Successful Use of Intrathecal Daptomycin to Treat Meningitis Due to Vancomycin-Resistant Enterococcus faecium

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CASE REPORT

A 59-year-old woman presented to the emergency department with acute onset of severe headache, followed by nausea, vomiting, and loss of consciousness. In the emergency department, she exhibited decerebrate posturing and had a fixed, dilated right pupil. A computed tomographic scan of the head revealed a subarachnoid bleed with a large right subdural hematoma. She underwent surgery, and a right craniotomy with drainage of the subdural hematoma was performed along with placement of a left EVD.

Three days later, the right craniotomy was reentered, and a ruptured right posterior communicating artery aneurysm was clipped. On hospital day 8, her EVD was exchanged; the EVD was removed on hospital day 13. Vancomycin was initiated on hospital day 21 after she developed a fever and exhibited CSF drainage from the EVD incision. A CSF culture was drawn on day 19 and was later confirmed as negative; however, the patient received a dose of gentamicin before the culture obtained.

On hospital day 24, a left ventriculoperitoneal shunt (VPS) was performed because of cerebral ventricular dilatation and development of a CSF leak from the previous EVD incision. Subsequently, on hospital day 36, fever developed and Staphylococcus hominis was isolated from the blood and the CSF. The VPS was externalized, but despite vancomycin therapy, the CSF drainage was persistently positive for S. hominis for 11 days.

On hospital day 47, the CSF culture from the VPS grew S. hominis and vancomycin-resistant Enterococcus faecium (VREF) (minimum inhibitory concentration [MIC] >16 μg/mL), which was susceptible to daptomycin (MIC = 2 μg/mL). The VPS was removed, and a new EVD was placed. Daptomycin was begun at a dose of 6 mg/kg IV daily for 2 weeks. The dose was increased to 10 mg/kg IV daily after the CSF culture remained positive for VREF. Despite 11 days of daptomycin therapy at 10 mg/kg, the CSF cultures remained positive for VREF.

On hospital day 73, daptomycin, 5 mg every 3 days, was instilled intrathecally via the EVD. Table 1 shows the CSF findings, where day 0 represents hospital day 73, when daptomycin was first administered intrathecally. On hospital day 89, the patient’s VPS was replaced (day 16 after starting IT daptomycin), and antibiotics were discontinued 3 days later. The patient was discharged to an extended-care facility on hospital day 94. She remained neurologically impaired as a result of the initial subarachnoid hemorrhage. Three months after discharge, she was being cared for by relatives and remained neurologically impaired...
Daptomycin, a cyclic lipopeptide, is a concentration-dependent antibiotic that is a potential option for the treatment of CNS infections. Daptomycin is approved by the US Food and Drug Administration for the treatment of complicated skin and soft tissue infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis, at recommended daily doses of 4 and 6 mg/kg, respectively.8

One concern regarding the potential use of daptomycin for CNS infections has been its relatively low CNS penetration. In an infant rabbit model of pneumococcal meningitis, daptomycin showed approximately 6% CSF penetration but was significantly more efficient at eliminating bacteria from the CSF compared with ceftriaxone (viable count, log_{10} 3.6 ± 1.0 vs 6.3 ± 1.4 CFU/mL; P < 0.02).8 Daptomycin also caused a greater reduction in the inflammatory host reaction assessed by matrix metalloproteinase-9 in CSF compared with ceftriaxone (P < 0.005).9

In a rabbit model of methicillin-susceptible S. aureus (MSSA) meningitis, daptomycin serum level after a single dose of 15 mg/kg peaked at 141 mg/L, and CSF level peaked at 4.5 mg/L, corresponding to approximately 5% and 2% penetration into the inflamed and uninfamed meninges, respectively, compared with serum levels.10,11 Riser et al12 reported a case of MSSA bacteremia with suspected MSSA meningitis in a 54-year-old man treated with once-daily high-dose IV daptomycin (800 mg, approximately 9 mg/kg based on 91 kg after aggressive volume resuscitation). Penetration was approximately 5% based on concurrent daptomycin trough serum and CSF concentrations of 11.2 μg/mL and 0.52 μg/mL, respectively.11 These results are consistent with those of another case report of a 78-year-old patient with VREF meningitis successfully treated with 9 mg/kg of IV daptomycin.12 Daptomycin penetration into the CSF was approximately 5% after 8 days of therapy.12 In contrast, in patients with indwelling external CSF shunts who had suspected or documented meningitis or ventriculitis, a single 10-mg/kg dose of IV daptomycin had minimal penetration (0.7%) into the CSF.13

Daptomycin displays several properties that make it an option for the treatment of CNS infections caused by gram-positive organisms. Daptomycin does not promote cell lysis, which may inhibit the release of bacterial molecules and lessen the inflammatory response.14 In vitro, daptomycin alone or in combination with vancomycin or oxacillin led to a diminished macrophage inflammatory response with reduced secretion of tumor necrosis factor and reduced accumulation of inducible nitric oxide synthase protein.14

Daptomycin is rapidly bactericidal, making it suitable for the treatment of severe, life-threatening infections.10,15 It exerts its bactericidal activity by irreversibly binding within the bacterial cell membrane in a calcium-dependent process, which leads to depolarization of the cell membrane and rapid cell death by inhibiting RNA, DNA, and protein synthesis.8 Unlike linezolid, the recommended therapy for treating VRE-associated CNS infections resistant to both vancomycin and daptomycin, daptomycin is not associated with myelosuppression.6,8,16

Daptomycin demonstrates a high level of in vitro activity against S. aureus, with a MIC90 of 0.5 μg/mL for MRSA.17 The MIC90 is 2 μg/mL for both Enterococcus faecalis and E. faecium.17 Because enterococci have a higher daptomycin susceptibility breakpoint of less than or equal to 4 μg/mL compared with that of S. aureus (≤1 μg/mL) as recommended by the Clinical and Laboratory Standards Institute and the US Food and Drug Administration, there may be a need for higher exposure to daptomycin when treating VRE-associated infections. In our patient, regimens of 6 mg/kg IV daptomycin and 10 mg/kg IV daptomycin failed to eradicate VREF. Intrathecal daptomycin at a dose of 5 mg every 3 days resulted in microbiological clearance of VREF from the CSF 6 days after the initiation of therapy. Creatine phosphokinase levels, which rose in a minority of patients taking daptomycin,8 became elevated in our patient while on IV daptomycin. However, the treating physician deemed this elevation not clinically significant. Despite an initial elevation, the patient’s creatine phosphokinase levels returned to the normal range after the addition of IT daptomycin.

This is the third published case of IT administration of daptomycin with no adverse events.1,18 Elvy et al1 described a 62-year-old patient with an EVD-associated ventriculitis associated with Klebsiella pneumoniae and meningitis due to E. faecalis that were successfully treated with intraventricular daptomycin, 10 mg every third day, later reduced to 5 mg every third day over a 2-week treatment period. Clinical and bacteriologic cures were sustained after follow-up for more than 1 year.1 Jaspan et al18 described a 21-month-old patient who had growth of vancomycin-resistant E. faecium after a peripheral blood stem cell transplant.18 Daptomycin administered intraventricularly via ventriculostomy tubing (2.5 mg in 5 mL of isotonic sodium chloride solution every 24 hours) achieved CSF concentrations of 24.44 mg/L (peak) and 2.97 mg/L (trough). Tigecycline, 2 mg/kg IV, was added after 3 days of daptomycin therapy. After 2 days on tigecycline, the CSF sterilized. Daptomycin was continued for 7 days after the last negative blood culture.

In conclusion, this case suggests that daptomycin is a safe and acceptable alternative for the treatment of CNS infections caused by VREF when traditional therapy fails or cannot be tolerated. In our case, IT combined with high-dose IV daptomycin resulted in an achievable exposure that adequately cleared VREF from the CSF. Further studies are necessary to assess more fully

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### TABLE 1. CSF Results

<table>
<thead>
<tr>
<th>Daptomycin dose IT, mg</th>
<th>Day –1</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 6</th>
<th>Day 9</th>
<th>Day 12</th>
<th>Day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF culture for VREF</td>
<td>Positive</td>
<td>N/D</td>
<td>N/D</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CSF WBC</td>
<td>45</td>
<td>N/D</td>
<td>N/D</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>CSF% neutrophils</td>
<td>100%</td>
<td>N/D</td>
<td>N/D</td>
<td>100%</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
</tr>
</tbody>
</table>

N/D indicates no data; WBC, white blood cell count.
daptomycin CNS penetration and efficacy in treating VRE-associated CNS infections.

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REFERENCES


