Linezolid: Its Role in the Treatment of Gram-Positive, Drug-Resistant Bacterial Infections

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While the choices available for the management of gram-positive, drug-resistant bacterial infections are becoming limited, antimicrobial resistance is becoming increasingly problematic because of the widespread overuse of antibiotics. Linezolid is a synthetic antibiotic belonging to a new class of antimicrobials called the oxazolidinones. Linezolid disrupts bacterial growth by inhibiting the initiation process of protein synthesis—a mechanism of action that is unique to this class of drugs. It is well absorbed with high bioavailability that allows conversion to oral therapy as soon as the patient is clinically stable. It has been approved for certain gram-positive infections including certain drug-resistant enterococcus, staphylococcus, and pneumococcus strains. It is generally well tolerated, with myelosuppression being the most serious adverse effect. As a nonselective inhibitor of monoamine oxidase, caution is recommended when used with adrenergic or serotonergic agents (e.g., tyramine, dopamine, pseudoephedrine, and selective serotonin reuptake inhibitors). Judicious use of this medication should help physicians treat patients with multidrug-resistant infections. (Am Fam Physician 2002; 65:663-70. Copyright© 2002 American Academy of Family Physicians.)

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The growing antimicrobial resistance of certain microorganisms is now a worldwide concern. The introduction of penicillin in 1944 was soon followed by reports of resistance to *Staphylococcus aureus.* Physicians have encountered problems with antimicrobial resistance ever since. During the 1970s, the problem of drug-resistant, gram-negative bacteria and of methicillin-resistant *S. aureus* emerged. Currently, the most pressing problem is that of multidrug-resistant, gram-positive bacteria.

Factors Responsible for Antimicrobial Resistance

Multiple factors contribute to the development of resistance to antibiotics. Their widespread and unnecessary use is the greatest contributing factor. It is estimated that 50 million pounds of antibiotics are taken annually in the United States[1] and 30 percent of antibiotic prescriptions are for respiratory tract infections, more than one half of which were probably viral.[2] The increasing problem of antimicrobial resistance in the hospital and the community parallels the over-prescribing of antibiotics. Other contributing factors that have led to changes in virulence, and thus, the development of resistance to antibiotics, include societal changes (e.g., population growth and migration), an increasing number of immunosuppressed patients, the globalization of food supplies and changes in the way food is grown and produced, human behavior (e.g., widespread and frequent international travel), and environmental changes (including long-standing use of antibiotics in animal husbandry and agriculture).[3]

Resistance Problems Among Gram-Positive Organisms

The increasing resistance among gram-positive species is concerning because they are responsible for one third of nosocomial infections.[4] During the past two decades, the prevalence of methicillin-resistant *S. aureus* increased from 2.0 to 39.7 percent in the United States.[5] Between 1980 and 1989, the incidence of bacteremia caused by coagulase-negative staphylococcal species, *S. aureus,* and enterococcus increased by 176 and 124 per-

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cent, respectively.[6] These three pathogens are now the most common nosocomial-acquired causes of bacteremia. Surveillance data report that nearly 79 and 25 percent of nosocomially acquired, coagulase-negative staphylococcal species and *S. aureus* are methicillin-resistant, respectively.[6]

The enterococcus species is recognized as a major nosocomial pathogen. During the period of methicillin-resistant *S. aureus* emergence, enterococci became the third most common cause of nosocomial infections.[5] In 1993, it was reported that 13.9 percent of all enterococcal isolates were resistant to vancomycin (Vancocin), representing a 20-fold increase from 1989.[5] Previously, vancomycin was often considered the final therapeutic option in cases in which resistance to all other antibiotics was present. Unfortunately, the arrival of vancomycin-resistant enterococcus changed this approach. Between 1990 and 1997, the percentage of enterococcal species resistant to vancomycin increased from less than 1 percent to 18 percent.[7] *Enterococcus faecalis* is responsible for 60 percent of these infections.[8] A new threat of decreased susceptibility of *S. aureus* to vancomycin now exists.[8] This emerging resistance to vancomycin is disturbing because it has been considered the last line of defense.

In the community setting, many antibiotic-resistant bacteria have emerged *(Table 1)*.[5] The prevalence of drug-resistant *Streptococcus pneumoniae* has increased 60-fold since 1980 with 51 percent and 8 percent of isolates demonstrating intermediate- or high-level resistance to penicillin or third-generation cephalosporins, respectively.[9] Thus, pneumococcal pneumonia is becoming more difficult to treat with first-line agents.

It is important to control the emergence of antimicrobial resistance and minimize the inappropriate use of antibiotics through education. This is not a small task and requires a multidisciplinary approach. All health care professionals need to work toward the same goal. Some principles to control antimicrobial resistance are outlined in *Table 2*.[5]

Against this background, newer therapeutic options are now available. Linezolid (Zyvox), a novel antimicrobial agent, has been approved by the U.S. Food and Drug Administration (FDA) primarily to fight resistant gram-positive cocci, such as vancomycin-resistant enterococcus, methicillin-resistant *S. aureus,* and penicillin-resistant pneumococci. Antibiotic therapy for these resistant infections must be guided by laboratory testing; thus, appropriate cultures should be obtained to determine the causative organism(s) and its susceptibility to linezolid.

TABLE 1
Common, Antibiotic-Resistant Microorganisms

Community-acquired resistant	Nosocomial-resistant
Escherichia coli	Bacteroides species
Haemophilus influenzae	Candida species
Methicillin-resistant *Staphylococcus aureus*	Coagulase-negative staphylococci
Multidrug-resistant tuberculosis	Enterobacter species
Neisseria gonorrhea	Klebsiella species
Neisseria meningitidis	Methicillin-resistant *S. aureus*
Salmonella species	Multidrug-resistant tuberculosis
Shigella species	Proteus species
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Streptococcus viridans	Serratia species
	Vancomycin-resistant enterococci

Adapted with permission from Hawkes CA. Antibiotic resistance: a clinician's perspective. Mil Med 2000;165(7 suppl 2):43-5.

Mechanism of Action

Linezolid is a synthetic antibiotic belonging to a new class of antimicrobials called the oxazolidinones. Linezolid disrupts bacterial growth by inhibiting the initiation process in protein synthesis. This site of inhibition occurs earlier in the initiation process than other protein synthesis inhibitors (e.g., chlo-

ramphenicol [Chloromycetin], clindamycin [Cleocin], aminoglycosides, and macrolides) that interfere with the elongation process.[10,11] Because the site of inhibition is unique to linezolid, cross-resistance to other protein synthesis inhibitors has not yet been reported.[12] Linezolid may also inhibit virulence factor expression and decrease toxin production in gram-positive pathogens.[13]

It is preferable to use an agent possessing bactericidal properties when possible. It has been demonstrated that linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal for the majority of streptococci.[14]

Pharmacokinetics

Linezolid is highly absorbed when administered orally, with a bioavailability of approximately 100 percent.[15] This allows conversion from intravenous to oral therapy as soon as the patient is clinically stable; thus, it provides an advantage over comparative therapy that can be delivered only parenterally (i.e., vancomycin or quinupristin/dalfopristin [Synercid]). Linezolid is metabolized via hepatic oxidation without any cytochrome P-450 pathways. Elimination occurs through nonrenal, renal, and fecal mechanisms accounting for 65, 30, and 5 percent, respectively. The half-life is approximately five hours.[15] Generally, the dosing interval for an antibiotic is three times the half-life—the dosing interval for linezolid is every 12 hours. Presently, no dosage adjustment is recommended for patients with renal insufficiency; however, linezolid is removed by hemodialysis and should be administered following dialysis.[14,15]

Indications

The FDA has approved linezolid for certain gram-positive infections in adult patients *(Table 3)*.[15] Other pathogens that linezolid has demonstrated in-vitro activity against include penicillin-resistant *S. pneumoniae,* vancomycin-sensitive *E. faecalis,* vancomycin-resistant *E. faecalis,* methicillin-susceptible *Staphylococcus epidermidis* and methicillin-resistant *S. epidermidis,* Corynebacterium sp, *Moraxella catarrhalis,* legionella species *Listeria monocytogenes, Pasteurella multocida,* and *Bacteroides fragilis.*[10,16]

Linezolid's high bioavailability allows for rapid conversion from intravenous to oral therapy.

Because of limited clinical data demonstrating activity against gram-negative organisms, it is recommended that coverage for these pathogens be added when indicated.[15] Clinical data in other special patient populations (i.e., children, pregnant women, or breastfeeding mothers) are limited. Linezolid is a pregnancy category C drug, and caution is urged if used in breastfeeding mothers. The safety and efficacy, and an appropriate dosage have not been established in children younger than 18 years.[15] Use in these patient populations cannot be recommended at this time.

TABLE 2
Principles to Control Antimicrobial Resistance

Appropriate antimicrobial use
Optimal use of antimicrobial agents—whether therapeutic, prophylactic, or empiric
Restriction of certain antimicrobial agents
Rotation of antimicrobial therapy
Combination of antimicrobial therapy
Implementation of guidelines for common antibiotic use
Antimicrobial resistance surveillance programs
Prompt detection and reporting of new resistance patterns
Rapid detection of resistant organisms
Physicians and paramedical staff education
Computer-based monitoring and feedback on use of microbial agents
Multidisciplinary approach in controlling antimicrobial resistance
Professional review of hospitals by oversight agencies such as the Joint Commission on Accreditation of Healthcare Organizations

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Dosing

The dosage regimen for linezolid is 400 mg or 600 mg every 12 hours for a duration of 10 to 28 days, with an intravenous or oral route of administration, based on the indication *(Table 4)*.[14] The 400-mg dose is approved for uncomplicated skin or skin structure infections; however, because many other antibiotic therapies are available, the authors strongly discourage the use of linezolid for this indication in order to reduce the potential for developing bacterial resistance. The intravenous infusion should be administered over a period of 30 to 120 minutes.[14] Several incompatibilities have been reported: amphotericin B (Fungizone), ceftriaxone (Rocephin), chlorpromazine (Thorazine), diazepam (Valium), erythromycin, phenytoin (Dilantin), and trimethoprim-sulfamethoxazole (Bactrim).[17] Because compatibility information changes, it is recommended that a pharmacist be consulted when there is doubt.

Adverse Effects

Adverse effects reported in clinical trials in more than 2 percent of patients include the following: rash, headache, diarrhea, nausea, vomiting, insomnia, constipation, and fever.[15]

TABLE 3
FDA Indications for Use of Linezolid

Vancomycin-resistant *Enterococcus faecium,* including cases with concurrent bacteremia
Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible strains only)
Complicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae*
Uncomplicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible strains only) or *S. pyogenes*
Community-acquired pneumonia caused by *S. pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *S. aureus* (methicillin-susceptible strains only)

Information from Zyvox (linezolid). Package insert. Peapack, N.J.: Pharmacia & Upjohn. Retrieved May 2001, from: www.zyvox.com/pdfs/zyvox_full_prescribe_012001.pdf.

The incidence was similar to the comparator groups: ceftriaxone, clarithromycin (Biaxin), dicloxacillin (Pathocil), oxacillin (Bactocill), and vancomycin.

Thrombocytopenia, defined as a decrease in platelet count below 75 percent of normal or baseline, was reported in 2.4 percent of patients receiving linezolid versus 1.5 percent in those in the comparator group.[14] This effect may be associated with the higher dose or treatment duration exceeding two weeks.

In addition, the FDA has recently reported cases of myelosuppression (anemia, leukopenia, and pancytopenia) warranting the monitoring of hematologic parameters and has issued a warning that myelosuppression is considered a potential adverse effect. The current recommendation is to monitor complete blood count status weekly, especially in patients receiving therapy longer than two

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weeks' duration, those with preexisting myelosuppression, those receiving drugs that produce bone marrow suppression, and those with a chronic infection who have received other antibiotic therapy recently or concurrently. If myelosuppression occurs, then discontinuation of therapy should be considered.

Drug-Drug Interactions

Linezolid does not affect cytochrome P-450; therefore, induced interactions are unlikely to occur.[10,11] No pharmacokinetic interaction was observed in patients taking warfarin (Coumadin) or phenytoin.[15]

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase (MOA), and a potential interaction with adrenergic or serotonergic agents is possible. A significant pressor response was observed when administered with tyramine; therefore, patients should avoid consuming food or beverages containing tyramine.[14,15] More commonly used agents such as dopamine (Intropin), epinephrine, or decongestants containing pseudoephedrine may also produce an exaggerated pressor response. In healthy normotensive subjects receiving linezolid and pseudoephedrine, the mean maximum increase in systolic blood pressure was 32 mm Hg.[11] Maximum elevation occurred at two to three hours and returned to baseline within three hours. No affect on heart rate was observed. Careful dosing titration is recommended when initiating dopamine or epinephrine.[14]

The potential for a serotonergic interaction with dextromethorphan (Robitussin DM) was evaluated in healthy subjects. No serotonin syndrome effects (confusion, delirium, tremors, restlessness, hyperpyrexia, or diaphoresis) were observed with this combination.[14] No effects of serotonin syndrome were observed during a phase III study of 52 patients comparing fluoxetine, paroxetine and sertraline with linezolid.[18] Nevertheless, caution is therefore recommended when using linezolid with agents such as citalopram (Celexa), fluvoxamine (Luvox), fluoxetine (Prozac), paroxetine (Paxil), or sertraline (Zoloft) until clinical safety is demonstrated.[14,15]

Linezolid is a nonselective inhibitor of monoamine oxidase; therefore, caution is recommended when used with adrenergic or serotonergic agents.

Clinical Studies

The FDA approved linezolid on the basis of nine unpublished, controlled clinical trials involving more than 4,000 patients.[19] Most published trials are either in-vitro studies or clinical studies involving a small sample size.

In all the therapeutic trials thus far, the 600-mg dosage was consistently more effective in the treatment of patients with vancomycin-resistant enterococcus infections than was the 200-mg dosage. Intravenous linezolid at twice daily dosages of 600 mg produced a clinical cure rate of 88.6 percent compared with

TABLE 4
Linezolid (Zyvox) Dosing Recommendations

Infection	*Dosage/route*	*Recommended duration (days)*
Nosocomial pneumonia	600 mg IV or PO every 12 hours	10 to 14
Complicated skin/skin structure infections	As above	As above
Community-acquired pneumonia, including concurrent bacteremia	As above	As above
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	600 mg IV or PO every 12 hours	14 to 28
Uncomplicated skin/skin structure infections	400 mg PO every 12 hours	10 to 14

IV = intravenous; PO = oral

Reproduced with permission from Zyvox (linezolid) approved as super antibiotic, new treatment option for hospital-acquired and drug-resistant bacteria. Pharmacia Corporation: Peapack, N.J.: April 18, 2000.

73.7 percent in the patients with vancomycin-resistant enterococcus infections who received 200 mg daily.[16]

Results from a compassionate use trial involving treatment of patients with bacteremia for resistant, gram-positive infections reveal that linezolid was well tolerated.[20] By the fifth day of the study, 75 percent of the bacteremia had resolved. It was concluded that linezolid is an excellent option for the treatment of patients with significant, resistant gram-positive bacteremic infections.

Eighty-one patients with community-acquired pneumonia were treated with linezolid, resulting in a 98 percent cure rate.[21] Of note, biologic eradication was achieved in all evaluated patients infected with *S. pneumoniae.* Linezolid demonstrated similar efficacy to ceftriaxone and/or cefpodoxime proxetil, with a clinical cure rate of approximately 90 percent for community-acquired pneumonia.[16] Interestingly, linezolid was clinically and microbiologically superior to ceftriaxone in treating patients with concurrent bacteremia (93 percent in the linezolid group versus 69.9 percent in the ceftriaxone/cefpodoxime proxetil group).[16]

Linezolid (600 mg twice a day) and van-

TABLE 5
Comparison of Linezolid (Zyvox) to Quinupristin/Dalfopristin (Synercid)

Drug/clinical significance	*Mechanism of action*	*FDA-approved spectrum of activity*	*Side-effect profile*	*FDA-approved indications*
Linezolid	Inhibits protein synthesis at initiation step.	*Streptococcus pneumoniae* (penicillin sensitive); *Staphylococcus aureus* (MSSA and MRSA); *Streptococcus pyogenes; Streptococcus agalactiae;* vancomycin-resistant *Enterococcus faecium*	Nausea, vomiting, thrombocytopenia (2.4 percent), myelosuppression	Vancomycin-resistant *E. faecium* infections; nosocomial pneumonia; complicated skin and skin structure infections; uncomplicated skin and skin structure infections; community-acquired pneumonia
Quinupristin/ dalfopristin	Inhibits protein synthesis at elongation step, similar to aminoglycosides, clindamycin (Cleocin), and chloramphenicol (Chloromycetin).	*S. aureus* (MSSA); *S. pyogenes;* vancomycin-resistant *Enterococcus faecium*	Phlebitis, arthralgias/ myalgias, hyperbilirubinemia (25 percent)	Vancomycin-resistant *E. faecium* infections; complicated skin and skin structure infections
Clinical significance	Similar site of inhibition may allow cross-resistance between Q/D, aminoglycosides, clindamycin, and chloramphenicol.	Q/D is not FDA approved for MRSA infections. Although not FDA approved for *Enterococcus faecalis,* linezolid has in-vitro activity against this pathogen. Q/D is not active against *E. faecalis.*	Lower infusion-related side effects with linezolid	Broader FDA indications may allow clinicians to feel more comfortable prescribing linezolid.

MSSA = methicillin-susceptible Staphylococcus aureus; *MRSA = methicillin-resistant* Staphylococcus aureus; *IV = intravenous; PO = by mouth; Q/D = quinupristin/dalfopristin; FDA = U.S. Food and Drug Administration.*

**—Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2001. Cost to the patient will be higher, depending on prescription filling fee.*

comycin (1 g twice a day) are similarly safe and efficacious in the treatment of patients with nosocomial pneumonia, including methicillin-resistant *S. aureus.* Patients were treated for seven to 21 days, with cure rates of 66.4 percent for patients treated with linezolid and 68.1 percent for patients treated with vancomycin.[22]

Linezolid therapy has been found to cure or improve more than 90 percent of patients treated for skin and soft tissue infections.[16] The 400-mg and 600-mg dosages twice daily produced clinical success rates exceeding 89 percent in patients with complicated and uncomplicated skin/soft tissue infections.[16] Linezolid also exhibited similar efficacy to oxacillin (Bactocill)/dicloxacillin and vancomycin.[16]

Dosage forms	*Daily cost ($)**
IV, PO (tablets, suspension)	IV = 143.74; tablet = 106.26 (600 mg every 12 hours)
IV	IV = 322.28 (500 mg every 8 hours)
Allows opportunity for conversion to oral therapy for outpatient treatment with linezolid	—

Comparison to Quinupristin/Dalfopristin

Quinupristin/dalfopristin (Synercid) was recently approved by the FDA for the treatment of patients with vancomycin-resistant *Enterococcus faecium,* methicillin-susceptible and methicillin-resistant infections. Although no randomized clinical trials have compared these agents, several notable differences exist *(Table 5).*

Final Comment

The oxazolidinones is a new class of antibiotics that are effective against many resurgent gram-positive organisms. The first of the oxazolidinones, linezolid, is available as an intravenous or oral agent. Its high bioavailability allows initial oral therapy for many infections and a convenient switch from intravenous to oral therapy when indicated. In addition, the every 12 hours dosing schedule improves compliance. Parallel to the increasing resistance among the common pathogens, linezolid is an exciting therapeutic option.

Nevertheless, there is no reason to believe that resistance will not emerge. This will depend on how responsibly and frequently linezolid is prescribed and how quickly bacteria can evolve a new defense. As emphasized earlier, linezolid should be reserved for the treatment of patients with infections caused by multidrug-resistant bacteria that are proved by laboratory testing, and to life-threatening or complicated infections associated with multiple resistances to first-line treatments. Thus far, it has demonstrated activity against all clinically significant, gram-positive bacteria. With its role in multidrug-resistant bacteria, linezolid will play a crucial role in both the community and the nosocomial setting. Physicians should prescribe this agent judiciously so as to minimize antimicrobial resistance.

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