Successful Treatment of Ceftazidime-Resistant Klebsiella pneumoniae Ventriculitis with Intravenous Meropenem and Intraventricular Polymyxin B: Case Report and Review

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Increasing prevalence of multidrug-resistant gram-negative organisms has led to a rise in clinically significant infections with these organisms and an increasing therapeutic dilemma. We present a case of a neurosurgical patient who developed ventriculoperitoneal shunt-associated ventriculitis due to ceftazidime-resistant Klebsiella pneumoniae susceptible to cefepime, imipenem, meropenem, and polymyxin B only. Successful management was accomplished by removal of the shunt and therapy with systemic meropenem and intraventricular polymyxin B. Rapid cerebrospinal fluid (CSF) sterilization occurred, with CSF bactericidal titers of 1:32 to 1:128. Polymyxin B should be considered as adjunctive therapy for life-threatening multidrug-resistant gram-negative infections. Prior literature on use of intrathecal polymyxin B in therapy for meningitis supports its potential efficacy.

The increasing prevalence of clinically significant multidrug-resistant bacteria has posed new therapeutic challenges. We are now forced to reconsider older therapies when the new antibacterial agents are rendered ineffective through plasmid- and chromosome-mediated resistance mechanisms. Recently reported nosocomial outbreaks of multidrug-resistant gram-negative bacilli have involved patients with pneumonia, bacteremia, and intra-abdominal abscesses [1–7]. We present a case of nosocomially acquired ceftazidime-resistant Klebsiella pneumoniae (CRKP) infection causing ventriculitis and ventriculoperitoneal shunt (VPS) infection. The therapeutic challenge was not only treatment of a multiply resistant organism but also achievement of sufficient bactericidal levels in the CSF to effect a cure.

Case report

The patient, a 55-year-old female school teacher, underwent craniotomy and resection of a meningioma. Her postoperative course was complicated by cerebrovascular hemorrhage, cardiac arrhythmias, renal insufficiency, and severe desquamating dermatitis following administration of several β-lactam antibiotics (including piperacillin/tazobactam, ceftazidime, and aztreonam). She was treated in the surgical intensive care unit for many weeks, during which several blood and sputum cultures yielded Pseudomonas aeruginosa (susceptible only to aminoglycosides) and/or CRKP (susceptible only to ceftazidime and imipenem). On postoperative day 64, a change in mental status secondary to hydrocephalus required placement of a VPS. After initial improvement, her neurological condition deteriorated, and a CSF culture yielded the same CRKP previously isolated from blood and sputum. The VPS was removed and a temporary external ventriculostomy opening was created for administration of intrathecal polymyxin B (50,000 U once daily). In addition, intravenous meropenem was administered (1 g every 12 hours, as adjusted for impaired renal function).

The patient’s mental status improved following removal of the VPS and start of antimicrobial therapy. Administration of polymyxin B was discontinued after a 7-day course, and meropenem was given for 21 days following the first negative CSF culture. Because of her debilitated condition and clinical improvement, the family refused further lumbar punctures to document eradication of infection. However, CRKP has not been cultured from her secretions subsequently, and she remained without clinical evidence of infection at 3 months following discontinuation of antibiotic therapy. A summary of her hospital course appears in table 1.

Methods

Initial identification of clinical isolates was performed with use of gram-negative GNI cards (Vitek Systems, Hazelwood, MO) and conventional Kirby-Bauer susceptibility testing. Broth macrodilution techniques to determine the MIC and MBC of meropenem (Zeneca Pharmaceuticals, Wilmington, DE) and polymyxin B (Pfizer, New York) were used according to standard methods [8, 9]. The MIC was recorded as the lowest concentration of antibiotic that completely inhibited visible growth; the MBC was defined as the lowest concentration at...
which 99.9% killing of the original inoculum could be demonstrated. The procedure for determining bactericidal titer in CSF was based on recommended guidelines, with use of serum [10]. The bactericidal titer was defined as the highest tube dilution in which 99.9% of the original inoculum was killed. Etest susceptibility testing was done in accordance with the directions of the manufacturer (AB BIODISK, Solna, Sweden) to determine MICs of other antimicrobials.

Three sequential isolates from different sources were selected for molecular typing by means of pulsed-field gel electrophoresis (PFGE) [11]. Enzyme restriction of bacterial chromosomes was done with use of Xba I (New England Biolabs, Beverly, MA). DNA separation by PFGE was achieved with the GenePath System (Bio-Rad, Hercules, CA). A DNA lambda ladder (Bio-Rad) was included to serve as a molecular weight reference.

Results

The susceptibility profile of CRKP with use of Etest and macrodilution methodologies appears in Table 2. The organism was susceptible to cefepime, imipenem, meropenem, and polymyxin B. CSF inhibitory and bactericidal titers appear in Table 1. The CSF colony count was markedly reduced (from >50,000 to 6,000 cfu/mL) 24 hours after administration of intravenous meropenem and intraventricular polymyxin B. Synergy studies for meropenem and polymyxin performed with use of broth microdilution checkerboard methodology revealed a sum of the fractional inhibitory concentration (ΣFIC) equal to 0.58. This represents partial or full synergy by the criteria for interpretation of checkerboard synergy testing (ΣFIC, ≤0.5) [12].

All CRKP strains were highly related by PFGE analysis, by >90% band correlation, as demonstrated in figure 1 [13].

Table 1. Hospital course of a patient with nosocomial ceftazidime-resistant *Klebsiella pneumoniae* infection causing ventriculitis and ventriculoperitoneal shunt infection.

<table>
<thead>
<tr>
<th>Date (1998)</th>
<th>Antibiotic therapy</th>
<th>WBCs/mm³ (% of PMNs)</th>
<th>Protein (mg/dL)</th>
<th>Glucose (mg/dL)</th>
<th>Colony count (cfu/mL)</th>
<th>Inhibitory titer</th>
<th>Bactericidal titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 May</td>
<td>iv Aztreonam, iv vancomycin</td>
<td>14,700 (90)</td>
<td>610</td>
<td>18</td>
<td>&gt;50,000</td>
<td>1:2</td>
<td>1:2</td>
</tr>
<tr>
<td>8 May</td>
<td>iv Meropenem, ith* polymyxin B (administered following LP)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>&gt;50,000</td>
<td>1:2</td>
<td>1:2</td>
</tr>
<tr>
<td>9 May</td>
<td>iv Meropenem, ith* polymyxin B</td>
<td>130 (98)</td>
<td>. . .</td>
<td>. . .</td>
<td>6,000</td>
<td>1:128</td>
<td>1:64</td>
</tr>
<tr>
<td>10 May</td>
<td>2,750 (95)</td>
<td>. . .</td>
<td>. . .</td>
<td>0</td>
<td>1:128</td>
<td>1:64</td>
<td></td>
</tr>
<tr>
<td>11 May</td>
<td>354 (98)</td>
<td>. . .</td>
<td>. . .</td>
<td>1,000</td>
<td>1:256</td>
<td>1:64</td>
<td></td>
</tr>
<tr>
<td>12 May</td>
<td>650 (98)</td>
<td>417</td>
<td>48</td>
<td>3,000</td>
<td>1:128</td>
<td>1:32</td>
<td></td>
</tr>
<tr>
<td>14 May</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>0</td>
<td>1:128</td>
<td>1:16</td>
<td></td>
</tr>
<tr>
<td>15 May</td>
<td>d/c ith* Polymyxin B</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>0</td>
<td>1:128</td>
<td>1:64</td>
</tr>
<tr>
<td>27 May</td>
<td>800 (83)</td>
<td>303</td>
<td>. . .</td>
<td>. . .</td>
<td>0</td>
<td>1:512</td>
<td>1:256</td>
</tr>
<tr>
<td>3 June</td>
<td>d/c iv Meropenem</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

NOTE. d/c = discontinued; LP = lumbar puncture; PMNs = polymorphonuclear leukocytes.

* Intrathecal (administered intraventricularly).

Table 2. Susceptibility profile of ceftazidime-resistant *Klebsiella pneumoniae* isolates.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Kirby-Bauer (mm)</th>
<th>Etest (µg/mL)</th>
<th>MIC</th>
<th>MBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>96</td>
<td>&gt;16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>32</td>
<td>&gt;32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>&gt;32</td>
<td>. . .</td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>. . .</td>
<td>&gt;4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin/clavulanate</td>
<td>128</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotetan</td>
<td>1</td>
<td>. . .</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>128</td>
<td>&gt;32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>&gt;32</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>2</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.125</td>
<td>≤0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.023</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>0.5</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. I = intermediate; NA = not applicable; R = resistant; S = susceptible.
penem (table 2). However, it was considered insufficient as a single form of therapy because of the potential for carbapenem resistance related to loss of an outer-membrane protein among strains of CRKP [22, 23].

In addition, recent evidence suggests that achievable CSF levels of meropenem in patients with hydrocephalus and external ventriculostomy openings may not be bactericidal in the treatment of infection due to multidrug-resistant gram-negative organisms [24]. In view of high-level aminoglycoside resistance, administration of intraventricular polymyxin B was chosen as adjunctive therapy. Suggestions that unidirectional circulation of CSF impedes entry of medications into the ventricular system when instilled via the lumbar space compelled us to administer the agent via an external ventriculostomy opening for optimal effect [20, 25].

From a large number of related compounds, only two polymyxins, B and E (colistin), have been produced commercially. However, polymyxin B has been used clinically more commonly. It was one of the earliest agents employed in the treatment of gram-negative bacillary meningitis, particularly that due to P. aeruginosa [14, 15, 18, 21, 26–30]. Polymyxin B demonstrates potent bactericidal activity against most strains of P. aeruginosa, Escherichia coli, Enterobacter species, and Klebsiella species, damaging the plasma membrane in a manner similar to that of cationic detergents. It penetrates poorly into CSF, and the presence of meningeal inflammation does not enhance absorption [31]. CSF levels range from 1.2 to 112 U/mL in children receiving 10,000 to 40,000 U intrathecally (1 mg of pure polymyxin B base is equivalent to 10,000 U of polymyxin B) [31]. Beneficial reduction in cerebral edema and endotoxin production have been demonstrated in experimental studies in rabbits when high-dose intravenous polymyxin is administered concurrently with another antibiotic [32].

Polymyxin B is nephrotoxic and neurotoxic and has been associated with renal insufficiency, giddiness, and neuromuscular blockade when used parenterally, and with pain, numbness, paresthesias, confusion, coma, and convulsions when used intrathecally [14, 21, 26–29, 31, 33]. The chemical arachnoiditis seen with polymyxin B use is dose-dependent. Parenteral dosing ranges from 2.5 to 3 mg/(kg·d), divided into twice daily doses. The intrathecal dosage is 5 mg once daily for adults, 2 mg daily for children ≤2 years of age, and 3–4 mg daily for older children [31]. Neurotoxicity is seen when the dosage exceeds 5 mg or 50,000 U a day.

Use of polymyxin B alone has been successful in therapy for >43 patients with meningitis and ventriculitis caused by a number of gram-negative bacteria [14, 16, 17, 21, 26–28, 30, 31, 34]. Although several authors advocate the separate use of polymyxin B intramuscularly, intravenously, or intrathecally, cures seemed to be more frequent among patients receiving combination systemic and local therapy (intrathecal or intraventricular) or local polymyxin B as an adjunct to other sys-

Figure 1. DNA fingerprinting of Klebsiella pneumoniae isolates from blood, sputum, and CSF. Lane 1, molecular weight markers. Lane 2, blood isolate. Lane 3, sputum isolate. Lane 4, CSF.
emetic therapy [15, 35]. Sterilization of CSF occurred promptly (within 24–48 hours) when therapy was given in conjunction with surgical repair and/or foreign-body removal [16, 21]. Nevertheless, the majority of patients received prolonged intrathecal or intraventricular therapy with polymyxin B (3–38 days; 13–205 mg). Most patients received 10–14 days of therapy with 30–50 mg. Our patient received a 7-day course for a total of 35 mg.

Bactericidal activity in CSF was assayed in one patient who received intrathecal polymyxin B and was cured [16]. The CSF trough was bacteriostatic at a 1:8 dilution and bactericidal at a 1:4 dilution. Our patient’s CSF was bacteriostatic at a 1:128 dilution and bactericidal at a 1:32–1:64 dilution because of the combined effect of polymyxin B and meropenem. Our synergy studies revealed the \( \Sigma \) FIC value was 0.58. In a recent report, in vitro \( \Sigma \) FIC values of 0.55 with administration of a combination of imipenem and polymyxin B for \( K. \) pneumoniae infection were considered synergistic [36].

More recently, intravenous and intrathecal polymyxin B was given to a patient infected with a resistant strain of \( A. \) baumannii whose systemic and intraventricular therapy with imipenem/cilastatin (intravenous), ticarcillin/clavulanate (intravenous, intrathecal), and amikacin (intravenous, intrathecal) failed [34]. Sterilization of CSF cultures was achieved within 24 hours following substitution of polymyxin B. This report and our experience suggest the benefit of reinstating polymyxin B in potential antimicrobial regimens as therapy for multiresistant gram-negative meningitis. When possible, polymyxin B should be combined with another effective agent in order to improve efficacy of therapy and minimize emergence of resistance to carbapenems.

References