

Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Eun Ju Choo¹, and Henry F. Chambers²

¹Division of Infectious Diseases, Department of Medicine, Soonchunhyang University Hospital, Bucheon, Korea; ²Division of Infectious Diseases, Department of Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant cause of health care-associated infections. Vancomycin remains an acceptable treatment option. There has been a welcome increase in the number of agents available for the treatment of MRSA infection. These drugs have certain differentiating attributes and may offer some advantages over vancomycin, but they also have significant limitations. These agents provide some alternative when no other options are available.

Key Words: Methicillin-resistant *Staphylococcus aureus*; Vancomycin; Treatment

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of serious nosocomial infections.

Vancomycin, a glycopeptide in clinical use for more than 50 years, still serves as the cornerstone of the treatment of drug-resistant Gram-positive infections. However, there are significant concerns owing to decreasing susceptibility to this agent among *S. aureus*. Furthermore, vancomycin is slowly bactericidal, which may be partly responsible for reported clinical failures in treatment of bacteremia and endocarditis. The growing awareness of the limitations of vancomycin has served as an impetus for development of newer agents. Emergence of non-susceptible MRSA strains and recognition of the

frequent failure of vancomycin treatment of MRSA infection regardless of the minimum inhibitory concentration (MIC) of the isolate, provides evidence of the need for more effective therapies and therapeutic approaches.

Linezolid, daptomycin, telavancin and ceftaroline are drugs that have received regulatory approval in the last decade for the treatment of infections caused by drug-resistant Gram-positive pathogens. Although these drugs do have certain differentiating attributes and may offer some advantages over vancomycin, they also have significant limitations. More importantly, data from randomized clinical trials to support greater therapeutic efficacy of the newer agents compared with vancomycin in the treatment of serious MRSA infections are limited.

Received: December 6, 2016 **Published online:** December 12, 2016

Corresponding Author : Henry F. Chambers, MD

Division of Infectious Diseases, Department of Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA

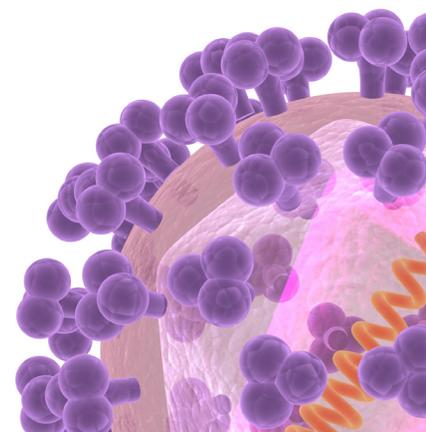
Tel: +1-415-206-5437, Fax: +1-415-648-8425

E-mail: Henry.Chambers@ucsf.edu

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyrights © 2016 by The Korean Society of Infectious Diseases | Korean Society for Chemotherapy

www.icjournal.org



Vancomycin or daptomycin are the agents of choice for treatment of invasive MRSA infections [1]. Alternative agents that may be used for second-line or salvage therapy include telavancin, ceftaroline, and linezolid. Recent studies of treatment of MRSA bacteremia are reviewed.

Vancomycin

Vancomycin is the agent for which there is the greatest cumulative clinical experience for the treatment of MRSA bacteremia. Although vancomycin has been used for over 50 years, controversies still exist about best to use it. Outcomes may be improved when vancomycin is dosed to achieve to a pharmacokinetics/pharmacodynamics (PK/PD) target, which requires serum concentration monitoring, particularly in the setting of renal dysfunction. Although several studies have suggested that vancomycin MIC = 2 µg/mL is associated with an increased risk of failure of treatment of these infections, a recent meta-analysis did not support this conclusion [2].

The pharmacokinetic driver of efficacy of vancomycin in bacteremia due to *S. aureus* is area under the plasma concentration time curve (AUC) values and an AUC_{0-24h} to MIC ratio of ≥400 µg·h/mL has been suggested as the target value. The measured trough concentration of 15-20 mg/L alone as been used as a surrogate as it was thought to be predictive of AUC/MIC; recent evidence suggests this may be incorrect. Modeling studies have demonstrated that unadjusted extrapolation of AUC from serum trough concentrations underestimate AUC by up to 25% and that AUCs varied between patients with similar trough results by up to 30-fold [3]. The increased accuracy of AUC estimations from serum vancomycin concentrations by the addition of Bayesian analysis may allow more precise individualized dosing, especially for targeting treatment of infections due to MRSA with an MIC = 2 µg/mL.

The use of loading dose and ongoing weight-based dosing are critical to rapid achievement of adequate serum concentrations, the importance of which has been demonstrated by the finding in patients with MRSA-associated septic shock that the highest survival rates were associated with an AUC_{0-24h}/MIC well in excess of 400 [4]. Individualized dosing should be explored in selected patients populations like the critically ill or in intensive care.

In general, if there is a poor clinical response to vancomycin regardless of MIC, but especially if vancomycin MIC approaches the upper limit of the susceptible ranges (2 µg/mL), it should discontinued and therapy switched to an alternative

agent, typically daptomycin.

Teicoplanin

Teicoplanin is a glycopeptides with slow bactericidal activity and a spectrum of activity and efficacy comparable to vancomycin. Some use it as the drug of choice for initial therapy of MRSA bacteremia, although good evidence to support this practice is lacking, while others favor its use for patients with intolerance to vancomycin [5]. Much debate has surrounded this antibiotic, however due to data showing inferior efficacy compared with vancomycin. These results can be explained by inadequate dosing of teicoplanin secondary to greater protein binding compared with vancomycin. Recent data and meta-analysis suggest that teicoplanin may not be inferior to vancomycin [6]. One meta-analysis noted a lower risk of nephrotoxicity with teicoplanin than with vancomycin [5].

Telavancin

Telavancin is a semisynthetic lipoglycopeptide that inhibits cell wall synthesis and disrupts cell membrane permeability [7]. The lipophilic side chain of telavancin confers enhanced potency, with approximately 10-fold more potency than vancomycin. It is bactericidal against MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA). It has a half-life of seven to nine hours, permitting once daily dosing. Telavancin should be avoided in patients at risk for nephrotoxicity.

Telavancin was approved in November 2009 in the United States for the treatment of acute bacterial skin and skin structure infections (ABSSSI), and in June 2013 in US for hospital-acquired pneumonia (HAP) caused by gram-positive pathogens including MRSA where alternative treatments are not suitable.

Telavancin may prove effective for treatment of MRSA bacteremia. In a phase 2 trial of telavancin for treatment of bacteremia including 17 patients, cure rates were comparable for telavancin and standard therapy (88 vs. 89%) [8]. A phase 3, multicenter, randomized, open-label, noninferiority trial of telavancin versus standard IV therapy in the treatment of patients with *S. aureus* bacteremia and right-sided infective endocarditis is ongoing [9]. This agent is an alternative when other options are not available.

Daptomycin

Daptomycin is a lipopeptide class antibiotic that disrupts cell membrane function via calcium-dependent binding, resulting in bactericidal activity in a concentration-dependent fashion. It is active against methicillin- and vancomycin-resistant staphylococci. It is the only new antibiotic that has a licensing indication for the treatment of *S. aureus* bacteremia (SAB) and right-sided endocarditis at 6 mg/kg/day [10]. It has the advantage of being a once-daily dosed, rapidly bactericidal agent. However, it lacks efficacy in pneumonia owing to its inactivation by pulmonary surfactant and it can cause muscle toxicity, so requires serum creatine kinase monitoring [11].

Daptomycin is currently the only antibiotic to have shown noninferiority to vancomycin in the treatment of MRSA bacteremia. A study comparing daptomycin versus initial low-dose gentamicin plus either an anti-staphylococcal penicillin or vancomycin in 124 patients with SAB and endocarditis demonstrated that daptomycin was not inferior to standard therapy [10]. Clinical success was low in the MRSA subset of patients but favored daptomycin (20 out of 45; 44.4%) over standard therapy (14 out of 44; 31.8%). However, five MRSA patients in the daptomycin group, most of whom had deep-seated infections or left-sided endocarditis, had microbiological failure with emergence on therapy of isolates with reduced daptomycin susceptibility (MIC increased from 0.25-0.5 to 2-4 µg/mL).

Daptomycin is an acceptable alternative to vancomycin for treatment of MRSA bacteremia. Historically, daptomycin has been used as salvage therapy in patients failing vancomycin therapy, particularly with high vancomycin MIC infections, but increasingly it is being used as initial therapy in high inoculum MRSA infections. A recent case-control study showed a possible advantage of daptomycin over vancomycin in infections caused by isolates with elevated vancomycin MIC [12]. Murray and colleagues reported 85 patients with MRSA bacteremia due to isolates with vancomycin MICs ≥ 1.5 µg/mL whose therapy was switched to daptomycin (median dose 8.4 mg/kg/d after median of 1.7 days of vancomycin) and compared their outcomes to 85 matched historical controls treated only with vancomycin (median trough 17.6 µg/mL). Patients treated with daptomycin experienced less frequent clinical failure and had a lower 30-day mortality. Limitations of this study were use of non-contemporaneous, historical vancomycin “control” group, and a much higher rate of infectious diseases consultation, which has been shown to improve outcomes in the daptomycin group [13].

Prior therapy with vancomycin, intermediate susceptibility to vancomycin (*i.e.* VISA) and retained prosthetic devices have been associated with an increased risk of daptomycin resistance. This is reflected in the Infectious Diseases Society of America guidelines for treatment of MRSA infections, where daptomycin dosing is recommended at 8 to 10 mg/kg for complicated bacteremia and in combination with other agents if there has been prior vancomycin treatment failure [1]. Laboratory data suggest that the administration of daptomycin in higher than approved doses may be superior to lower doses in terms of efficacy and reducing the risk of selection of resistance, but clinical data to support this hypothesis are largely lacking. Daptomycin resistance and cross-resistance in the setting of reduced vancomycin susceptibility raises concerns about widespread use of this agent.

Ceftaroline

Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA and VISA as well as Gram-negative pathogens [14]. Ceftaroline fosamil, the pro-drug of ceftaroline, received approval by the US Food and Drug Administration (FDA) in 2010. The activity of ceftaroline against MRSA is the result of its high affinity for penicillin-binding proteins, but especially to an allosteric site of PB-P2a near the transpeptidase domain. Binding to this site causes a conformational change that opens the active site of the molecule, allowing binding of a second ceftaroline molecule with consequent inhibition of its enzymatic activity [15]. Ceftaroline is active *in vitro* against VISA and heterogeneous VISA (hVISA), as well as VRSA, and exhibits a “see-saw” effect in which there is an inverse correlation between the MICs of ceftaroline and vancomycin [16].

Ceftaroline has been approved for use in the treatment of ABSSSI and community-acquired pneumonia (CAP). In a phase 4 registry study of *S. aureus* bacteremia secondary to either bacterial SSTIs or to community-acquired bacterial pneumonia, clinical success in those with MRSA infection was reported in 18 of 32 [17]. Data for use of ceftaroline for treatment of MRSA bacteremia are limited to small retrospective case series.

In one study, ceftaroline therapy was reported to achieve clinical success in 101 of the 129 patients with SAB, 92% of whom had endocarditis [18]. For many patients, however, ceftaroline was administered together with a second antibiotic. Ceftaroline in combination with a second agent, most com-

monly daptomycin, has been effective as a salvage regimen in patients with persistent MRSA bacteremia.

Oxazolidinones

Linezolid is a bacteriostatic oxazolidinone that inhibits initiation of protein synthesis at the 50S ribosome [19]. This drug class may have enhanced efficacy against strains producing toxins such as Panton-Valentine leukocidin, α -hemolysin, and toxic shock syndrome toxin 1 [20]. Unlike vancomycin, linezolid achieves high levels in the epithelial lining fluid of the lungs, making it a promising candidate for treatment of patients with HAP, including MRSA.

Linezolid has been compared with vancomycin for SAB in several case series and observational cohorts [21]. In a prospective open randomized trial, clinical success at test of cure was achieved in 19 of 24 (79.2%) linezolid recipients and 16 of 21 (76.2%) of those given vancomycin [22]. In patients with persistent (≥ 7 days) MRSA bacteremia while receiving vancomycin for at least 5 days, a switch to linezolid therapy led to similar outcomes as seen in those in whom vancomycin was continued [23]. Linezolid resistance and linezolid failure have been described [24]. Thus, an increasing frequency of resistance may potentially accompany more widespread use of this drug.

Tedizolid, the second drug of oxazolidinones, has key structural differences that allow additional target binding site interactions, accounting for its greater potency (2- to 8-fold lower MICs than linezolid against staphylococci) [25]. The FDA approved tedizolid in 2014 for use in acute bacterial SSTI caused by susceptible organisms, including MRSA. Published information regarding the use of tedizolid for the treatment of bacteremia is exceedingly limited. Like linezolid, tedizolid is bacteriostatic, making its use in endocarditis problematic. When administered in a dose consistent with human exposure, tedizolid exerted only a modest bactericidal effect that was inferior to both vancomycin and daptomycin in a rabbit model of experimental endocarditis, a result similar to that previously observed with linezolid [26]. Further study of tedizolid for treatment of MRSA bacteremia is needed.

Tigecycline

The first of a new generation of tetracyclines, glycylicyclines, tigecycline inhibits bacterial protein synthesis. Tigecycline's

distinctive feature is that it confers broad antibiotic coverage of drug-resistant Gram-positive bacteria and certain, but not all, species of multidrug-resistant Gram-negative bacteria, although it is a bacteriostatic agent.

There are substantial clinical trial data available on the use of tigecycline for intra-abdominal infections, complicated ABSSSIs, and nosocomial pneumonia, but there are insufficient data available specifically assessing the role of tigecycline in invasive MRSA infections. The use of tigecycline in bacteremia is controversial because of its low serum levels with standard dosing [27]. In a pooled, retrospective data analysis of phase 2 clinical trials, 91 patients being treated with tigecycline had secondary bacteremia detected. In the subset of patients with *S. aureus* infection ($n = 10$), cure rates were 83.3% and 75% in the tigecycline and comparator arms, respectively [28]. The paradox of higher mortality and lower cure despite excellent *in vitro* activity is thought to be due to PK/PD considerations including high protein binding, an inadequate AUC/MIC with standard dosing, poor serum concentrations, and penetration into some tissues [29].

Combination Therapy

1. Combination with vancomycin

Synergistic interactions between vancomycin and a wide variety of β -lactams, have been demonstrated *in vitro*. The mechanisms for this synergy are not clear but may include β -lactam induced potentiation of host defense peptide activity against *S. aureus*, and a "see-saw" effect whereby reduced vancomycin susceptibility results in reduced transcription of *mecA* and increased susceptibility to β -lactams. A retrospective study found a higher rate of clearance of MRSA bacteremia in patients receiving empiric vancomycin plus a β -lactam than in patients receiving vancomycin alone [30]. A pilot randomized clinical trial comparing an antistaphylococcal β -lactam in combination with vancomycin to vancomycin alone found that the duration of MRSA bacteremia was shorter by about a day 3.00 days with vancomycin alone versus 1.94 days with the combination [31]. There is a lack of evidence of benefit of vancomycin combined with other antistaphylococcal antibiotics. In a retrospective study, 35 patients with persistent (≥ 7 days) MRSA bacteremia while receiving vancomycin had their therapy altered. In 12 cases, vancomycin was continued, with an aminoglycoside added in 6, rifampin in 4, and both an aminoglycoside and a rifampin added in 2, but bacteremia

cleared within 72 hours in only 2 (17%) [21].

2. Combination with daptomycin

The combination of daptomycin and β -lactam enhances killing against daptomycin-susceptible and daptomycin-nonsusceptible MRSA, increases daptomycin binding to the bacterial cell membrane, and prevents the development of daptomycin resistance. Experiments in the rabbit model of endocarditis caused by a daptomycin-nonsusceptible strain of MRSA have shown that the combination of daptomycin with β -lactam reduced bacterial densities in all tissues compared to single agents [32]. Case reports describe the successful clearance of persistent bacteremia caused by MRSA strains, including strains that are nonsusceptible to daptomycin [33].

Summary

Treatment of MRSA bacteremia requires prompt source control and initiation of active antimicrobial therapy. Vancomycin remains the initial antibiotic of choice for the treatment of patients with MRSA bacteremia and endocarditis due to isolates with vancomycin MIC ≤ 2 $\mu\text{g/mL}$. Daptomycin is an effective, although more costly alternative, and ceftaroline appears promising. Although often attributed to antibiotic failure, persistent MRSA bacteremia more often is due to inadequate poor source control of foci of infection. The optimal salvage regimen for persistent MRSA bacteremia is uncertain. Treatment options for persistent MRSA bacteremia or bacteremia due to VISA or VRSA include daptomycin, ceftaroline, and combination therapies.

The need for antibiotics that are more efficacious than vancomycin has never been greater. Fortunately, several agents have become available for the treatment of MRSA. Compelling evidence of the improved efficacy of the newer agents against MRSA infections complicated by bacteremia in prospective, randomized, double-blind studies is lacking and even in observational studies the total number of MRSA is relatively small. The exact role and choice of agent needs to be defined.

Conflicts of Interest

No conflicts of interest.

ORCID

Eun Ju Choo

<https://orcid.org/0000-0003-2842-7041>

Henry F. Chambers

<https://orcid.org/0000-0003-4372-0780>

References

1. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF; Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18-55.
2. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA* 2014;312:1552-64.
3. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob Agents Chemother* 2014;58:309-16.
4. Zelenitsky S, Rubinstein E, Ariano R, Iacovides H, Dodek P, Mirzanejad Y, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock-CATSS Database Research Group. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant *Staphylococcus aureus*-associated septic shock. *Int J Antimicrob Agents* 2013;41:255-60.
5. Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DD, Silva E. Teicoplanin versus vancomycin for proven or suspected infection. *Cochrane Database Syst Rev* 2010:CD007022.
6. Yoon YK, Park DW, Sohn JW, Kim HY, Kim YS, Lee CS, Lee MS, Ryu SY, Jang HC, Choi YJ, Kang CI, Choi HJ, Lee SS, Kim SW, Kim SI, Kim ES, Kim JY, Yang KS, Peck KR, Kim MJ. Multicenter prospective observational study of the comparative efficacy and safety of vancomycin versus teicoplanin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2014;58:317-24.
7. Karlowsky JA, Nichol K, Zhanel GG. Telavancin: mechanisms of action, in vitro activity, and mechanisms of resistance. *Clin Infect Dis* 2015;61 (Suppl 2):S58-68.
8. Stryjewski ME, Lentnek A, O'Riordan W, Pullman J, Tambayah PA, Miró JM, Fowler VG Jr, Barriere SL, Kitt MM, Corey

- GR. A randomized Phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. *BMC Infect Dis* 2014;14:289.
9. National Institutes of Health. A phase 3 telavancin *Staphylococcus aureus* (S. Aureus) bacteremia trial. Available at: <https://clinicaltrials.gov/ct2/show/NCT02208063>. Accessed June 30 2015.
 10. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, Levine DP, Chambers HF, Tally FP, Vigiiani GA, Cabell CH, Link AS, DeMeyer I, Filler SG, Zervos M, Cook P, Parsonnet J, Bernstein JM, Price CS, Forrest GN, Fätkenheuer G, Gareca M, Rehm SJ, Brodt HR, Tice A, Cosgrove SE; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006;355:653-65.
 11. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. *Clin Infect Dis* 2004;38:994-1000.
 12. Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clin Infect Dis* 2012;54:51-8.
 13. Murray KP, Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, Rybak MJ. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis* 2013;56:1562-9.
 14. Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: a novel cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2011;52:1156-63.
 15. Otero LH, Rojas-Altuve A, Llarrull LI, Carrasco-López C, Kumarasiri M, Lastochkin E, Fishovitz J, Dawley M, Hessek D, Lee M, Johnson JW, Fisher JE, Chang M, Mobashery S, Hermoso JA. How allosteric control of *Staphylococcus aureus* penicillin binding protein 2a enables methicillin resistance and physiological function. *Proc Natl Acad Sci U S A* 2013;110:16808-13.
 16. Espedido BA, Jensen SO, van Hal SJ. Ceftaroline fosamil salvage therapy: an option for reduced-vancomycin-susceptible MRSA bacteraemia. *J Antimicrob Chemother* 2015;70:797-801.
 17. Vazquez JA, Maggione CR, Cole P, Smith A, Jandourek A, Friedland HD. Ceftaroline fosamil for the treatment of *Staphylococcus aureus* bacteremia secondary to acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia. *Infect Dis Clin Pract (Baltim Md)* 2015;23:39-43.
 18. Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, Kaye KS, Mynatt RP, Molloy LM, Pogue JM, Rybak MJ. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. *Antimicrob Agents Chemother* 2014;58:2541-6.
 19. Moellering RC. Linezolid: the first oxazolidinone antimicrobial. *Ann Intern Med* 2003;138:135-42.
 20. Stevens DL, Wallace RJ, Hamilton SM, Bryant AE. Successful treatment of staphylococcal toxic shock syndrome with linezolid: a case report and in vitro evaluation of the production of toxic shock syndrome toxin type 1 in the presence of antibiotics. *Clin Infect Dis* 2006;42:729-30.
 21. Jang HC, Kim SH, Kim KH, Kim CJ, Lee S, Song KH, Jeon JH, Park WB, Kim HB, Park SW, Kim NJ, Kim EC, Oh MD, Choe KW. Salvage treatment for persistent methicillin-resistant *Staphylococcus aureus* bacteremia: efficacy of linezolid with or without carbapenem. *Clin Infect Dis* 2009;49:395-401.
 22. Wilcox MH, Tack KJ, Bouza E, Herr DL, Ruf BR, Ijzerman MM, Croos-Dabrera RV, Kunkel MJ, Knirsch C. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. *Clin Infect Dis* 2009;48:203-12.
 23. Park HJ, Kim SH, Kim MJ, Lee YM, Park SY, Moon SM, Park KH, Chong YP, Lee SO, Choi SH, Woo JH, Kim YS. Efficacy of linezolid-based salvage therapy compared with glycopeptide-based therapy in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteremia. *J Infect* 2012;65:505-12.
 24. Sánchez García M, De la Torre MA, Morales G, Peláez B, Tolón MJ, Domingo S, Candel FJ, Andrade R, Arribi A, García N, Martínez Sagasti F, Fereres J, Picazo J. Clinical outbreak of linezolid-resistant *Staphylococcus aureus* in an intensive care unit. *JAMA* 2010;303:2260-4.
 25. Rybak JM, Marx K, Martin CA. Early experience with tedizolid: clinical efficacy, pharmacodynamics, and resistance. *Pharmacotherapy* 2014;34:1198-208.
 26. Chan LC, Basuino L, Dip EC, Chambers HF. Comparative efficacies of tedizolid phosphate, vancomycin, and daptomycin in a rabbit model of methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2015;59:3252-6.

27. Stein GE, Babinchak T. Tigecycline: an update. *Diagn Microbiol Infect Dis* 2013;75:331-6.
28. Gardiner D, Dukart G, Cooper A, Babinchak T. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials. *Clin Infect Dis* 2010;50:229-38.
29. Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 2013;57:1756-62.
30. Dilworth TJ, Ibrahim O, Hall P, Sliwinski J, Walraven C, Mercier RC. beta-Lactams enhance vancomycin activity against methicillin-resistant *Staphylococcus aureus* bacteremia compared to vancomycin alone. *Antimicrob Agents Chemother* 2014;58:102-9.
31. Davis JS, Sud A, O'Sullivan MV, Robinson JO, Ferguson PE, Foo H, van Hal SJ, Ralph AP, Howden BP, Binks PM, Kirby A, Tong SY; Combination Antibiotics for Methicillin Resistant *Staphylococcus aureus* (CAMERA) study group; Australasian Society for Infectious Diseases Clinical Research Network. Combination of vancomycin and beta-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicenter randomized controlled trial. *Clin Infect Dis* 2016;62:173-80.
32. Chambers HF, Basuino L, Hamilton SM, Choo EJ, Moise P. Daptomycin- β -lactam combinations in a rabbit model of daptomycin-nonsusceptible methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2016;60:3976-9.
33. Sakoulas G, Moise PA, Casapao AM, Nonejuie P, Olson J, Okumura CY, Rybak MJ, Kullar R, Dhand A, Rose WE, Goff DA, Bressler AM, Lee Y, Pogliano J, Johns S, Kaatz GW, Ebright JR, Nizet V. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clin Ther* 2014;36:1317-33.