Bacteremia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: the potential role of daptomycin

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Abstract: *Staphylococcus aureus* bacteremia is a common disease with a high risk of mortality and complications. An increasing proportion of cases are methicillin-resistant *S.aureus* (MRSA), and methicillin-resistance is being observed from both community-acquired bacteremias and in healthcare-associated infections. The duration of bacteremia and transesophageal echocardiographic findings are useful in predicting the likelihood of complications including endocarditis. Therapy with vancomycin has been the mainstay in the treatment of MRSA bacteremias, but is associated with a long duration of bacteremia on therapy and relapses. Loss of susceptibility to vancomycin, due to thickened cell walls and through the acquisition of the *vanA* gene, has been described. Daptomycin is newly approved lipopeptide that is highly bactericidal against most strains of MRSA. In a randomized trial, daptomycin was demonstrated to be effective in the treatment of *S. aureus* bacteremia and right-sided endocarditis. However treatment failures associated with isolates with daptomycin non-susceptibility are reported, and there is a correlation between isolates with reduced vancomycin susceptibility and reduced daptomycin susceptibility. Daptomycin is a useful alternative to vancomycin in the therapy of MRSA bacteremia and endocarditis. However the appropriate role of daptomycin in optimizing therapy with MRSA bacteremia and endocarditis remains to be elucidated.

Keywords: methicillin-resistant *Staphylococcus aureus*, bacteremia, endocarditis, daptomycin

Introduction

In a national survey in the United States conducted in 2000–2001, *Staphylococcus aureus* infections were reported as a discharge diagnosis in 0.8% of all inpatients, and were associated with a five-fold increased risk of in-hospital mortality (Noskin 2005). Methicillin-resistant *S. aureus* (MRSA) isolates were reported within a year of the initial use of semi-synthetic penicillins for the treatment of beta-lactamase producing staphylococci in 1960 (Jevons 1961). The incidence of methicillin resistance among *S. aureus* has been steadily rising over the last thirty years. In 2003, among nosocomial infections in intensive care unit patients in the national nosocomial infections surveillance system report, the proportion of methicillin-resistant isolates among *S. aureus* strains comprised 59.5% of isolates (NNIS System Report 2004). The expanding use of intravascular catheters, prosthetic devices, invasive procedures and broad spectrum antimicrobial use has resulted in an increased population of patients at risk for MRSA bacteremia.

Beginning in the mid-1990s, MRSA infections were also recognized in those without any of the healthcare associated risk factors, particularly as a cause of skin and soft-tissue infections, and included severe cases associated with bacteremia and mortalities. The incidence of community-acquired MRSA infections has steadily risen

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over the past ten years. The infections were initially recognized more commonly in children, athletes, military recruits, Pacific Islanders, Alaskan Natives, Native Americans, men who have sex with men, and prisoners (CDC 2004). Among adult patients with acute purulent skin and soft-tissue infections presenting in 2004 to academic emergency departments in the United States, 59% of the patients had infections due to MRSA (Moran 2006). Pulsed-field type USA300 isolates accounted for 97% of these MRSA isolates. These strains contain the SCC*mec*IV element and usually the Panton-Valentine leucocidin. Most hospital acquired MRSA contain SCC*mec* elements I, II, and III. At a large urban hospital in Atlanta, Georgia, 6.79 per 1000 hospital admissions were associated with a MRSA bacteremia (Seybold 2006). Of these patients, 8% had community-acquired infections with no health care associated risk factors, 42% were nosocomial with onset of bacteremia >48 hours after hospital admission, and 50% were community-onset but had healthcare-associated risk factors. USA300 genotype was found in all of the patients without healthcare-associated risk factors, and in 20% of the nosocomial isolates, indicating that the USA300 genotype which is commonly associated with community-acquired MRSA infections also has now emerged as a pathogen in nosocomial disease.

S. aureus bacteremia

Studies have suggested a crude in-hospital mortality rate for MRSA bacteremia of 22 to 24.5%, and an attributable mortality of 12.2% (Khatib 2006, Seybold 2006). Although studies have reported higher mortality rates with MRSA compared to methicillin-susceptible strains (odds ratio [OR] 1.93, 95% confidence interval [CI] 1.54–2.42) (Cosgrove 2003), this may represent differences in the host or efficacy of treatment and not necessarily related to enhanced virulence associated with susceptibility to methicillin. Animal models have suggested that the presence of the *mecA* gene complex per se is not associated with increased virulence of the organism (Voyich 2005).

In addition to a high mortality rate, complications associated with *S. aureus* bacteremia are common. Complications reported in a prospective study of 724 patients with *S. aureus* bacteremia in a single academic medical center include endocarditis in 89 (12%), septic arthritis in 54 (7.5%), deep tissue abscesses in 41 (5.7%) vertebral osteomyeltis in 22 (3.0%), epidural abscesses in 18 (2.5%), septic thrombophlebitis in 17 (2.3%), psoas abscess in 13 (1.7%), and meningitis in 12 (1.7%). Seventy patients (9.7%) developed a recurrent *S. aureus* infection, including 49 (6.7%) recurrent bacteremias (Fowler 2003). In another prospective study at six teaching hospitals, 66 of 505 (13%) consecutive patients with *S. aureus* bacteremia were found to have endocarditis, including 21% of patients with community acquired infections (11 of 95), 5% of nosocomial infections (10 of 204), and 12% of those on hemodialysis (11 of 95). Forty-two of 505 patients (8.3%) had recurrent infections, of which 79% had relapse with the same organism documented by pulsed-field gel electrophoresis. The median time relapse was 36 days (range 10–190 days). Thirty-one percent of the cases of endocarditis were due to MRSA (Chang 2003b).

Identifying complications and providing appropriate therapy to prevent relapse are key elements in the management of *S. aureus* bacteremia. The presence of community-acquired bacteremia (OR 3.08; 95% CI, 1.80–5.28), skin examination findings suggestive of the presence of acute infection (petechiae, vasculitis, infarcts, ecchymoses and pustules) (OR 1.80; 95% CI 1.10–2.95), positive follow-up blood cultures obtained 48 to 96 hours after antimicrobial administration (OR 4.94; 95% CI 3.37–7.25), and persistent fever at 72 hours (OR 2.00; 95% CI, 1.36–7.25) are all predictive of the presence of complications in a multivariate model (Fowler 2003). However 16% of patients without any of these risk factors still had complicated infections. In a study conducted at six teaching hospitals, the following risk factors are associated with endocarditis among patients with *S. aureus* bacteremia in a multivariate analysis: native valve disease (OR 4.5; 95% CI 2.0–9.9), the presence of a prosthetic valve (OR 10.5; 95% CI ,7.5–43.7), positive blood cultures on appropriate therapy for >3days (OR 7.4; 95% CI, 3.3–16.6), intravenous drug use (OR 3.2; 95% CI, 1.2–8.6) , and an unidentifiable portal of entry (OR 3.3; 95% CI 1.3–6.6), history of prior endocarditis (OR 10.0; 95% CI 2.0–50.0), community acquisition (OR 2.9; 95% CI 1.4–4.9), and nonwhite race (OR 2.5; 95% CI 1.2–5.3) (Chang 2003a). MRSA endocarditis was more likely in those with persistent bacteremia and with serum creatinine >2 mg/dl. Native valve disease and cirrhosis were significantly associated with a relapse of bacteremia (Chang 2003b).

The duration of bacteremia is associated with metastatic infections and complications. Complications and metastatic infections increased from 6.6% among those with bacteremias persisting from 1 to 2 days, to 24.0% among those with bacteremias for 3 days, and 37.7% among those with bacteremias persisting >4 days ($p = 0.05$) (Khatib 2006). Of note is that there may not be a strong correlation between the duration of fever and bacteremia

($r = 0.121$, $p = 0.094$), and bacteremia may continue after resolution of fever in more than half of cases (Khatib 2006). Persistent bacteremia for more than 3 days correlates with the presence of endovascular sources, having a cardiovascular prosthesis, a metastatic infection and diabetes. A length of time of incubation before detection of a positive blood culture using a blood culture system that monitors CO2 production every 10 minutes (time to positivity) of less than 14 hours is an independent predictor of an endovascular source of infection, prolonged bacteremia, metastatic infection, and attributable mortality (Khatib 2005). Because of concerns of unrecognized endocarditis among patients with intravascular catheter-associated *S. aureus* bacteremia, the Infectious Diseases Society of America, in conjunction with the American College of Critical Care Medicine and the Society for Healthcare Epidemiology of America has recommended routine use of transesophageal echocardiography (TEE). TEE is helpful in the diagnosis of endocarditis, is more sensitive than transthoracic echocardiography, and has been demonstrated to be cost-effective compared to empiric short-course (2 week) or long course (4 week) therapy (Rosen 1999). The use of TEE in this setting has not been studied prospectively, however, and it remains unclear if empiric short-course therapy can be safely utilized without a TEE among patients with a removable focus of infection and without the risk factors associated with endocarditis and complications identified above.

Endocarditis

The large International Collaboration on Endocarditis (ICE) merged database study has suggested that *S. aureus* has become the most common microbiologic cause of endocarditis observed in tertiary referral centers, occurring in 31.6% of cases of endocarditis (Fowler 2005). Compared to non-*S. aureus* endocarditis, patients with *S. aureus* endocarditis were more likely to have intravenous drug use (OR 9.3; 95% CI 6.3–13.7), a first clinical presentation less than 1 month after first symptoms (OR 5.1; 95% CI 3.2–8.2), health-care associated infections (OR 2.9; 95% CI 2.–3.8), persistent bacteremia defined as positive blood cultures more than 12 hours apart or all of three or a majority of four or more separate blood cultures, with first and last drawn at least one hour apart (OR 2.3; 95% CI 1.2–2.6), presence of a presumed intravascular device as a source (OR 1.7; 95% CI 1.2–2.3), a stroke (OR 1.6; 95% CI 1.2–2.3), and diabetes mellitus (OR 1.3; 95% CI 1.1–1.8). In-hospital mortality was 22.4%, and was higher among those with health-care associated disease, and among those with cardiac devices. 27.4% of cases were due to MRSA, and patients with MRSA endocarditis had higher rates of persistent bacteremia compared to those with MSSA (42.6% vs 8.8%, $p < 0.001$), a presumed intravascular device as a source (60.3% vs 30.7%, $p < 0.001$), chronic immunosuppressive therapy (17.7% vs 3.5%, $p < 0.001$), and diabetes mellitus (34.0% vs 18.0%, $p < 0.001$). Within the ICE study among patients with *S. aureus* native valve endocarditis, characteristics associated with mortality in a multivariate analysis included increasing age (OR, 1.38; 95% CI, 1.15–1.66), presence of heart failure (OR, 3.90; 95% CI 2.27–6.68), periannular abscess (OR, 2.34: 95% CI, 1.05–5.64), and an aortic valve vegetation (OR, 1.91; 95% CI, 1.00–3.66). Receiving surgical therapy was associated with reduced in-hospital mortality (OR 0.43; 95% CI 0.24–0.79) (Miro 2005). Among patients with prosthetic valve endocarditis in the ICE study, overall mortality was 47.5%. Among those with prosthetic valve endocarditis, stroke appeared to be associated with a higher mortality in multivariate analysis (OR 30.4, 95% CI 0.8–11.6, $p = 0.09$), and although early valve replacement was not associated with improved survival in the whole population, there was a trend towards it benefiting those who developed congestive heart failure and/or an intracardiac abscess (28.6% mortality vs 53.3%, $p = 0.09$) (Chirouze 2004). American Heart Association guideline indications for surgical therapy in patients with MRSA infective endocarditis include congestive heart failure, infections with strains not fully susceptible to vancomycin, persistent bacteremia greater than one week on therapy, one or more embolic events during the first two weeks of therapy, valvular dehiscence, perforation, rupture or fistula formation, perivalvular abscess greater than 1 cm, anterior leaflet of mitral value vegetation size greater than 1 cm, and an increase in vegetation size despite appropriate antimicrobial therapy (Baddour 2005).

Therapy of MRSA bacteremia and endocarditis with vancomycin

Vancomycin is the drug of choice as recommended by current guidelines by the Infectious Diseases Society of America in the treatment of catheter-associated MRSA bacteremia (Mermel 2001), by the American Heart Association and Infectious Diseases Society in the treatment of MRSA endocarditis (Baddour 2005), and by the British Society for Antimicrobial Chemotherapy in the treatment of MRSA bacteremia (Gemmell 2006). However there are concerns about the efficacy of vancomycin. Compared to nafcillin, vancomycin has slower in vitro killing of *S. aureus* when measured at 24 hours and vancomycin therapy for methicillin-susceptible *S. aureus* endocarditis in intravenous drug users was associated with

a higher than expected failure rate compared to historical controls treated with beta-lactams (Small and Chambers 1990). In a study of MRSA endocarditis, the mean duration of bacteremia on vancomycin therapy was seven days (95% CI 6–11). The duration of bacteremia was similar (9 days) when combining vancomycin with rifampin (95% CI 6–13) (Levine 1991). In two prospective studies of methicillin-susceptible *S. aureus* bacteremia, nafcillin was superior to vancomycin in preventing persistent bacteremia (62.5% vs 52.6%, $p = 0.04$) or relapse (OR, 6.5; 95% CI, 1.0–52.8; $p < 0.048$) (Chang 2003b; Khatib 2006).

In addition to slow or inadequate response rates associated with vancomycin therapy, more recently concerns have emerged regarding the development of strains of *S. aureus* that are not fully susceptible to vancomycin. In 1996 the first clinical isolate of *S. aureus* with intermediate susceptibility to vancomycin, vancomycin intermediate *S.aureus* (VISA) was noted in Japan. As of 2002, eight cases had been identified, and the number of cases has been steadily growing. In 2002 the first clinical case of *S. aureus* with full resistance to vancomycin occurred (CDC 2002). In addition a growing concern regarding poor vancomycin response rates among isolates with a MIC of 4 μg/ml prompted a change by the Clinical and Laboratory Standards Institute in defining vancomycin susceptibility to isolates with a MIC of ≤2 μg/ml, intermediate susceptibility for isolates of 4–8 μg/ml, and resistance for isolates ≥16 μg/ml (CLSI 2006). VISA strains have developed thickened cell walls, and vancomycin becomes clogged within the cell wall, preventing it from reaching its target in the cytoplasmic membrane (Cui 2006). Another feature of VISA strains is their association with group II polymorphism at the accessory gene regulator (agr) locus (Sakoulas 2002). Vancomycin efficacy has also been inversely correlated with MIC values within the susceptible range, and the higher failure rates among the isolates with MIC values of 2μg/ml has been correlated with this polymorphism. In one study the vancomycin response rates was 61% among patients with isolates with a MIC of 0.5 μg/ml, 28% among patients with a MIC of 1.0 μg/ml, and 11% among isolates with a MIC of 2 μg/ml (Moise-Broder 2004). In another study the final response rate with vancomycin therapy was 85% among isolates with MIC1 μg/ml and 62% among isolates with a MIC of 2 μg/ml even among patients who reached a trough level of vancomycin of >15 μg/ml ($p = 0.02$). Attainment of a target vancomycin trough level of >15 μg/ml vancomycin did not improve final response rates among isolates with a MIC of 2 μg/ml (Hidayat 2006). Vancomycin-resistant *S.aureus* (VRSA) isolates do not have enlarged cell walls, but have acquired the *vanA* vancomycin resistance gene from enterococci, which alters the vancomycin target (Cui 2006, CDC 2002). Resistance in these isolates is due to the synthesis of an alternative terminal peptide D-ala-D-lac instead of D-ala-D-ala. Vancomycin is unable to bind to D-ala-D-lac.

Daptomycin: mode of action, resistance, pharmacokinetics, and pharmacodynamics

Because of concerns about the utility of vancomycin in the treatment of MRSA, development of additional agents has been undertaken by the pharmaceutical industry. Daptomycin is a cyclic lipopeptide, derived from a fermentation product of *Streptomyces roseosporus* initially discovered by Eli Lilly and Company in the early 1980s. It has a unique mechanism of action, and is only active against Gram-positive bacteria. It acts at the cytoplasmic membrane, binding but not penetrating the membrane via a calcium-dependent insertion of its lipid tail. It forms an ion-conduction structure, resulting in an efflux of ions, including potassium. Cell death occurs associated with widespread inhibition of synthesis of DNA, RNA, and protein, but cell lysis and release of large molecules from the cytoplasm does not occur. The activity of daptomycin is dependent on the presence of calcium. It is 2–4 fold more active in Mueller-Hinton media supplemented to 50 μg/ml Ca^{2+} per mL, compared to the usual 20–25 μg/ml in usual resistance testing (Carpenter and Chambers, 2004).

Prior to 2003, there had been no reports of initial clinical isolates of *S. aureus* without previous exposure to daptomycin that were resistant to daptomycin, although mutants of *S. aureus* resistant to daptomycin could be derived by serial passage in liquid media containing incremental subinhibitory concentrations (Carpenter and Chambers, 2004). With the emergence of an increasing number of strains of *S. aureus* with vancomycin intermediate susceptibility, a correlation has been noted between acquisition of vancomycin intermediate susceptibility and non-susceptibility of daptomycin. Daptomycin susceptibility is defined as a MIC of ≤1 μg/ml (CSLI 2006). Among *S. aureus* strains fully susceptible to vancomycin, 97% are susceptible to daptomycin. However among strains with a vancomycin MIC of 4 μg/ml, only 20% are susceptible to daptomycin, and among strains with a vancomycin MIC of 8–16 μg/ml only 7% are susceptible to daptomycin (Patel 2006). All 5 VRSA isolates tested with vancomycin MIC ≥32 μg/ml remain susceptible to

daptomycin. Daptomycin heteroresistance is also found among strains that develop vancomycin heteroresistance during treatment with vancomycin, even when the MIC of the organisms remains within the susceptible range. In vitro killing assays demonstrate less rapid killing of these heteroresistant isolates (Sakoulas 2006). Cui, et al also found a strong correlation ($R = 0.814$, $p < 0.0001$) between daptomycin reduced susceptibility and vancomycin resistance among VISA strains, and correlated this loss of susceptibility with the degree of cell wall thickening ($R = 0.883$, $p < 0.0001$) (Cui 2006). They postulated that the mechanism of the loss of daptomycin susceptibility was due to the inability of daptomycin, which has a molecular weight of 1,620, to pass through the physical barrier of the enlarged cell wall. VRSA isolates which have vancomycin resistance as a result of acquisition of the *vanA* gene and have normal size cell walls remain susceptible to daptomycin. In clinical isolates, prior patient exposure to vancomycin is associated with isolates with a small but statistically significant rise in daptomycin MIC (mean 0.599 vs 0.726 μg/ml $p = 0.019$) even among strains that remain within the susceptible range (Moise-Broder 2006).

Daptomycin exhibits linear pharmacokinetics at doses up to 12 mg/kg with a maximum concentration (C_{max})of 93.9 μg/ml, minimum concentration (C_{min}) of 6.7 μg/ml, and area under the concentration curve (AUC_{0-tau}) of 631.8 μg·h/ml at steady state with a dose of 6 mg/kg per day. The half-life of approximately 8 hours, volume of distribution of 100 ml/kg, and protein binding of 90–93% are independent of dose (Benvenuto 2006). Protein binding is reduced to 84–88% among patients with a creatinine clearance of less than 20 ml/min. Approximately 78% of daptomycin is excreted via the kidney, two-thirds of which is intact drug (Carpenter and Chambers 2004). It is not extensively metabolized. The dose for bacteremia and right-sided endocarditis is 6 mg/kg administered once daily. The dose for skin and soft tissue infections is 4 mg/kg administered once daily. For patients with creatinine clearance of <30 ml/minute the same dose is administered every 48 hours. It should be administered after hemodialysis because approximately 15% of the dose is removed by 4h of hemodialysis. No clinically significant drug interactions have been identified. No dose adjustment is needed for mild to moderate hepatic insufficiency. Dosage has not been evaluated in severe hepatic insufficiency.

Daptomycin is more rapidly bactericidal than vancomycin in vitro (Tally and DeBruin 2000). In vitro time-kill studies using exponential growth phase MRSA there is more than a 3 $\log_{10}$ fall in CFU/ml by only 2 hours at a 20 μg/ml concentration of daptomycin compared to a less than 1 $\log_{10}$ fall with 20 μg/ml vancomycin (Lamp 1992). It has concentration dependent killing in vitro and in pharmacodynamic studies in mice (Tally and DeBruin 2000). Similarly in an in vitro pharmacodynamic model with simulated endocardial vegetations it had concentration dependent killing, and against both a MRSA and a MSSA strain was more rapidly bactericidal than vancomycin over a 4 to 96 hour time course (Tsuji and Rybak 2005). It produces a post-antibiotic effect (PAE) of over 6 hours at 16 μg/ml that is concentration dependent compared to a 1.3–1.8 hour PAE of vancomycin that is non-dose-dependent (Hanberger 1991). Unlike vancomycin, it maintains high level bactericidal activity when tested against a high inoculum of 9.5 $\log_{10}$ cfu/g of MRSA in an in vitro simulated endocardial vegetation model, and has activity against stationary phase growth organisms (LaPlante 2004, French 2006). Similar to vancomycin, it is less active in more acidic pH within pH ranges of 6.4 to 8.0 (Lamp 1992). The clinical relevance of this finding in the management of infections associated with intracellular organisms within the phagolysosome or in the treatment of abscesses remains speculative. The addition of gentamicin to daptomycin is synergistic in some in vitro time-kill studies and in an in vitro pharmacodynamic model with simulated endocardial vegetations, but was not beneficial in improving human serum bactericidal activity of daptomycin against MRSA (Tsuji and Rybak 2005; DeRyke 2006).

Clinical studies of efficacy

The initial clinical studies of daptomycin were performed by Eli Lilly and Company. Efficacy in small studies was comparable to conventional therapy in the treatment of skin and soft-tissue infections, and it was effective in 17 of 19 patients with bacteremia treated with a 6 mg/kg load followed by 3 mg/kg every 12 h for up to 34 days (Tally and DeBruin 2000). Daptomycin was dropped from further development by Lilly because of concerns regarding skeletal muscle toxicity with higher-dose regimens when utilized every 12 hours, and failures among patients treated for *S. aureus* endocarditis (Lamp 1992). Cubist Pharmaceuticals, Inc. licensed daptomycin from Lilly in 1997, and initiated clinical trials in 1999 in patients with complicated skin and soft-tissue infections, community-acquired pneumonia, urinary tract infections, bacteremia and endocarditis utilizing once daily-dosing. Once daily dosing may increase the therapeutic-toxicity ratio because of the concentration dependent killing, prolonged post-antibiotic effect, and in animal models, less skeletal muscle toxicity associated with once-daily administration

(Tally and DeBruin 2000). In the complicated skin and soft-tissue infection trial, among 902 evaluable patients, the 83.4% clinical response with daptomycin given at 4 mg/kg every 24h was similar to the 84.2% response rate (95% CI for the difference, –4.0 to 5.6) with the comparator drugs (either vancomycin given at 1 gm every 12h or a penicillinase-resistant penicillin given at 4–12 gm intravenously daily in divided doses). Among patients successfully treated, 63% of those required only 4–7 days of therapy and were able to switch to an oral drug at that time, compared to 33% of the comparator drug ($p < .0001$) (Arbeit 2004). Response rates were similar between daptomycin and the comparator arm among those who had infections with MRSA (21/28 [75%] vs 25/36, [69.4%], 95% CI –28.5 to17.4) and among those who received vancomycin as the comparator drug (90 of 111 [81.1%] patients vs 127 of 172 [73.8%] patients, 95% CI –17.4 to 2.9). Studies in the treatment of pneumonia were halted when pooled data revealed that daptomycin was inferior to ceftriaxone (Carpenter and Chambers 2004). Daptomycin has low concentrations in bronchial-alveolar lining fluid and lung parenchyma, and is inactivated by surfactant (Silverman 2005). Daptomycin should not be utilized in the treatment of pneumonia. A phase III trial investigating the use of daptomycin in the treatment of complicated urinary tract infections due to gram-positive organisms was terminated early because of difficulty enrolling patients.

Daptomycin was evaluated for the treatment of *S. aureus* bacteremia and endocarditis in a recently published prospective randomized trial (Fowler 2006). The trial was open-labeled, but an adjudication committee which was blinded to treatment arm determined outcome. Patients were excluded if their age was <18 years, they had a creatinine clearance less than 30 ml/min, known osteomyelitis, polymicrobial bacteremia, or pneumonia. Patients were randomized 1:1 to either daptomycin 6 mg/kg daily or standard therapy with either vancomycin 1 g every 12 hours (adjusted to renal function) or a penicillinase-resistant penicillin (nafcillin, oxacillin, or flucloxacillin) 2 g every 4 hours, depending on the results of methicillin susceptibility testing. Serum vancomycin levels were monitored according to standard practice of each participating site.

Length of therapy was determined by the investigator depending on the working diagnosis. Patients assigned to standard therapy and all patients with left-sided endocarditis were given gentamicin 1 mg/kg every 8h (adjusted to renal function) for the first four days. Patients were required to undergo TEE within the first five days of therapy. Blood cultures were performed daily until negative, at the end of therapy, and at day 42. The primary outcome was clinical success at day 42, and failure at that time was defined as clinical failure (no response to the study drug on the basis of ongoing signs an symptoms of infection), microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective non-study antimicrobial agent, or premature discontinuation of the study medication because of clinical failure, microbiologic failure, or an adverse event. The study was designed as a non-inferiority trial, and was powered to detect a difference of 20% between the two treatment groups.

MRSA was isolated in 89 of 235 (38%) of patients, and 53 (22.5%) of patients had endocarditis. The overall success rates was 53/120 (44.2%) in the daptomycin arm, and 48/115 (41.7)% in the comparator arm, including a 37.7% (20/53) response among those that received vancomycin, and 45.2% (28/62) among those that received an antistaphylococcal penicillin. The differences were not statistically significant, and there were no statistical differences among patients infected with MRSA (44.4% success with daptomycin and 31.8% with standard therapy, 95% CI –7.4 to 32.6), among those with complicated bacteremias, or endocarditis. Only 1 of 9 patients with left-sided endocarditis was treated successfully with daptomycin, compared to 2 of 9 treated successfully with the comparator arm. Among those infected with MRSA, the median time to clearance of bacteremia did not differ between the daptomycin arm and the comparator arm (8 days and 9 days, respectively, $p = 0.25$). 19 of 120 patients (15.8%) had treatment failures due to persistent or relapsing *S. aureus* infections in the daptomycin arm compared to 11 of 115 patients (9.6%) in the standard therapy arm ($p = 0.17$). 8 patients (6.7%) had treatment-related adverse events in the daptomycin arm compared to 17 patients (14.8%) in the standard therapy arm ($p = 0.06$). Of the 19 patients in the daptomycin arm who had microbiologic failure, 6 had increases in daptomycin MICs to the non-susceptible range, and 5 of these isolates were MRSA. This represents 11% of the patients with MRSA treated with daptomycin. Overall gentamicin was administered to 107 of 115 patients in the standard-therapy group (93%) and in 1 of 120 patients in the daptomycin group. In a substudy analysis, study drug MIC shifts to ≥2 μg/ml occurred in 7/120 patients treated with daptomycin, and in 7/53 patients treated with vancomycin and gentamicin (Luperchio 2006). None of the vancomycin isolates had a shift to the non-susceptible range (4 μg/ml). Baseline MIC values did not predict MIC shifts. Patients

with MIC shifts in both arms typically did not or could not receive appropriate adjunctive therapy, such as surgery or drainage of sequestered foci of infection, including osteomyelitis, and removal of indwelling prostheses or devices. Microbiologic treatment failure did not correlate with levels of plasma antimicrobials in either arm.

In a retrospective report of use of daptomycin in the treatment of bacteremia and endocarditis at one university-affiliated hospital and one regional hospital, eleven patients had MRSA bacteremia with or without endocarditis, and all were treated successfully with daptomycin. Most of the patients had received vancomycin prior to initiation of daptomycin and had persistent bacteremia (≥5 days) on vancomycin prior to initiation of daptomycin (Segreti 2006). In a preliminary report from a multicenter retrospective observation chart review evaluating outcomes of patients receiving daptomycin, a 76% success rate was achieved among patients with endocarditis. Among patients with all infections, success rates were lower among patients with creatinine clearance less than 30 ml/min (McKinnon 2006). There are case reports, especially among patients with osteomyelitis and endovascular infections who had previously failed therapy with vancomycin, that have failed therapy with daptomycin associated with bacteremia with isolation of MRSA that developed reduced susceptibility to daptomycin (Hayden 2005; Vikram 2005; Mangill 2005; Paez 2006).

Safety

During the early development of daptomycin, dosing of daptomycin at 4 mg/kg every 12 hours resulted in myopathy in 2 of 5 subjects. An investigation in dogs found that the skeletal muscle myopathy was more related to the higher sustained trough concentration than the peak drug concentration or the area under the curve (Oleson 1999). Along with the pharmacodynamic properties of the drug, this led to the development of daptomycin using once daily dosing. In the complicated skin and soft tissue infection trial utilizing a dose of 4 mg/kg per day, elevations of creatinine kinase levels were found in 15 of 534 (2.8%) of patients in the daptomycin arm, and in 10 of 558 (1.8%) of patients in the comparator arm (Arbeit 2004). Only 1 of 534 patients receiving daptomycin had an elevation of creatinine kinase associated with weakness and muscle pain that was felt to be drug related. After discontinuation of the drug, symptoms resolved over the following 72 hours. In the bacteremia trial utilizing a 6 mg/kg per day dose, creatinine kinase elevations of >500 IU/L were observed in 11 of 116 (9.5%) of evaluable patients in the daptomycin group compared to 2 of 111 (1.5%, $p = 0.02$) in the standard-therapy group (Fowler 2006). 10 of 120 (8.3%) patients receiving daptomycin stopped study drug because of a drug-related adverse event, compared to 13 of 116 (11.2%, $p = 0.51$) in the standard-therapy group. Discontinuation of daptomycin was due to elevated creatinine kinase levels in 3 of 120 patients treated with daptomycin. Daptomycin induced rhabdomyolysis including rhabdomyolysis induced acute renal failure has now been reported in case reports (Edwards 2006, Kazory 2006). Patients receiving daptomycin should be monitored for signs and symptoms of myopathy and receive a weekly creatinine kinase level. Daptomycin should be discontinued in patients who develop an otherwise unexplained myopathy with elevated creatinine kinase levels (≥5 times the upper limit of normal or ≥1000 IU/L) or an isolated increase in creatinine kinase ≥10 times the upper limit of normal. There were no reports of skeletal myopathy in a phase I trial of daptomycin dosed at 4 mg/kg/d among patients receiving concomitant simvastatin. In the bacteremia/endocarditis trial 5 of 22 patients who received prior or concomitant HMG-CoA reductase inhibitors and daptomycin developed creatine phosphokinase (CPK) elevations of >500 U/L. Consideration should be given to suspending HMG-CoA reductase inhibitors during therapy with daptomycin (Cubist 2006).

Other side-effects related to daptomycin are unusual and have not been associated with significant increases in events compared to comparator arms in randomized trials. An exception is events related to the peripheral nervous system, including paresthesias, dysesthesia, and peripheral neuropathy, which was observed in 9.2% of patients receiving daptomycin in the bacteremia trial, compared to 1.7% of the comparator arm ($p = 0.02$). These events were felt to mild to moderate, and most were transient and resolved during continued treatment (Fowler 2006).

Keys in the therapy of bacteremia due to MRSA

Effective antimicrobial therapy should be initiated promptly after obtaining appropriate cultures, including at least 2 sets of blood culture from separate sticks, when there is a reasonable likelihood of MRSA bacteremia. Delays in therapy have been associated with higher mortality, especially among patients with higher APACHE II scores (Lodise 2003). Either vancomycin or daptomycin should be initiated unless the source of bacteremia is due to pneumonia, in which case daptomycin

should not be used. A thorough investigation should be performed to determine the source of the bacteremia, recognizing the possibility of endocarditis, catheter and prosthetic device infections, septic arthritis, osteomyelitis (including vertebral osteomyeltis), epidural, psoas muscle or deep tissue abscesses, and septic thrombophlebitis, which may not be clinically obvious. Intravascular catheters that are potential sources of the bacteremia should be removed. Attempts at salvage of tunneled catheters in stable patients in whom there is no tunnel, pocket or exit-site infection and a negative transesophageal echocardiogram using an antibiotic lock therapy have been suggested by guidelines, but in limited trials has been generally unsuccessful in infections due to *S. aureus* (Mermel 2001; Forun 2006). All attempts should be made to debride infected tissues, appropriately drain abscesses, and remove infected hardware. Patients with endocarditis, particularly left-sided endocarditis, should be considered for valve replacement based on current guidelines (Baddour 2005). Blood cultures in all patients with bacteremia should be repeated every 72 hours until negative.

The duration of therapy for MRSA bacteremia is controversial, and is dependent on the source of the bacteremia. Most authorities have recommended at least two weeks of intravenous therapy for *S. aureus* bacteremia (Mermel 2001). However seven days of therapy may be adequate in patients with bacteremia due to a removable focus when the device is promptly removed, a transesophageal echocardiogram is negative, there are no heart valve abnormalities, no indwelling prosthetic devices, follow-up blood cultures at 72 hours are negative, and there are no features of metastatic infection (Fowler 1998). Patients with persistent bacteremias beyond 72 hours, those with osteomyelitis, septic thrombophletibis, infective endocarditis and deep tissue infections should be treated with four to six weeks of intravenous antibiotics.

Therapy of MRSA not fully susceptible to vancomycin also remains controversial. Vancomycin MICs between 2 and 8 μg/ml have been correlated with daptomycin non-susceptibility. Linezolid, quinupristin-dalfopristin, tigecycline and trimethoprim-sulfamethoxasole are alternatives for patients with VISA strains. High dose daptomycin at doses of up to 12 mg/kg per day could be considered (Benenuto 2006), but would likely risk a greater chance for skeletal muscle toxicity. VRSA strains could be treated with daptomycin, with linezolid, quinupristin-dalfopristin, tigecycline and trimethoprim-sulfamethoxasole as alternatives, but among these only daptomycin and quinupristin-dalfopristin are bactericidal agents (Cha 2003). Of high controversy is the optimal treatment of MRSA bacteremia due to strains with vancomycin MIC of 1–2 μg/ml, especially in the setting of persistent bacteremia on vancomycin therapy with appropriate trough levels. Most important for patients with isolates with reduced susceptibility to vancomycin is appropriate surgical therapy including debridement of abscesses and necrotic infected tissue, and removal of infected hardware and catheters. Whether there is a benefit to switching patients to daptomycin is remains speculative, and should be investigated in clinical trials.

Table 1 Daptomycin summary information

Structure	Cyclic lipopeptide
Mechanism of action	Bactericidal, binds cytoplasmic membrane, with resultant depolarization of membrane potential, cellular ion efflux and cell death
In vitro activity	Gram positive organisms, including MRSA, VRSA, and vancomycin resistant enterococci
CSLI susceptibility cutoff	≤1 μg/ml; supplementation to 50 μg/ml Ca^{2+} required for testing in Muellar-Hinton broth
Pharmacokinetics	Given intravenously, half- life 8 hours, volume of distribution 100 ml/kg, protein biding 90%–93%, C_{max} 94 μg/ml with 6 mg/kg dose at steady state, linear kinetics through 12 mg/kg
Excretion	78% renal
Pharmacodynamics	Concentration dependent killing, post-antibiotic effect of 6 hours against *S. aureus*
US FDA approved indications	Treatment of complicated skin and skin structure infections (caused by susceptible strains of Gram-positive microorgansisms, including MSSA and MRSA); *S. aureus* bacteremia, including those with right-sided endocarditis, caused by MSSA and MRSA
FDA approved dose	4 mg/kg q24h for skin and soft tissue infections; 6 mg/kg q24h for bacteremia and endocarditis
Dose for renal dysfunction	Creatinine clearance ≤30 ml/min: 4 mg/kg q48h for skin and soft tissue infections; 6 mg/kg q48h for bacteremia and endocarditis; for hemodialyis, dose after hemodialysis
Adverse reactions	CPK elevation with and without myopathy, transient neuropathy
Drug interactions	HMG-CoA inhibitors
Cost	$171 for 500 mg
Pregnancy	Class B

Abbreviations: CSLI, Clinical and Laboratory Standards Institute; CPK, creative phosphokinase; FDA, Food and Drug Administration; MRSA, methicillin-resistant *S.aureus*; MSSA, methicillin-sensitive *S.aureus*; VRSA, vancomycin-resistant *S.aureus*

Summary of potential role of daptomycin for *S. aureus* bacteremia and endocarditis

Key summary information regarding daptomycin use is provided in Table 1. Daptomycin provides a needed alternative to vancomycin in the therapy of *S. aureus* bacteremia and endocarditis for those with either methicillin-resistant organisms or intolerance to beta-lactams. Beta-lactams such as nafcillin or cefazolin remain the drug of choice for bacteremia or endocarditis due to methicillin-susceptible *S. aureus*. Daptomycin would be a drug of choice for patients with MRSA bacteremia who are either intolerant to vancomcyin or infected with daptomycin susceptible strains of VRSA. Further clinical studies should be performed to define groups of patients infected with MRSA, based on either microbiological characteristics of the infecting strain or clinical characteristics of the patients, who could potentially benefit from daptomycin as compared to vancomycin among organisms that demonstrate in vitro susceptibility to both agents.

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