Journal of Microbiology, Immunology and Infection (2012) 45, 52–57

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Safety and efficacy of daptomycin for the treatment of hospitalized adult patients in Taiwan with severe staphylococcal infections

Chung-Chih Lai [a], Wang-Huei Sheng [a], Jann-Tay Wang [a], Chun-Hsin Liao [b], Mao-Wang Ho [c], Chwen-Je Chen [d], Der-Li Chen [e], Ming-Uen Chou [f], Chien-Ming Lee [g], Yee-Chun Lin [h], Ming-Ye Pong [i], Shan-Chwen Chang [a,*]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Internal Medicine, Far-East Memorial Hospital, Taipei, Taiwan*
[c] *Department of Internal Medicine, Chinese Medical University Hospital, Taichung, Taiwan*
[d] *Department of Internal Medicine, Kaoshiung Medical University Hospital, Kaoshiung, Taiwan*
[e] *Department of Internal Medicine, Veterans General Hospital, Taipei, Taiwan*
[f] *Department of Internal Medicine, Jeng-Shin Medical Center, Taipei, Taiwan*
[g] *Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan*
[h] *Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[i] *Department of Internal Medicine, Triservice General Hospital, Taipei, Taiwan*

Received 19 May 2010; received in revised form 9 September 2010; accepted 20 October 2010

KEYWORDS
Daptomycin;
Methicillin-resistant *Staphylococcus aureus*;
Serious infection

Background and Purpose: The safety and efficacy of treating serious infections caused by *Staphylococcus aureus* with daptomycin in a Taiwanese population were studied.
Methods: A retrospective, multicenter study was performed in Taiwan between December 2007 and June 2009. This study included adult hospitalized patients who had received intravenous daptomycin therapy for infections caused by *S aureus*. All patients were followed until discharge from the hospital or death.
Results: A total of 52 patients (males, $n = 44$; median age: 62 years) were evaluated. Infections included complicated skin and soft-tissue infections ($n = 14$), catheter-related bacteremia ($n = 14$), osteomyelitis and septic arthritis ($n = 12$), endovascular infections and endocarditis ($n = 11$), and urinary tract infections ($n = 1$). Overall, 47 (90.4%) patients were successfully treated and their clinical symptoms were resolved. Adverse effects related to daptomycin were detected in nine patients, but none were required to discontinue daptomycin.

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: changsc@ntu.edu.tw (S.-C. Chang).

doi:10.1016/j.jmii.2011.09.018

Conclusion: The results support daptomycin as an effective and safe treatment for staphylococcal infections in Taiwanese populations.

Introduction

Infections caused by Gram-positive bacteria are increasingly more common and remain one of the leading causes of morbidity and mortality in hospitalized patients. Many Gram-positive pathogens are resistant to common classes of antimicrobial agents, including methicillin and vancomycin. In the United States (US), the proportion of clinical *Staphylococcus aureus* isolates with methicillin resistance increased from 22% in 1995 to 57% in 2001. Vancomycin resistance was identified in 60% of *Enterococcus faecium* isolates, and methicillin resistance was identified in 75% of coagulase-negative staphylococcal isolates.[1] Although vancomycin remains the first-line drug of choice for treating methicillin-resistant *S aureus* (MRSA), recurrent bacteremia and mortality due to MRSA infections are increasingly on the rise, despite the use of vancomycin.[2,3] In such cases, vancomycin may have an inadequate bactericidal activity against MRSA, particularly for isolates with an elevated minimum inhibitory concentration (MIC).[4]

Daptomycin belongs to a new class of antimicrobial agents—the cyclic lipopeptides—and demonstrates a rapid, concentration-dependent bactericidal activity against a broad spectrum of Gram-positive organisms. Daptomycin is also fully active against drug-resistant strains, including MRSA and vancomycin-resistant enterococci (VRE).[5] Daptomycin has been approved by the US Food and Drug Administration (FDA) for treating complicated skin and soft-tissue infections, bacteremia, and right-sided endocarditis caused by MRSA.[6] Therefore, daptomycin appears to be a promising agent for the treatment of patients with severe infections due to antimicrobial-resistant, Gram-positive strains of bacteria. Although there are reports regarding the safety and efficacy of daptomycin for the treatment of various infections in Western countries, daptomycin is new to clinical use in Taiwan and only limited data exist regarding the use of daptomycin in Asian populations.[7–13] In this study, the safety and efficacy of daptomycin for the treatment of serious infections were evaluated in hospitalized patients at nine medical centers in Taiwan.

Methods

Patient enrollment

In this investigator-initiated study, we retrospectively reviewed the medical charts of hospitalized patients who were treated with daptomycin (Cubicin, Cubist Pharmaceuticals, Lexington, MA, USA) at nine medical centers in Taiwan (National Taiwan University Hospital, Taipei; Chinese Medical University Hospital, Taichung; Kaoshiung Medical University Hospital, Kaoshiung; Taipei Veterans General Hospital, Taipei; Far-East Memorial Hospital, Panchiao; Jen-Shin Medical Center, Taipei; Chi-Mei Medical Center, Tainan; Taipei Medical University Hospital, Taipei; and Triservice General Hospital, Taipei) from December 2007 through June 2009. Patients were treated with daptomycin if they presented with one of the following criteria: (1) documented MRSA infection that was not responding to treatment with glycopeptides (i.e., vancomycin or teicoplanin); (2) documented methicillin-susceptible *S aureus* (MSSA) or MRSA infection with a significant allergic reaction to β-lactams or glycopeptides (e.g., rash, anaphylaxis, etc.); (3) intolerable glycopeptide-related adverse effects (e.g., hypotension, increase in serum creatinine level, etc.); or (4) failure of alternative agents, such as vancomycin, teicoplanin, or linezolid. A standard case record form was used to collect patient information, including age, sex, primary and secondary diagnoses, previous antibiotic treatments, and daptomycin regimens. Microbiological results were evaluated in all patients in order to determine the identity of each pathogen and its susceptibilities. The isolates were identified and tested for susceptibility using the Vitek system (bioMerieux, Hazelwood, MO, USA). Daptomycin (4–10 mg/kg, administered intravenously [IV] every 24 hours) was administered to all patients. The dose was adjusted by the attending physicians according to the clinical condition of each patient, the presence of any co-morbidities, and renal functions. Daptomycin was administered every 48 hours to patients undergoing hemodialysis or those with a creatinine clearance <30 mL/min. All patients were hospitalized in order to complete their IV therapy regimen with daptomycin. The primary outcome was the resolution of the signs and symptoms associated with infection after discharge from the hospital.

Antimicrobial susceptibility tests

Susceptibility tests for all isolates were initially performed using the disc diffusion method, according to the Clinical and Laboratory Standards Institute (CLSI) guidelines used at each hospital.[14] The MICs of vancomycin and daptomycin were checked in the isolates obtained from patients who failed to respond to daptomycin treatment. The MIC of vancomycin was determined by the broth microdilution method using Mueller-Hinton broth (BBL, Becton Dickinson, Sparks, MD, USA). An initial inoculum of 5×10^5 colony-forming units (CFU)/mL was utilized, according to CLSI guidelines.[14] When the MIC of daptomycin was tested, the medium consisted of Mueller-Hinton broth and physiological levels of calcium (50 μg/mL), as previously recommended.[15] S aureus ATCC 29213 was used as a quality control strain in each run. S aureus Mu3 and Mu50 strains

were used for comparison with our vancomycin-intermediate *S aureus* (VISA) isolates. The MIC for S aureus ATCC 29213 was within the control ranges reported by CLSI.[14]

Definition

Clinical failure was defined as follows: (1) infection-related death, (2) persistence of the signs and symptoms of infection after 14 days of therapy with daptomycin, (3) readmission to the hospital due to a relapse of the initial infection, or (4) replacement of daptomycin with other antimicrobial agents due to persistent infection. Microbiological failure was defined as persistently obtaining positive cultures from blood or infection sites of patients who were receiving daptomycin.

Results

During the study period, a total of 52 adult patients (44 males and 8 females) were hospitalized with serious Gram-positive bacterial infections and received daptomycin therapy for at least 48 hours. The demographic data are shown in Table 1. The ages of the patients ranged from 17 to 90 years with a median age of 62 years. Most of the patients had underlying medical conditions, such as malignancy, congestive heart failure, diabetes mellitus, cerebrovascular accident, liver cirrhosis, uremia, or chronic lung disease. The administered dosages of daptomycin were 4 mg/kg/d ($n = 11$), 6 mg/kg/d ($n = 30$), 8 mg/kg/d ($n = 8$), or 10 mg/kg/d ($n = 3$). The highest doses were received by one patient with endocarditis and two patients with osteomyelitis. Daptomycin was used as replacement therapy after the failure of previous antimicrobial treatments ($n = 32$) or intolerance to prior antibiotic therapies due to adverse effects ($n = 20$). The duration of daptomycin treatment ranged from 4 to 116 days with a median duration of 14 days.

Table 1 Demographic characteristics of 52 patients who received daptomycin therapy

Demographic data	No. of patients (%)
Gender; no. of male/female (% male)	44/8 (84.6)
Mean age, y (range)	62 (17–90)
Body weight, kg (range)	63 (41–83)
Presenting with chronic medical illness	48 (92.3)
Previous uses of anti-gram positive antibiotics	
Oxacillin	5 (9.6)
Vancomycin	24 (46.2)
Teicoplanin	18 (34.6)
Linezolid	5 (9.6)
Median duration of previous antibiotic use, d (range)	12 (2–165)
Reason for change to daptomycin	
Prior antimicrobial treatment failure	32 (61.5)
Adverse effects from prior antibiotic use	20 (38.5)
Daptomycin dosage	
4 mg/kg/d	11 (21.1)
6 mg/kg/d	30 (57.7)
8 mg/kg/d	8 (15.4)
10 mg/kg/d	3 (5.8)
Median daptomycin treatment, d (range)	14 (4–116)

The types of infections and microbiological results are shown in Table 2. Complicated skin and soft-tissue infections ($n = 14$) and catheter-related bacteremia ($n = 14$) were the most common infections, followed by osteomyelitis and septic arthritis ($n = 12$), endovascular infection and endocarditis ($n = 11$), and urinary tract infection ($n = 1$). Thirty-six patients (69.2%) were diagnosed with bacteremia. The identified pathogens included MRSA (47 patients) and MSSA (5 patients). Mixed infections were found in five patients and included *Acinetobacter baumannii* ($n = 2$), *Pseudomonas aeruginosa* ($n = 1$), *Klebsiella pneumoniae* ($n = 1$), and *Escherichia coli* ($n = 1$).

The clinical and microbiological outcomes are shown in Tables 2 and 3. Forty-seven (90.4%) patients were treated successfully. There were no differences in treatment outcomes between those patients who received < 6 mg/kg/day and those who received ≥ 6 mg/kg/day daptomycin. (Table 3) Adverse effects related to daptomycin were detected in nine patients (17.3%), including elevated serum creatine kinase [CK] levels ($n = 5$), leukopenia ($n = 3$), elevated liver aminotransferase levels ($n = 2$), elevated serum creatinine levels ($n = 1$), and pruritis ($n = 1$). All of the adverse effects were mild and tolerable. There were no grade 3 or 4 adverse effects, with the exception of one patient who developed mild myalgia and an increased serum CK level that rose from 20 IU/L to 1487 IU/L (normal upper limit: 167 IU/L). No patient required discontinuation of daptomycin because of adverse effects. The five patients with elevated CK levels required 4–13 days (median: 6 days) for their levels to normalize. Five patients failed to respond to daptomycin treatment (Table 4). Patients who failed to respond to daptomycin treatment had previously received a prolonged administration of glycopeptides (median: 47 days; range: 14–165 days). Three of those patients had documented MRSA isolates with increased MICs for both vancomycin (4 μg/mL) and daptomycin (2–4 μg/mL) recorded during their treatment regimens with vancomycin and daptomycin.

Discussion

Although vancomycin remains the first-line drug of choice for treating many antimicrobial-resistant, Gram-positive bacterial infections, its efficacy against MRSA infections is declining. The reduced susceptibility of MRSA to vancomycin[16] and the inability of antimicrobials to remove of *S aureus*-produced biofilms, which may facilitate resistance by promoting horizontal gene transfer, allow MRSA to escape lysis and death by vancomycin.[17,18] The results presented here support daptomycin as a highly efficacious agent for the treatment of serious infections caused by MRSA in the Taiwanese population.

Table 2 Infections and post-daptomycin treatment outcomes

Characteristics	No. of patients(%)
Type of infection	
Complicated skin and/ or soft-tissue infection[a]	14 (26.9)
Catheter-related bacteremia	14 (26.9)
Osteomyelitis and septic arthritis[c]	12 (23.1)
Bacteremia from endovascular infection or endocarditis[b]	11 (21.2)
Urinary tract infection[d]	1 (1.9)
Causative microorganism	
Methicillin-susceptible *Staphylococcus aureus*	5 (9.6)
Methicillin-resistant *Staphylococcus aureus*	47 (90.4)
Clinical outcomes (%)	
Cure	47 (90.4)
Failure	5 (9.6)
Microbiological outcomes (%)	
Eradication	24 (46.2)
Presumed eradication	23 (44.2)
Persisted infection	5 (9.6)
Microbial superinfection[e]	11 (21.2)

[a] Includes four patients (three with necrotizing fasciitis and one with a deep neck infection) diagnosed with bacteremia
[b] Includes two patients with aortic mycotic aneurysm and nine with endocarditis
[c] Includes six patients diagnosed with bacteremia
[d] Patient had methicillin-resistant *Staphylococcus aureus* bacteremia and renal abscess
[e] Superinfectious pathogens encountered during daptomycin treatment included *Acinetobacter baumannii* ($n = 3$), *Klebsiella pneumoniae* ($n = 2$), *Pseudomonas aeruginosa* ($n = 2$), *Enterobacter cloacae* ($n = 1$), *Escherichia coli* ($n = 1$), *Serratia marcescens* ($n = 1$), and *Stenotrophomonas maltophilia* ($n = 1$).

With the rising prevalence of MRSA in hospitalized patients, effective treatment depends on the availability of antimicrobials with potent activities against these drug-resistant pathogens. The *in vitro* potency of daptomycin has been demonstrated against a wide range of aerobic and anaerobic Gram-positive bacteria, including MRSA, VISA, methicillin-resistant coagulase-negative staphylococci (MRCNS), and VRE.[19] In a time-kill study performed on MRSA, MRSE, VRE, and VISA, daptomycin demonstrated a more rapid bactericidal activity (≥3 log CFU/mL within 8 hours) than vancomycin, linezolid, and quinupristin-dalfopristin.[20,21] Daptomycin also exhibits a dose-dependent, postantibiotic effect against *E. faecalis* and *S aureus* that lasts between 1 and 6 hours.[22] These characteristics suggest that daptomycin is a promising agent for use against various Gram-positive bacterial infections.

The approved dose of daptomycin for complicated skin and soft-tissue infections is 4 mg/kg.[7] A previously reported clinical study demonstrates the efficacy of higher doses (6 mg/kg) of daptomycin for treating bacteremia and infective endocarditis.[8] Most patients in this study received ≥6 mg/kg. Compared to other reports, the use of higher dosages of daptomycin for patients with severe MRSA infections has been shown to be safe and well tolerated, even for longer durations of therapy.[10–13,21,23] The pharmacokinetic profile and concentration-dependent antimicrobial properties of daptomycin suggest that higher doses (≥6 mg/kg/day) may be beneficial for treating severe infections.

Resistance to daptomycin in MRSA isolates has been reported in patients with bacteremia and osteomyelitis.[24–27] Interestingly, almost all of these patients had received previous treatment with vancomycin. Not unlike other studies, our results also demonstrate a correlation between reduced daptomycin susceptibility and vancomycin resistance in VISA after prolonged vancomycin therapy.[28–31] A thickened cell wall may contribute to the resistance of *S aureus* against daptomycin.[27] Although glycopeptide-intermediate *S aureus* (GISA) has been noted since 1997, the isolation of GISA has been rare until quite recently (≤0.3% of all strains of *S aureus*).[32] As reported in the SENTRY Antimicrobial Surveillance Program, of 15 identified GISA isolates, 86.7% were susceptible to daptomycin.[33] Out of almost 10,000 isolates of *S aureus* tested, only four (0.04%) had a daptomycin MIC of 2 μg/mL (all four of these isolates were glycopeptide-susceptible *S aureus*) and only two (0.02%) GISA isolates were identified (vancomycin MIC: 4 μg/mL; daptomycin MIC: 0.5–1 μg/mL).[34–36] Although the strains of *S aureus* that are insusceptible to daptomycin are rare, our results recommend testing MRSA isolates for

Table 3 Daptomycin dosages, infection sites, and treatment outcomes[a]

	Daptomycin dosage (mg/kg/d)							
	4		6		8		10	
	Cured	Failed	Cured	Failed	Cured	Failed	Cured	Failed
Complicated skin and soft-tissue infection	10	0	3	0	1	0	0	0
Catheter-related bacteremia	1	0	12	0	1	0	0	0
Osteomyelitis and septic arthritis	0	0	5	1	4	0	2	0
Bacteremia due to endovascular infection or endocarditis	0	0	4	4	2	0	1	0
Urinary tract infection	0	0	1	0	0	0	0	0

[a] There were no differences in treatment outcomes between those patients who received <6mg/kg/d and those who received ≥6 mg/kg/d ($p = 0.57$).

Table 4 Clinical and microbiologic characteristics of patients who failed to respond to daptomycin treatment (n=5)

Case no. age/sex [Ref.]	Underlying systemic illness	Prior antibiotic usage/reason for daptomycin	Infections	Pathogen	Daptomycin dosage, duration	Reason of failure of daptomycin treatment
1. 66/M [28]	Chronic hepatitis C with cirrhosis, end-stage renal disease postendovascular graft	Vancomycin and teicoplanin, 47 d/ Treatment failure	Graft septic thromboplebitis with bacteremia, left-sided endocarditis	MRSA (VISA)[a]	6 mg/kg/ q2d, 12 d	Persistent MRSA bacteremia died of candidemia, septic shock and multiple organ failure
2. 57/M [29]	Congestive heart failure, post-heart transplantation	Vancomycin and teicoplanain, 165 d/ Treatment failure	Mycotic aortic aneurysm with bacteremia	MRSA (VISA)[a]	6 mg/kg/d, 4 d	Persistent MRSA infection, died of aortic aneurysm rupture
3. 17/F	Traffic accident, post-knee joint prosthesis implantation	Vancomycin, teicoplanin, and linezolid, 77 d/ Treatment failure	Osteomyelitis of femoral prosthesis	MRSA	6 mg/kg/d, 62 d	Prosthesis not removed, persistent MRSA infection
4. 85/M [30]	Chronic kidney disease, long-term total parenteral nutrition	Vancomycin plus gentamicin, 14 d/ Treatment faiure	Catheter-related bacteremia, infective endocarditis, septic shock	MRSA (VISA)[a]	6 mg/kg/ q2d, 13 d	No surgical intervention died of persistent MRSA infection, and multiple organ failure
5. 86/M [31]	Coronary arterial disease, diabetes, end-stage renal disease	Vancomycin plus rifampin, 19 d/ Treatment failure	Hickman catheter-related bacteremia, infective endocarditis, lung abscess, septic shock	MRSA	6 mg/kg/ q2d, 5 d	Successful treated with linezolid, fusidic acid, and teicoplanin

[a] Elevated minimal inhibitory concentrations of vancomycin (4 μg/mL) and daptomycin (2–4 μg/mL) of three *Staphylococcus aureus* isolates that were identified.

susceptibility to daptomycin and glycopeptides, especially those obtained from patients who initiate daptomycin after prolonged glycopeptide therapy.

The adverse effects of daptomycin, including increased CK levels and associated myopathy, are concerning.[7,10–13] However, in this case series, only one patient with an elevated CK level $> 5\times$ the normal upper limit and generalized myalgia was identified. No patient was required to discontinue daptomycin treatment due to its adverse effects. The tolerability of long-term treatment is an important concern for patients with severe infections, such as infective endocarditis and septic arthritis/osteomyelitis; these patients must be treated with antibiotics for 4–6 weeks in order to completely eradicate the pathogen. The high tolerability and safety of daptomycin make it a useful antimicrobial agent against difficult-to-treat infections.

In conclusion, this report demonstrates that daptomycin is safe and well tolerated by Taiwanese populations, even for extended treatment periods. Daptomycin may prove to be an effective option for treating bacteremia and serious drug-resistant staphylococcal infections. Increased dosages and the susceptibility of MRSA and/or VISA isolates to daptomycin are important considerations that warrant further study, especially when considering daptomycin as a salvage therapy for MRSA and/or VISA bacteremia with difficult-to-eradicate foci.

References

1. National nosocomial infections surveillance (NNIS) system report. Data summary from January 1992 through June 2004. *Am J Infect Control* 2004;**32**:470–85.
2. González C, Rubio M, Romero-Vivas J, González M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis* 1999;**29**: 1171–7.
3. Fowler VG, Kong LK, Corey GR, Gottlieb GS, McClelland RS, Sexton DJ, et al. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. *J Infect Dis* 1999;**179**:1157–61.
4. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004;**42**:2398–402.
5. Thorne GM. Daptomycin: a novel lipopeptide antibiotic. *Clin Microbiol News* 2002;**24**:33–40.
6. Cubist Pharmaceuticals. *Cubicin (daptomycin for injection) product information*. Lexington, MA: Cubist Pharmaceuticals; 2003.
7. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004;**38**:1673–81.

8. Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. *N Engl J Med* 2006;**355**:653—65.
9. Rehm SJ, Boucher H, Levine D, Campion M, Eisenstein BI, Vigliani GA, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: subset analysis of patients infected with methicillin-resistant isolates. *J Antimicrob Chemother* 2008;**62**:1413—21.
10. Crompton JA, North DS, McConnell SA, Lamp KC. Safety and efficacy of daptomycin in the treatment of osteomyelitis: results from the CORE registry. *J Chemother* 2009;**21**: 414—20.
11. Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or = 8 mg/kg) daptomycin therapy. *Ann Pharmacother* 2009;**43**:1211—9.
12. Chamberlain RS, Culshaw DL, Donovan BJ, Lamp KC. Daptomycin for the treatment of surgical site infections. *Surgery* 2009;**146**:316—24.
13. Figueroa DA, Mangini E, Amodio-Groton M, Vardianos B, Melchert A, Fana C, et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. *Clin Infect Dis* 2009;**49**:177—80.
14. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A7, 7th ed. Wayne, PA: CLSI 2009.
15. Fuchs PC, Barry AL, Brown SD. Daptomycin susceptibility tests: interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect Dis* 2000;**38**:51—8.
16. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, et al. Emergence of vancomycin resistance in Staphylococcus aureus. *N Engl J Med* 1999;**340**:493—501.
17. Nishimura S, Tsurumoto T, Yonekura A, Adachi K, Shindo H. Antimicrobial susceptibility of *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms isolated from infected total hip arthroplasty cases. *J Orthop Sci* 2006;**11**:46—50.
18. Weigel LM, Donlan RM, Shin DH, Jensen B, Clark NC, McDougal LK, et al. High-level vancomycin-resistant *Staphylococcus aureus* isolates associated with a polymicrobial biofilm. *Antimicrob Agents Chemother* 2007;**51**:231—8.
19. Woodworth JR, Nyhart Jr EH, Brier GL, Wolny JD, Black HR. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob Agents Chemother* 1992;**36**:318—25.
20. Rybak MJ, Hershberger E, Moldovan T, Grucz RG. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against staphylococci and enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother* 2000;**44**:1062—6.
21. Rose WE, Leonard SN, Rybak MJ. Evaluation of daptomycin pharmacodynamics and resistance at various dosage regimens against *Staphylococcus aureus* isolates with reduced susceptibilities to daptomycin in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother* 2008;**52**:3061—7.
22. Tally FP, DeBruin MF. Development of daptomycin for Gram-positive infections. *J Antimicrob Chemother* 2000;**46**:523—6.
23. Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of Gram-positive bacteremia and infective endocarditis: a retrospective case series of 31 patients. *Pharmacotherapy* 2006;**26**:347—52.
24. Vikram HR, Havill NL, Koeth LM, Boyce JM. Clinical progression of methicillin resistant *Staphylococcus aureus* vertebral osteomyelitis associated with reduced susceptibility to daptomycin. *J Clin Microbiol* 2005;**43**:5384—7.
25. Marty FM, Yeh WW, Wennersten CB, Venkataraman L, Albano E, Alyea EP, et al. Emergence of a clinical daptomycin resistant *Staphylococcus aureus* isolate during treatment of methicillin resistant *Staphylococcus aureus* bacteremia and osteomyelitis. *J Clin Microbiol* 2006;**44**:595—7.
26. Sakoulas G, Alder J, Thauvin-Eliopoulos C, Moellering RC, Eliopoulos GM. Induction of daptomycin heterogeneous susceptibility in *Staphylococcus aureus* by exposure to vancomycin. *Antimicrob Agents Chemother* 2006;**50**:1581—5.
27. Cui L, Tominaga E, Neoh HM, Hiramatsu K. Correlation between reduced daptomycin susceptibility and vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2006;**50**:1079—82.
28. Huang YT, Hsiao CH, Liao CH, Lee CW, Hsueh PR. Bacteremia and infective endocarditis caused by a non-daptomycin-susceptible, vancomycin-intermediate, and methicillin-resistant *Staphylococcus aureus* strain in Taiwan. *J Clin Microbiol* 2008;**46**:1132—6.
29. Kuo CC, Wu V, Tsai CW, Chou NK, Wang SS, Hsueh PR. Fatal bacteremic mycotic aneurysm complicated by acute renal failure caused by Daptomycin-nonsusceptible, vancomycin-intermediate, and methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2008;**47**:859—60.
30. Kuo CC, Wu VC, Huang YT, Liao CH, Hsueh PR. Fatal bacteraemia caused by daptomycin-non-susceptible, vancomycin-intermediate, methicillin-resistant *Staphylococcus aureus* in a patient with chronic kidney disease. *Int J Antimicrob Agents* 2009;**33**:96—8.
31. Liu CY, Wang JL, Huang YT, Hsueh PR. Development of multiple lung abscesses during daptomycin treatment for right-sided endocarditis caused by methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents* 2008;**32**:544—5.
32. Tenover FC, Moellering RC. The rationale for revising the clinical and laboratory standards institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. *Clin Infect Dis* 2007;**44**:1208—15.
33. Wootton M, MacGowan AP, Walsh TR. Comparative bactericidal activities of daptomycin and vancomycin against glycopeptide-intermediate *Staphylococcus aureus* (GISA) isolates. *Antimicrob Agents Chemother* 2006;**50**:4195—7.
34. Sader HS, Jones RN. The activity of daptomycin against wild-type *Staphylococcus aureus* and strains with reduced susceptibility to vancomycin. *Clin Infect Dis* 2006;**43**:798—9.
35. Sader HS, Fritsche TR, Jones RN. Antimicrobial activity of daptomycin tested against clinical strains of indicated species isolated in North American medical centers (2003). *Diagn Microbiol Infect Dis* 2005;**53**:329—32.
36. Pfaller MA, Sader HS, Jones RN. Evaluation of the in vitro activity of daptomycin against 19615 clinical isolates of Gram-positive cocci collected in North American hospitals (2002—2005). *Diagn Microbiol Infect Dis* 2007;**57**:459—65.