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Newer antibiotics for serious gram-positive infections

ABSTRACT

Four newer antibiotics are available to treat gram-positive bacterial infections that are resistant to traditional antibiotics and to vancomycin. They should preferably be used with the help of an infectious-disease consultant: specific therapy should be chosen on the basis of the bacteria involved, the site of infection, whether the patient has kidney or liver disease, other medications the patient is taking, and side effects that develop.

KEY POINTS

Vancomycin and the new antibiotics should be used judiciously to forestall further resistance.

Linezolid is effective against gram-positive organisms that are resistant to many antibiotics, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Patients taking linezolid for more than 2 weeks should have their blood monitored for cytopenia.

Quinupristin-dalfopristin is active against MRSA and vancomycin-resistant *Enterococcus faecium*. Its use is limited because it often causes myalgia and arthralgia and has numerous drug interactions.

Daptomycin is an option for treating endovascular infection due to MRSA. The drug is inactivated by surfactant, so it should not be used to treat pneumonia.

Tigecycline can cause permanent tooth discoloration and should not be used in young children and pregnant women.

GRAM-POSITIVE BACTERIA have become common causes of hospital-acquired infections. Friedman et al,[1] in a study of 361 patients with nosocomial bloodstream infections, found that the top three organisms were *Staphylococcus aureus*, *S epidermidis*, and enterococcal species.[1]

At the same time, antibiotic resistance is on the rise, often leaving few therapeutic options.[1,2] Resistance is even being seen in community-acquired infections: methicillin-resistant *S aureus* (MRSA) infections are now also found in people who have not recently received health care.[3]

Although vancomycin remains effective, several new antibiotics have become available to assist in the management of serious gram-positive infections. This article uses two case scenarios to discuss when and how to use these agents and how to monitor for and respond to their adverse effects.

CASE 1: ACUTE ILLNESS AFTER OUTPATIENT SURGERY

An 18-year-old woman is admitted because of fever, cough, and left knee pain that began 7 days ago after she underwent an outpatient surgical procedure. She appears very ill, has a rapid heart beat, and has a murmur at the lower left sternal border (grade 3 on a scale of 6).

Computed tomography of the chest reveals bilateral peripheral infiltrates: the largest, in the right lung field, is cavitary. Transesophageal echocardiography shows a

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large vegetation on the tricuspid valve. Synovial fluid aspirated from her left knee has a white blood cell count of 66 × 10^9/L. Cultures of her blood and synovial fluid grow MRSA.

The patient is treated with vancomycin and gentamicin. She improves but requires open-heart surgery because of severe tricuspid insufficiency.

VANCOMYCIN SHOULD BE USED JUDICIOUSLY

Discovered in 1952, vancomycin is produced by the mold *Streptomyces orientalis*.[4] It was originally developed to combat penicillin-resistant *S aureus*. However, it is active against most gram-positive aerobic and anaerobic organisms. It works by binding to D-alanyl-D-alanine peptide precursors in the bacterial cell wall, preventing the cross-linking of peptidoglycan side chains and therefore inhibiting cell-wall synthesis. It is bactericidal and may trigger cell autolysis.

The use of vancomycin has increased significantly over the past 25 years, and it remains the workhorse agent for beta-lactam-resistant staphylococcal and enterococcal infections in most hospitals. Its empiric use has also increased, owing to an increase in penicillin-resistant *Streptococcus pneumoniae* infections.

Vancomycin remains the workhorse agent for resistant infections in most hospitals

Although we rely on vancomycin for treating gram-positive infections, it should be used judiciously to forestall the further development and spread of vancomycin-resistant enterococci (VRE) and *S aureus*.[5]

Vancomycin is not absorbed across the bowel wall and therefore it is limited to parenteral administration for all infections other than *Clostridium difficile*-associated diarrhea.

Dosage is based on body weight. Because it is eliminated almost exclusively by the kidneys, the dosage should be adjusted for patients with reduced creatinine clearance and can be calculated with the use of nomograms.[6] Although the need to routinely monitor blood levels of vancomycin is debatable, a target trough level of at least 15 µg/mL can help ensure that the dosage is adequate in patients with bacteremia, endocarditis, and hospital-acquired pneumonia.[7]

The main adverse reaction to vancomycin is "red man syndrome," an infusion-related toxicity characterized by fevers, chills, and flushing of the upper trunk and face. Nephrotoxicity and ototoxicity sometimes occurred in the past, most likely because early preparations contained impurities.[6] Vancomycin still appears to potentiate aminoglycoside nephrotoxicity.

CASE 2: FEVER IN A LIVER TRANSPLANT RECIPIENT

A 55-year-old woman who received a liver transplant because of primary biliary cirrhosis is hospitalized for fever. She is again on the transplant list because of graft failure. She is jaundiced and appears ill. Her temperature is 39°C (102.2°F), pulse 120 beats/minute, and blood pressure 88/42 mm Hg.

A large liver abscess is found on computed tomography. The abscess is aspirated percutaneously, and *Enterococcus faecium*, *Escherichia coli*, and *Candida glabrata* are identified. Blood cultures grow *E faecium* that is resistant to ampicillin and vancomycin.

The patient's condition improves after treatment with liposomal amphotericin B, ciprofloxacin, and linezolid.

LINEZOLID CAN CAUSE MYELOSUPPRESSION

Linezolid, an oxazolidinone antibiotic, was approved by the US Food and Drug Administration (FDA) in early 2000. Its current indications are to treat community-acquired and hospital-acquired pneumonia and uncomplicated and complicated skin and skin-structure infections. It is effective against gram-positive organisms, including MRSA and VRE, that are resistant to many antibiotics.[8]

Linezolid works by binding to a subunit (designated 23S) of the bacteria's ribosomal RNA, preventing the final ribosomal complex from forming and thereby blocking protein synthesis. It is bacteriostatic, kills in a time-dependent fashion, and has a postantibiotic effect (ie, it continues to suppress bacterial growth even after the drug concentration in the blood falls to undetectable levels).[9]

TABLE 1

Agents active against beta-lactam-resistant gram-positive bacteria

AGENT	ROUTE	DOSAGE	RENAL DOSE ADJUSTMENT	HEPATIC DOSE ADJUSTMENT	COST/DAY*
Linezolid (Zyvox)	IV, PO	600 mg every 12 hours	No	No	IV: $180 PO: $140
Quinupristin-dalfopristin (Synercid)	IV	7.5 mg/kg every 8 hours	No	May be necessary†	$140‡
Daptomycin (Cubicin)	IV	4–6 mg/kg every 24 hours	Yes§	No	$150‖
Tigecycline (Tygacil)	IV	100 mg loading dose, then 50 mg every 12 hours	No	Yes¶	$110
Vancomycin (Vancocin)	IV	Various nomograms are available	Yes	No	$14–$25#

IV = intravenous, PO = oral
*Actual wholesale price rounded to the nearest $10
†Specific recommendations are not available
‡Based on a person weighing 70 kg
§If creatinine clearance < 30 mL/minute, give 4–6 mg/kg every 48 hours
‖Based on 6 mg/kg for a person weighing 70 kg
¶Severe hepatic impairment only (Child-Pugh class C); give 100 mg × 1, then 25 mg every 12 hours
#Based on 1 g every 12 hours; various generic products available, costs vary

Linezolid is 100% orally bioavailable and is metabolized in the liver to inactive byproducts. Although 30% to 40% of a dose is eliminated unchanged by the kidneys, no dosage adjustment is necessary for patients with renal impairment.[10]

Adverse effects, drug interactions, resistance

Treatment-limiting toxicities include myelosuppression, which manifests as thrombocytopenia and anemia. Peripheral and optic neuropathy may also occur.[11–13] Patients should have their blood monitored for cytopenias weekly, especially if they receive the drug for longer than 2 weeks.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may interact with adrenergic and serotonergic agents. A mild pressor effect has been observed in normotensive patients taking linezolid with pseudoephedrine but not with dextromethorphan. Patients taking linezolid with selective serotonin reuptake inhibitors should be closely observed for serotonin syndrome (ie, cognitive dysfunction, fever, incoordination).[10]

When linezolid was first introduced, experts hoped that resistance would be slow to develop. Unfortunately, there are already reports of resistance in VRE and MRSA isolates in patients previously exposed to linezolid. Resistance is associated with mutations of the domain V region of 23S rRNA, where linezolid binds.[14]

CASE 2 CONTINUED: HER PLATELET COUNT DROPS

In the hospital, the patient's jaundice and malaise persist, although her fever abates and her blood pressure and other hemodynamic measures stabilize.

At 3 weeks, her platelet count has dropped: on admission it was 95 × 10^9/L, but now it is 19. An evaluation for reversible causes of thrombocytopenia does not reveal anything besides her liver dysfunction and line-

zolid use. Although ongoing liver dysfunction is believed to be contributing to her thrombocytopenia, her linezolid is stopped and quinupristin-dalfopristin is started. Over the next week, her platelet count increases back toward the admission value.

QUINUPRISTIN-DALFOPRISTIN FOR SERIOUS VREF INFECTIONS

Quinupristin-dalfopristin consists of two streptogramins that inhibit protein synthesis by binding to the 50S subunit of the bacteria's ribosomes.[15] It is active against MRSA and vancomycin-resistant *E faecium* (VREF) but not against *E faecalis*. It is bactericidal against staphylococci and streptococci and is bacteriostatic for enterococcal species.

Quinupristin-dalfopristin was granted accelerated approval by the FDA for the treatment of serious or life-threatening VREF infections. Its current indications are to treat adults with serious VREF infections associated with bacteremia and complicated skin infections and skin-structure infections due to group A streptococci or methicillin-susceptible *S aureus*.[15,16]

Up to 30% of patients on quinupristin-dalfopristin develop treatment-limiting myalgia and arthralgia

Myalgia, arthralgia, and drug interactions

Up to 30% of patients who receive quinupristin-dalfopristin develop treatment-limiting myalgia and arthralgia[17] that are typically refractory to standard pain treatment, including opioids and nonsteroidals, but resolve when quinupristin-dalfopristin is stopped.

The clinical utility of quinupristin-dalfopristin is further limited by numerous drug interactions: the drug inhibits the cytochrome P450 3A4 isoenzyme and therefore can increase the serum levels of drugs that are metabolized by this enzyme, eg, astemizole, cisapride, cyclosporine, disopyramide, lidocaine, midazolam, nifedipine, quinidine, and terfenadine.[16]

CASE 2 CONTINUED: MYALGIA DEVELOPS

The patient remains afebrile on a regimen of amphotericin B lipid complex, ciprofloxacin, and quinupristin-dalfopristin. A small residual fluid collection remains in her liver. Her status on the liver transplantation list is upgraded to the highest priority (status 1A).

However, the patient develops disabling myalgias. She cannot walk (even moving about in bed is painful), and she requires continuous opioid analgesia. Her physicians obtain approval for compassionate use of daptomycin (it is in phase 3 trials at the time of this case), her quinupristin-dalfopristin is stopped, and the myalgia abates. A donor liver becomes available, and it is successfully transplanted.

DAPTOMYCIN

Daptomycin was approved in September 2003 and is currently indicated for complicated skin and skin-structure infections caused by daptomycin-susceptible staphylococcal and streptococcal species, as well as vancomycin-susceptible *E faecalis*.[18] Studies in patients with bloodstream and endovascular infection due to *S aureus* are in progress. Daptomycin is inactivated by surfactant, so it is not appropriate for treating pneumonia.

Daptomycin was discovered in the 1980s, but its development was suspended because of skeletal muscle toxicity. This toxic effect was found to be due to high trough concentrations, so further investigations used a different dosing schedule.

Daptomycin is a cyclic lipopeptide that is active against gram-positive organisms only. It is thought to act by forming an ion conduction structure in the cytoplasmic membrane that dissipates the ion concentration gradient.[18]

The pharmacodynamics depend on drug concentration, and there is a significant postantibiotic effect.

Side effects, drug interactions, and resistance

Patients receiving daptomycin should be monitored for skeletal myopathy by measuring their serum creatine phosphokinase levels every week. In addition, one should consider temporarily discontinuing agents that can cause rhabdomyolysis, such as statins.

Resistance to daptomycin has emerged in patients treated for bloodstream MRSA and VRE infections.[19,20] The mechanism of resis-

tance has not yet been elucidated, and cut points for defining susceptibility and resistance have not been fully validated.

TIGECYCLINE: THE NEWEST AGENT

Tigecycline is the newest FDA-approved agent with activity against multidrug-resistant, gram-positive pathogens. It is the first available glycylcycline, a synthetic analogue of tetracycline that has similar antibacterial activity but circumvents the two major mechanisms of tetracycline resistance: efflux and ribosomal protection.[21]

Tigecycline is effective against complicated skin and skin-structure infections and intra-abdominal infections. It is active against VRE strains and MRSA, as well as certain *Enterobacteriaceae* and anaerobes.[22] However, tigecycline has been shown to be affected by multidrug efflux pumps in gram-negative organisms, particularly *Proteus mirabilis* and *Citrobacter freundii*.

Adverse effects

The main adverse reactions are nausea and vomiting. As with tetracyclines, tigecycline may cause permanent tooth discoloration, so it should not be taken by young children or pregnant women.

Drug interactions have not been observed. Dosage should be adjusted for patients with hepatic insufficiency.[22]

THERAPEUTIC APPROACH

Sensitive gram-positive infections: Use beta-lactam antibiotics

Beta-lactam antibiotics are preferred for gram-positive infections in which no resistant organisms are identified. If a broader-spectrum agent is used initially, it should later be changed to the agent with the narrowest spectrum indicated by susceptibility testing. For example, oxacillin or nafcillin should be used for methicillin-susceptible *S aureus* infections, and ampicillin should be used for sensitive enterococcal species.

Beta-lactam antibiotics are often avoided because a patient reports a history of penicillin allergy. But the validity of such a history is often difficult to confirm. Vancomycin use can be reduced by consistently performing penicillin skin testing in patients with suspected allergy: most patients with "penicillin allergy" can actually take a beta-lactam antibiotic safely.[23,24]

Resistant gram-positive infections: Start with vancomycin

Serious infections due to beta-lactam resistant, gram-positive bacteria require a multifaceted therapeutic approach.

S aureus and enterococcal species tend to cause endovascular infections with subsequent metastatic foci. Therefore, patients with bacteremia due to these pathogens—especially those with prosthetic heart valves or cardiac devices—should be thoroughly evaluated for endocarditis. The use of central vascular catheters should be limited, and existing lines should be removed. Suppurative collections should be drained either surgically or percutaneously whenever possible.

Vancomycin is still the first-line therapy for hospitalized patients with beta-lactam-resistant, glycopeptide-sensitive, gram-positive infections.

If an oral agent is needed

The emergence of community-acquired MRSA has affected the treatment of patients who present with a skin or skin-structure infection. Those patients who do not require hospital admission may need an oral antibiotic. Linezolid covers a very broad spectrum, but its high cost is often prohibitive. Doxycycline, clindamycin, and trimethoprim-sulfamethoxazole are possible choices for likely MRSA; however, soft-tissue infections can be caused by *Streptococcus pyogenes*, which trimethoprim-sulfamethoxazole does not reliably cover. To treat outpatient infections effectively, one should follow up with the patient closely, control the source of infection, and attempt to make a microbiological diagnosis.

Most 'penicillin-allergic' patients are not

Using new antibiotics

Therapy with antibiotics other than vancomycin must be individualized (as in the above case of the liver transplant recipient), preferably with the help of an infectious disease consultant.

Daptomycin's bactericidal activity may make it a good choice for treating endovascular MRSA infections, but it is not an option for pneumonia. For treating VRE, there is more experience with linezolid than with daptomycin; as far as we know, no head-to-head clinical trials have compared the two. The use of quinupristin-dalfopristin is limited by its toxicity and infusion-associated vein irritation. Tigecycline's broad spectrum of activity provides the ability to use a single agent for complicated polymicrobial infections that include gram-positive infections.

Will new antibiotics supplant vancomycin for treating glycopeptide-sensitive gram-positive infections? Two clinical syndromes due to MRSA deserve mention:

Hospital-acquired pneumonia due to suspected MRSA. Recent consensus guidelines for treating hospital-acquired pneumonia recommend vancomycin or linezolid for empiric therapy if MRSA is suspected.[25] This recommendation is based in part on a retrospective subgroup analysis of two prospective clinical trials that actually showed linezolid to be associated with a higher survival rate than vancomycin in patients with nosocomial MRSA pneumonia.[26] Although this finding has not been prospectively confirmed, it raises the question of whether linezolid should be the first-line drug in hospitals in which nosocomial MRSA pneumonia is common.

New guidelines recommend vancomycin or linezolid for suspected nosocomial MRSA pneumonia

Prolonged MRSA bacteremia. Although the evidence is mixed, some studies indicate that patients with MRSA bacteremia fare worse than those with methicillin-sensitive *S aureus* bacteremia.[27] A possible explanation is that vancomycin is not as effective as nafcillin or oxacillin. Alternatives to vancomycin might better treat MRSA, particularly for patients with endovascular infections.

FUTURE DIRECTIONS

Recent evidence shows that a polymorphism in the *agr*II operon of certain MRSA strains is associated with prolonged bacteremia.[28] This phenotype, characterized by decreased production of autolysin and increased cell surface virulence factors, may be the first step towards vancomycin-intermediate *S aureus*.[29] Further work in this area, along with the results of a trial of daptomycin for the treatment of *S aureus* bacteremia, may help guide treatment decisions in the future.

REFERENCES

1. **Friedman ND, Kaye KS, Stout JE, et al.** Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137:791–797.
2. **Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP.** Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999; 29:239–244.
3. **Said-Salim B, Mathema B, Kreiswirth BN.** Community-acquired methicillin-resistant *Staphylococcus aureus*: an emerging pathogen. Infect Control Hosp Epidemiol 2003; 24:451–455.
4. **Levine DP.** Vancomycin: a history. Clin Infect Dis 2006; 42(suppl 1):S5–S12.
5. **Recommendations for preventing the spread of vancomycin resistance.** Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 1995; 44(RR-12):1–13.
6. **Fekety R.** Vancomycin, teicoplanin, and the streptogramins: quinupristin and dalfopristin. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 5th ed. Philadelphia: Churchill Livingstone; 2000:382–391.
7. **Rybak MJ.** The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006; 42(suppl 1):S35–S39.
8. **Noskin GA, Siddiqui F, Stosor V, Hacek D, Peterson LR.** In vitro activities of linezolid against important gram-positive bacterial pathogens including vancomycin-resistant enterococci. Antimicrob Agents Chemother 1999; 43:2059–2062.
9. **Clemett D, Markham A.** Linezolid. Drugs 2000; 59:815–827.
10. Linezolid [package insert]. New York, NY: Pharmacia & Upjohn; 2005.
11. **Moellering RC.** Linezolid: the first oxazolidinone antimicrobial. Ann Intern Med 2003; 138:135–142.
12. **Rho JP, Sia IG, Crum BA, Dekutoski MB, Trousdale RT.** Linezolid-associated peripheral neuropathy. Mayo Clin Proc 2004; 79:927–930.
13. **Lee E, Burger S, Shah J, Melton C, Mullen M, Warren F, Press R.** Linezolid-associated toxic optic neuropathy: a report of 2 cases. Clin Infect Dis 2003; 37:1389–1391.
14. **Meka VG, Gold HS.** Antimicrobial resistance to linezolid. Clin Infect Dis 2004; 39:1010–1015.
15. **Eliopoulos GM.** Quinupristin-dalfopristin and linezolid: evidence and opinion. Clin Infect Dis 2003; 36:473–481.
16. **Delgado G Jr, Neuhauser MM, Bearden DT, Danziger LH.** Quinupristin-dalfopristin: an overview. Pharmacotherapy 2000; 20:1469–1485.
17. **Olsen KM, Rebuck JA, Rupp ME.** Arthralgias and myalgias related to quinupristin-dalfopristin administration. Clin Infect Dis 2001; 32:e83–e86.
18. **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.
19. **Mangili A, Bica I, Snydman DR, Hamer DH.** Daptomycin-resistant, methicillin-resistant *Staphylococcus aureus* bac-

teremia. Clin Infect Dis 2005; 40:1058–1060.
20. **Long JK, Choueiri TK, Hall GS, Avery RK, Sekeres MA.** Daptomycin-resistant *Enterococcus faecium* in a patient with acute myeloid leukemia. Mayo Clin Proc 2005; 80:1215–1216.
21. **Zhanel GG, Homenuik K, Nichol K, et al.** The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004; 64:63–88
22. Tigecycline [package insert]. Philadelphia, PA: Wyeth; 2005.
23. **Arroliga ME, Radojicic C, Gordon SM, et al.** A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. Infect Control Hosp Epidemiol 2003; 24:347–350.
24. **Li JT, Markus PJ, Osmon DR, Estes L, Gosselin VA, Hanssen AD.** Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. Mayo Clin Proc 2000; 75:902–906.
25. **American Thoracic Society, Infectious Diseases Society of America.** Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171:388–416.
26. **Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH.** Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 2003; 124:1789–1797.
27. **Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y.** Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 2003; 36:53–59.
28. **Moise-Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC Jr.** Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. Clin Infect Dis 2004; 38:1700–1705.
29. **Sakoulas G, Moellering RC Jr, Eliopoulos GM.** Adaptation of methicillin-resistant *Staphylococcus aureus* in the face of vancomycin therapy. Clin Infect Dis 2006; 42(suppl 1):S40–S50.

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