Use of Linezolid, an Oxazolidinone, in the Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

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We report our experience with linezolid in an investigation of its use against resistant gram-positive bacterial infections. Fifteen patients who had renal failure ($n = 6$), recent liver transplantation ($n = 5$) or surgery ($n = 6$), cancer ($n = 3$), endocarditis ($n = 2$), or human immunodeficiency virus infection ($n = 1$), along with infections due to vancomycin-resistant enterococcus (VRE), and 2 patients with infections due to methicillin-resistant *Staphylococcus* species who had adverse reactions to vancomycin were treated with linezolid (600 mg every 12 h for 5–42 days (mean ± SD, 20.5 ± 3.5 days). Abscess drainage or prosthetic device removal was undertaken. Microbiological cure occurred in all 10 patients who completed therapy, and all 7 patients alive at follow-up were free of infection. No deaths were attributable to the index infection. Adverse events associated with linezolid use were mild leukopenia in 1 patient and nausea in another. It appears that administration of linezolid, in conjunction with surgical intervention or device removal, is an effective treatment option for serious resistant gram-positive bacterial infections.

The incidence of nosocomially acquired gram-positive bacterial infections has dramatically increased since the early 1980s. Between 1980 and 1989, the incidence of bacteremia due to coagulase-negative *Staphylococcus* species increased 754%, that due to *Staphylococcus aureus* increased 176%, and that due to enterococci increased 124% [1]. These 3 pathogens are now the most common nosocomially acquired causes of bloodstream infections [2, 3].

Unfortunately, antimicrobial resistance among nosocomially acquired gram-positive organisms is also rising. For instance, it is estimated that 79% and 25% of all nosocomially acquired coagulase-negative *Staphylococcus* species and *S. aureus,* respectively, are methicillin-resistant [3]. VRE, which now accounts for up to 47% of all *Enterococcus faecium* isolates, is of particular concern because of its increasing prevalence among severely ill patients [3–5], including orthotopic liver transplant (OLT) recipients. Because of the extensive abdominal surgery, selective pressures of perioperative broad-spectrum antibiotics, high-dose immunosuppressive therapy, and prolonged postoperative stay in the intensive care unit, OLT recipients are at high risk for becoming colonized with VRE and developing serious VRE-related complications [6].

The increasing rate of VRE infection may also lead to increasing morbidity and mortality. Multiple retrospective analyses comparing clinical outcomes in cases of vancomycin-susceptible and vancomycin-resistant bacteremia have suggested that despite the differences in patient populations and study methodologies, VRE bacteremia was consistently associated with higher mortality [4, 7–12]. Other retrospective studies have also demonstrated that OLT recipients who were colonized with VRE were more likely to develop VRE bacteremia. When OLT recipients who developed VRE infection were compared to OLT recipients without VRE infection, the former group had a higher incidence of retransplantation, biliary complications, requirement for reexploration, and death [6, 7].

A major contributing factor to this increase in morbidity and mortality is the lack of effective therapy. Because of the emergence of *S. aureus* strains with intermediate-level resistance to vancomycin (MIC, 8 μg/mL) and the increased frequency of serious VRE infections, vancomycin is becoming a less dependable therapeutic option. Although chloramphenicol and rifampin, doxycycline, novobiocin, high-dose ampicillin/sulbactam, gentamicin, and bacitracin have been used to treat VRE infections, the development of resistance during treatment and clinical failure are common [13–16].

Quinupristin/dalfopristin, which was recently approved by the US Food and Drug Administration for use against VRE infection, has been demonstrated to have clinical efficacy [17, 18]. However, this agent causes multiple adverse effects and has already become associated with a significant resistance pattern [19–22]. Thus, there are presently no consistently effective ther-

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apeutic options for serious multidrug-resistant gram-positive bacterial infections.

Oxazolidinones are a new class of synthetic antibiotics unrelated to other antibiotics presently on the market. They inhibit protein synthesis by binding to the 50s ribosome subunit and preventing formation of the initiation complex. In vitro and in vivo studies have demonstrated that linezolid, an oxazolidinone analog, has significant bacteriostatic activity against multiresistant gram-positive pathogens such as coagulase-negative *Staphylococcus* species, *S. aureus,* VRE, and *Streptococcus pneumoniae* through inhibition of protein synthesis [14, 23, 24]. This strongly suggests that linezolid has promise for the clinical treatment of resistant gram-positive infections. We report results for a series of patients treated prospectively with linezolid for serious multidrug-resistant gram-positive bacterial infections.

Patients and Methods

Patient selection. All patients in our series were treated at the University Hospitals of Cleveland, a 974-bed tertiary care center. All inpatient microbiological samples are submitted to and evaluated by the clinical microbiology department. If a sample was positive for VRE and obtained from a normally sterile site, the patient information was reported to and investigated by the Infectious Disease Consultation Service (IDCS). In addition, the consultation team was notified by the primary care services of any patient who had a serious methicillin-resistant staphylococcal bacterial infection but was unable to tolerate vancomycin.

If the patient was aged ⩾18 years and had symptoms and a clinical presentation consistent with active infection, the IDCS was involved in the management of the patient. Once it was determined that the case was a true infection and either that it was refractory to conventional therapy (i.e. surgical drainage/debridement, percutaneous drainage, prosthetic device removal, and/or administration of antibiotics other than linezolid) or that the patient was unable to tolerate vancomycin, the patient was eligible for treatment with linezolid, according to compassionate-use protocol (see below).

Definitions. A culture specimen was considered to be obtained from a normally sterile body site if its source was the blood, peritoneal space, or an organ other than lung or bladder, or if it was obtained during a surgical procedure or an initial percutaneous aspiration. Cases were considered to be true VRE infections if the organisms were isolated from >1 normally sterile body site, if all other isolated organisms considered clinically significant were adequately treated against, if other possible causes of fever were investigated and excluded, if cultures did not become VRE-negative despite removal of a prosthetic device (i.e., iv catheter or urinary catheter), or if the infection persisted despite surgical drainage procedures.

Bacteremia was defined by the culture-positivity of blood obtained from 2 separate sites. An intravascular catheter infection was defined by the culture-positivity of a catheter tip, blood obtained through the catheter, and blood from a peripheral site. Infective endocarditis was defined according to the Duke criteria [25].

All organisms were demonstrated to be susceptible to linezolid by disk diffusion (⩾21 mm) in the clinical microbiology department at UHC, and these findings were confirmed by a central study center.

Serious adverse reactions to vancomycin that were considered to be indications for substitution with linezolid were neutropenia, thrombocytopenia, rash, and renal failure. In the cases in which an adverse reaction to vancomycin was suspected, all other possible causes of the adverse reactions were investigated and excluded. An adverse reaction to linezolid was defined as any clinical event that could not be easily or temporally attributed to concomitant medications or other aspects of the patient's hospital care.

Treatment. Patients who met the above criteria were eligible for treatment with linezolid. The treatment protocol and patient consent forms were approved by the Institutional Review Board at University Hospitals of Cleveland. After informed consent was obtained, patients were treated with iv linezolid at a dosage of 600 mg every 12 h according to an open-label, noncomparative, compassionate-use treatment protocol facilitated by a central study center. The duration of therapy was determined by the IDCS in conjunction with the primary service. If the intended duration of therapy extended beyond the necessary hospital stay, linezolid therapy was continued at home as an oral preparation and the patient was monitored as an outpatient.

All classes of antibacterial antibiotics that were to be used were tested for effectiveness against the resistant gram-positive organism. Antibacterial agents with exclusive activity against gram-negative organisms, antivirals, and antifungals were permitted for use whenever deemed necessary by the IDCS.

Evaluation of outcome. All patients were followed by the IDCS during the duration of the therapy and followed as outpatients for at least 1 month after the completion of therapy. After the 1-month period, patients were followed by their primary care physicians, and the IDCS was notified of any recurrent infections.

Antimicrobial effectiveness was evaluated microbiologically and clinically. Microbiological cure was determined at the end of the treatment period and was demonstrated by negative repeated cultures of specimens from the original site of infection, when samples were available. Clinical cure was determined at 2 times: at short-term follow-up, 7–10 days after completion of therapy, and at long-term follow-up, 15–30 days after completion of therapy.

The patient was considered to be clinically cured if all signs and symptoms of infection noted at the time of enrollment completely resolved. Persistence of presenting signs or symptoms and/or new unfavorable findings consistent with recurrent infection were considered to be representative of clinical failure. If clinical failure occurred, the patient was eligible for a second course of linezolid, the duration of which was again determined by the IDCS. In these cases, microbiological and clinical cures were reassessed after completion of the second course of therapy. If the patient died before completion of the intended course of therapy or before short-term or long-term follow-up, then the microbiological and/or clinical outcome was categorized as indeterminate.

Results

Between September 1997 and October 1998, the IDCS was involved in the care of 17 patients who were ultimately treated

with linezolid. Fifteen of these patients had serious VRE infections, 1 patient had methicillin-resistant coagulase-negative staphylococcus infection, and 1 patient had methicillin-resistant *S. aureus* infection.

VRE-infected patients. The median (±SEM) age of the 15 VRE-infected patients was 52.3 (±3.4) years; 46.7% were male and 73.3% were white (table 1). All 15 patients were debilitated hosts with multiple preexisting medical conditions. Eleven of the patients (73.3%) had recently undergone a major surgical procedure, including 5 (33.3%) who were recent OLT recipients. Twelve of the patients (80.0%) were in an intensive care unit when the VRE infection was diagnosed. The mean duration of hospitalization prior to VRE infection was 19.4 (±3.1) days.

VRE was routinely isolated from multiple sites (table 2). The mean number of infected sites per patient was 2.6 (±0.2). Bacteremia, which was the most common type of VRE infection, developed in 10 patients (66.7%). The second most common source of VRE isolates was the urine; such isolations were documented for 6 patients (40%), of whom 5 also had VRE bacteremia and the sixth also had VRE peritonitis. Five of the 11 patients who had recently undergone major surgery developed wound infections with VRE. Of these, 1 patient had a wound infection alone, 2 had concurrent VRE peritonitis, and 2 also had VRE bacteremia.

VRE peritonitis developed in 4 of the 5 OLT recipients. Three of these OLT recipients also had VRE bacteremia. Four patients had an intraabdominal abscess from which VRE was isolated. Two of these patients also had VRE bacteremia. Despite multiple attempts at surgical drainage or debridement of the abscesses and peritoneal infections, all of the infections ultimately required linezolid therapy.

The mean duration of therapy was 20.5 (±3.5) days (range, 5–42 days). The longest duration of iv therapy was 42 days, for VRE endocarditis. In addition to linezolid therapy, 10 patients (73.3%) underwent either surgical drainage or debridement of the infection or removal of an infected prosthetic device (table 2). Three patients (20%) required a second course of therapy because the VRE infection recurred (patients 5, 12, and 15). All of these recurrences occurred in patients with intraabdominal abscesses and were secondary to incomplete evacuation of the infected-fluid collections.

Ten patients (66.7%) were alive at the end of the intended treatment period. Microbiological cure was achieved in all of these patients. Eight patients (53.3%) were alive at short-term follow-up, all of whom were determined to be clinically cured at that time. This included our case of VRE endocarditis, which is to our knowledge the first successfully treated case. Seven patients (46.6%) were alive at long-term follow-up, and all were still considered clinically cured. Of the 3 patients who required retreatment, only 1 survived to complete the second course of therapy. This patient was considered microbiologically and clinically cured at both short-term and long-term follow-up.

Overall, 8 patients died before long-term follow-up (table 2).

Table 1. Demographic characteristics of patients infected with a vancomycin-resistant enterococcus.

Characteristic	No. of patients (n = 15) or other value
Sex (male : female)	7 : 8
Race (black : white)	4 : 11
Age in years (mean ± SEM)	52.3 ± 3.4
Preexisting medical condition	
Dialysis-dependent renal failure	6
Orthotopic liver transplantation	5
Abdominal or thoracic surgery	6
Malignancy	3
Bacterial endocarditis	2
HIV infection	1
Hospital location at diagnosis of infection	
Medical ICU	3
Surgical ICU	10
Medical floor	2
Days in hospital prior to infection (mean ± SEM)	19.4 ± 3.1

NOTE. ICU, intensive care unit.

Five of these patients (66.7%) died before completing the intended course of therapy. None of the deaths were attributable to VRE infection. The causes of death were overwhelming infection (patients 5, 11, 14, and 15), terminal oncological illness (patients 3 and 8), and multiple organ failure (patients 5, 9, and 13). When possible, the original site of infection was assessed for VRE clearance before death. Five patients who originally had VRE bacteremia had VRE clearance from the bloodstream documented before their deaths. VRE infection was also demonstrated to be cleared from 3 patients who originally had a VRE-infected abscess. Overall, clearance of the original VRE infection was demonstrated for all but 1 of the patients who died before long-term follow-up.

Two patients developed probable adverse reactions to linezolid therapy. Patient 2 developed leukopenia (nadir WBC count, 1900/mL) on day 12 of therapy. The patient was able to complete a 14-day course of therapy despite the leukopenia, which resolved 3 days following completion of therapy. Patient 8 developed mild nausea, which resolved after linezolid treatment was completed. Although patients were concurrently treated with a variety of drugs that could have been associated with these toxic effects, it was only with the introduction of linezolid that these adverse reactions were seen, and these side effects resolved with discontinuation of the oxazolidinone.

Recurrent parotitis due to methicillin-resistant S. aureus. A 58-year-old woman with a history of transverse myelitis, pulmonary *Mycobacterium avium* complex infection, celiac sprue, recurrent urinary tract infections, and right methicillin-resistant *S. aureus* parotitis was admitted for acute left-parotid swelling. The parotid fluid yielded methicillin-resistant *S. aureus.* Despite a history of severe reaction to vancomycin that included neutropenia, thrombocytopenia, and acute renal failure, treatment with vancomycin was initiated. Shortly thereafter, the patient developed a generalized erythematous, blanching maculopapular rash and leukopenia (WBC count, 1300/mL).

A reaction to vancomycin was suspected, and the patient was

Table 2. Clinical data concerning patients infected with a vancomycin-resistant enterococcus (VRE).

Patient no.	Preexisting medical condition	Site(s) of VRE infection	Days of linezolid therapy	Additional intervention(s)	Concomitant antimicrobials[a]	Micro-biological cure	Clinical cure, STF/LTD	Outcome	Cause of death
1	Recent OLT for HBV, peritonitis[b]	Ascites,[b] blood, catheter tip, surgical drains	14	Peritoneal dbdr, biliary leak repair	Gan, Cpfx, Pip/Taz, Imi, AmB	Y	Y/Y	Alive at LTF	
2	Recent OLT for HCV, peritonitis[b]	Ascites,[b] blood	14	Peritoneal dbdr	AmB, Acy, Gan, Mero	Y	Y/Y	Alive at LTF	
3	Recent thoracic surgery for esophageal cancer, wound infection[b]	Abdominal wound,[b] ascites	14	Wound dbdr	Cpfx, Imi, Flu	Y	I/I	Died before STF	Esophageal cancer
4	Renal failure during peritoneal dialysis, diabetes, bacteremia[b]	Percutaneous iv central catheter,[b] blood	14	Catheter removal	Gm, AmB, Chl	Y	Y/Y	Alive at LTF	
5	Recent gastric resection for peptic ulcer disease, hepatic necrosis, subhepatic abscess[b]	Hepatic abscess,[b] percutaneous drain, wound	9, 25	Surgical drainage of abscess	Cpfx, Imi, AmB, Czid, Chl	I	I/I	Died during therapy	Overwhelming sepsis and MOF
6	Recent exploratory laparotomy for trauma wound infection[b]	Abdominal wound	12	Dbdr	None	Y	Y/Y	Alive at LTF	
7	Recent OLT for seroclosing cholangitis, liver abscess[b]	Ascites,[b] urine, wound	14	Peritoneal dbdr	Mtz, Etz, Acy, CMZ, Clo	Y	Y/Y	Alive at LTF	
8	Recent resection of metastatic colon cancer, subhepatic abscess	Subhepatic abscess[b]	12	Percutaneous catheter drainage	Pip/Taz, Flu, Vm, CMZ, Gm	Y	Y/I	Died before LTF	Metastatic colon cancer
9	*Enterococcus faecium* (susceptible to Vm), pulmonic valve endocarditis, bacteremia[b]	Blood[b] catheter tip, urine	21	None		I	I/I	Died during therapy	Cardiac and renal failure
10	Recent abdominal aortic repair, diabetes, renal failure during hemodialysis[b]	Blood,[b] urine, wound	42	None	Vm, Alfx	Y	Y/Y	Alive at LTF	
11	HIV infection, sepsis, bacteremia[b]	Blood,[b] urine	19	None	Cpfx, Flu, Atm, Azm, Pip/Taz, AmB	I	I/I	Died during therapy	Overwhelming sepsis
12	Recent OLT for alcoholic cirrhosis, infected peritoneal hematoma[b]	Peritoneal hematoma,[b] blood, ascites, urine	21, 25	Surgical dbdr at each trmt	Flu, CMZ, Acy, Cpfx, Pip/Taz, Gan, Em, CMZ, Amik, Amp, AmB	Y	Y/Y	Alive at LTF	
13	Recent valve replacement and aortic graft placement, *Staphylococcus aureus* prosthetic aortic valve endocarditis with aortic abscess, bacteremia[b]	Blood,[b] sternal wound, urine, catheter tip	7	None	Cfaz, AmB, Imi, Amik	Y	I/I	Died before STF	MOF
14	Acute myelogenous leukemia, recent bone marrow transplantation, renal failure, bacteremia[b]	Blood,[b] catheter tip	5	Catheter removal	Tm, Cpfx, Acy, Imi, AmB	I	I/I	Died during therapy	Aspergillar pneumonia
15	Recent OLT for HCV, cirrhosis, hepatocellular carcinoma, fungal peritonitis, perirectal abscess[b]	Perirectal abscess,[b] blood	21, 18	Abscess drainage	Acy, Flu, Cpfx, CMZ, Imi, AmB, Gan, Vm, Mero	I	I/I	Died during therapy	Aspergillar pneumonia

NOTE. HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; debr, debridement; I, indeterminate; ICU, intensive care unit; iv, intravenous; LTF, long-term follow-up; MOF, multiple-organ failure; OLT, orthotopic liver transplantation; STF, short-term follow-up; trmt, treatment; Y, yes.

[a] Acy, acyclovir; Alfx, alatrofloxacin; AmB, amphotericin; Amp, ampicillin; Amik, amikacin; Atm, aztreonam; Azm, azithromycin; Cefz, ceftazidime; CMZ, cotrimoxazole; Cpfx, ciprofloxacin; Clo, clotrimazole; Chl, chloramphenicol; Em, erythromycin; Flu, fluconazole; Gan, ganciclovir; Gm, gentamicin; Imi, imipenem; Mero, meropenem; Mtz, metronidazole; Pip/Taz, piperacillin/tazobactam; Vm, vancomyin.

[b] Primary site or type of infection.

switched to therapy with iv linezolid (600 mg every 12 h). Within 48 h, the rash and leukopenia resolved and the parotid swelling diminished significantly. The patient was discharged and was to continue oral therapy at the same dose for a total of 3 weeks; microbiological cure was determined at completion of therapy. At short-term and long-term follow-up, the patient was considered to be clinically cured and the parotid gland was normal.

Epidural abscess due to methicillin-resistant coagulase-negative Staphylococcus *species.* A 38-year-old woman was admitted because of back pain and fevers. She had a history of stage IIIB adenocarcinoma of the cervix, status post radiation and cisplatin therapy, placement of bilateral ureteral stents secondary to recurrent hydronephrosis, recurrent urinary tract infections, and status post recent permanent epidural-catheter placement for analgesic administration. MRI showed an epidural abscess at the site of the epidural catheter. The epidural catheter was removed and the tip yielded methicillin-resistant coagulase-negative *Staphylococcus* species.

A percutaneous iv central catheter was placed and the patient was discharged; she was to continue iv vancomycin therapy. However, despite 1 week of vancomycin treatment, hectic fevers persisted and the patient developed progressive agranulocytosis (absolute neutrophil count, 720/mL). The patient was readmitted and MRI was repeated; it showed a decrease in the epidural fluid collection. Blood cultures yielded methicillin-resistant coagulase-negative *Staphylococcus* species, and percutaneous iv central catheter–related bacteremia was suspected.

The suspect catheter was removed, and vancomycin treatment was continued. Still, the fevers and neutropenia persisted. Vancomycin-induced fever and neutropenia were suspected, so the patient was switched to iv linezolid (600 mg every 12 h). Within 24 h, the patient defervesced. The neutropenia also resolved shortly thereafter. After completing 3 weeks of linezolid therapy, the patient was microbiologically cured. At short-term and long-term follow-up, it was determined that the patient was also clinically cured, with complete resolution of the epidural abscess.

Discussion

To our knowledge, this is the largest reported series of patients infected with multidrug-resistant gram-positive organisms who were treated with an oxazolidinone. The clinical profiles of the patients we treated are consistent with those of previously described populations at risk for serious multidrug-resistant gram-positive infections; all 17 patients were debilitated hosts with multiple underlying medical problems, and most of them had recently undergone extensive surgical procedures or were immunosuppressed. It is also no surprise that all of these patients had either a prolonged hospital stay or multiple previous hospitalizations, placing them at higher risk for colonization with nosocomial organisms. The large majority of these patients were also in intensive care units at the time of infection, where the incidence of these infections and its attributable morbidity and mortality are typically the highest [7–12].

It is unlikely that any of these infections represented a colonizing state or would have resolved without the use of linezolid. We were careful to explore all treatment alternatives before starting linezolid therapy. In patients whose site of infection was surgically accessible, multiple incision and drainage or percutaneous procedures were attempted first. For instance, multiple attempts were made to drain the hepatic abscess, subhepatic abscess, infected intraabdominal hematoma, and perirectal abscess in patients 5, 8, 12, and 15, respectively. If there was any suspicion that a prosthetic device was infected, it was removed as well.

Persistent infection was documented after all conventional therapeutic options for treatment of VRE infections had failed. Even for patient 6, who only had an abdominal wound infection, multiple debridements of the wound over a prolonged period of time did not result in healing, a circumstance suggesting that the VRE was more than just a colonizing organism. It is also unlikely that the microbiological and clinical outcomes are attributable to the use of other antibiotics that may have contributed to the eradication of the VRE infection. All antibacterials that were used at some time during each patient's hospitalization were determined to be ineffective against VRE.

Serious linezolid-associated adverse events reported to an independent evaluator have included rashes, liver abnormalities, anemia, leukopenia, hypertension and hypotension, renal insufficiency, elevated amylase levels, serum sickness, CNS toxic effects (headache, sleepiness, and confusion), and hemorrhagic mucositis [26]. As with these serious adverse events, those we report were considered to be attributable to linezolid only because we could not determine an alternative cause and the temporal relationship of these toxic effects to initiation of oxazolidinone therapy was clear. However, it should be remembered that the majority of these patients were critically ill and that it is often difficult to determine the cause of every clinical abnormality in such patients.

The limitations of our limited case-series are obvious. Without a control or comparative group, we cannot definitively determine if linezolid therapy had an impact on the clinical outcome. In addition, the mortality rate among our patients was extremely high (53.3% at long-term follow-up). This was most likely secondary to 2 main factors. First, our patients were severely debilitated; many had terminal illnesses, had multiorgan failure, and/or were receiving immunosuppressive agents that placed them at an immunologic disadvantage. Second, our thorough efforts in trying all other available options before linezolid therapy may have imposed additional morbidity and mortality risks and may have delayed linezolid therapy long enough to result in a less-than-optimal outcome.

In spite of these factors, it is critical to note that all survivors at long-term follow-up were clinically cured. In addition, all

but 1 of the patients who did not survive to long-term follow-up had documented clearance of VRE from the original site of infection. Therefore our data have significant clinical implications. Bacteremia, peritonitis, and abscesses secondary to multidrug-resistant gram-positive organisms, especially VRE, are serious infections that are unlikely to resolve without definitive antimicrobial therapy. There is no doubt that if these infections had been permitted to persist unchecked, they would have ultimately resulted in the demise of all the patients.

The lack of effective therapy against gram-positive bacteria has led to serious limitations in our treatment of critically ill patients. As the trend of multidrug-resistant gram-positive infections progresses, multidrug-resistant gram-positive organisms will most likely continue to cause significant morbidity and mortality. New compounds active against these resistant microbes are desperately needed.

Although linezolid is still under investigation in clinical trials, this report presents initial information crucial to determining the role linezolid will play in the battle against nosocomial infections. Ultimately, administration of linezolid, in conjunction with surgical intervention or prosthetic device removal, will probably be a reasonable option for the treatment of serious multidrug-resistant gram-positive bacterial infections. Prospective randomized controlled trials will be necessary to confirm the efficacy of this agent.

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