Case Report

The Use of Daptomycin and Linezolid to Treat Vancomycin-Intermediate *Staphylococcus haemolyticus* Infection in a Premature Infant

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Infections with staphylococcal species, especially coagulase-negative staphylococci are common after neurosurgical procedures. We report a case of a coagulase-negative staphylococci infection of a ventricular shunt site in a 105-day-old, premature infant born at 25 weeks gestation with multiple medical problems. The patient was successfully treated with a combination of daptomycin and linezolid for the persistent infection, which was increasingly resistant to vancomycin. The patient was initially treated with a combination of vancomycin and rifampin; however, the course of therapy had to be changed when the bacteria was identified as having intermediate resistance to vancomycin. Therapy was initially changed to linezolid monotherapy, but culture results continued to be positive for the bacteria, necessitating removal of an external ventricular drain and combination therapy of daptomycin and linezolid for 2 weeks before insertion of a new ventricular shunt. The patient received 4 weeks of therapy with no further positive results of the culture analysis. To our knowledge, this is the first published case report of the use of daptomycin to successfully treat a central nervous system infection in a premature infant.

KEYWORDS daptomycin, linezolid, premature infant, *Staphylococcus*

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CASE REPORT

The infant patient was born at an outside facility at 25 weeks gestation (birth weight, 568 g) and transferred to our institution on day of life (DOL) 9 for management of possible necrotizing enterocolitis, grade 3 intraventricular hemorrhage (IVH), and hydrocephalus. She was noted to have an intestinal perforation; therefore, a peritoneal drain was placed on DOL 10. A subgaleal shunt was placed in the infant on DOL 21 because of worsening IVH (from grade 3 to grade 4) and hydrocephalus. One month after the shunt placement (DOL 54), the infant was noted to have an increasing head circumference and a bulging fontanelle. Consequently, a fontanelle tap was performed, and 25 mL of cerebrospinal fluid (CSF) were aspirated with the following results: white blood cell (WBC) count, 8 cells/mm^3 (14% neutrophils, 1% bands, 26% lymphocytes, 52% monocytes); glucose, 22 mg/dL; and protein, 134 mg/dL. However, the CSF had no growth on culture. The patient was receiving vancomycin and rifampin at the time of the tap because of a positive blood culture of coagulase-negative *Staphylococcus* 1 week before the tap (DOL 47). Three days after the tap, the patient's shunt was revised.

When the infant's body weight had reached 2 kg, a more permanent ventriculo-peritoneal (VP) shunt was placed on DOL 72. During the period after the shunt revision and placement of the VP

ABBREVIATIONS CNS, central nervous system; CSF, cerebrospinal fluid; DOL, day of life; EVD, external ventricular drain; FDA, Food and Drug Administration; IVH, intraventricular hemorrhage; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; VP, ventriculoperitoneal; VRE, vancomycin-resistant enterococcus; WBC, white blood cell

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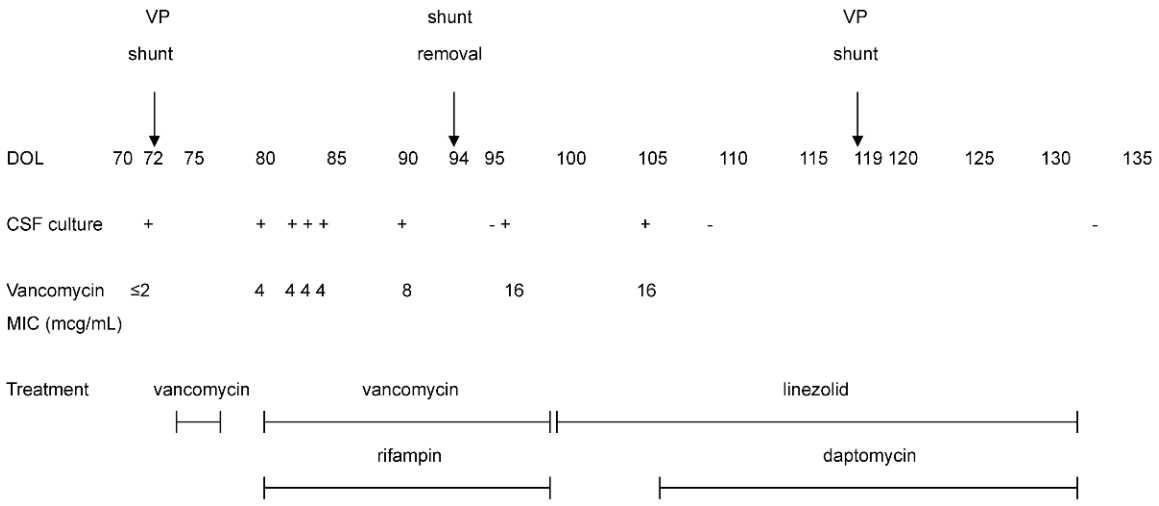

Figure. CSF indicates cerebrospinal fluid; DOL, day of life; MIC, minimum inhibitory concentration; VP, ventriculoperitoneal shunt.

shunt, the patient remained stable, and the daily head circumferences reported were 29.5 cm. The CSF fluid taken on the day of shunt placement had the following: WBC count, 28 cells/mm^3 (2% neutrophils, 40% lymphocytes, 46% monocytes); glucose, 31 mg/dL; and protein, 219 mg/dL. The CSF culture grew coagulase-negative *Staphylococcus*, which was isolated only after broth enrichment 6 days after the culture was drawn. This organism was reported to be sensitive to vancomycin with a minimum inhibitory concentration (MIC) less than or equal to 2 mg/L.

After the shunt placement, the patient received ampicillin (100 mg/kg/dose every 8 hours) and gentamicin (4 mg/kg/dose every 24 hours). Two days after the shunt placement, the course of therapy was changed to vancomycin (10 mg/kg/dose every 12 hours) because the patient was noted to have a full abdomen, oxygen desaturations despite mechanical ventilation, and a heart rate in the 190s. The vancomycin was discontinued 48 hours later when blood cultures were negative but vancomycin was restarted at a dose of 15 mg/kg/dose every 8 hours when the CSF culture grew coagulase-negative staphylococci. Rifampin (5 mg/kg/dose every 12 hours) was also started at this time. The vancomycin dose was increased to 20 mg/kg/dose every 8 hours because the steady-state serum concentrations (trough=10 mg/L and peak=26 mg/L) on the previous dose were lower than our institutional goals (goal trough=10-15 mg/L and goal peak=35-40 mg/L). Despite attaining goal steady-state vancomycin serum concentrations on the new dose (initial: trough=12 mg/L, peak=33 mg/L; week 2: trough=12 mg/L, peak=38 mg/L), the infant continued to have growth of coagulase-negative staphylococcus, which was later identified to be *Staphylococcus haemolyticus*. The VP shunt was externalized in the abdomen soon after the initial culture result was available. The original shunt was maintained in place for an additional 2 weeks. During therapy with vancomycin, there was demonstration of vancomycin MIC creep, confirmed by E test (Figure).

On day 20 of therapy (DOL 94), the original shunt was removed, and an external ventricular drain (EVD) was placed because the organism—namely, *S haemolyticus*—was determined to be intermediately sensitive to vancomycin. On day 25 of therapy (DOL 99), the course of therapy was changed from vancomycin and rifampin to linezolid (10 mg/kg/dose every 8 hours) because the organism was sensitive to linezolid in all cultures, with a MIC of 1 mg/L. The plan was to continue linezolid for 1 week, then remove the EVD and replace it with a new shunt. However, after 6 days of treatment with linezolid, the patient's repeat CSF cultures from the EVD continued to grow *S haemolyticus*. At this time (DOL 106), a decision was made to add daptomycin (6 mg/kg/dose every 24 hours) to the current antimicrobial regimen even though the organism had not been tested specifically for daptomycin sensitivity. In addition, the EVD was removed on the same day as the daptomycin was added. Repeat CSF cultures drawn on DOL 109 remained negative for the bacteria. On day 14 of combined daptomycin

and linezolid therapy (DOL 119), a new shunt was placed. The patient received 4 weeks of combination therapy with daptomycin and linezolid and had no further positive CSF cultures or adverse effects from the antibiotics.

DISCUSSION

An infection after VP shunt placement occurs in approximately 5% to 15% of pediatric patients. Coagulase-negative *Staphylococcus* species and *Staphylococcus aureus* are reported to be the most common causative organisms.[1] Current recommendations for the management of ventriculostomy-related CNS infections include removal of the infected shunt and treatment with an intravenously administered antibiotic.[2] Vancomycin is usually the drug of choice.[3] Immediate removal of a shunt is not always possible in some patients for various reasons, including prematurity and technical difficulties related to prematurity. Despite starting our patient on appropriate empiric therapy with vancomycin and rifampin, the initial treatment unfortunately failed because the organism—*S haemolyticus*—became resistant to vancomycin during therapy, necessitating the use of alternative antimicrobial therapy that is currently not approved by the FDA for use in this age group.

In recent years, the use of both daptomycin and linezolid for the treatment of invasive infections with gram-positive organisms has been on the rise because of the development of multiple resistant strains of staphylococci. *S haemolyticus* is a highly resistant, coagulase-negative staphylococcal species, which accounts for approximately 10% of clinical isolates of coagulase-negative staphylococci.[4] *In vitro* studies with both daptomycin and linezolid have shown activity against *S haemolyticus* with MIC_{90} of 1 and 2 mg/L, respectively.[5] Neither daptomycin nor linezolid is approved for use with CNS infections.

Daptomycin is a lipopeptide antibiotic with rapid bactericidal activity against resistant gram-positive organisms. However, it is not approved for use in pediatric patients. Current data on the use of daptomycin in pediatric patients are limited. Furthermore, the use of daptomycin in infants has been reported in only 3 patients.[6,7] These infants were treated with daptomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, an MRSA cervical abscess, and vancomycin-resistant enterococcus (VRE) bacteremia. The pharmacokinetics of daptomycin in pediatric patients has been studied in a small group of patients. Abdel-Rahman and colleagues conducted a single-dose pharmacokinetic study in 25 children aged 2 to 17 years and found that systemic exposure to daptomycin decreased with decreasing age, suggesting an increased clearance in younger children compared with clearance patterns in adolescents and adults.[8] For this reason neonates and young infants may require higher mg/kg doses compared with adults. In 2 of the infant cases reported in the literature, clinicians used a dose of 6 mg/kg/dose every 12 hours with peak and trough concentrations drawn that were comparable with those drawn in adults using a dose of 4 mg/kg/dose every 24 hours.[6] In a third case report, a neonate received a range of doses, from 4 mg/kg/dose every 48 hours to 6 mg/kg/dose every 24 hours, adjusting for renal function.[7] The higher dose resulted in negative blood cultures and an appropriate peak concentration compared with published data. Our patient received the same dose that has been reported in the medical literature; however, no blood concentrations or drug susceptibilities were obtained.

Daptomycin has not been extensively studied for CNS infections in either pediatric or adult patients. In an experimental meningitis model in a rabbit, CSF concentrations for daptomycin were approximately 5% with inflamed meninges and 2% for noninflamed meninges.[9] In addition, daptomycin was found to be more efficacious than vancomycin for sterilization of the CSF in the rabbit model. The only data we identified regarding pediatric patients are limited to a single case series describing a single center's experience with daptomycin for infections of invasive gram-positive bacteria in 16 pediatric patients, ranging in age from 5 months to 15 years.[10] Six of these patients had possible CNS involvement.

Linezolid is an oxazolidinone antibiotic with bacteriostatic activity against resistant gram-positive organisms. It is approved for use in both adult and pediatric patients (including neonates). Although it demonstrates bacteriostatic activity, linezolid has favorable characteristics for treatment of a CNS infection. It is a small molecule, neutral at physiologic pH, and crosses the blood brain barrier readily even when there is no inflammation. Linezolid has been more extensively studied than daptomycin for CNS infections in

humans. In adults, linezolid achieves excellent CSF penetration with reported CSF/plasma ratios exceeding 1. In addition, time above the MIC was 99.8% for organisms with a MIC of 2 mg/L.[11] Langgartner and colleagues recently reported their success with linezolid either alone or in combination with other antibiotics for ventriculostomy-related CSF infections in 5 premature infants.[12] They concluded that linezolid should be considered as an alternative to vancomycin for this indication.

To our knowledge, our case is the first report of daptomycin treatment in a premature infant with a CNS infection. Since combination therapy was used, it is difficult to determine the specific role of each antibiotic in the successful outcome of this patient. Another confounder is that the contaminated EVD was removed on the same day that daptomycin was started. Daptomycin was added because it demonstrates rapid bactericidal activity against resistant gram-positive organisms. It is possible that the addition of daptomycin might have also contributed to the rapid sterilization of the CSF. A new shunt was placed 2 weeks after the initiation of the combination therapy, and there were no further positive culture results. Infections caused by resistant gram-positive bacteria continue to be a significant source of morbidity and mortality among premature infants. With increasing reports of vancomycin-resistant strains of staphylococcal species, alternative therapies need to be explored. Both daptomycin and linezolid represent excellent alternatives to vancomycin for treatment of infections caused by resistant gram-positive bacteria and need to be further studied in neonates and infants with CNS infections.

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