Quinupristin-Dalfopristin and Linezolid: Evidence and Opinion

George M. Eliopoulos
Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Quinupristin-dalfopristin and linezolid demonstrate in vitro activity against a wide range of gram-positive bacteria, including many isolates resistant to earlier antimicrobials. Quinupristin-dalfopristin is inactive against Enterococcus faecalis but has been effective for treatment of infections due to vancomycin-resistant Enterococcus faecium associated with bacteremia. In comparative trials, linezolid proved to be equivalent to comparator agents, resulting in its approval for several clinical indications. The almost-complete bioavailability of linezolid permits oral administration. Each agent can cause adverse effects that may limit use in individual patients. Resistance to these drugs has been encountered infrequently among vancomycin-resistant E. faecium. Resistance to quinupristin-dalfopristin is rare among staphylococci in the United States, and resistance to linezolid is very rare. Whether there is any benefit to use of these agents in combination regimens, and whether there are circumstances in which they might be alternatives to cell-wall active antibiotics for treatment of bone or endovascular infections, are questions that deserve further study.

In anticipation of the importance of infections due to gram-positive bacteria, pharmaceutical companies committed resources to the development of antimicrobials with activity against such organisms. As a result of these efforts, 2 new antimicrobials were introduced in the United States: quinupristin-dalfopristin, in 1999, and linezolid, in 2000. Recent trends in the prevalence of antibiotic-resistant strains [1, 2] and new observations concerning their epidemiology [3] confirm that decisions to develop such compounds were both prescient and justified. The isolation of clinical strains of vancomycin-resistant Staphylococcus aureus in 2002 proves this point [4].

Quinupristin-dalfopristin and linezolid demonstrate activity in vitro against important gram-positive pathogens, including most strains that are resistant to older antibiotics. These agents may also be useful for treating many patients who are intolerant of previously available agents. The bioavailability of orally administered linezolid extends treatment options for patients who do not require parenterally administered antibiotics. For these reasons, it is appropriate to consider the potential roles of these agents in current clinical practice.

BACKGROUND

Quinupristin-dalfopristin. This antibiotic is a 30:70 mixture of quinupristin and dalfopristin, which are semisynthetic antibiotics of streptogramin groups B and A, respectively. Although the individual components are primarily bacteriostatic, the combination is often bactericidal, is more potent, and may be active even when there is resistance to 1 component. The synergistic activity of the compound is ascribed to conformational change in the bacterial ribosome after dalfopristin binding [5]. Resistance determinants for the individual components specify inactivating enzymes (e.g., vat), efflux (e.g., lsa), or target modification (e.g., erm) and can occur on transmissible elements [6-8].

The criteria of the National Committee for Clinical Laboratory Standards [9] for susceptibility, intermediate susceptibility, and resistance to quinupristin-dalfopristin are \( \leq 1 \), \( 2 \), and \( \geq 4 \) \( \mu g/mL \), respectively. Surveys of isolates recovered through the year 2000 indicate that almost all strains of S. aureus (in-
Table 1. Representative studies of in vitro activity of quinupristin-dalfopristin and linezolid against selected bacterial species.

| Organism                        | No. of isolates | Quinupristin-dalfopristin | Linezolid |
|--------------------------------|-----------------|---------------------------|-----------|
|                                |                 | Susceptible, % | Resistant, % | Susceptible, % | Resistant, % | Reference |
| **Staphylococcus aureus**       |                 |               |             |               |             |           |
| Methicillin susceptible         | 3296            | 99.7          | —           | 99.8          | —           | [1]       |
|                                 | 1819            | 99.8          | —           | 100           | —           | [16]      |
|                                 | 4317            | 99.9          | —           | 100           | —           | [2]       |
|                                 | 610             | 99.9          | —           | 100           | —           | [17]      |
| Methicillin resistant           | 2557            | 99.0          | —           | 100           | —           | [1]       |
|                                 | 574             | 96.7          | —           | 100           | —           | [16]      |
|                                 | 2721            | —             | 0.1–0.3     | 100           | —           | [18]      |
| **Coagulase-negative staphylococci** |             |               |             |               |             |           |
| Methicillin susceptible         | 592             | 99.3          | —           | 100           | —           | [1]       |
|                                 | 1360            | 99.6          | 0.1         | 100           | —           | [2]       |
| Methicillin resistant           | 828             | 98.0          | —           | 100           | —           | [1]       |
|                                 | 3273            | 98.3          | 0.6         | 100           | —           | [2]       |
| **Any**                         | 6177            | —             | 0.1–0.3     | 100           | —           | [18]      |
|                                 | 769             | —             | 0           | 100           | —           | [17]      |
| **Streptococcus pneumoniae**    | 4626            | 97.7          | 0.2         | 100           | —           | [1]       |
|                                 | 2598            | 93–96         | 0.2–1.1     | 100           | —           | [2]       |
|                                 | 1057            | —             | 0           | —             | 0           | [18]      |
| Other streptococci              | 2647            | 97.0          | 0.3         | —             | 0           | [1]       |
|                                 | 761             | 95.4          | 2.7         | 100           | —           | [2]       |
|                                 | 988             | —             | 0           | 100           | —           | [2]       |
| **Enterococcus faecium**        |                 |               |             |               |             |           |
| Vancomycin susceptible          | 632             | 87            | 0.2         | 95.5          | 0           | [1]       |
| Vancomycin resistant            | 310             | 70.3          | 13.2        | 95.5          | 0           | [2]       |
| **Enterococcus faecalis**       |                 |               |             |               |             |           |
| Vancomycin susceptible          | 598             | 90.6          | 3.8         | 97.7          | 0           | [2]       |
| Vancomycin resistant            | 2308            | 2.9           | 92.5        | 96.5          | 0           | [2]       |
|                                 | 61              | 3.2           | 96.8        | 95.6          | 0           | [18]      |
| **Enterococcus species**        |                 |               |             |               |             |           |
| Vancomycin susceptible          | 4664            | 97.1          | 0           | —             | 0           | [18]      |
| Vancomycin resistant            | 439             | 97.5          | 0           | —             | 0           | [18]      |

**NOTE.** Totals may not equal 100% because of variable numbers of isolates in the “intermediate” category. An entry of 0 indicates that there was an explicit statement that strains meeting criteria for resistance were not encountered; otherwise, a dash is shown.
isms. Pneumococci may be killed in human stool samples obtained in the same regions. Pristin-dalfopristin–resistant strains were found in only 1% of a significant source of human colonization, because quinupristin-dalfopristin for MRSA infection because of intolerance or failure of conventional therapy, MLSB phenotype did not in others, it did not [39]. In 90 patients treated with quinupristin-dalfopristin for MRSA infection because of intolerance to or failure of conventional therapy, MLSB phenotype did not have an obvious effect on outcome [40].

Quinupristin-dalfopristin is approved in the United States for treatment of adults with serious infections due to VREF associated with bacteremia and for complicated skin and skin-structure infections due to group A streptococci or methicillin-susceptible S. aureus (MSSA) [41]. Patients treated for VREF infections in emergency use protocols typically had major underlying illnesses or risk factors, including organ failure or transplantation, hematologic malignancy, or diabetes [42–44]. The recommended dosage was 7.5 mg/kg given every 8 h, and patients actually received an average of ~20 mg/kg per day [43, 44]. The overall success rate (clinical response plus bacterial eradication or presumed eradication) in the evaluable population was ~65% (table 2). In randomized trials involving skin and soft-tissue infections in hospitalized adults, clinical success rates for evaluable patients were comparable between quinupristin-dalfopristin (7.5 mg/kg q12h) and comparators (oxacillin, cefazolin, or vancomycin; table 2). Although bacteriologic success rates were lower for quinupristin-dalfopristin, the authors thought that this could be explained in part by more frequent polymicrobial infection in this group and by assessment as presumed bacteriologic failure when treatment was changed because of an adverse effect [45]. For treatment of gram-positive nosocomial pneumonia, quinupristin-dalfopristin (7.5 mg/kg q12h) was found to be equivalent to vancomycin (table 2). Clinical success rates among the microbiologically evaluable patients infected with MRSA did not differ between the 2 treatment groups, but the rates for both treatments were lower than for patients with MSSA infection [46]. Among 19 pediatric liver transplant recipients, complete resolution of VREF infection was noted in 74% [47].

The emergence of resistance to quinupristin-dalfopristin was reported from Taiwan [28]. Genes mediating dalfopristin inactivation have been found in resistant strains of E. faecium recovered from humans and animals [7, 29–31]. Quinupristin-dalfopristin–resistant E. faecium isolates were recovered from 58% of retail chickens [32]. However, this did not seem to be a significant source of human colonization, because quinupristin-dalfopristin–resistant strains were found in only 1% of human stool samples obtained in the same regions.

Quinupristin-dalfopristin is bactericidal against some organisms. Pneumococci may be killed ≤3 h after exposure to the drug at the MIC [33, 34]. For 16 strains of Streptococcus pneumoniae, killing ≤6 h after exposure occurred more frequently with quinupristin-dalfopristin (15 strains) than with amoxicillin, vancomycin, or levofloxacin (≤6 strains) at 2 or 4 times the MIC [34]. Quinupristin-dalfopristin was not bactericidal against VREF with high levels of erythromycin resistance (MIC, >256 μg/mL) [35]. Quinupristin-dalfopristin kills some but not all staphylococci [36]. Clindamycin-susceptible (i.e., not constitutive macrolide-lincosamide–streptogramin B [MLSb]–resistant) S. aureus were killed by quinupristin-dalfopristin, whereas erythromycin- and clindamycin-resistant strains were only inhibited [37]. The significance of such in vitro observations is unclear. In some animal models, constitutive MLSb resistance predicted failure of the combination [38], whereas, in others, it did not [39]. In 90 patients treated with quinupristin-dalfopristin for MRSA infection because of intolerance to or failure of conventional therapy, MLSb phenotype did not have an obvious effect on outcome [40].

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The emergence of resistance to quinupristin-dalfopristin was

Table 2. Clinical outcomes reported in representative studies of quinupristin-dalfopristin therapy.

| Reference | Observations |
|-----------|--------------|
| [42]      | 19 Bloodstream and 5 localized infections in VREF emergency use protocol, 63% of which were associated with liver failure; 63% patients were cured or improved. |
| [43]      | VREF emergency use protocol. Clinical success was noted for 55.3% of all treated patients and in 73.6% of clinically evaluable patients; overall success (clinical response and bacteriological eradication) was noted for 65.4% of evaluable patients. |
| [44]      | Second VREF emergency use protocol (396 patients). Clinical response occurred in 51% of all treated patients and in 68.8% of clinically evaluable patients; overall success was noted in 65.6% of patients. |
| [45]      | Complicated skin and skin-structure infection, quinupristin-dalfopristin compared with oxacillin or vancomycin in United States, and it was compared with cefazolin or vancomycin elsewhere. Clinical success was noted for 68.2% vs. 70.7% of clinically evaluable patients and by-pathogen eradication was noted for 66.6% vs. 77.7% for quinupristin-dalfopristin vs. comparators, respectively. |
| [46]      | Comparison with vancomycin in patients with nosocomial pneumonia; aztreonam, imipenem, or tobramycin could be added. Clinical success rates for all treated and bacteriologically evaluable patients were 43.3% and 56.3%, respectively, for quinupristin-dalfopristin, and 45.3% and 58.3%, respectively, for vancomycin; by-pathogen eradication rates were 58.6% and 64.3%, respectively; for methicillin-susceptible Staphylococcus aureus, clinical success rates among bacteriologically evaluable patients were 66.7% for quinupristin-dalfopristin and 58.1% for vancomycin; for methicillin-resistant S. aureus, results were 30.9% vs. 44.4%, respectively. |

NOTE. VREF, vancomycin-resistant Enterococcus faecium.
rare in comparative trials; in emergency use studies, resistance developed in 5 of 338 patients with VREF infection, 4 of whom had therapy failure [48]. Bacteremia due to E. faecalis, which is inherently resistant to quinupristin-dalfopristin, has occurred during its use for treatment of VREF or staphylococcal infection [49].

Safety and tolerability data from clinical trial experience have been reviewed elsewhere [50]. Quinupristin-dalfopristin significantly interferes with the metabolism of agents cleared through the cytochrome P<sub>450</sub> (3A4) system, with important implications for drug interactions. Venous intolerance is common when the antibiotic is administered via peripheral vein. The drug is incompatible with saline, so it is given in 5% dextrose. Quinupristin-dalfopristin has been administered intrathecally or intraventricularly (together with intravenously administered therapy) to treat device-related VREF meningitis [51, 52]. These routes of administration have not been approved by the US Food and Drug Administration.

Variable numbers of patients receiving quinupristin-dalfopristin develop myalgias and/or arthralgias that may be severe. These symptoms were noted in 7%–10% of patients in non-comparative protocols, and they were noted less frequently in comparative trials [50]. In a clinical trial in which quinupristin-dalfopristin was administered together with minocycline, cases were also encountered more frequently in this study than in clinical trials [57]. Case reports describe reversible hyponatremia and anemia with reticulocytopenia [55, 56]. Despite these challenges, quinupristin-dalfopristin has been used successfully in the home as antibiotic therapy after initial inpatient treatment. In one study, myalgias (18.9% of patients) and arthralgias (13.5% of patients) were more common than reported in most other studies, but these symptoms did not necessitate discontinuation of therapy; nausea was also encountered more frequently in this study than in clinical trials [57].

**Linezolid.** Linezolid is a synthetic oxazolidinone antimicrobial that binds to the ribosome and inhibits protein synthesis [58, 59]. No cross-resistance between linezolid and drugs of other classes is exhibited [60]. Efflux accounts for resistance of gram-negative bacteria to linezolid. In gram-positive organisms, resistant mutants can be generated at low frequency in the laboratory; these have mutations involving the domain V peptidyltransferase center of 23S rRNA [61]. Resistance has been encountered among VREF isolates, and nosocomial spread of linezolid-resistant strains has been documented [62–64]. Linezolid-resistant VREF has demonstrated a G2576U mutation in 23S rRNA also seen in laboratory mutants [62, 64]. A linezolid-resistant MRSA clinical isolate demonstrated the same G2576U mutation [65].

The breakpoints of the National Committee for Clinical Laboratory Standards [9] for enterococci are as follows: susceptible, $\leq 2 \mu g/mL$; intermediate, $4 \mu g/mL$; resistant, $\geq 8 \mu g/mL$. For staphylococci, the breakpoint for susceptibility is $\leq 4 \mu g/mL$, and, for pneumococci and other streptococci, it is $\leq 2 \mu g/mL$. Surveys (table 1) have shown almost 100% susceptibility among staphylococci (including MRSA), enterococci (including VREF), Streptococcus pyogenes, and pneumococci [22, 66]. Linezolid is bacteriostatic against enterococci [67]; combinations with ampicillin, gentamicin, or streptomycin are indifferent [68]. At concentrations of 4 $\mu g/mL$, linezolid demonstrated bactericidal activity at 24 h against only 1 of 14 strains of S. aureus, whereas vancomycin killed 18 of 25 strains at its breakpoint concentration [36]. In volunteers, peak serum bactericidal titers against S. aureus and E. faecalis were $<1:4$, even at dosages of 625 mg given 3 times per day [69]. At 4 times the MIC, linezolid killed 12 of 16 strains of pneumococci [34].

In the United States, linezolid is indicated for treatment of VREF infection; nosocomial pneumonia caused by S. aureus (including MRSA) or penicillin-susceptible S. pneumoniae; uncomplicated skin and skin-structure infections caused by MSSA or S. pyogenes; complicated skin and skin-structure infections caused by MSSA, MRSA, or streptococci of groups A or B; and community-acquired pneumonia caused by S. pneumoniae or MSSA. In adults with complicated skin or skin-structure infections who require hospitalization, linezolid, 600 mg iv q12h, followed by the same dosage given orally after initial improvement, was as effective, clinically and microbiologically, as intravenously administered oxacillin followed by orally administered dicloxacinil (table 3) [70]. In nosocomial pneumonia, the cure rates for linezolid or vancomycin were comparable for the intention-to-treat and clinically and microbiologically evaluable populations [71]. Linezolid was compared with vancomycin for treatment of MRSA infection in a randomized, open-label study [72]. Skin and skin-structure infections were the most common, but pneumonia and urinary tract infections were also represented. For evaluable patients, rates of clinical cure (73%) and microbiological success (≈60%) were similar for patients in both treatment arms.

Case reports describe use of linezolid for treatment of purulent exacerbations due to MRSA in cystic fibrosis [73], hip prosthesis infection due to MRSA or VREF [74, 75], coagulase-negative staphylococcal epidural catheter infection [76], and endovascular infections due to VREF [76–78]. A preliminary...
report indicated that ~85% of patients with MRSA infection who experienced treatment failure or who were intolerant of vancomycin treatment were clinically cured with linezolid [79]. Of 32 patients with definite endocarditis treated with linezolid, 50% were considered to be cured at 6 months [80]. In the latter report, 78% of the subjects were enrolled after therapy with other antibiotics had failed. Linezolid appears to penetrate well into bone, fat, and muscle in patients undergoing hip replacement [81]. Given the primarily bacteriostatic activity of linezolid against enterococci, most surprising have been several reports of successful treatment with linezolid of patients with VREF meningitis, including patients in the postoperative period, persons with infection associated with a device, and patients with infections resulting from Strongyloides hyperinfection syndrome [82–84].

The pharmacokinetics of linezolid are summarized elsewhere [41]. Orally administered linezolid is virtually completely bioavailable. One adult given a standard dosage (600 mg b.i.d. iv or po) did not achieve adequate serum concentrations [85]. Symptoms associated with linezolid, including nausea, headache, diarrhea, rash, and altered taste, have generally been mild [70, 72, 76]. Nervous system effects, including peripheral neuropathy, have been noted in a few patients [86]. Linezolid is a weak monoamine oxidase inhibitor, and, in volunteers, it can potentiate adrenergic effects of phenylpropanolamine or pseudoephedrine [41]. This appears not to have been a problem in clinical studies. Linezolid did not precipitate serotonin syndrome in volunteers receiving dextromethorphan [41], and this did not appear to be a problem in clinical studies that included patients receiving drugs that had the potential to interact with monoamine oxidase inhibitors [71, 72]. However, in patients receiving selective serotonin reuptake inhibitors with linezolid, there have been subsequent reports of confusional states involving agitation, fever, or tachycardia, which is consistent with the serotonin syndrome [87, 88].

The labeling of linezolid indicates the potential to cause reversible myelosuppression and advises monitoring of hematologic parameters in patients who receive treatment for ≥2 weeks or who might be predisposed to marrow dysfunction [89]. The hematologic effects observed during clinical studies of ~2000 linezolid-treated patients and an equal number of subjects who received comparator agents were reviewed [90]. The percentage of patients who developed substantially low platelet counts while receiving linezolid treatment began to increase to more than seen in subjects who received comparator agents at ~2 weeks of therapy. The cumulative percentage of patients with substantially low platelet counts was 2.4% for the linezolid arm and 1.5% for the comparator arm; the difference was not significant. Reticulocyte indices, measured in ~600 patients in each treatment arm, were significantly decreased compared with baseline values at the end of treatment with linezolid, whereas indices increased in patients in the comparator arm. Case studies suggest that thrombocytopenia may occur earlier and in a larger proportion of patients than has been reported in the comparative trials [91, 92]. In these studies, platelet counts of <100,000 platelets/mm³ were noted in 20%–30% of treated patients. The risk of developing thrombocytopenia while receiving linezolid treatment may depend not only on total duration of therapy but also on drug exposure, reflected by the 24-h area under the curve averaged over the first few days of therapy [93].

Several articles have reported anemia, which may be associated with increases in serum iron saturation or thrombocytopenia, or both, in linezolid-treated patients [72, 92, 94–97]. Neutropenia appears to be less common [76]. Reversible pan- cytopenia has been reported [98]. One patient died of myelodysplastic syndrome after receiving multiple antibiotics, including linezolid [99]. Other reports document successful use of linezolid in patients who had been persistently thrombocytopenic at baseline [78] or who had previously developed thrombocytopenia while receiving chloramphenicol therapy [84].

Table 3. Clinical outcomes reported in representative studies of linezolid therapy.

| Reference | Observations |
|-----------|--------------|
| [70]      | Complicated skin and skin-structure infections treated with linezolid (600 mg iv followed by po q12h) vs. iv oxacillin and oral dicloxacillin. Respective clinical success rates for linezolid vs. oxacillin were 69.8% vs. 64.9% for intention-to-treat, 88.6% vs. 85.8% for clinically evaluable, and 88.1% vs. 86.1% for microbiologically evaluable populations |
| [71]      | Linezolid vs. vancomycin, each with aztreonam, for treatment of nosocomial pneumonia. Respective clinical cure rates for linezolid vs. vancomycin were 53.4% vs. 52.1% for intention-to-treat, 66.4% vs. 68.1% for clinically evaluable, and 69.8% vs. 68.4% for microbiologically evaluable patients |
| [72]      | Linezolid (iv followed by po) vs. vancomycin only for treatment of methicillin-resistant Staphylococcus aureus infection. Respective clinical cure rates were 73.2% vs. 73.1% for clinically evaluable patients and 58.9% vs. 63.2% for microbiologically evaluable patients |
OPINION

The evidence above suggests that both quinupristin-dalfopristin and linezolid are effective antimicrobials, each with its own benefits and limitations. There are clearly circumstances in which one or both of these agents would be useful additions to a hospital pharmacy. MRSA infections are now common in US hospitals and have begun to appear increasingly in the community. Although vancomycin remains the standard treatment for most MRSA infections, and although it is less expensive than either new drug, treatment failures have occurred despite in vitro susceptibility of the infecting strain. Furthermore, some patients cannot tolerate this agent [76]. Although VREF are less aggressive pathogens than MRSA, they are clinically important organisms. Strains of S. aureus with intermediate resistance to glycopeptides, although uncommon at present, are a very real threat, and the appearance of vancomycin-resistant strains of S. aureus is ominous.

If one considers the properties of both agents, linezolid would be found to be the more versatile of the drugs. Its antibacterial spectrum is at least as broad as that of quinupristin-dalfopristin, and it is active against both E. faecalis and E. faecium. It can be given orally, with the potential to enhance patient comfort and decrease costs and risks of intravenous therapy. On the other hand, in some patients, myelosuppression or other effects will constrain the use of this agent, especially in long courses of treatment. In a few persons taking other medications, monoamine oxidase–inhibitory effects, however modest, may precipitate symptoms. Linezolid exhibits limited in vitro bactericidal activity against enterococci, and the time it takes to kill staphylococci can be described as “slow.” Resistance has been encountered among enterococci and in S. aureus. The former have demonstrated capacity to spread in the hospital environment. Comparative clinical studies have shown that resistance is unlikely to emerge in the patient with a straightforward infection that can be managed under optimal circumstances. However, for those occasional patients whose condition cannot be managed with optimal debridement or removal of foreign material, long courses of therapy with an orally administered antimicrobial might offer special hope. It is precisely such conditions that would favor emergence of linezolid-resistant strains.

The great majority of strains of MRSA, VREF (not, however, E. faecalis), and other common or problematic gram-positive pathogens are susceptible to quinupristin-dalfopristin. Linezolid-resistant VREF can be susceptible to quinupristin-dalfopristin, as was the linezolid-resistant MRSA strain reported elsewhere by myself and colleagues [65]. Although resistance has emerged in a few patients during therapy with quinupristin-dalfopristin, the incidence appears to be within the range observed for other antimicrobials. Resistant enterococci are found in poultry; such strains could constitute a reservoir of resistance genes for the future. Quinupristin-dalfopristin is bacteriostatic against the great majority of VREF strains but in vitro data show bactericidal potential against staphylococci that are not constitutively MLS	extsubscript{B} resistant. At present, there is a paucity of clinical information on how well this drug might work in specific infections caused by MRSA—an area of perceived need for which there is currently no US Food and Drug Administration indication. Small case studies provide tantalizing evidence that combinations of quinupristin-dalfopristin and vancomycin may be effective against MRSA infections that fail to respond to a glycopeptide alone [100, 101].

Several practical issues complicate use of quinupristin-dalfopristin, one of which is the limited number of approved indications. It must be given intravenously, generally by deep catheter, to avoid venous irritation. Quinupristin-dalfopristin affects clearance of medications via the cytochrome P	extsubscript{450} system, with the potential for major drug interactions. A variable number of patients will experience myalgias and/or arthralgias that can be severe enough to require dose reduction or administration of opiate analgesics. Despite these challenges, the drug has been used successfully both in the hospital and in outpatient settings.

A number of questions remain. Particularly relevant for linezolid, which has an oral formulation, is under what circumstances this drug can be used in place of cell wall–active agents to treat serious infections requiring long courses of therapy, such as osteomyelitis, in an effort to minimize the inconvenience, risks, and costs of parenteral treatment. Would either agent prove able to prevent the development of endocarditis, infection of biomedical prostheses, or other deep infection when used to treat staphylococcal bacteremia related to intravascular catheters or other removable foci? Would combination therapies improve the bactericidal activity of either agent or prevent the emergence of resistance in challenging circumstances? Most important, can we identify patients who are at greatest risk of developing serious adverse effects associated with these agents before use, and can any steps minimize or completely avert the risk of such events?

At the moment, we await data to define the circumstances under which either drug might be superior to previously available antimicrobials for treatment of infections susceptible to both new and old agents. However, because we are faced today with organisms that are resistant to other antibiotics or with patients intolerant of or experiencing failure of therapy with older agents (despite susceptibility in vitro), these new antimicrobials offer value.

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