Successful Treatment of Vancomycin-Resistant Enterococcus faecium Bacteremia with Linezolid after Failure of Treatment with Synercid (Quinupristin/Dalfopristin)

The emergence of vancomycin-resistant Enterococcus faecium (VRE) as an increasingly common cause of nosocomial infections has spurred renewed interest in the development of novel antimicrobial agents [1]. Quinupristin-dalfopristin (Synercid, Rhône-Poulenc Rorer, Paris) is a combination of 2 chemically distinct streptogramins, streptogramin A (dalfopristin) and streptogramin B (quinupristin), which act synergistically to inhibit bacterial protein synthesis [2]. Synercid has bactericidal activity against most drug-resistant staphylococci, streptococci, and pneumococci; appears to be bacteriostatic against E. faecium; and is not active against Enterococcus faecalis [2, 3].

Linezolid (Pharmacia & Upjohn, Piscataway, NJ) is an oxazolidinone analogue, the first of a novel antimicrobial class that inhibits bacterial protein synthesis. Linezolid demonstrates bacteriostatic activity against gram-positive organisms, including vancomycin-resistant strains of E. faecium and E. faecalis [4, 5].

We describe a patient with persistent bacteremia due to VRE who was successfully treated with linezolid after the failure of prolonged treatment with Synercid, initially in combination with chloramphenicol and later with doxycycline.

A 51-year-old man with acute myelogenous leukemia underwent a matched, unrelated-donor bone marrow transplantation on 2 April 1998. His immediate posttransplantation course was uneventful, but on 16 April he developed left-arm swelling, and a Doppler ultrasonographic examination demonstrated a left-subclavian deep venous thrombosis that was believed to be secondary to a central venous catheter. The catheter was removed, and systemic urokinase therapy was initiated but discontinued in <24 h because of nosebleed.

Two sets of blood cultures from 16 April yielded VRE. Therapy with iv Synercid (575 mg every 8 h) was begun on 24 April. The organism was susceptible by Kirby-Bauer testing. Chloramphenicol (1 g every 6 h) was given from 22 April to 30 April (figure 1).

Engraftment and defervescence occurred on 26 April, and blood cultures remained negative until 7 May, when they again showed VRE (figure 1). Transesophageal echocardiography showed no cardiac vegetations, and an indium-111-labeled WBC scan revealed no uptake. Administration of chloramphenicol was started again on 11 May, and on 5 June doxycycline (100 mg every 12 h) was added to the regimen. Blood cultures continued to yield VRE.

On 8 June, upper gastrointestinal bleeding and Clostridium difficile colitis were documented. Multiple cultures of blood again yielded VRE. A venogram demonstrated progression of the left-subclavian thrombus with extension to the innominate, axillary, and internal jugular veins; MRI showed occlusion of the left great veins and extension into the right subclavian and

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Relationship between antimicrobial therapy and blood cultures yielding vancomycin-resistant enterococci (VRE) in a bone marrow transplantation (BMT) patient who developed septic thrombophlebitis following placement of a Hickman catheter. Cm, clindamycin; Chl, chloramphenicol; Czid, ceftazidime; Dox, doxycycline; Gm, gentamicin; Imi, imipenem; Vm, vancomycin; +, 2 sets of blood cultures positive for VRE; −, 2 sets of blood cultures negative for VRE; †, time of marrow engraftment.
axillary veins. Repeated transesophageal echocardiography and labeled WBC scanning failed to identify an alternative source of the bacteremia.

Surgery and radiology consultants determined that no surgical or angiographic therapeutic option existed, given the extensive thrombus and the patient’s persistent, refractory thrombocytopenia.

From 16 to 29 June, all 16 sets of blood cultures that were performed yielded VRE; at that point the patient was receiving Synercid and doxycycline. On 30 June, Synercid and doxycycline were withdrawn, and administration of iv linezolid (600 mg every 12 h) was initiated. The MICs of linezolid and Synercid against the isolate recovered on 16 June were each 1 μg/mL.

Blood cultures remained positive for VRE until 8 July; 22 sets of blood cultures performed between 9 July and 20 December yielded no growth. The patient received iv linezolid for 6 weeks, followed by oral linezolid for 6 weeks, until 30 September 1998, when therapy was stopped. He remained well at his last follow-up visit, on 28 July 1999.

This patient had persistent bacteremia for 12 weeks. The presumed source of infection was the central venous thrombus. Preferred treatment would have been removal of the thrombus, but this was believed to be impossible, given its extent and the patient’s thrombocytopenia. Throughout this illness, he had few systemic symptoms and no embolic events occurred.

Synercid had been used in appropriate dosages for ~10 weeks, and chloramphenicol and doxycycline, often used to treat infections due to VRE, had been added. It is surprising that this infection was not cured with Synercid, which has been noted to cure prosthetic valve endocarditis caused by VRE [6]. Combining Synercid with doxycycline has resulted in enhanced killing of VRE in a simulated endocardial vegetation model in vitro [7]. The VRE infecting our patient remained susceptible to Synercid 2 months into therapy, a circumstance suggesting that treatment failure was not related to the development of resistance.

Linezolid, generally considered to be bacteriostatic [8], finally cleared this patient’s bacteremia. Noskin et al. also reported cure of persistent bacteremia due to VRE, but they added gentamicin to the regimen of linezolid [9]. Linezolid has not been studied with regard to the treatment of endocarditis, and no studies have examined the penetration of linezolid into intravascular lesions. The rapid clearance of this patient’s bacteremia in the continued presence of extensive intravascular thrombus could potentially be explained by superior penetration of linezolid (over that of Synercid) into the clot.

Shelly A. McNeil,¹ Nina M. Clark,¹
P. H. Chandrasekar,² and Carol A. Kauffman¹
From the ¹Division of Infectious Diseases, Department of Internal Medicine, Veterans Affairs Healthcare System, University of Michigan Medical School, Ann Arbor; and ²Division of Infectious Diseases, Department of Internal Medicine, Wayne State University Medical Center, Detroit, Michigan

References