.0                    |
| \textit{S. pyogenes}\textsuperscript{19, 22, 25, 30} | 340             | 0.06                    | 0.015–0.5                   |
| \textit{S. viridans}\textsuperscript{19, 22, 23, 30} | 126             | 1.0–2.0                 | 0.016–8.0                   |
| \textit{S. agalactiae} \textsuperscript{22} | 81              | 0.25                    | 0.12–0.25                   |
| \textit{Streptococcus pneumoniae} \textsuperscript{22} |                 |                        |                             |
| Penicillin intermediate\textsuperscript{19, 24, 25, 28} | 389             | 0.25–1.0               | 0.008–1.0                   |
| Penicillin resistant\textsuperscript{19, 24, 25, 28} | 267             | 0.25–1.0                | 0.015–1.0                   |
| Penicillin susceptible\textsuperscript{19, 24, 25, 28} | 1166           | 0.25–0.5               | 0.015–0.5                   |

MIC\textsubscript{90} = minimum inhibitory concentration for 90% of strains tested; NA = not applicable.

\textsuperscript{a} Based on two isolates, Michigan and Pennsylvania.
activity in vitro. In a study of the drug's activity against clinical gram-positive anaerobic bacteria and Corynebacteria, daptomycin was active against all tested strains of Clostridium difficile, Clostridium perfringens, and Propionibacterium sp, and several strains of peptostreptococci and the Eubacterium group. Table 3 shows reported MICs for this group.

**Pharmacokinetics**

The pharmacokinetics of daptomycin are summarized in Table 4. In ongoing clinical
trials, the intravenous dose of 6 mg/kg actual body weight administered once/day has demonstrated promising results with few adverse effects. With once-daily administration, daptomycin has linear kinetics, as seen with intravenous doses of 1–8 mg/kg given after repeated once-daily doses.\textsuperscript{60–62} In healthy men and women, first doses of 4, 6, and 8 mg/kg body weight yielded mean plasma daptomycin maximum concentration ($C_{\text{max}}$) values of 55, 86, and 116 µg/ml, respectively, with a mean area under the plasma concentration–time curve from 0–24 hours (AUC\textsubscript{0–24}) ranging from 425–1127 µg•hour/ml; protein binding ranged from 90–94%, and the mean ± SD elimination half-life was $7.74 ± 0.63$ hours with minor individual variations.\textsuperscript{51, 63, 64} After 7 days of once-daily administration of 4 mg/kg, $C_{\text{max}}$ values were 57.8, 98.6, and 133 µg/ml, respectively.\textsuperscript{61} Mean urine recovery of unchanged drug over 24 hours ranged from 53–59.7 ± 10.2%.\textsuperscript{64} In the same study daptomycin 4 mg/kg had penetration into skin inflammatory fluid blisters at 1 and 2 hours of 9.4 and 14.5 µg/ml, respectively. When penetration of inflammatory fluid was compared with plasma concentrations, the mean AUC\textsubscript{0–24} ratio was 68.4% (coefficient of variation 29.1%).\textsuperscript{64}

In early clinical trials, daptomycin's pharmacokinetics in sick patients did not differ noticeably from those in healthy volunteers.\textsuperscript{64} However, in a study of the agent's pharmacokinetics and bactericidal killing rates in six intravenous drug abusers, peak serum concentrations were lower and volumes of distribution were higher than reported in healthy volunteers.\textsuperscript{65} In addition, but not statistically different, daptomycin’s clearance was 22% higher than reported in healthy volunteers.\textsuperscript{65} In this study and later efficacy studies, the pharmacodynamic properties of daptomycin in S. aureus were assessed in a neutropenic mouse thigh model.\textsuperscript{71} In single doses ranging from 0.1–200 mg/kg, daptomycin’s dose-response was best described by a maximal effect ($E_{\text{max}}$) sigmoidal curve. Investigators performed dose-fractionated studies with doses given every 24 hours and divided doses given every 12 and 6 hours; they reported no difference in effect at each fraction of the total dose, concluding that the AUC:MIC ratio predicts the agent's pharmacodynamic activity. Another dose-fractionated study tested daptomycin’s efficacy

### Pharmacodynamics

Pharmacodynamic and toxicology studies were pivotal in establishing daptomycin’s once-daily dosing regimen. In the early 1980s, regimens ranging from 2–4 mg/kg every 12 hours were tested in clinical trials and were successful in treating a variety of gram-positive infections.

| Parameter Value |
|-----------------|
| Maximum concentration (µg/ml) | 77.5 |
| Half-life (hrs) |
| Healthy volunteers | 8 |
| Patients with renal failure | 28 |
| Serum protein binding (%) | 92 |
| Volume of distribution (L) | 7 |
| AUC\textsubscript{0–24} (mg•hr/L) | 468 |
| Systemic clearance (ml/hr/kg) | 8.2 |
| Urinary excretion (%) | 60 |

$\text{AUC}_{0–24} = $ area under the plasma concentration–time curve from 0–24 hours.

However, these regimens caused effects on skeletal muscle as seen by increases in creatine kinase levels. Fortunately, these effects were reversible with discontinuation of the drug. There were few reported cases of clinical failure at suboptimal serum concentrations with dosages of 2 mg/kg/day for sequestered infections.\textsuperscript{68} Several key pharmacodynamic efficacy investigations\textsuperscript{13, 62, 69, 70} reported that once-daily administration optimized daptomycin’s pharmacodynamic properties while diminishing dose-dependent side effects, hence maximizing both safety and efficacy.

A series of studies reevaluated the pharmacodynamics with dosing once/day.\textsuperscript{62} Two combined studies were conducted in beagle dogs to help guide clinical dosing schedules that allowed for the most effective dose with the least effect on skeletal muscle. Data from this study suggested that skeletal muscle effects were more closely related to the dosing interval than to $C_{\text{max}}$ or AUC.\textsuperscript{62} Based on the information provided in this study and later efficacy studies, once-daily intravenous doses of 4 mg/kg actual body weight were evaluated in clinical trials with promising results and few adverse effects.

The pharmacodynamic properties of daptomycin in S. aureus were assessed in a neutropenic mouse thigh model.\textsuperscript{71} In single doses ranging from 0.1–200 mg/kg, daptomycin’s dose-response was best described by a maximal effect ($E_{\text{max}}$) sigmoidal curve. Investigators performed dose-fractionated studies with doses given every 24 hours and divided doses given every 12 and 6 hours; they reported no difference in effect at each fraction of the total dose, concluding that the AUC:MIC ratio predicts the agent’s pharmacodynamic activity. Another dose-fractionated study tested daptomycin’s efficacy
against vancomycin-resistant isolates of *E. faecalis* and MRSA using targeted and clinically achievable doses in humans (4–6 mg/kg). It also reported that the AUC/MIC ratio had the closest correlation to bactericidal activity.

Further characterizing the pharmacodynamics of daptomycin, modeling studies reported the efficacy of once-daily dosing. Investigators examined regimens of 0–9 mg/kg/day against clinical *Staphylococcus* and *Enterococcus* isolates. A sigmoid dose-response model was used to estimate the effective doses required to achieve 50% kill (ED$_{50}$) and 80% kill (ED$_{80}$). Doses of 3–7 mg/kg produced significant bactericidal activity (ED$_{80}$) against MSRA and *E. faecium* isolates tested. A Monte Carlo prediction model analysis was conducted using data obtained from this study to determine if AUC/MIC targets could be achieved in a clinical setting. An AUC$_{free}$:MIC of 189 generated maximum-kill ED$_{80}$ in the model against all pathogens. The Monte Carlo simulations predicted the probability of achieving an AUC$_{free}$:MIC ratio of 189 to be predictive of 80.4%, 91.06%, and 95.64% for doses of 4, 6, and 8 mg/kg once/day. Data from several pharmacodynamic studies support the once-daily regimen and suggest that efficacy against *S. aureus* will be achieved at 4 mg/kg/day.

**Bactericidal Activity**

Several in vitro studies comparing antibiotics typically administered to treat gram-positive infections showed daptomycin to have the most rapid and consistent bactericidal activity against all organisms tested. In time-kill analyses comparing daptomycin with vancomycin, linezolid, and quinupristin-dalfopristin against *Staphylococcus* and *Enterococcus* sp, including vancomycin-intermediate and -resistant strains, daptomycin had greater bactericidal activity than the other drugs, with 3 log kill or greater in 8 hours. Other studies expanded these findings and found daptomycin to be active against most clinical isolates tested, with MICs of 0.006–2.0 µg/ml. Investigators assessed the impact of high-inoculum (9 log$_{10}$ colony-forming units [cfu]/g) *S. aureus* on the activities of nafcillin, vancomycin, linezolid, gentamicin, and daptomycin in an in vitro pharmacodynamic model with simulated endocardial vegetations over 72 hours. High inoculum had a major impact on nafcillin and vancomycin against methicillin-susceptible *S. aureus* (MSSA) and MRSA, respectively, over the 72-hour experiment. The drugs’ bactericidal activity improved with the addition of gentamicin. When tested at a moderate inoculum (6 log$_{10}$ cfu/g), nafcillin and vancomycin mimicked the efficacy of daptomycin and demonstrated bactericidal kill. Daptomycin was minimally affected by a high inoculum. These findings may be helpful in sequestered high-inoculum infections, which are often difficult to eradicate due to an inoculum effect, antibiotic penetration, and stationary-phase organisms.

**Postantibiotic Effect**

Daptomycin had a dose-dependent postantibiotic effect (PAE) in pharmacodynamic studies. Postantibiotic effect is defined as bacterial growth suppression that persists after exposure to an antimicrobial agent. It reflects the time it takes for an organism to recover from the effects of the drug and resume normal growth. This effect varies depending on the pharmacodynamic interaction for each microorganism-antimicrobial combination. Daptomycin has a dose-dependent PAE that lasts over 6 hours in the presence of physiologic free calcium concentrations. It was evaluated at clinically achievable levels of 8–16 µg/ml with both *S. aureus* and *E. faecalis* isolates.

**Protein Binding**

Daptomycin has a high affinity for protein, with in vivo protein binding of 90–94%. In the presence of albumin, there is little effect on daptomycin’s MIC values, with only a 2-fold increase. However, the MICs in the presence of 50% serum against MSSA, MRSA, methicillin-sensitive *S. epidermidis* (MSSE), methicillin-resistant *S. epidermidis* (MRSE), *E. faecium*, and vancomycin-intermediate *S. aureus* (VISA) isolates increased 1–8-fold.

Another in vitro study examined the effect of daptomycin in the presence of albumin in a time-kill model. The medium was infused to obtain physiologic concentrations of albumin (4 g/dl) in the presence of cryoprecipitate AHF (coagulation factor VIII:c, factor XIII, fibrinogen, von Willebrand factor, and fibronectin). Daptomycin concentrations mimicked total peaks of 80 µg/ml, which are equivalent to concentrations achieved by dosages of 6 mg/kg/day in healthy volunteers. The killing curves showed no difference in kill rates between the albumin supplemental medium...
A related pharmacodynamic study assessed the efficacy of low-dose (2 mg/kg) and high-dose (6 mg/kg) once-daily daptomycin against a clinical isolate of *S. aureus*, each in the presence and absence of physiologic human albumin concentrations. The average time required for a 99.9% kill of the initial *S. aureus* inocula at 2 mg/kg was 0.81 hours without albumin and 7.66 hours with albumin, indicating that albumin has a significant effect on delaying the drug’s activity. At 6 mg/kg the average time required for 99.9% kill of the initial *S. aureus* inocula without albumin was 0.33 hours and 0.95 hours with albumin. Thus in the presence of albumin, time to bactericidal activity (99.9% kill) was delayed at doses equivalent to 2 mg/kg. However, the end point was not different when doses were equivalent to 2 mg/kg with or without the presence of albumin.

**Synergy**

Several studies investigated combination therapy with daptomycin, most commonly against *Enterococcus* sp. Enterococci, although susceptible, have a traditionally higher MIC₉₀, therefore making it easier to demonstrate additivity or synergy to these isolates. The rapid bactericidal activity seen with daptomycin against staphylococci and streptococci alone make it difficult to demonstrate additivity or synergy.

Synergy was noted in 68% of 18 VRE isolates when daptomycin was combined with rifampin, using an agar Etest screening method; that result was confirmed with traditional time-kill methodologies. An earlier study reported similar results with slightly enhanced activity when combining rifampin or tobramycin with daptomycin. The in vitro synergistic activities of daptomycin were determined for 44 *E. faecalis*, *E. faecium*, and *Enterococcus avium* isolates. Daptomycin monotherapy had excellent bactericidal activity against all enterococci tested by time-kill curves, and when combined with ampicillin, daptomycin had synergistic bactericidal activity against *E. faecalis* isolates. All published works expressed additivity, synergy, or enhanced effect when combining various concentrations of daptomycin with ampicillin against *E. faecium*.

Daptomycin alone or in combination with an aminoglycoside was investigated as an alternative therapy for ampicillin-resistant enterococci. In an in vitro time-kill experiment, daptomycin alone had marked activity against an ampicillin-resistant *E. faecium*, and the addition of gentamicin resulted in synergistic killing. A similar bactericidal response to gentamicin-daptomycin combination therapy was suggested against *Enterococcus* sp by both checkerboard assay method and time-kill studies. A handful of studies tested daptomycin against gentamicin or tobramycin and found greater or enhanced bactericidal activity. No antagonism has been noted with daptomycin and aminoglycosides against *Enterococcus* sp and MRSA isolates.

Combination therapy with daptomycin and aminoglycosides is effective against *Staphylococcus* sp. Combination of daptomycin and the aminoglycoside arbekacin resulted in synergistic activity against Mu-50 and HIP5836, which are GISA isolates from Japan and New Jersey. An additional result of this study was no antagonism with vancomycin and gentamicin in combination with daptomycin. However, a comparable study with both MRSA and MSSA isolates showed no greater additivity at the 72-hour point when gentamicin was added to daptomycin. Bactericidal activity (99.9% kill) was seen as early as 12 hours with combination therapy, whereas daptomycin alone demonstrated bactericidal activity at 24 hours.

**Administration**

Daptomycin 4 mg/kg once/day for complicated skin and soft tissue infections is undergoing phase III trials. A dosage of 6 mg/kg once/day in endocarditis and bacteremia also is being studied. The intravenous infusion has been well tolerated at 30-minute intervals.

**Renal Insufficiency and End-Stage Renal Disease**

Daptomycin is excreted primarily through the kidneys and is concentrated during glomerular filtration. In animals and humans, approximately 80% is excreted by the kidneys, with 50% of the total dose recovered in urine as intact, active drug. Dosage adjustment is necessary in patients with decreased or nonexistent renal function. Investigators evaluated 44 subjects aged 35–75 years who were assigned to one of four treatments based on creatinine clearance (Clₑ). Subjects given daptomycin 4 mg/kg intravenously over 30 minutes were placed into one of the following groups: Clₑ greater than 80 ml/minute, Clₑ between 40 and 80 ml/minute,
and Cl\textsubscript{cr} below 40 ml/minute. Also included were patients with end-stage renal disease and 13 receiving hemodialysis and 5 continuous ambulatory peritoneal dialysis (CAPD) with exchanges containing daptomycin remaining in the abdomen for 6 hours. The half-life of daptomycin in patients undergoing hemodialysis was 36.7 hours and the volume of distribution was 0.154 L/kg. Respective figures in patients receiving CAPD were 31.3 hours and 0.125 L/kg. Daptomycin’s clearance was correlated with Cl\textsubscript{cr}. The authors recommended that patients with end-stage renal disease or an estimated Cl\textsubscript{cr} of 40 ml/minute or below require a dosage adjustment of 4 mg/kg once every 48 hours.

Hepatic Failure

The pharmacokinetics of daptomycin are not significantly altered in patients with hepatic impairment; therefore, no dosage adjustments are necessary.

Mechanisms of Antimicrobial Resistance

In vitro studies showed conflicting results regarding resistance with daptomycin.\textsuperscript{85–87} Typically, in vitro emergence of bacterial resistance most commonly occurs by spontaneous mutations, serial passage, or chemical mutagenesis and often can be reproduced in laboratory settings. Daptomycin’s mechanism of action is directed at the bacterial cell wall, which typically has a relatively slow rate of inheriting resistance, whereas agents targeting ribosomal DNA usually acquire mutational resistance at a much faster rate. In a clinical trial in the 1990s, development of resistance in an S. aureus isolate was thought to have resulted in treatment failure in an intravenous drug user with S. aureus endocarditis.\textsuperscript{85–87} The patient had persistent bacteremia, with low daptomycin dosages and blood levels (peak 22.5 µg/ml, 9.1 µg/ml at 8 hrs, 6.7 µg/ml at 12 hrs). The starting dosage of daptomycin was 3 mg/kg every 12 hours but was adjusted shortly after admission to less than 1.6 mg/kg due to the patient’s decreased renal function. Once the patient was rehydrated and the calculated creatinine clearance was within the normal range, the dosage was not increased. Throughout the duration of this patient’s treatment, blood cultures remained positive and the MIC for daptomycin increased from 1.56 µg/ml at baseline to 12.5 µg/ml on day 12. When the same parent S. aureus isolate was rechallenged, mimicking the same conditions in a rabbit endocarditis model, MICs for daptomycin increased to 5 mg/ml, with subpopulation MICs as high as 8 µg/ml.\textsuperscript{87} Further examination was conducted with this mutant isolate, and electron microscopy revealed no differences between the parent isolate and the daptomycin-resistant mutant with respect to morphology of the cell wall; however, exposure to subinhibitory concentrations of this isolate to daptomycin did result in some cell wall thickening.\textsuperscript{87}

Emergence of resistance with daptomycin against S. aureus, S. epidermidis, vancomycin-resistant E. faecium, and S. pneumoniae was determined by observing for spontaneous mutations.\textsuperscript{88} No resistance was identified when concentrations as high as 10\textsuperscript{9} cfu and greater were tested. However, one mutant daptomycin-resistant S. aureus was obtained after 21 days serial passage in liquid culture. The MICs increased 8–32-fold and heterogeneous susceptibility patterns were identified. The phenotypes displayed by these mutant isolates were complex. When preliminary analyses were completed, the potential mechanism of resistance patterns supported an alteration of membrane potential, which causes reduced binding of daptomycin. None of the mutants showed antibiotic cross-resistance to any other class of antibiotic.

Animal Studies

Several animal studies reported daptomycin’s effectiveness in infection. Dosages used in earlier studies varied from the current recommendation of 4 mg/kg once/day for humans, as the drug originally was developed to be given twice/day. In animal models the drug was effective against gram-positive infections in blood, thigh, renal, pulmonary, cardiac, and bone tissue. In a bacteremia study in immunosuppressed mice challenged intraperitoneally with lethal bacterial concentrations, daptomycin eradicated infections with Streptococcus pyogenes, S. pneumoniae, MSSA, and vancomycin-resistant E. faecalis, which had ED\textsubscript{50}\textsubscript{s} of less than 2 mg/kg.\textsuperscript{14} The agent also had protective effects against disseminated VRE infection significantly better than those of either vancomycin or ciprofloxacin.\textsuperscript{89} All animals were protected from lethal inocula of a VRE by prophylactic daptomycin 5 mg/kg. In contrast, neither vancomycin nor ciprofloxacin protected the animals from VRE infection at doses up to 50 mg/kg.
Skin and Soft Tissue Infections

Daptomycin was effective against both drug-susceptible and -resistant S. aureus, S. pneumoniae, and E. faecium in soft tissue and bacterial abscesses in the immunosuppressed mouse model of bacterial thigh infection. In one model of MRSA or MSSA bacterial abscess, the agent produced a 5–7 log₁₀ reduction against S. aureus strains, consistent with its rapid bactericidal activity. The animals received daptomycin 10 mg/kg, which is equivalent to concentrations achieved in humans, compared with vancomycin 125 mg/kg subcutaneously every 12 hours for 5 or 10 days. In a similar model of delayed therapy against MRSA or MSSA bacterial abscess, combination therapy of daptomycin plus rifampin or daptomycin plus rifampin and tobramycin produced significant reductions, again suggesting that daptomycin may be useful in combination therapy.

Pyelonephritis and Urinary Tract Infections

The drug had efficacy in several animal models of pyelonephritis caused by both vancomycin-susceptible and -resistant strains of Enterococcus sp. Its efficacy compared favorably with that of vancomycin in several investigations, as well as synergy with gentamicin. Daptomycin resulted in dose-dependent reductions in bacterial counts in infected kidneys and a significant percentage of sterile kidneys. It produced the most rapid response of antibiotics tested (ampicillin, vancomycin, vancomycin-gentamicin), with significant reduction of E. faecalis after 2 days of therapy. A dosage of 10 mg/kg twice/day was more effective than 20 mg/kg once/day, again suggesting the AUC:MIC ratio is a key pharmacodynamic parameter. As monotherapy, daptomycin was more effective than gentamicin 4–6 mg/kg (0.6 mg/rat) intramuscularly twice/day, and the combination of daptomycin and gentamicin was more effective than either drug alone in reducing bacterial counts in kidney tissue. Efficacy against both vancomycin-sensitive and -resistant enterococci is consistent with the equal potency of daptomycin against these isolates. The agent's efficacy in treating renal infections is likely enhanced by excretion of intact drug in urine.

Pneumonia

Daptomycin was effective against MRSA pneumonia in a hamster model system. The combination of daptomycin and vancomycin produced similar increases in survival, but daptomycin produced greater reductions of MRSA from the lungs. It had high distribution to hamster lung tissue. After intravenous administration of radiolabeled daptomycin to rats, the lungs had the second highest drug concentration of 34 tissues analyzed. After repeated administration, the total exposure (AUC) of radiolabeled drug in the lungs was 240% of corresponding plasma values. Thus daptomycin partitions effectively from blood into lung tissue. Its favorable distribution could be an important factor in controlling both pulmonary infection and concurrent septicemia.

Endocarditis

In rat and rabbit animal models of aortic valve endocarditis, daptomycin was effective against drug-susceptible and -resistant gram-positive organisms. Efficacy was observed against staphylococcal, streptococcal, and enterococcal species. Daptomycin resulted in sterilization of cardiac vegetations or reductions in bacterial titers in vegetations. Its activity in both treating and preventing bacterial endocarditis was equal to or better than that of vancomycin. Its efficacy in challenging models of endocarditis suggests clinical potential for this difficult infection.

In rats, the effective daptomycin dosage was 5–10 mg/kg once or twice/day by subcutaneous injection, which provides C_{max} values of 30 µg/ml, and AUC₀–₂₄ values of 200 µg•hour/ml or less. These dosages resulted in exposures less than 50% of those achieved with the clinical regimen. The agent achieved sterilization of cardiac vegetations in up to 100% of animals infected with Staphylococcus or Streptococcus sp, but the sterilization rate was lower in rats infected with Enterococcus sp. Daptomycin produced significant 5–6 log₁₀ reductions in staphylococcal, streptococcal, and enterococcal titers of cardiac vegetations, including strains resistant to penicillins and aminoglycosides. Despite the lower rate of vegetation sterilization in enterococcal endocarditis, the bacterial load was significantly reduced across all studies. Synergistic efficacy was observed when daptomycin was administered in combination with gentamicin.

The efficacy of an antibiotic in the treatment of endocarditis depends on penetration and distribution of the drug within infected vegetations. Aortic valve vegetations that occur in endocarditis are not vascularized; therefore,
antibiotic diffusion into the infected site is gradient driven. In a model of *E. faecium* endocarditis in rabbits, $^{13}$C-daptomycin penetrated and was consistently homogeneously distributed throughout all aortic valve vegetations at 30 minutes after the dose. Thus daptomycin can penetrate into poorly vascularized vegetations, suggesting the potential for effective treatment of endocarditis.

Osteomyelitis

Daptomycin reduced *S. aureus* bacterial titers in bone infected with experimental osteomyelitis in an in vivo rabbit model. Chronic osteomyelitis was induced by inoculating MSSA and MRSA into tibiae in the presence or absence of a sclerosing agent. Treatment was begun 14 or 21 days later and continued for 14–28 days. Greatest efficacy was observed in animals in which the time between inoculation and start of treatment was 14 days and in which therapy continued for 28 days. Daptomycin was as efficacious as vancomycin at comparable peak plasma levels of approximately 33 µg/ml for the two drugs. Similarly, the efficacy of daptomycin plus rifampin was comparable with that of vancomycin plus rifampin; both combinations were more effective than vancomycin or rifampin alone. The efficacy achieved by daptomycin at relatively low dosages in animal models of osteomyelitis suggests clinical potential.

Clinical Efficacy Trials

Daptomycin’s promise against both drug-susceptible and drug-resistant gram-positive bacteria at dosages of 4–6 mg/kg intravenously once/day are being investigated in phase II and III clinical trials of skin and soft tissue infections, community-acquired pneumonia, and endocarditis.

Complicated Skin and Soft Tissue Infections

The agent is approved for therapy of serious skin and soft tissue infections. Two large, randomized, multicenter, investigator-blinded, phase III studies with over 1000 subjects recently were completed. Adults aged 18–85 years were enrolled if they had a complicated skin and soft tissue infection with known or suspected gram-positive organisms, including abscesses, surgical and traumatic wound infections, and infected diabetic foot ulcers. Subjects were randomized to receive daptomycin 4 mg/kg once/day, or standard therapy of antistaphylococcal semi-

synthetic penicillin 4–12 g/day or vancomycin 1 g every 12 hours. Aztreonam and/or metronidazole was added as deemed necessary. Daptomycin was as effective as standard therapy when measured by clinical success rates and microbiologically evaluable rates in all populations tested (intent-to-treat 74% vs 73%, 95% confidence interval [CI] -5.6–5.0; modified intent-to-treat 76% vs 76%, 95% CI -4.0–5.6). Adverse event rates were similar for daptomycin and standard therapy. Of interest, subjects receiving daptomycin achieved equivalent results as those given standard therapy after fewer days; 63% and 33%, respectively, reached goal by 4–7 days (p<0.001).

In a randomized, evaluator-blinded study, 468 patients with dual complicated skin and soft tissue infections with *S. aureus* and/or hemolytic streptococci were randomized to receive either daptomycin 4 mg/kg once/day or standard therapy of antistaphylococcal semisynthetic penicillin 4–12 g/day or vancomycin 1 g every 12 hours. Aztreonam and/or metronidazole was added as indicated. Independent of daptomycin, infections in diabetics persisted longer than those in nondiabetics. Daptomycin was comparable with standard therapy, and a trend was seen toward more rapid clearance of *S. aureus* in diabetics (20 vs 31 days, p=0.17) with an additional trend of improved success in nondiabetics (82% vs 71%, p=0.29). Other studies with similar enrollment criteria consistently showed equal efficacy comparing daptomycin against standard therapy and a trend toward shorter duration with a more rapid microbiologic and clinical response.

Bacteremia

Clinical trials were performed to determine the efficacy of daptomycin in patients with gram-positive bacteremia. There is one published case report of a liver transplant recipient having VRE bacteremia that later developed linezolid resistance. This case is consistent with a description of linezolid resistance in a patient with VRE infection after 21–40 days of linezolid therapy. This patient was unable to tolerate quinupristin-dalfopristin 7.5 mg/kg intravenously every 8 hours due to severe myalgias on days 13–16 of treatment. She responded to intravenous daptomycin once/day, her myalgias resolved with discontinuation of quinupristin-dalfopristin, and blood cultures remained sterile with 16 days of therapy. Additional bacteremia data will be gained from the endocarditis trial (see below).
Community-Acquired Pneumonia

One large phase III clinical trial evaluating daptomycin’s efficacy in community-acquired pneumonia has been completed. This was an international (North America, western Europe, eastern Europe, Australia, New Zealand, South Africa), multicenter, randomized, double-blind study that enrolled over 900 patients. The primary end point was noninferiority in clinical efficacy, defined as resolution of signs and symptoms, compared with standard therapy, ceftriaxone. The secondary end point was bacteriologic efficacy. Patients were randomized to receive either daptomycin 4 mg/kg once/day or ceftriaxone 2 g once/day, both intravenously. In clinically evaluable populations daptomycin and ceftriaxone had 85.7% and 84.8% (95% CI -10.9–9.0) clinical success rates in North American and western European populations. In the North American intent-to-treat population, daptomycin achieved higher success rates than ceftriaxone (72% vs 62%). However, in the eastern European trial the primary end point was not met, and clinical success rates of daptomycin and ceftriaxone were 74.3% and 85.3%, respectively (95% CI 2.1–19.8). No significant differences were seen in demographic parameters, although there were strong geographic differences in this study. The reason for the latter is not known.

Complicated Urinary Tract Infections

A phase II study of daptomycin’s effectiveness in complicated urinary tract infection showed promising results. The randomized, open-label, microbiologist-blinded trial enrolled patients with febrile neutropenia with complicated urinary tract infections caused by gram-positive pathogens. Patients were randomized to receive either daptomycin 4 mg/kg once/day or ciprofloxacin, both intravenously. The primary end point was bacteriologic efficacy, and the secondary end point was clinical efficacy based on signs and symptoms. Daptomycin’s outcomes were similar to those of ciprofloxacin, with daptomycin’s clinical and microbiologic cure rates being 55% (5/9 patients) and 33% (3/9), respectively.

Endocarditis

Phase III clinical trials continue to investigate the efficacy of daptomycin in patients with endocarditis or bacteremia. One is an open-label study of daptomycin 6 mg/kg every 24 hours versus vancomycin 1 g every 12 hours or nafcillin 2 g every 4 hours. Patients are enrolled if they have a positive S. aureus blood culture and if endocarditis is confirmed. If endocarditis is not confirmed, patients may continue in the study and be treated for bacteremia. This study must prove daptomycin to be noninferior to comparator within a ±20% change in infective endocarditis. Recently, an independent data-monitoring committee recommended continuation of this trial.

Safety

In early clinical trials, daptomycin dosages of 3 mg/kg every 12 hours caused reversible effects in skeletal muscle as measured by creatine kinase isoenzymes specifically released by skeletal muscle. The effects were not progressive, were reversible on discontinuing the drug, and were related to dosing frequency. It is recommended that the drug be discontinued in patients with unexplained signs of myopathy in conjunction with creatine kinase elevations greater than 1000 U/L or approximately 5 times the upper limit of normal.

A study was conducted to establish the pharmacokinetics and safety of escalating once-daily doses of daptomycin in 24 healthy subjects. Subjects were equally and randomly divided to receive daptomycin 4, 6, or 8 mg/kg or normal saline by 30-minute intravenous infusion every 24 hours for 7–14 days. Pharmacokinetics were assessed by blood and urine samples taken at several times throughout the study. All subjects completed the 14-day treatment with minimal adverse events (e.g., gastrointestinal upset), none reported events consistent with daptomycin-related myopathy.

A phase III, multicenter, randomized, international trial enrolled over 500 subjects with complicated skin and soft tissue infections to assess outcomes and adverse events associated with daptomycin. Daptomycin 4 mg/kg intravenously once/day was compared with standard therapy of a semisynthetic penicillin 4–12 g/day or vancomycin intravenously 1 g every 12 hours for a planned duration of 7–14 days. Vancomycin and daptomycin dosages were adjusted based on patient-specific pharmacokinetics by an unblinded coinvestigator according to local practices. A blinded investigator at each site assessed adverse events. Success rates were equal for both treatments, with a 67% successful
clinical response at test of cure (95% CI: 9.0–9.0). Discontinuation due to adverse events was reported for 9 subjects receiving daptomycin and 12 receiving standard therapy. Two patients receiving daptomycin withdrew due to hypersensitivity (fever, rash, urticaria). Additional discontinuations reported as due to drug-related adverse events with daptomycin were an acute sickle cell crisis, an asymptomatic creatine kinase elevation in a subject receiving intramuscular drug injections, and a creatine kinase elevation associated with muscle symptoms. Subjects receiving daptomycin required less drug monitoring, infrequent interval adjustments, fewer daily doses, and fewer discontinuations due to adverse events than those receiving comparator drugs combined.

Daptomycin reduced gentamicin toxicity in animal studies. One study assessed this protective effect in female rats with both high and low dosages of aminoglycosides and found a significantly smaller increase in serum creatinine at 10 days when renal function was already compromised.

Phase II trials indicate that the drug is safe at 6 mg/kg. Earlier clinical studies created concern regarding a higher dose and more frequent dosing schedule. Once-daily administration appears to minimize the potential for drug-related skeletal-muscle effects while maintaining efficacy. Less frequent dosing may allow for repair of subclinical effects.

Adverse Events

Table 5 shows the frequency of adverse events that occurred in 2% or more of patients treated with either daptomycin or a comparator.

| Adverse Event                  | Daptomycin (n=534) | Comparator (n=558) |
|--------------------------------|--------------------|--------------------|
| Constipation                   | 6.2                | 6.8                |
| Nausea                         | 5.8                | 9.5                |
| Injection site reaction        | 5.8                | 7.7                |
| Headache                       | 5.4                | 5.4                |
| Diarrhea                       | 5.2                | 4.3                |
| Insomnia                       | 4.5                | 5.4                |
| Rash                           | 4.3                | 3.8                |
| Vomiting                       | 3.2                | 3.8                |
| Abnormal liver function tests  | 3.0                | 1.6                |
| Pruritus                       | 2.8                | 3.8                |
| Elevated creatine kinase       | 2.8                | 1.8                |
| Fungal infections              | 2.6                | 3.2                |
| Hypotension                    | 2.4                | 1.4                |
| Urinary tract infections       | 2.4                | 0.5                |
| Renal failure                  | 2.2                | 2.7                |
| Dizziness                      | 2.2                | 2.0                |
| Anemia                         | 2.1                | 2.3                |
| Dyspnea                        | 2.1                | 1.6                |
| Fever                          | 1.9                | 2.5                |
| Limb pain                      | 1.9                | 2.0                |
| Hypertension                   | 1.1                | 2.0                |
| Dyspepsia                      | 0.9                | 2.5                |
| Arthralgias                    | 0.9                | 2.2                |

Data are percentages.

Pregnancy

There have been no adequate, well-controlled studies of daptomycin reporting safety in pregnant or breastfeeding women. Small studies in rats and rabbits receiving up to 75 mg/kg/day during organogenesis reported no ill effects in either species.

Drug Interactions

No cross-resistance with other drug classes has been reported. Since daptomycin does not induce or inhibit cytochrome P450 enzymes and has no appreciable metabolism in the liver, drug-drug interactions by this mechanism are unlikely. When the drug was coadministered in healthy volunteers with warfarin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, aztreonam, and probenicid, its pharmacokinetic profiles were not altered. However, this fact is not well established, and patients should be monitored for the first few days after starting any new therapies.

In Vitro Considerations

Daptomycin's in vitro activity is known to be affected by variations in free calcium ion content of the media. For broth microdilution susceptibility tests, several in vitro studies showed that it requires calcium supplementation to total 50 µg/ml. Studies using broth supplemented with 50–75 µg/ml reported no difference in MICs. In addition, E-strips have been manufactured with calcium added to the strip to compensate for varying levels of calcium in media, which may resolve problems created by variability in calcium levels of agar media that are available in the United States. When broth microdilution MICs (National Committee for Clinical Laboratory Standards, 50 µg/ml calcium supplementation) were compared with calcium supplemented Etest MICs, results of Etests varied
by 1 dilution both above and below broth MIC values.

Summary

Daptomycin is a concentration-dependent, rapidly bactericidal agent that has excellent activity against virtually all susceptible and multidrug-resistant gram-positive bacteria. Preliminary data suggest that it will be highly effective in the treatment of complicated skin and soft tissue infections. The potential for shorter regimens should result in faster resolution of symptoms and faster cure rates, and may decrease the likelihood of the development of resistance. The drug will require less frequent dosing intervals and less drug monitoring. Continuing studies in serious infections such as bacteremia and endocarditis should increase daptomycin’s utility and its potential as an alternative to vancomycin, linezolid, and quinupristin-dalfopristin.

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56

PHARMACOTHERAPY Volume 24, Number 1, 2004

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DAPTOMYCIN  Tedesco and Rybak

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