MAJOR ARTICLE

Vancomycin-Resistant *Enterococcus faecium* Meningitis Successfully Managed with Linezolid: Case Report and Review of the Literature

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Enterococci cause serious illness in immunocompromised patients and severely ill, hospitalized patients. Resistance to vancomycin has increased in frequency during the past few years. Limited therapeutic options are available for vancomycin-resistant enterococcal infections and the optimum therapy has not been established. We report a case of nosocomial vancomycin-resistant *Enterococcus faecium* meningitis in the setting of hyperinfection with *Strongyloides stercoralis* that was successfully treated with linezolid. We also review the previously reported cases of vancomycin-resistant *E. faecium* meningitis.

Enterococci are associated with infections of the urinary tract, wound, and bloodstream; infective endocarditis; and, rarely, meningitis [1]. The prevalence of nosocomial infections caused by *Enterococcus* species has increased during the past few years. According to data generated by the National Nosocomial Infection Surveillance System (NNIS), enterococci were the second most common nosocomial pathogens in 1986–1989 [2, 3]. According to a more recent NNIS report that was published in 1999, enterococcal species were the second most common pathogenic causes of bloodstream infections in patients in intensive care units [4].

From 1969 through 1988, a significant increase in resistance to antibiotics occurred in clinical isolates of *Enterococcus faecium* [5]. The emergence of resistance to multiple antibiotics, including vancomycin, has made management of enterococcal infections a challenge [5, 6]. Linezolid is a new oxazolidinone antibiotic with activity against vancomycin-resistant *E. faecium* (VREF). We report a case of nosocomial *E. faecium* meningitis in a patient with *Strongyloides* hyperinfection who was successfully treated with intravenously administered linezolid.

CASE REPORT

A 69-year-old man who was originally from the Dominican Republic presented with a 4-day history of fever, malaise, and abdominal pain. His medical history was remarkable for diabetes mellitus, hypertension, coronary artery disease, and autoimmune hemolytic anemia, for which he had been receiving long-term steroid therapy for the past 6 years. Surgical history was notable for a splenectomy that had been performed 2 months prior to admission to the hospital. At admission, the medications he was receiving included prednisone (60 mg q.d.), metoprolol, glyburide, furosemide, and insulin. He had no history of recent travel (his last visit to the Dominican Republic occurred 8 years before admission to the hospital).

The patient's physical examination at admission was

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significant for fever (temperature, 38.9°C [102°F]), icterus, and left upper quadrant pain on palpation. Initial laboratory studies revealed the following values: WBC count, 3.3×10^4 cells/mm^3 (64% neutrophils, 17% bands, 10% lymphocytes, and 3% eosinophils); hemoglobin level, 7 g/dL; platelet count, 2.7×10^5 platelets/mm^3; serum creatinine level, 0.9 mg/dL; aspartate aminotransferase level, 249 U/L; alanine aminotransferase level, 27 U/L; total bilirubin level, 6 mg/dL; indirect bilirubin level, 0.5 mg/dL; and lactate dehydrogenase level, 3900 U/L. A CT scan of the abdomen showed a fluid collection at the splenectomy site. The patient was admitted to the intensive care unit and began receiving piperacillin-tazobactam therapy as well as therapy with high-dose steroids for his acute hemolytic episode. The fluid collection was drained, his clinical condition improved, and antibiotic therapy was continued for a total of 14 days. The results of cultures of blood, urine, and fluid samples remained negative. Immunosuppression with prednisone, 40 mg b.i.d., was continued in an attempt to control his hemolysis.

Two weeks after the completion of antibiotic therapy, the patient developed an erythematous rash on his chest and abdomen, fever, shortness of breath, and diarrhea. A chest radiograph showed new bilateral patchy infiltrates, and the CT scan of the chest revealed bilateral nodular densities consistent with an inflammatory process. The results of cultures of blood, sputum, urine, and stool samples remained negative, but examination for ova and parasites revealed *Strongyloides stercoralis* larvae in stool and sputum samples. The appearance of a skin biopsy specimen from the site of the rash was consistent with *Strongyloides* hyperinfection. The patient received 2 doses of ivermectin as well as vancomycin, ciprofloxacin, and metronidazole for a total of 7 days, with marked improvement in symptoms. The results of an HIV antibody test were negative.

On day 45 of hospitalization, the patient became febrile (temperature, 39.4°C [103°F]), agitated, and disoriented; signs of meningismus were not evident on examination. A lumbar puncture was performed. The opening pressure was 250 mm Hg, and analysis of CSF revealed the following values: WBC count, 289 cells/mm^3 (50% segmented neutrophils and 48% lymphocytes); glucose level, 18 mg/dL; and protein level, 195 mg/dL. The findings of an examination of the CSF for ova and parasites were normal. The patient was given ampicillin, ceftazidime, and vancomycin for possible bacterial meningitis. The results of serial cultures of blood samples remained negative. Two days later (hospital day 47), the culture of the CSF specimen yielded VREF. By use of the Kirby-Bauer disk method, the isolate was found to be resistant to ampicillin, vancomycin, minocycline, and levofloxacin and sensitive to chloramphenicol, quinupristin-dalfopristin, and linezolid. The MICs of chloramphenicol and linezolid were reported to be <4 μg/mL and 1–2 μg/mL, respectively, by use of the E-test. Therapy with ampicillin, ceftazidime, and vancomycin was discontinued, and the patient began to receive iv chloramphenicol, 750 mg given every 6 h. A 7-day course of albendazole was initiated at this time, despite the negative results of a stool examination for *Strongyloides* species. A transthoracic echocardiogram showed no valvular abnormality or vegetation. A head CT scan without contrast was unremarkable.

The patient's clinical condition did not improve after 2 days of chloramphenicol therapy. On hospital day 49, the results of analysis of fluid obtained from a second lumbar puncture were still positive for VREF, with MICs that were similar to the initial isolate. Therapy with iv linezolid, 600 mg every 12 h, was added at this time. Because the patient's thrombocytopenia worsened, chloramphenicol was discontinued 4 days later (hospital day 53), and the patient's platelet count stabilized. The results of repeated analyses of CSF showed improvement, and the results of cultures of CSF samples remained negative after the addition of linezolid (table 1). The increase in RBCs in the CSF that had been observed in lumbar punctures performed at follow-up was attributed to procedural trauma in the setting of thrombocytopenia. Linezolid was well tolerated, and the patient's clinical condition markedly improved. Intravenous linezolid was continued for a total of 28 days. The levels of linezolid in the plasma and CSF were determined 7 and 21 days into linezolid therapy. After completion of therapy, the patient remained asymptomatic, with no recurrence of VREF infection. Follow-up CSF analysis that was performed 10 days after linezolid was discontinued revealed the following values: WBC count, 5 cells/mm^3 (12% neutrophils and 78% lymphocytes); glucose level, 72 mg/dL; and protein level, 24 mg/dL.

DISCUSSION

Enterococci occur naturally among the normal flora in the human gastrointestinal tract. Initially thought to be harmless commensal organisms in hospitalized patients, enterococci have emerged as significant nosocomial pathogens. Enterococci are intrinsically resistant to several antibiotics and possess the ability to acquire resistance through the exchange of genetic material [7]. As a result, they have become more resistant to multiple antibiotics. Resistance to vancomycin increased 43% in 1999, compared with the 5-year period that ended in 1998 (NNIS semiannual report, 1999; at http://www.cdc.gov/ncidod/hip/SURVEILL/NNIS.HTM). In 1997, the Surveillance Network database reported that 52% of *E. faecium* isolates were resistant to vancomycin [7]. Colonization and infection with vancomycin-resistant enterococci are associated with prolonged hospitalization, exposure to cephalosporins and vancomycin, and the use of antianaerobic agents [6]. Cases of nosocomial transmission have been reported [6].

Enterococci are unusual etiologic agents of bacterial meningitis. In a review of 151 cases of nosocomial meningitis, entero-

Table 1. Drug therapy and results of analysis of the CSF for a patient with vancomycin-resistant *Enterococcus faecium* (VREF) meningitis.

	Day of hospitalization								
Drug or laboratory value	45	47	49	50	53	58	71	77	88
Ampicillin	X								
Ceftazidime	X								
Vancomycin	X								
Chloramphenicol		X	X	X	X				
Linezolid			X	X	X	X	X	X	
Results of culture for VREF	+			+	−	−	−		−
WBC count, cells/mm^3	289			403	215	100	15		5
Neutrophils, %	50			3	2	5	1		12
RBC count, cells/mm^3	32			1	2910	5000	75		1
Glucose level, mg/dL	18			76	94	41	66		72
Protein level, mg/dL	195			86	163	57	34		24

NOTE. X, drug used for therapy; +, positive; −, negative.

cocci accounted for only 3% of the cases [8]. Enterococcal meningitis tends to occur in patients with chronic medical conditions that are often associated with the use of immunosuppressive therapy, underlying CNS disease (trauma, surgery, and epidural catheter), gastrointestinal pathology, and *Strongyloides* species [3]. The typical presentation of enterococcal meningitis is rapid onset of fever, signs of meningeal irritation, and altered sensorium, but a subacute presentation has also been described [3, 9]. CSF findings are usually consistent with infection demonstrated by pleocytosis with neutrophil predominance, elevated protein levels, and hypoglycorrhachia [3]. The mortality rate of patients with enterococcal meningitis is high, ranging from 13% to 33% [3, 10]. Most cases of enterococcal meningitis are caused by *Enterococcus faecalis. E. faecium* is responsible for only 10% of the cases of enterococcal meningitis, but it poses a treatment challenge, because the rates of resistance to ampicillin and vancomycin are increasing. An association of *E. faecium* meningitis with *Strongyloides* hyperinfection has been reported [3, 11, 12]. The presumed pathogenesis is enterococcal bacteremia originating from the gastrointestinal tract with secondary seeding of the meninges [13].

A total of 9 cases of VREF meningitis have been reported in the literature (table 2). At the 1999 meeting of the Infectious Diseases Society of America, a case report describing a patient with VREF meningitis who was treated with linezolid (with limited follow-up) was presented [12]. All 9 previously reported cases occurred in a nosocomial setting. The age of the patients ranged from 16 days to 71 years. The most common underlying conditions and causes were shunt infections ($n = 3$), neurosurgery ($n = 1$), chemotherapy ($n = 1$), gastrointestinal disease ($n = 1$), HIV ($n = 1$), and aspergillosis ($n = 1$). Concurrent VREF bacteremia was reported in 3 cases. The initial CSF profiles of the reported cases and of our patient were consistent with bacterial meningitis and were usually characterized by pleocytosis with neutrophilic predominance, a low glucose level ($\leqslant$45 mg/dL), and a high protein level (>170 mg/dL).

Different agents in various combinations have been used to treat patients with VREF meningitis, including teicoplanin, chloramphenicol, rifampin, clindamycin, streptomycin, penicillin, amikacin, and quinupristin-dalfopristin in various combinations. Chloramphenicol, which was chosen as the initial agent for the patient we studied, has good CSF penetration but is bacteriostatic against enterococci and is associated with hematologic adverse effects. There are case reports describing patients with VREF meningitis who were treated with chloramphenicol for whom this agent failed to sterilize the CSF and resulted in poor clinical outcomes [16, 18, 20]. Optimal therapy for vancomycin-resistant *Enterococcus* and VREF meningitis has not been established. Recent clinical experience with newer agents suggests that these agents may be preferred in the treatment of patients with VREF CNS infections.

To our knowledge, this is the first published description of a patient with VREF meningitis who was successfully treated with linezolid. Linezolid is an oxazolidinone antibiotic that has recently been approved for management of complicated and uncomplicated skin and soft-tissue infections, community- and hospital-acquired pneumonia, and drug-resistant, gram-positive infections, including infections with vancomycin-resistant enterococci. Linezolid, like other available agents with activity against vancomycin-resistant enterococci, is bacteriostatic, with a MIC of $\leqslant 4$ μg/mL. Pharmacokinetic studies have demonstrated that linezolid distributes well into tissues. Steady-state concentrations are achieved after 2–4 doses. In healthy volunteers, serum levels ($\pm$SD) reported with iv dosing, 600 mg b.i.d., have a maximum concentration (C_{max}) of ~15.1 $\pm$ 2.52 μg/mL and a minimum concentration (C_{min}) of ~3.7 $\pm$ 2.36

Table 2. Summary of reported cases of vancomycin-resistant *Enterococcus faecium* (VREF) meningitis.

Patient	Age, sex	Underlying condition(s)	Isolates from cultures of CNS samples	Other culture-positive site	CSF profile	Previous unsuccessful therapy	Therapy for VREF infection (duration, days)	Outcome	Duration of follow-up, months	Reference
1	16 d, NA	Necrotizing enterocolitis	VREF	Blood	WBC count, 3.8×10^5 cells/mm^3; RBC count, 1.6×10^4 cells/mm^3		iv Chl, 75 mg/kg/d; iv Quin-Dalf, 7 mg/kg/d (13)	Cured		[14]
2	3 mo, F	Ventriculoperitoneal shunt	VREF	—	WBC count, 5.3×10^2 cells/mm^3 (36% neutrophils); protein level, 438 mg/dL; glucose level, 22 mg/dL	Amp-Sulb; Gm	iv Chl, 100 mg/kg/d (21)	Cured	4	[15]
3	8 mo, F	CNS shunt	VREF	—	WBC count, 58 cells/mm^3; RBC count, 81 cells/mm^3; glucose level, 4 mg/dL; protein level, 217 mg/dL	Chl	IT Quin-Dalf, 1 mg q.d.; iv Quin-Dalf, 7.5 mg/kg q8h (28)	Cured	8	[16]
4	6 y, M	S/p frontal and temporal grid removal and cortical resection	VREF	—	WBC count, 8.8×10^3 cells/mm^3 (83% neutrophils); glucose level, <20 mg/dL; protein level, 678 mg/dL		IT Teic, 10 mg; iv Rif, 15 mg/kg/d; iv Stm, 20 mg/kg/d (changed to iv Cm, 40 mg/kg/d) (14)	Cured	8	[17]
5	23 y, M	Ventriculoperitoneal shunt	VREF	—		Chl	IT Quin-Dalf, 2 mg (5); iv Quin-Dalf, 7.5 mg/kg q8h; iv Chl, 1 g q6h (10)	Died		[18]
6	29 y, M	None	VREF and *A. calcoaceticus*	—	WBC count, 8×10^6 cells/mm^3 (60% neutrophils); RBC count, 4×10^6 cells/mm^3; glucose level, 31 mg/dL; protein level, 238 mg/dL		iv Chl, 1 g q6h (10)	Cured	2	[19]
7	42 y, F	CML s/p bone marrow transplant	VREF	Peripheral and catheter blood	WBC count, 60 cells/mm^3 (78% neutrophils); protein level, 234 mg/dL	Chl	iv Quin-Dalf, 7.5 mg/kg q8h (12)	Died		[20]
8	63 y, F	HIV infection	VREF	—	WBC count, 15 cells/mm^3 (91% neutrophils); RBC count, 2.1×10^3 cells/mm^3; glucose level, 45 mg/dL		iv Pen, 4 million units q4h; iv Amik, 500 mg q12h (5)	Died		[21]
9	71 y, F	Invasive aspergillosis	VREF	Blood			iv Quin-Dalf, 7.5 mg/kg q8h (22)	Died		[22]
10	69 y, M	Steroids, strongyloides	VREF	—	WBC count, 289 cells/mm^3; RBC count, 32 cells/mm^3; glucose level, 18 mg/dL; protein level, 195 mg/dL	Chl	iv Lin, 600 mg q12h (28)	Cured	6	This report

NOTE. *A. calcoaceticus, Acinetobacter calcoaceticus;* Amik, amikacin; Amp-Sulb, ampicillin-sulbactam; Chl, chloramphenicol; Cm, clindamycin; CML, chronic myelogenous leukemia; d, day(s); IT, intrathecal; Lin, linezolid; mo, month(s); NA, not available; Pen, penicillin; Quin-Dalf, quinupristin-dalfopristin; Rif, rifampin; s/p, status post; Stm, streptomycin; Teic, teicoplanin; VREF, vancomycin-resistant *Enterococcus faecium;* y, year(s).

μg/mL, with an estimated half-life of 4.8 $\pm$ 1.7 h [23]. Similar concentrations are achieved with orally administered doses.

In healthy volunteers with noninflamed meninges, linezolid concentrations in the CSF were 70% of plasma concentrations (Pharmacia & Upjohn, data on file). The concentrations of linezolid that are achievable in the CSF of patients with meningitis are unknown. Concentrations in plasma and corresponding CSF samples were determined in our patient by use of HPLC and HPLC coupled with mass spectrometry, respectively (performed by Pharmacia & Upjohn, Kalamazoo, Michigan). One week into the course of therapy, the level of linezolid in the plasma that was obtained 7 h after the dose was administered was reported to be 7.32 μg/mL; the corresponding level in the CSF was reported to be 5.4 μg/mL (74% of plasma concentration). This degree of CSF penetration is comparable to that reported in healthy volunteers. It is unknown to what extent steroids might have decreased the CSF penetration of linezolid in our patient.

Additional samples were obtained 3 weeks after the start of linezolid therapy. At this time, the linezolid plasma C_{min} and C_{max} were reported to be 12.1 μg/mL and 25.9 μg/mL, respectively. The level of linezolid in the CSF corresponding to the plasma C_{max} was 12.5 μg/mL. Assuming an instantaneous equilibrium between plasma and CSF, these levels can be extrapolated to a linezolid CSF C_{min} of ~6 μg/mL. Although these levels must be interpreted with caution, the linezolid concentrations in both the plasma and the CSF remained greater than the MIC. This is important, considering the in vitro time-dependent killing exhibited by linezolid. This patient's adequate systemic exposure and CSF penetration may have been important factors in the resolution of this infection, and the patient's outcome holds promise for the role of linezolid in the treatment of patients with meningitis caused by resistant gram-positive organisms.

Although formal clinical studies are necessary, linezolid appears to be a promising new antimicrobial agent for the treatment of patients with vancomycin-resistant enterococcal CNS infections. Enterococcal resistance to linezolid, however, has already been reported in clinical trials [24]. In vitro, linezolid resistance occurs at a frequency of 1×10^{-9} to 1×10^{-11} with point mutations in the 23S rRNA [23]. The control of vancomycin-resistant enterococci and the emergence of resistance to newer agents will rely on judicious use of antibiotics, improved surveillance, and the development of new drugs that will target these resistant pathogens.

Our case report highlights 3 interesting aspects of resistant enterococcal infections for the clinician, including the nosocomial nature of meningitis due to vancomycin-resistant enterococci, its association with *Strongyloides* hyperinfection, and linezolid as a new treatment option for CNS infections with this pathogen.

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