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Current and Future Antibiotics for Treatment of Resistant Gram-Positive Infections

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Introduction

For most American clinicians, antimicrobial resistant gram-positive infections are a fact of life. Recent events suggest that the clinical utility of vancomycin, long the antimicrobial agent of last resort for resistant gram positive infections, may be eroding. Increasing rates of vancomycin resistance in enterococci, vancomycin tolerance in Streptococcus pneumoniae, and the identification of clinical Staphylococcus aureus isolates with reduced susceptibility or full resistance to vancomycin mandate new additions to our antimicrobial armamentarium. In addition, infections involving indwelling pros-

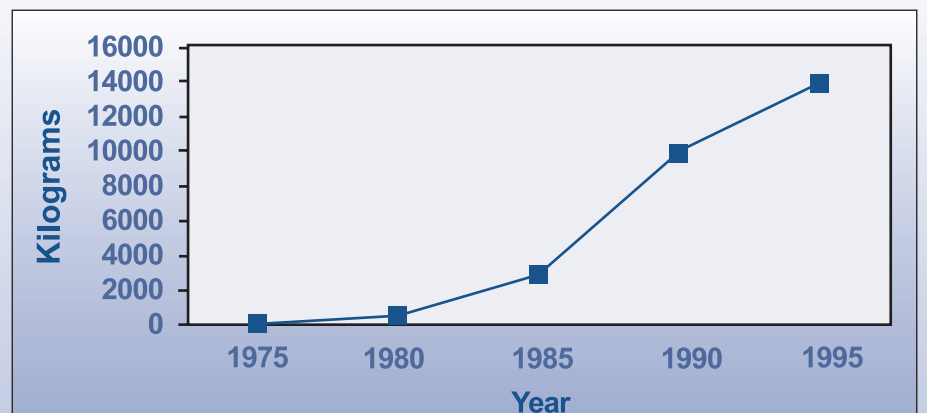
thetic devices caused by resistant gram-positive pathogens are also increasing in frequency and complexity. Finally, the aging American population and the ever-increasing number of medical indications for indwelling prosthetic devices assures that the number and complexity of infections due to resistant gram-positive infections will only increase. Thus, there is an urgent public health need for new antimicrobial options for the treatment and prevention of resistant gram-positive pathogens.

Currently Available Antibiotics

Our arsenal for the treatment of resistant gram-positive infections

Figure 1

Total Usage of Vancomycin (US and Europe)3



Adapted from Kirt HA, Thompson DG, Nicas TI. Antimicrob Agents Chemother 1998; 42(5):1303-1304

may be grouped into two broad categories: vancomycin and alternatives to vancomycin. Vancomycin is currently the treatment of choice for methicillin resistant *S. aureus* (MRSA) and most other resistant Gram-positive pathogens because it is convenient, inexpensive, safe, available, and effective. Because of these attributes, our reliance upon vancomycin has increased dramatically. For example, the total usage of vancomycin in the United States and Western Europe is estimated to have increased from essentially negligible quantities in 1975 to over 14,000 kilograms in 1995<sup>4</sup> (Figure 1). This extensive reliance upon vancomycin has in large part been driven by the lack of better alternative antibiotics. Despite this increasing reliance, vancomycin is generally regarded as an inferior anti-staphylococcal antibiotic. Vancomycin for the treatment of *S. aureus* infections has been associated with high clinical failure rates, prolonged durations of bacteremia<sup>5</sup>, higher rates of relapsing infections<sup>6</sup>, and worse clinical outcomes<sup>7</sup>. This impression has been underscored by the recent reports of vancomycin resistance among a growing number of gram-positive pathogens, making alternatives to vancomycin increasingly desirable.

### Alternatives To Vancomycin

Currently, three alternatives to vancomycin are available: quinupristin/dalfopristin (Synercid®), linezolid (Zyvox®), and daptomycin (Cubicin®). The profiles of quinupristin/dalfopristin and linezolid have been recently reviewed<sup>8</sup>. Quinupristin/dalfopristin is FDA approved for vancomycin-resistant *Enterococcus faecium* skin and soft tissue infections. It is bactericidal against *Streptococcus pneumoniae*, bacteriostatic against *S. aureus* isolates possessing resistance to the macrolide/lincosamide/ streptogramin antibiotics and *E. faecium*, and has no efficacy against *Enterococcus faecalis*. Resistance to quinupristin/dalfopristin may occur in both enterococci and *S. aureus*. Administration of quinupristin/dalfopristin requires central venous access because of local irritation at the infusion site when given by peripheral vein. Other side effects include hyperbilirubinemia, and myalgias and arthralgias, which can be severe<sup>9</sup>. Although limited data from expanded access programs are available<sup>10</sup>, data from randomized clinical trials are required to clarify the role of quinupristin/dalfopristin in treatment of *S. aureus* infections.

Linezolid is currently indicated for VRE infections, nosocomial pneumonia due to methicillin-sensitive *S. aureus* or MRSA, skin and soft tissue infections, and community-acquired pneumonia due to either *S. pneumoniae* or *S. aureus*. Linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal against *S. pneumoniae*. Because of its excellent oral bioavailability (100%), linezolid may be administered either orally or intravenously. Antimicrobial resistance to linezolid has been documented for both *S. aureus* and in enterococci. Although apparent clinical failures involving patients with *S. aureus*

endocarditis treated with linezolid have also been reported, an open-label randomized clinical trial comparing linezolid to vancomycin for the treatment of known or suspected *S. aureus* infections other than endocarditis revealed similar outcomes for patients treated with either drug<sup>11</sup>. The risk for myelosuppression, the primary side effect associated with linezolid, increases with prolonged durations of therapy<sup>12</sup>, generally beyond two weeks. Important unresolved questions surrounding quinupristin/dalfopristin and linezolid include the role of these agents in combination regimens and/or the circumstances in which they might be alternatives to vancomycin or other traditional antibiotics for the treatment of deep-seated or endovascular infections.

Daptomycin, a “first in class” lipopeptide class antibiotic originally discovered by Eli Lilly and developed by Cubist Pharmaceuticals, received approval by the Food and Drug Administration in late 2003 for the treatment of complicated skin and soft tissue infections caused by gram-positive pathogens. Daptomycin exhibits rapid bactericidal activity against a wide variety of Gram-positive organisms. The mechanism of action involves cell membrane disruption and depolarization. *In vitro* data, animal model data, and two well-designed phase three trials for the indication of complicated skin and soft tissue infections have been highly encouraging. An important clinical trial evaluating daptomycin in the treatment of *S. aureus* bacteremia is currently underway, and the results of this trial are eagerly anticipated. When daptomycin was first being evaluated over a decade ago, skeletal muscle injury was observed with twice daily administration of daptomycin. This toxicity appears to be related to high trough drug concentrations. Based upon data from over 1,000 patients receiving daptomycin to date, given as a once daily dose, the risk of skeletal muscle toxicity appears to be minimal. Additional studies will be required to confirm these observations, and to better define dosing in patients with renal insufficiency.

### Future Antimicrobial Agents

While quinupristin/dalfopristin, linezolid, and daptomycin offer readily available alternatives to vancomycin, other antimicrobial agents are desperately needed for the treatment of resistant gram-positive organisms. Fortunately, a number of exciting new antimicrobial agents are currently undergoing clinical trials as future alternatives to vancomycin.

*Glycopeptide class compounds.* Oritavancin is currently being developed by InterMune. This glycopeptide class compound is likely to be intravenously administered in a daily or alternate day schedule, and it is primarily eliminated via the gastrointestinal route. *In vitro* data for oritavancin against resistant gram-positive pathogens, including vancomycin-resistant *E. faecium*, is also quite promising. Clinical trials in skin and soft tissue

infections comparing oritavancin to conventional therapies to date have also been favorable. Unresolved issues with oritavancin are likely to include the impact of a prolonged half-life on the development of both resistance in bacteria and adverse events in patients. Another glycopeptide agent, dalbavancin, is currently being developed by Vicuron. Appealing characteristics of dalbavancin include rapid cidal activity against *S. aureus* and a prolonged half-life, allowing intravenous dosing as infrequently as once weekly. Although dalbavancin also has a broad-spectrum activity against a variety of gram-positive pathogens *in vitro*, it does not have efficacy against VanA-type enterococci. Clinical trials of dalbavancin are currently underway. A third glycopeptide-class antibiotic, TD-6424, is being developed by Theravance. TD-6424 also exhibits rapid concentration dependent killing *in vitro* against a wide range of gram-positive bacteria. Clinical trials involving the use of TD-6424 in a variety of clinical indications are underway.

**Tetracycline class compounds.** Tigecycline, a tetracycline derivative antibiotic under development by Wyeth, has broad-spectrum activity against gram-positive, gram-negative, anaerobic, and fastidious organisms including mycoplasma and legionella. It is currently undergoing late phase clinical trials for the treatment of several clinical indications. *In vitro* activity of tigecycline against a wide variety of gram-positive pathogens, including VanA-, VanB-, and VanC-constitutive enterococci is encouraging. Administration is anticipated to be both via intravenous and oral routes. The clinical significance of tigecycline's bacteriostatic mechanism of action remains to be defined.

**Immunotherapeutic compounds.** In addition to conventional antimicrobial agents, a variety of innovative immunotherapeutic agents are currently under development. In my opinion, the ultimate role of these interesting immunotherapeutic agents will primarily be the prevention of infection. Two such immunotherapeutic products are currently under development. Altastaph®, produced by Nabi, consists of pooled antibodies to *S. aureus* capsular polysaccharide types five and eight. These capsule polysaccharide types are present in a majority of *S. aureus* isolates responsible for human disease. A phase two trial is currently underway for this product in the setting of *S. aureus* bacteremia. Aurexis®, a monoclonal antibody produced by Inhibitex, targets clumping factor A, a protein on the surface of *S. aureus* which binds to human fibrinogen. Phase two trials are currently under development for this product.

**Vaccines.** Because the best way to combat infections due to resistant Gram-positive pathogens is to prevent them in the first place, the possibility of a clinically available vaccine for *S. aureus* is one of the most interesting developments in the whole area of Gram-positive therapeutics in recent years. This

vaccine, produced by Nabi, targets *S. aureus* capsular polysaccharides five and eight. A recent study in 1800 hemodialysis patients produced promising results, but the study failed to meet its primary endpoint of reducing staphylococcal sepsis episodes in the first year after vaccination (relative risk reduction, 26%;  $P=0.23$ )<sup>13</sup>. A *post hoc* analysis showed a relative reduction in sepsis episodes of 57% (nominal  $P=0.02$ ) in the first 40 weeks after vaccination, but this analysis was not pre-specified and the hazard of this type of analysis is well known<sup>14</sup>. Thus, this work remains hypothesis-generating and a repeat trial is eagerly anticipated.

### Summary

Resistant Gram-positive infections represent a growing public health threat. The benefits offered by vancomycin, long the antibiotic of last resort against these pathogens, have been eroded by suboptimal clinical performance and increasing resistance rates. Currently available alternatives to vancomycin are insufficient due to high cost, significant side effects, and incomplete clinical outcomes data for the treatment of complex endovascular infections. Several promising compounds are currently in various stages of clinical development. These new compounds on the horizon promise to provide important new additions to our armamentarium in the fight against resistant gram-positive bacteria.

## REFERENCES:

1. Novak R, Henriques B, Charpentier E, Normark S, Tuomanen E. Emergence of vancomycin tolerance in *Streptococcus pneumoniae* [see comments]. *Nature* 1999; 399(6736):590-593.
2. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E, Jarvis WR. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group.[comment]. *New England Journal of Medicine* 1999; 340(7):493-501.
3. *Staphylococcus aureus* resistant to vancomycin—United States, 2002. *MMWR - Morbidity & Mortality Weekly Report* 2002; 51(26):565-567.
4. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. *Antimicrobial Agents & Chemotherapy* 1998; 42(5):1303-1304.
5. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis [see comments]. *Annals of Internal Medicine* 1991; 115(9):674-680.
6. Fowler VGJ, Kong LK, Corey GR, Gottlieb GS, McClelland, RS, Sexton DJ, Gesty-Palmer D, Harrell LJ. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. *Journal of Infectious Diseases* 1999; 179(5):1157-1161.
7. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clinical Infectious Diseases* 1999; 29(5):1171-1177.
8. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clinical Infectious Diseases* 2003; 36(4):473-481.
9. Olsen KM, Rebuck JA, Rupp ME. Arthralgias and myalgias related to quinupristin-dalfopristin administration. *Clinical Infectious Diseases* 2001; 32(4):e83-e86.
10. Drew RH, Perfect JR, Srinath L, Kurkimilis E, Dowzicky M, Talbot GH. Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid Emergency-Use Study Group. *Journal of Antimicrobial Chemotherapy* 2000; 46(5):775-784.
11. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections.[comment]. *Clinical Infectious Diseases* 2002; 34(11):1481-1490.
12. Attasi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy.[comment]. *Clinical Infectious Diseases* 2002; 34(5):695-698.
13. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, Ordonez J, Yeoh H, Law D, Robbins JB, Schneerson R, Muenz L, Fuller S, Johnson J, Fireman B, Alcorn H, Naso R. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. *New England Journal of Medicine* 2002; 346(7):491-496.
14. Moye LA, Deswal A. The fragility of cardiovascular clinical trial results. [Review] [40 refs]. *Journal of Cardiac Failure* 2002; 8(4):247-253.

**Target Audience:** practicing physicians, infectious disease physicians, physicians specializing in travel medicine, clinical microbiologists, pharmacists, public health authorities, and others interested in the diagnosis and management of enteric infections and the growing problem of antimicrobial resistance in enteric infections

**Learning Objectives:** After reading this publication, the reader should be able to:

- List recently marketed or soon-to-be marketed antimicrobials for treating gram-positive infections.
- Understand the advantages and disadvantages of the recently marketed antimicrobials for treating serious gram-positive infections.

### CME Self Assessment Examination

Volume VI, Issue 5

See instructions and pertinent information on the reverse before requesting credit.

1-3) Questions 1-3 refer to the antimicrobial activity of quinupristin/dalfopristin (Synercid®). Circle **S** if quinupristin/dalfopristin has **BACTERIOSTATIC** activity or **C** if it has **BACTERICIDAL** activity against the following Gram-positive bacteria:

- 1) *Streptococcus pneumoniae* **S C**
- 2) *Staphylococcus aureus* resistant to macrolide/lincosamide/streptogramin **S C**
- 3) *Enterococcus faecium* **S C**

4) Which of the following conditions is a potential side effect of quinupristin/dalfopristin?

- a) Local irritation of peripheral vein
- b) Hyperbilirubinemia
- c) Myalgia and arthralgia
- d) Red man syndrome
- e) A, b, and c
- f) All of the above

Answer: \_\_\_\_\_

5-7) Questions 5-7 refer to the antimicrobial activity of linezolid (Zyvox®). Circle **S** if linezolid has **BACTERIOSTATIC** activity or **C** if it has **BACTERICIDAL** activity against the following Gram-positive bacteria:

- 5) Enterococci **S C**
- 6) Staphylococci **S C**
- 7) *Streptococcus pneumoniae* **S C**

8) The following antibiotic which has gained FDA approval represents a "first in class," that is, the first antibiotic of its type in a class of antimicrobials?

- a) Quinupristin/dalfopristin
- b) Linezolid
- c) Daptomycin
- d) Vancomycin
- e) All of the above

Answer: \_\_\_\_\_

9) Which of the following statements least likely characterizes the antibiotic?

- a) A potential side effect of linezolid is thrombocytopenia and myelosuppression
- b) Skeletal muscle toxicity with daptomycin administered twice daily seemed to be associated with high trough drug concentrations
- c) A potential drawback of oritavancin is its short half-life
- d) Tigecycline has broad spectrum activity against Gram-positive, Gram-negative, anaerobic, and fastidious microorganisms such as Mycoplasma and Legionella
- e) None of the above

Answer: \_\_\_\_\_

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