

# 리네졸리드로 치료한 반코마이신 내성 *Enterococcus faecium* 뇌수막염: 증례보고 및 문헌고찰

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## Vancomycin-Resistant *Enterococcus faecium* Meningitis Treated with Linezolid: A Case Report and Review of the Literature

Vancomycin-resistant enterococci (VRE) infection is a serious problem because optimal therapy has not been established. Different agents in various combinations, including teicoplanin, chloramphenicol, and quinupristin/dalfopristin, have been used to treat patients with VRE meningitis, but the efficacy of these agents is not satisfactory because of their limited ability to penetrate into the cerebrospinal fluid. We report a case of nosocomial vancomycin-resistant *Enterococcus faecium* meningitis in a patient with ventriculoperitoneal shunt that was successfully treated with linezolid. We will also review previously reported cases of vancomycin-resistant *E. faecium* meningitis treated by linezolid.

**Key Words :** Vancomycin, *Enterococcus faecium*, Meningitis, Linezolid

## Introduction

*Enterococci* continue to be an unusual pathogen of bacterial meningitis. *Enterococcal meningitis* is associated with a high mortality rate, reaching up to 33%(1). Vancomycin-resistance rate of *Enterococcus faecium* has risen significantly, but this rate in Korea differ significantly from that of western countries because of the different types of selective pressure or patterns of nosocomial spread (2). Linezolid, the first available oxazolidinone for clinical use, has been shown to be effective in treating serious methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) infections (3). Herein, we report a case of vancomycin-resistant *E. faecium* (VREF) meningitis secondary to infected ventriculoperitoneal (VP) shunt, which was successfully treated with linezolid, along with a review of previous reported cases of VREF meningitis treated by linezolid.

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## Case Report

A 57-year-old man visited our emergency department due to intermittent fever and decline of consciousness that had been present for two weeks. The patients received a craniotomy with VP shunt to remove hematoma for acute epidural, subdural, and intracerebral hemorrhage caused by traffic accident three months ago. On admission, the patient's body temperature was 37.5°C, blood pressure 115/80 mmHg, pulse rate 93/min, and respiration rate 30/min. Cerebrospinal fluid (CSF) analysis revealed WBC 185 cells/mm<sup>3</sup> (80% neutrophils and 20% lymphocytes), protein 20.5 mg/dL, and glucose 60 mg/dL (serum glucose, 108 mg/dL). The shunt catheter was removed, and vancomycin was introduced. No microorganism was cultured from the tip of the shunt catheter. After treatment with vancomycin for two weeks, fever subsided and CSF pleocytosis with neutrophil dominance almost normalized. Therefore, VP shunt was placed again 8 weeks later.

On the 136th day from his first visit for treatment of meningitis, the body temperature rose to over 38.5°C and the patient became nervous and grew restless again. Erythematous swelling of the skin at abdominal insertion site of VP shunt was detected, and subcutaneous abscess formation was confirmed on ultrasonography. Surgical incision and drainage of the abscess was performed. The drained fluid was a mixture of pus and peritoneal fluid. Because fever was persistent for 6 days despite complete drainage of the abscess, lumbar puncture was performed. Analysis of CSF revealed WBC 1,346 cells/mm<sup>3</sup> (90% neutrophils and 10% lymphocytes), protein 123 mg/dL, and glucose 24 mg/dL (serum glucose, 121 mg/dL). The culture of the CSF and another peritoneal fluid specimen yielded VREF with a minimal inhibitory concentration (MIC) of >32 µg/mL vancomycin by VITEK (BioMerieux, Hazelwood, MO, USA). The isolate was found to be resistant to vancomycin and teicoplanin by the Kirby-Bauer disk diffusion method. Ceftriaxone and levofloxacin were

changed to meropenem (1 g every 8 hours) and quinupristin/dalfopristin (7.5 mg/kg every 8 hours). After 5 days of quinupristin/dalfopristin treatment, his clinical condition did not improve and subsequent CSF cultures were still positive for VREF. Intravenous linezolid, 600 mg every 12 hours, was challenged (Table 1). The patient's clinical status progressively improved, and subsequent CSF cultures became negative after linezolid treatment for 5 days. Intravenous linezolid was continued for 12 days and then changed to oral linezolid (600 mg every 12 hours) for additional 10 days. Linezolid was well tolerated, and adverse effects such as nausea, vomiting, skin rash, and bone marrow suppression were not observed. After successful treatment of meningitis using linezolid, the patient was operated to remove VP shunt after 3 months and remained stable with no recurrence of VREF infection for 2 years.

## Discussion

Enterococci have become a common pathogen for nosocomial infections of the urinary tract, wound, bloodstream, heart, and rarely, meninges (1). Enterococci are naturally resistant to several antibiotics and possess the ability to acquire resistance through the exchange of genetic material (4).

A total of 7 cases of VRE meningitis treated by linezolid have been reported in the literature, in addition to the present case (5–12) (Table 2). The median age was 59.5 years and the six of them were male. Of them, 7 cases were cured and only one died. Underlying diseases included 3 ventriculostomy, 2 VP shunt, and 3 steroid users. The median duration of treatment was 21.5 days. The median WBC, glucose, and protein levels were 875 cells/mm<sup>3</sup>, 24 mg/dL, and 243 mg/dL, respectively. There is also one report that the VREF meningitis was successfully treated with linezolid in Korea (12).

**Table 1.** Summary of Antibiotic Therapy and the Results of CSF Analysis during Admission

Admission day		1st	8th	136th	140th	145th	147th	164th
Antibiotics		VAN	VAN	MRP+ SYN	Lin	Lin	Lin	Lin
Serum	WBC	8800	7500	10400	6300	4300	3300	56
CSF	Culture	Negative	Negative	VREF	VREF	Negative	Negative	Negative
	RBC (/mm <sup>3</sup> )	2	20	11	11	8	11	5
	WBC (/mm <sup>3</sup> )	185	3	1346	1280	35	8	2
	Neutrophil (%)	80	0	90	95	70	0	0
	Lymphocyte (%)	20	0	10	5	30	0	0
	Protein (mg/dL)	20	19	123	136	86	55	22
	Glucose (mg/dL)	60	63	24	40	34	40	53

VAN, vancomycin; MRP, meropenem; SYN, synercid(quinupristin/dalfopristin); Lin, linezolid

**Table 2.** Summary of Reported Cases of Vancomycin-resistant *Enterococcus faecium* (VREF) meningitis Treated with Linezolid

Patients	Age (year)	Sex	Underlying disease	CSF profile	Therapy for VREF infection (duration, days)	Outcome	Reference
1	56	F	Ventriculostomy	WBC 1200 cells/mm <sup>3</sup> ; glucose 25 mg/dL; protein 155 mg/dL	Lin, 600 mg q 12h (42), IV	Cured	5
2	69	M	Steroid, tronyloides	WBC/RBC 289/32 cells/mm <sup>3</sup> ; glucose 18 mg/dL; protein 195 mg/dL	Lin, 600 mg q 12h (28), IV	Cured	6
3	62	M	Ventriculostomy	WBC 550 cells/mm <sup>3</sup> ; glucose 103 mg/dL; protein 58 mg/dL	Lin, 600 mg q 12h (21), Gen 5 mg q 12h (5), , IV	Died	7
4	35	M	Ventriculostomy	WBC/RBC 62/575 cells/mm <sup>3</sup>	Lin, 600 mg q 12h (28), IV	Cured	8
5	69	M	Steroids, COPD	WBC/RBC 1300/100 cells/mm <sup>3</sup> ; glucose 24 mg/dL; protein 565 mg/dL	Lin, 600 mg q 12h (14), IV	Cured	9
6	6 wk	F	VP shunt	WBC 1957 cells/mm <sup>3</sup> ; glucose < 20 mg/dL; protein 496 mg/dL	Lin, 10 mg/kg q 8h (21) and 12 mg/kg q 8h (14), IV	Cured	10
7	82	M	Steroid, COPD	WBC 12,300 cells/mm <sup>3</sup> ; glucose 28 mg/dL; protein 291 mg/dL	Lin and ampicillin (21), IV	Cured	11
8	57	M	VP shunt	WBC/RBC 185/2 cells/mm <sup>3</sup> ; glucose 60 mg/dL; protein 20 mg/dL	Lin, 600 mg q 12h (22), IV	Cured	this study

COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; RBC, red blood cell count; IV, intravenous; Lin, linezolid; Gen, gentamicin; VP shunt, ventriculoperitoneal shunt; Lin, linezolid; Gen, gentamicin

VREF meningitis has rarely been documented (5–8) and represents a therapeutic challenge because of limited treatment options (13). Chloramphenicol, which was chosen as the initial agent, has good CSF penetration but it is bacteriostatic against enterococci and associated with serious hematologic adverse effects. There are case reports describing patients with VREF meningitis who were treated with chloramphenicol, which failed to sterilize the CSF resulting in poor clinical outcomes (14, 15). Quinupristin/dalfopristin has been approved by the U.S. Food and Drug Administration for treatment of severe VREF infection. There are several reports that VRE meningitis was successfully treated with quinupristin/dalfopristin (14–17). However, in most cases, quinupristin/dalfopristin was administered intravenously and intraventricularly because of its poor CSF penetration (14–18).

Linezolid, like other available agents that have activity against VRE, is bacteriostatic. Pharmacokinetic studies have shown that linezolid distributes well into the tissues (6). In healthy volunteers without meningitis, linezolid concentrations in the CSF were 70% of plasma concentrations (6). In patients with meningitis, linezolid concentrations in the CSF was over 70% of plasma concentrations (6). In our case, intravenous linezolid was changed to oral form because the patient was very stable clinically, VREF was not cultured from the CSF, and bioavailability of linezolid was known to be excellent (6).

Although only very few clinical cases have been reported, linezolid appears to be an excellent antimicrobial agent for the treatment of central nervous system infections caused by VRE.

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