National Foundation for Infectious Diseases

CLINICAL UPDATES IN Infectious Diseases

Supported by an unrestricted educational grant from **Cubist Pharmaceuticals**

Volume X Issue 1 December 2006

# Treatment Options for Management of *Staphylococcus aureus* Bacteremia and Endocarditis: *Past, Present and Future*

**George M. Eliopoulos, M.D.**
*Professor of Medicine*
Department of Medicine, Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA USA

## Introduction

The detection of *Staphylococcus aureus* bactermia in any patient represents a serious development. The mortality rate associated with *S. aureus* native valve endocarditis can exceed 20% (1-3). Even in non-fatal cases, the morbidity resulting from local or systemic complications of the infection, such as perivalvular abscess or stroke, is significant (4). Additional adverse effects and complications may arise from the required antimicrobial and surgical treatments. *S. aureus* bacteremia, even without evident endocarditis, can lead to serious suppurative complications (5). The latter events may have devastating clinical consequences, particularly in individuals with indwelling bioprosthetic material. As the proportion of *S. aureus* bacteremias caused by methicillin-resistant strains increases over time, clinicians will be further challenged to deliver appropriate therapy from a more selective list of options.

## Anti-staphylococcal penicillins

No other antimicrobial agent has proven superior to intravenously administered anti-staphylococcal penicillins (*e.g.*, nafcillin, oxacillin) for use in the treatment of most patients with bacteremia or endocarditis due to methicillin-susceptible isolates of *S. aureus* (MSSA). In a prospective observational study of patients with MSSA bacteremia who were followed for at least six months, Chang *et al.* (4) found that none of the patients treated with nafcillin experienced persistent ( >7 days) bacteremia or relapsed after therapy. This was in contrast to patients treated with vancomycin, of whom 19% had prolonged bacteremia or relapsed after treatment.

Several important points emerged from a prospective treatment study of MSSA endocarditis presented by Korzeniowski and Sande almost 25 years ago (3). Patients enrolled in this study were randomized to treatment with nafcillin alone for six weeks or to nafcillin for six weeks combined with gentamicin for the first two weeks of therapy. As might be expected, individuals using parenteral drugs (total, 48 patients) presented substantially more often with right-sided endocarditis, while those who were not using injection drugs (total, 30 patients) primarily had left-sided disease. Of the former group, those receiving gentamicin defervesced sooner (median, three days versus seven days), but there was no difference in days to clearance of bacteremia (median, three days) and only two of the 48 were known to have died or relapsed. In contrast, for the non-injection drug users, cure rates were lower than those obtained in the drug-user population, but within this group were comparable whether or not gentamicin was added (73% for nafcillin alone versus 68% for the combination). The duration of blood culture positivity was shorter in the gentamicin-treatment arm (mean, 2.8 days versus 4.1 days, a statistically significant difference), but this small advantage came at a cost of significant nephrotoxicity, which was seen in more than one-third of those receiving gentamicin, but in none of those treated with nafcillin alone.

## Vancomycin

As mentioned above, vancomycin treatment of MSSA bacteremia was more likely than therapy with nafcillin to result in prolonged duration of positive blood cultures or relapse (4). In their retrospective review of *S. aureus* endocarditis, Gentry *et al.* (2) found that patients with MSSA infections treated with nafcillin had significantly shorter duration of bacteremia than those treated with vancomycin (mean, 5.2 versus 9.5 days) and experienced fewer complications of endocarditis. However, because patients were not randomly allocated to these treatment groups, it was apparent that those treated with vancomycin had on average twice as many chronic medical conditions—including chronic renal insufficiency—as those treated with nafcillin, and were only half as likely to have been users of intravenous drugs. It could be expected that both of these factors might have skewed the

results in favor of nafcillin. The mortality rates observed in this study, 22% for those treated with nafcillin and 28% for those receiving vancomycin, were not statistically different.

Nafcillin treatment of *S. aureus* bacteremia and endocarditis was examined in a VA cooperative study (6). One result of that study, in which nafcillin two grams intravenously every four hours was the only antimicrobial therapy given, was that patients infected with organisms tolerant to the drug (*i.e.*, inhibited but not well killed by the drug, with nafcillin minimal bactericidal concentration ≥ 32 times the minimal inhibitory concentration) experienced a longer time to defervescence than those with organisms killed more rapidly. However, tolerance to the bactericidal effects of the drug did not influence the ultimate treatment outcome. This result is consistent with observations comparing vancomycin and nafcillin treatment. Because vancomycin tends to kill staphylococci more slowly than do anti-staphylococcal penicillins, relative tolerance to killing by vancomycin may also explain the reports noted above of slower clinical response of *S. aureus* (MSSA) bacteremia or endocarditis treated with vancomycin compared with nafcillin, an observation that does not always result in worse outcomes.

When vancomycin has been studied in the treatment of endocarditis due to methicillin-resistant strains of *S. aureus* (MRSA), the duration of fever and of positive blood cultures has generally been longer than seen when MSSA endocarditis is treated with an anti-staphylococcal penicillin. Levine *et al.* (7) randomized patients with MRSA endocarditis, the vast majority of whom had right-sided disease, to treatment with vancomycin alone or with rifampin. The median duration of positive blood cultures for patients in the vancomycin treatment arm was seven days. The addition of rifampin did not improve these results, with a median duration of positive cultures of nine days in that arm. For comparison, in the prospective study of Korzeniowski and Sande (3), intravenous drug users with predominantly right-sided MSSA endocarditis remained culture positive for an average of only 3.4 days after nafcillin therapy. In part, the duration of bacteremia in patients with MRSA endocarditis appears to depend upon a number of characteristics of the infecting organism (8). What has emerged is a general sense that treatment of serious MRSA infections with vancomycin is associated with slower response and is often less successful than treatment of MSSA infections with anti-staphylococcal penicillins (9). At the present time, it appears that a number of factors may account for the sometimes disappointing results seen when bacteremic *S. aureus* infections are treated with vancomycin, which include: characteristics specific to the infecting organisms; host factors in patients at risk for infection with MRSA versus MSSA; and any differences that might exist in the bactericidal properties of the antimicrobials themselves.

National Foundation for Infectious Diseases
EDUCATION · PREVENTION · RESEARCH
*Infectious Diseases*

**Senior Editor**
Susan J. Rehm, M.D.

**Managing Editor**
Sheena L. Majette

**Published by National Foundation for Infectious Diseases**
**4733 Bethesda Avenue, Suite 750**
**Bethesda, MD 20814**
**301-656-0003 • www.nfid.org**


### Trimethoprim-sulfamethoxazole

A randomized, prospective clinical trial compared trimethoprim-sulfamethoxazole (TMP-SMX) with vancomycin for treatment of serious staphylococcal infections in intravenous drug users (10). In that study, TMP-SMX was given at a dosage of 320 mg TMP plus 1600 mg SMX twice daily, while vancomycin was administered at one gram twice daily, with adjustments for renal function and serum levels. Approximately two-thirds of patients were bacteremic. The study showed that although serum bactericidal titers with TMP-SMX therapy exceeded those obtained with vancomycin, higher cure rates were obtained with vancomycin. Bacteremia cleared approximately two days earlier with vancomycin therapy (mean, 4.3 days versus 6.7 days), although this difference was not statistically significant. The inferiority of TMP-SMX was limited to patients with MSSA infections, however, because all patients with MRSA infections were cured with this drug.

**Table 1**

**Antimicrobial agents approved since 1999 with activity in vitro against *Staphylococcus aureus***

| Antimicrobial | Mechanism of action | Primary activity* |
|---|---|---|
| Quinupristin-dalfopristin | Protein synthesis inhibition | Bacteriostatic, or bactericidal if organism is susceptible to both components |
| Linezolid | Protein synthesis inhibition | Bacteriostatic |
| Daptomycin | Membrane depolarization | Bactericidal |
| Tigecycline | Protein synthesis inhibition | Bacteriostatic |

*The designation of bacteriostatic and bactericidal is somewhat arbitrary, and often reflects rate of killing in addition to extent of killing of a bacterial population.

### Quinupristin-dalfopristin

Quinupristin-dalfopristin, which became available in the US in 1999 (**Table 1**), is active in vitro against both MRSA and MSSA, and the combination is bactericidal against some isolates (11,12). In the US, the drug is not approved for treatment of MRSA infections. There are very limited published data on the use of this agent for treatment of MRSA bacteremias. In the summary of treatment courses in patients who failed or were intolerant of prior therapy, reported by Drew *et al.* (13), clinical success

rates with this agent were described in 13 of 22 "all treated" cases of MRSA endocarditis, catheter-related infection, and bacteremia of unknown source; but only three of these cases were clinically and microbiologically evaluable, with the only success in a catheter-related infection. A few cases have been reported in which the addition of quinupristin-dalfopristin to failing courses of vancomycin has resulted in control of MRSA bacteremia (14,15). The use of quinupristin-dalfopristin requires deep venous access, carries the risk of drug-drug interactions, and is associated with a high rate of adverse effects, especially the myalgia-arthralgia syndrome (16).

### Linezolid

With rare exceptions, linezolid demonstrates predictable in vitro antimicrobial activity against clinical isolates of *S. aureus*, including both MSSA and MRSA. Although the drug is bacteriostatic against *S. aureus* in vitro (12), in compassionate use experience, linezolid was used successfully to treat three of four cases of *S. aureus* endocarditis and 18 of 21 bacteremias (17). Case reports describe successful use of linezolid to treat MRSA bacteremias due to isolates demonstrating reduced susceptibility (18) or heteroresistance (19) to vancomycin. Linezolid was used successfully to treat four of eight patients with endocarditis due to MRSA with reduced susceptibility to vancomycin (MICs 2-4 µg/mL and a population analysis profile consistent with heteroresistance) (20). In two of the four cured patients, linezolid was used alone for 40 or 49 days, and in the other two patients linezolid was given for 38 or 42 days, followed by 8-11 days of therapy with fusidic acid plus rifampin.

Linezolid given orally is almost completely absorbed, and thus offers the possibility for oral therapy of serious infections. However, treatment lasting two weeks or more requires monitoring for myelosuppressive effects of linezolid, and long courses have been associated with the development of peripheral or optic neuropathy or both (21, 22). Lactic acidosis has been described very rarely in patients treated with this drug (23). Resistance to linezolid has been reported among clinical isolates of *S. aureus*. One case report documents the emergence of linezolid resistance in an isolate recovered from a patient after many months of suppressive therapy for an intractable endovascular infection (24).

### Daptomycin

The cyclic lipopeptide antibiotic, daptomycin, was approved in the US in 2003 for treatment of complicated skin and skin structure infections, including those due to MRSA and MSSA. The daily dose used in studies leading to that indication was 4 mg/kg for patients with normal renal function (25). Daptomycin acts uniquely among currently available antimicrobials. In a calcium-dependent process, the lipid tail of daptomycin inserts into the bacterial cytoplasmic membrane. It is believed that, subsequently, oligomerization of drug units and channel formation leads to membrane depolarization, leakage of intracellular ions, and eventually cell death (26). Daptomycin is broadly active in vitro against gram-positive organisms and demonstrates substantially greater bactericidal activity than vancomycin against staphylococci (12, 26).

A randomized clinical trial compared daptomycin at 6 mg/kg once daily with either an anti-staphylococcal penicillin or vancomycin, pre-specified by the investigator, for treatment of *S. aureus* bacteremia or right-sided endocarditis. Gentamicin was added in the comparator arms for the first three to five days. The results of this trial showed that daptomycin was not inferior to standard therapy for both MSSA and MRSA infections (27). This resulted in the approval in 2006 by the US FDA of daptomycin for treatment of *S. aureus* (MSSA or MRSA) bacteremia and right-sided endocarditis.

The daptomycin package insert advises clinicians to monitor patients for muscle pain or weakness, and to check creatine kinase (CK) levels weekly during therapy, or more frequently for patients with renal insufficiency, because muscle weakness associated with elevated CK were noted in a small proportion of treated patients. These changes are expected to be reversible upon discontinuation of the drug. Two case reports suggest the possibility that muscle injury can on rare occasions rise to levels associated with myoglobinuria (28, 29). Mild, reversible symptoms related to the peripheral nervous system have occasionally been noted.

A few isolates of MRSA with reduced susceptibility to daptomycin after exposure to the drug have been reported (30, 31). This increase in MICs of daptomycin was seen in about one-third of the *S. aureus* isolates recovered from patients who failed to respond to treatment with the lipopeptide in the *S. aureus* bacteremia/endocarditis trial (27).

### Tigecycline

In 2005, tigecycline was approved in the US for treatment of intra-abdominal infections, including those due to MSSA, and complicated skin and skin structure infections, including those due to MSSA or MRSA. This drug of the glycylcycline class is an inhibitor of bacterial protein synthesis. In vitro, tigecycline demonstrates potent inhibitory activity against MSSA and MRSA isolates (32). At the present time, the drug does not have a defined role in the treatment of *S. aureus* bloodstream infections.

### Investigational Antimicrobial Agents

Three other antibiotics with in vitro anti-staphylococcal activity in advanced phases of clinical investigation will be discussed. These are the glycopeptides, dalbavancin and telavancin, and the cephalosporin, ceftobiprole (**Table 2**).

Dalbavancin is a glycopeptide with an antibacterial spectrum similar to that of vancomycin, but with substantially greater potency: *e.g.*, $MIC_{90}$s against both MSSA and MRSA of 0.06 µg/ml for dalbavancin versus 1-2 µg/ml for vancomycin (33). Another important difference between the two drugs is the very long elimination half-life of dalbavancin, approximately nine days. Taking advantage of the prolonged serum concentrations that are achieved after an intravenous dose, successful studies in complicated skin and skin structure infections have been carried out using only two doses of the drug, administered one week apart (34, 35). At present, the only published data on the use of dalbavancin versus vancomycin for treatment of bacteremia is the report of a small, randomized, open-label study in catheter-related bloodstream

**Table 2**

**In vitro activity of vancomycin and investigational agents against methicillin–susceptible and –resistant strains of *Staphylococcus aureus*.**

| | $MIC_{90}$ (µg/mL) against* | | |
|---|---|---|---|
| Antimicrobial | MSSA | MRSA | Reference |
| Vancomycin | 1-2 | 1-2 | 33, 37, 42 |
| Dalbavancin | 0.06 | 0.06 | 33 |
| Telavancin | 0.5 | 0.5 | 37 |
| Ceftibiprole | 0.5 | 2 | 42 |

*MIC is the lowest drug concentration that inhibited 90% of isolates in the collections studied. For each of the investigational agents, vancomycin was also tested and included in the results shown.

infections (including both *S. aureus* and coagulase-negative staphylococci) in which promising results were presented (36).

Telavancin is a lipoglycopeptide that is also somewhat more potent than vancomycin ($MIC_{90}$ for MSSA and MRSA of 0.5 µg/ml, versus 1-2 µg/ml) (37). However, in contrast to vancomycin, telavancin appears not only to inhibit peptidoglycan synthesis, but also to disrupt the bacterial cell membrane (38). A study in our own laboratory found telavancin to have greater bactericidal activity than vancomycin against *S. aureus* isolates that were selected for relative resistance to killing by vancomycin (39). Initial clinical studies have documented the effectiveness of this agent in the treatment of complicated skin and skin structure infections (40, 41). At present, there are no published studies that examine the role of telavancin in bloodstream infections.

A number of ß-lactam antibiotics have been developed, which have the property of enhanced binding to penicillin-binding protein 2' that is the product of the *mecA* gene in MRSA. As a result, such agents defy the dictum that MRSA must be considered resistant to all ß-lactams, irrespective of apparent in vitro activity. One such agent in advanced stages of development is ceftobiprole. $MIC_{90}$s of this agent against MSSA and MRSA were 0.5 and 2 µg/ml, which contrasts with $MIC_{90}$s of ceftriaxone, which were four and >32 µg/ml (42). In a rabbit model of MRSA endocarditis, ceftobiprole demonstrated activity comparable to that of vancomycin, and the ß-lactam proved superior to vancomycin for treatment of experimental endocarditis due to a vancomycin-intermediate MRSA isolate (43). As yet, there are no published studies examining the effectiveness of ceftobiprole in *S. aureus* bacteremia in patients. Because of the success of anti-staphylococcal penicillins in the treatment of infections due to MSSA, results of such studies would be of great interest.

## Conclusions

For MSSA bacteremia or endocarditis, anti-staphylococcal penicillins remain the agents of choice. For MRSA bacteremia, no agent has yet proven superior to vancomycin. Linezolid has been used successfully for some cases of MRSA bacteremia, but the agent is primarily bacteriostatic and does not have an indication for bloodstream infections. Daptomycin has recently earned approval for treatment of *S. aureus* bacteremia and right-sided endocarditis due to MRSA and MSSA. A number of investigational agents have interesting properties and may eventually prove useful for treatment of serious infections due to MRSA, including bacteremia.

## REFERENCES:


1. Fowler VG Jr, Miro JM, Hoen B, *et. al. Staphylococcus aureus* endocarditis. A consequence of medical progress. *JAMA* 2005; 293: 3012-3021.
2. Gentry CA, Rodvold KA, Novak RM, Hershow RC, Naderer OJ. Retrospective evaluation of therapies for *Staphylococcus aureus* endocarditis. *Pharmacotherapy* 1997; 17:990-997.
3. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts. *Ann Intern Med* 1982; 97:496-503.
4. Chang F-Y, Peacock JE Jr, Musher DM, *et al. Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine* 2003 ; 82:333-339.
5. Lowy, FD. *Staphylococcus aureus* infections. *New Engl J Med* 1998; 339:520-532.
6. Rahal JJ Jr, Chan YK, Johnson G. Relationship of staphylococcal tolerance, teichoic acid antibody, and serum bactericidal activity to therapeutic outcome in *Staphylococcus aureus* bacteremia. *Am J Med* 1986; 81:43-52.
7. Levine DP, Fromm BS, Reddy BR Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med* 1991; 115:674-680.
8. Fowler VG Jr, Sakoulas G, McIntyre LM, *et al.* Persistent bacteremia due to methicillin-resistant *Staphylococcus aureus* infection is associated with *agr* dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. *J Infect Dis* 2004; 190:1140-1149.
9. Eliopoulos GM. Antimicrobial agents for treatment of serious infections caused by resistant *Staphylococcus aureus* and enterococci. *Eur J Clin Microbiol Infect Dis* 2005; 24:826-831.
10. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* 1992; 117:390-398.
11. Jones RN, Ballow CH, Biedenbach DJ, *et al.* Antimicrobial activity of quinupristin-dalfopristin (RP 59500, Synercid) tested against over 28,000 recent clinical isolates from 200 medical centers in the United States and Canada. *Diagn Microbiol Infect Dis* 1998; 31:437-451.
12. Fuchs PC, Barry AL, Brown SD. *In vitro* bactericidal activity of daptomycin against staphylococci. *J Antimicrob Chemother* 2002; 49:467-470.
13. Drew RH, Perfect JR, Srinath L, *et al.* Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. *J Antimicrob Chemother* 2000; 46:775-784.
14. Moise-Broder PA, Forrest A, Schentag JJ. Clinical experience with quinupristin/dalfopristin and vancomycin in combination against persistent methicillin-resistant *Staphylococcus aureus* infections expressing the accessory gene regulator (agr) group II polymorphism. Abstracts 41st Annual Meeting of the Infectious Diseases Society of America, San Diego, Oct 9-12, 2003, abst. no. 486.
15. Moyenuddin M, Ohl CA, Williamson JC, Peacock JE. Disseminated oxacillin-resistant *Staphylococcus aureus* infection responsive to vancomycin and quinupristin-dalfopristin combination therapy. *J. Antimicrob Chemother* 2003; 51:202-203.
16. Eliopoulos GM. Quinuprisitin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis* 2003; 36:473-481.
17. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J Antimicrob Chemother* 2002; 50:1017-1022.
18. Fridkin SK, Hageman J, McDougal LK, *et al.* Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997-2001. *Clin Infect Dis* 2003; 36:429-439.
19. Charles PG, Ward PB, Johnson PD, *et al.* Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus.* *Clin Infec Dis* 2004; 38:448-451.
20. Howden BP, Ward PB, Charles PG, *et al.* Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. *Clin Infect Dis* 2004; 38:521-528.
21. Rho JP, Sia IG, Crum BA, *et al.* Linezolid-associated peripheral neuropathy. *Mayo Clin Proc* 2004; 79:927-930.
22. Lee E, Burger S, Shah J, *et al.* Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; 37:1389-1391.
23. De Vriese AS, Van Coster R, Smet J, *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006; 42:1111-1117.

24. Meka VG, Gold HS. Antimicrobial resistance to linezolid. *Clin Infect Dis* 2004; 39:1010-1015.
25. Arbeit RD, Maki D, Tally FP, *et al*. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004; 38:1673-1681.
26. Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious gram-positive infections. *J. Antimicrob Chemother.* 2005; 55:283-288.
27. Fowler VC, Jr., Boucher HW, Corey GR, *et al*. Daptomycin vs. standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *New Engl J Med* 2006; 355:653-665.
28. Kazory A, Dibadj K, Weiner ID. Rhabdomyolysis and acute renal failure in a patient treated with daptomycin. *J Antimicrob Chemother* 2006; 57:578-579.
29. Echevarria K, Datta P, Cadena J, Lewis JS II. Severe myopathy and possible hepatotoxicity related to daptomycin. *J Antimicrob Chemother* 2005; 55:599-600.
30. Mangili A, Bica I, Snydman DR, Hamer DH. Daptomycin-resistant, methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2005; 40:1058-1060.
31. Hayden MK, Rezai K, Hayes RA, *et al*. Development of daptomycin resistance in vivo in methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol* 2005; 43:5285-5287.
32. Fritsche TR, Kirby JT, Jones RN. In vitro activity of tigecycline (GAR-936) tested against 11,859 recent clinical isolates associated with community-acquired respiratory tract and gram-positive cutaneous infections. *Diagn Microbiol Infect Dis* 2004; 49:201-209.
33. Streit JM, Fritsche TR, Sader HS, Jones RN. Worldwide assessment of dalbavancin activity and spectrum against over 6,000 clinical isolates. *Diagn Microbiol Infect Dis* 2004; 48:137-143.
34. Jauregui LE, Babazadeh S, Seltzer E, *et al*. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005; 41: 1407-1415.
35. Seltzer E, Dorr MB, Goldstein BP, *et al*. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 2003; 37:1298-1303.
36. Raad I, Darouiche R, Vazquez J, *et al*. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis* 2005; 40:374-380.
37. King A, Phillips I, Koniga K. Comparative *in vitro* activity of telavancin (TD-6424), a rapidly bactericidal, concentration-dependent anti-infective with multiple mechanisms of action against gram-positive bacteria. *J Antimicrob Chemother* 2004; 53:797-803.
38. Higgins DL, Chang R, Debabov DV, *et al*. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2005; 49:1127-1134.
39. Eliopoulos GM, Wennersten CB, Sakoulas G, Moellering RC Jr. *In vitro* bactericidal activity of telavancin against *S. aureus* with relative tolerance to vancomycin. Progr. Abstr. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct 30-Nov 2, 2004, Washington, DC, abstr. no. E-2011.
40. Stryjewski ME, O'Riordan WD, Lau WK, *et al*. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. *Clin Infect Dis* 2005; 40:1601-1607.
41. Stryjewski ME, Chu VH, O'Riordan WD, *et al*. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. *Antimicrob Agents Chemother* 2006; 50:862-867.
42. Jones RN, Deshpande LM, Mutnick AH, Biedenbach DJ. In vitro evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci. *J Antimicrob Chemother* 2002; 50:915-932.
43. Chambers HF. Evaluation of ceftobiprole in a rabbit model of aortic valve endocarditis due to methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2005; 49:884-888.

**Target Audience:** Practicing physicians, infectious disease physicians, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, and others interest in the treatment of S. aureus bacteremia and endocarditis.

**Learning Objective:** After reading this publication, the reader should be able to list current and future antimicrobial therapies for *S. aureus* bacteremia and endocarditis.

## Self Assessment Examination

**Volume X, Issue 1**

**(At least three of the five answers must be correct in order to obtain a CME certificate)**
See mailing instructions and other pertinent information on the reverse side.

1) Native valve *S. aureus* endocarditis proves fatal in approximately what proportion of patients:
   a) ≥ 80%
   b) 60%
   c) 20%
   d) ≤ 5%

   Answer: _____

2) Which of the following statements about MSSA native valve endocarditis is true:
   a) No agent has proven to be more effective than an anti-staphylococcal penicillin for therapy of this condition.
   b) The addition of a 2-week course of an aminoglycoside to nafcillin therapy enhances survival and is devoid of serious toxicity.
   c) When a patient becomes clinically stable, it is appropriate to switch to oral oxacillin to minimize the risk of venous irritation.
   d) Rifampin is an essential component of successful treatment.

   Answer: _____

3) MRSA infections are accurately characterized by which of the following statements:
   a) MRSA bacteremia treated with vancomycin tends to resolve more slowly than MSSA bacteremia treated with an anti-staphylococcal penicillin.
   b) The addition of rifampin to vancomycin when treating MRSA native valve endocarditis predictably hastens clearance of blood cultures.
   c) Quinupristin-dalfopristin is usually active in vitro against MRSA, but is not approved for treatment of MRSA bacteremia.
   d) Trimethoprim-sulfamethoxazole is active in vitro, but has never been studied clinically for treatment of serious MRSA infections.

   Answer: _____

4) Which of the following is true about antimicrobials used to treat infections caused by MRSA or MSSA:
   a) Daptomycin is FDA approved for treating bacteremia and right-sided endocarditis due to these organisms.
   b) Linezolid resistance is rare among clinical isolates of *Staphylococcus aureus*.
   c) Tigecycline inhibits growth of MRSA in vitro.
   d) Periodic measurements of plasma drug concentrations are not required when using daptomycin or linezolid for indicated infections.
   e) all of the above

   Answer: _____

5) True statement(s) concerning investigational antimicrobial agents include the following:
   a) Dalbavancin is unique among ß-lactams because of its long elimination half-life.
   b) Telavancin is a lipoglycopeptide that has more than one mechanism of antibacterial action.
   c) Ceftobiprole is highly active against MSSA in vitro, but like all other ß-lactams must be considered inactive against MRSA.
   d) Published studies support the superiority of anti-MRSA ß-lactams over vancomycin for the treatment of MRSA bacteremia.

   Answer: _____

## Evaluation

Your input is important to us in improving this publication and identifying areas of need for other educational programs. Please circle the choice that best answers the following:

1. This content meets the educational objectives.
   A. Agree B. Neutral C. Disagree
2. Considering my experience, the material presented was:
   A. Satisfactory B. Too Elementary C. Too Technical
3. I gained information which will be of use to me.
   A. Agree B. Neutral C. Disagree
4. The format is clear, readable, and useful.
   A. Agree B. Neutral C. Disagree
5. There was commercial bias in this publication.
   A. Yes B. No

**If yes, please give examples:** _____

_____

Suggested topics for future issues or other comments about this publication:_____

_____

Please provide all the information below so that you may obtain CME credit **(Please print legibly or we will be unable to process your certificate)**.

Name/Degree _____

Title _____

Affiliation _____

Address _____

City_____ State_____ Zip_____

E-Mail _____

Telephone _____ Fax _____

Check the appropriate box:

☐ I am an MD and/or DO and wish to receive 1.0 (one) AMA/PRA Category 1 credit.

☐ I am not an MD and/or DO but wish to receive a certificate of completion.

☐ I am a nurse and wish to receive 1.2 contact hours for completion.

Signature/Date _____

**Please Fax to NFID 301-907-0878**

National Foundation for Infectious Diseases
EDUCATION PREVENTION RESEARCH

4733 Bethesda Avenue, Suite 750
Bethesda, MD 20814

**Return Service Requested**



## Accreditation

**Physicians**

The National Foundation for Infectious Diseases (NFID) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide Continuing Medical Education (CME) for physicians. NFID takes responsibility for the content, quality, and scientific integrity of this CME activity.

NFID designates this educational activity for a maximum of one 1.0 *AMA PRA Category 1 credit*™. Each physician should only claim credit commensurate with the extent of their participation in the activity. The 1.0 Category 1 credit is based upon the approximate time it should take to read this publication and complete the self-assessment examination and evaluation.

CME Credits will be granted only up to six months following the publication date. **Requests for CME credit must be received no later than June 30, 2007.**

**Nurses**

This offering has been approved for 1.2 contact hours by the Maryland Nurses Association which is accredited as an approver of continuing education in nursing by the American Nurses' Credentialing Center's Commission on Accreditation.

Nursing Credits will be granted up to one year following the publication date. **Requests for nursing credits must be received no later than December 31, 2007.**

## CME Disclosure

As a sponsor accredited by the ACCME, NFID must ensure balance, independence, objectivity, and scientific rigor in its educational activities. All authors are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any product or service discussed in an educational presentation and with the commercial supporter of this activity. Disclosure information is reviewed in advance to manage and resolve any conflict of interest that may affect the balance and scientific integrity of an educational activity.

**Dr. Eliopoulos** has received research contracts from and/or consulted for the following: Aventis Pharmaceuticals [now Sanofi-Aventis], Cubist Pharmaceuticals, Johnson & Johnson Pharmaceutical Research, Pfizer, Inc., Theravance, Inc., Wyeth Pharmaceuticals

## CME Instructions

To receive credits after reading this publication, complete the self-assessment examination, the evaluation, and your contact information. Return the examination and evaluation form, including your complete contact information, **via fax to 301-907-0878** or by mail to:

NFID Office of CME
4733 Bethesda Avenue, Suite 750
Bethesda, Maryland 20814

No fee is required. Please allow 4-6 weeks for processing your certification. Inquiries may be directed by phone to 301-656-0003 ext. 19 or by email to info@nfid.org.