Successful Treatment of Vancomycin-Resistant Enterococcus Ventriculitis in a Child

Paulo Sérgio Lucas da Silva, Henrique Monteiro Neto and Lílian Márcia Sejas
Pediatric Intensive Care Unit, Department of Pediatrics, State Hospital of Diadema, Federal University of São Paulo; São Paulo, SP, Brazil

Enterococci are an uncommon cause of CNS infection. A 20 month-old boy, diagnosed with hydrocephalus with ventriculoperitoneal shunt and history of lengthy hospitalization and use of wide spectrum antibiotics, was admitted to the pediatric intensive care unit diagnosed with ventriculitis. On the 14th day of empirical antibiotic therapy (vancomycin and meropenem) the child presented fever while the CSF sample culture evidenced vancomycin-resistant *Enterococcus faecium*. The patient received intravenous linezolid achieving cerebrospinal fluid sterilization. Conclusion: Intravenous linezolid appears to be a safe and effective therapy for vancomycin-resistant enterococcus ventriculoperitoneal shunt infection.
Key-Words: Vancomycin, resistance, treatment.

Enterococci are known for causing urinary tract infection, infections of surgical wounds, nosocomial bacteremia, infectious endocarditis and, rarely, central nervous system infections [1]. Over the past decade, enterococcus has become a significant nosocomial pathogen, particularly given their resistance to multiple antimicrobial agents, and thus represents a challenge due to the limited therapeutic options available [2].

Only a few studies [3-9] have reported the use of linezolid in the treatment of central nervous system infection by vancomycin-resistant enterococcus (VRE), and only one case reported a pediatric patient [4]. The present study described treatment of ventriculitis caused by vancomycin-resistant enterococcus in an infant with multiple comorbidities.

Case Report

A 20 month-old boy, with underlying diagnosis of neurodevelopmental delay and hydrocephalus with ventriculoperitoneal shunt (VPS) secondary to *Pneumococcus meningitis* at 6 months of life, presented a cardiorespiratory arrest on his arrival in hospital, and was then resuscitated over 23 minutes. The infant remained hospitalized for 10 days within the pediatric intensive care unit (PICU), diagnosed with aspirative pneumonia and cardiogenic shock, receiving oxacillin and ceftriaxone.

On the 18th day, the patient was readmitted to the PICU with a diagnosis of septic shock due to central venous catheter-related infection, being discharged from the PICU on the 7th day, having received vancomycin and cefepime for a total of 3 weeks. On the 39th day he was readmitted to the PICU diagnosed with ventriculitis. The cerebrospinal fluid (CSF) sample obtained by reservoir puncture revealed 71 cells/mm^3 (72% neutrophils; glucose 13 mg/dL and protein 69 mg/dL). Cultures were negative. The patient received external ventricular drain associated with vancomycin and meropenem empirically for 4 weeks, undergoing a VPS on the 30th PICU day. On the 14th postoperative (PO) day, the patient developed perivalvular abscess, the CSF obtained from the shunt reservoir presented 74 cells/mm^3 (79% neutrophils), upon which the patient was submitted to external ventricular shunt (EVS) whilst vancomycin and meropenem were resumed. On the 6th PO day after EVS, fluconazole was associated due to the presence of yeast in a routine CSF sample. Cultures for fungus were negative. On the 14th day of antibiotic therapy, the patient evolved with fever (39ºC), presenting the following laboratorial exams: white blood cells (WBC) 23,000/mm^3, platelets 156,000/mm^3, C-reactive protein 20 mg/dL, CSF with 15 cells (90% neutrophils), glucose 45 g/dL, protein 910 g/dL, Gram stain showed Gram-positive cocci in chains, and 2 serial CSF cultures yielded *Enterococcus faecium* resistant to vancomycin, ampicillin, streptomycin, ciprofloxacin, chloramphenicol and susceptible to gentamicin. The vancomycin minimum inhibitory concentration (MIC) of this isolate was > 32 μg/mL (using an E-test method with an inoculum density of 0.5 McFarland standard). Based on this information, he was switched to linezolid monotherapy, dosed at 10 mg/kg intravenously every 8 hours.

Following the 2nd day of linezolid, the patient became afebrile, and after the 3rd day had sterile CSF. Following 4-week treatment with linezolid, the patient had a new VPS in place (CSF: 1 cell/mm^3, glucose 54 g/dL and protein 90 g/dL) and C-reactive protein of 1.78 mg/dL. Treatment continued for a further 2 weeks, during which time CSF samples remained sterile. Concentrations of linezolid in CSF were not recorded. The patient tolerated the 6-week treatment without showing evidence of bone marrow suppression. Fecal cultures obtained during treatment with linezolid were negative. The patient evolved requiring ventilation assistance due to neurologic compromise, and was cared for in an intermediate care unit.

Discussion

The emergence of nosocomially acquired vancomycin-resistant enterococci has become a significant concern and a treatment challenge to physicians [3]. Approximately 12% to 18% of enterococci in the United States exhibit vancomycin resistance [3].

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Address for correspondence: Dr. Paulo Sérgio Lucas da Silva. Rua Aroeiras 30 apt. 22, Santo Andre, São Paulo, Brazil. Zip code: 09090-000. Phone/Fax number: +55 11 32889928. E-mail: psls.nat@terra.com.br.

Risk factors for vancomycin-resistant enterococcus (VRE) colonization in children include young age, use of invasive devices, antimicrobial drug administration, immunosuppression, low birth weight, and underlying malignancy [10]. Such patients have commonly been treated with vancomycin or broad-spectrum antibiotics before VRE isolation [11]. Two important factors predisposing patients to VRE infection are the percentage of hospital days receiving antimicrobial therapy of any type and the number of days receiving intravenous vancomycin [7]. Our patient had received several weeks of broad-spectrum antibiotics before developing VRE meningitis; this prolonged use of antibiotics, associated with the long stay in hospital were likely contributory factors in both colonization and subsequent infection with VRE. However, treatment with lengthy courses of broad-spectrum antibiotics is often unavoidable in critically ill patients.

The National Nosocomial Infections Surveillance system of the Centers for Disease Control and Prevention reported vancomycin resistance in 28.5% of nosocomial enterococcal intensive care unit infections in 2003 [12]. In a recent study, 14% of VRE-colonized patients progressed to infection within 15 days of a positive surveillance culture [13]. A recent review noted that, although *Enterococcus faecalis* is responsible for 80% of enterococcal infections, *E. faecium* strains account for 98% of vancomycin-resistant cases [14].

There are no established guidelines for the treatment of central nervous system infection caused by VRE. Therapeutic options for vancomycin-resistant enterococci are limited because these organisms are usually resistant to multiple antimicrobial agents. Treatment often has to include investigational drugs or less tested new drugs. In our patient the therapy included intravenous linezolid. To the best of our knowledge, there has only been 1 previous case report of ventriculitis due to enterococcus in a child treated successfully with linezolid [4].

Linezolid, the first member of the oxazolidinones class of antibiotics licensed by the U.S. Food and Drug Administration (FDA), inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. It is approved for use in adults and children for serious infections caused by *Enterococcus faecium* or *Enterococcus faecalis* including vancomycin-resistant strains (VRE), *Staphylococcus aureus* including methicilllin-resistant strains (MRSA), coagulate-negative staphylococci and streptococci including penicillin-resistant *Streptococcus pneumoniae* [15]. Linezolid is essentially bacteriostatic. *In vitro* time-kill experiments against multidrug-resistant (including vancomycin-resistant) enterococci, linezolid was not bactericidal but had greater bacteriostatic activity against these organisms [16].

CSF penetration of linezolid suggests utility in treatment of meningitis and intracranial prosthetic device infections. In individuals with noninflamed meninges, linezolid concentrations in CSF were 70% of plasma concentrations [17]. In adults, reversible thrombocytopenia is the major hematologic consequence of linezolid use, generally occurring after ≥ 2 weeks of treatment and thought to be due to transient bone marrow suppression. In children, thrombocytopenia is less common; however, a complete blood count should be monitored weekly while children are receiving linezolid [17]. In adults, linezolid-induced neuropathy has been reported among patients receiving the drug for > 6 months.

Vancomycin and aminoglycosides with variable penetration of the blood-brain barrier and monitoring CSF levels is recommended. Intraventricular administration of antimicrobials with irregular penetration of blood-brain barrier makes theoretical sense but is controversial [18]. Problems with intraventricular antibiotics include allergic reactions, drug-induced inflammation and toxic or inadequate concentrations [18]. Even though our case presented gentamycin-susceptible enterococcus, the patient was successfully treated without needing intraventricular administration of drugs.

Optimal management of ventricular shunt infection requires removal of the shunt, placement of a temporary external ventricular drain (EVD), followed by reinternalization after CSF sterilization. A recent analysis strongly confirmed this as the most effective treatment method [19].

Length of time on antibiotic therapy in patients with ventriculoperitoneal shunt infection remains controversial. Studies employing linezolid for the treatment of VPS infections range from 3 to 12 weeks in length [4,8,20,21]. Despite receiving prolonged treatment, our patient presented no bone marrow compromise according to serial hemograms. However, peripheral neuropathic signs could not be assessed in this case because the patient presented severe neurologic compromise due to the underlying disease and comorbidity. In conclusion, intravenous linezolid appears to be a safe and effective therapy for vancomycin-resistant enterococcus ventriculitis. Our success with linezolid in this instance is encouraging for the future role of this class of drugs for the treatment of shunt infections.

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