Treatment of Multidrug-Resistant *Acinetobacter baumannii* Meningitis with Amoxicillin/Sulbactam


The clinical features and the outcomes of eight cases of nosocomial *Acinetobacter baumannii* meningitis treated with amoxicillin/sulbactam are reported. All the patients had fever, neck stiffness or meningeal signs, and a low consciousness level, and in their cerebrospinal fluid (CSF), pleocytosis, a low glucose level, and an elevated protein level were noted. For all CSF isolates of *A. baumannii*, the MIC of amoxicillin/sulbactam was \( \leq 8/4 \mu g/mL \). The MICs of sulbactam by microdilution in two cases were \( 4 \mu g/mL \). All isolates were resistant to cefotaxime, ceftriaxone, ceftazidime, ureidopenicillins, ciprofloxacin, and gentamicin. Seven isolates were resistant to imipenem. *A. baumannii* was isolated from other samples in seven episodes. All patients were treated with amoxicillin/sulbactam (seven with 2 g/1 g every 6 hours and one with 2 g/1 g every 8 hours). Six patients were cured and two patients died of meningitis. There were no side effects with the amoxicillin/sulbactam treatment.

**Methods**

We performed a retrospective clinical study to evaluate the outcome of eight cases of postneurosurgical meningitis caused by multiresistant *A. baumannii* during the period between January 1993 and December 1995.

All patients met the following inclusion criteria: (1) clinical signs of meningitis (fever, meningeal signs, low consciousness level); (2) pleocytosis, low glucose level, and elevated protein level in the CSF; (3) isolation of *A. baumannii* from CSF; and (4) treatment with amoxicillin/sulbactam.

All CSF cultures were processed by the hospital laboratory with use of the Bactec NR860 system (Becton Dickinson, Cockeysville, MD). *A. baumannii* was identified by the MicroScan system (Baxter Health Care, West Sacramento, CA), the API 20 NE system (bioMérieux, Marcy l’Etoile, France), and temperature growth tests [15]. Susceptibility to antimicrobial agents was determined by the MicroScan system, with use of the Neg Breakpoint Combo Panel 21 (Baxter Health Care), according to the norms established by the National Committee for Clinical Laboratory Standards [16]. Susceptibility to sulbactam was also determined by microdilution in Mueller-Hinton broth [16].

Clinical cure was considered to be the disappearance of fever and meningeal signs, improvement of consciousness level (in cases of low consciousness directly related to meningitis), and remission of CSF alterations at the time the therapy was discontinued. Bacteriologic cure was defined as elimination of *A. baumannii* from CSF during therapy. Death was considered to be related to meningitis if it occurred during treatment for meningitis.
A. baumannii meningitis was considered to be related to a CSF shunt if it appeared following placement of the CSF shunt, if the CSF at the time of placement was sterile, and if there were no other neurosurgical procedures in the period of time between the shunt placement and the onset of meningitis. The results of analyses of continuous variables are expressed herein as mean ± SD.

Results

Eight patients (four men and four women) between 30 and 74 years of age were included. The most common underlying condition was intracerebral or subarachnoid hemorrhage (six cases) (table 1). All patients underwent surgical procedures, involving 3 craniotomies, 2 burr hole drillings, and 6 placements of external CSF shunts, which were in place for 3–17 days (10.5 ± 6.3 days) before onset of meningitis. The external CSF shunt was directly related to A. baumannii meningitis in five cases (83%). Four patients had CSF fistulae at the craniotomy and/or burr hole sites. One case had A. baumannii surgical wound infection prior to meningitis. Seven patients had been in the intensive care unit and seven had received antimicrobial treatment prior to onset of meningitis.

All the patients had fever (39.06 ± 0.69°C), neck stiffness or meningeal signs, and a low consciousness level (coma in six cases and stupor and somnolence in one case each). Five patients had nausea and/or vomiting and three suffered seizures. The neurological deficits and the headaches were difficult to evaluate because of the underlying conditions.

Leukocytosis (18,817 ± 6,101/μL) with a polymorphonuclear predominance was noted in seven patients. In all CSF specimens, pleocytosis (4,383 ± 6,927 cells/μL) with a polymorphonuclear predominance, an elevated protein level (415 ± 219 mg/dL), and a low glucose level (14 ± 15 mg/dL) were noted.

In seven episodes, additional A. baumannii isolates were recovered from other samples (table 1). All A. baumannii isolates were susceptible to ampicillin/sulbactam (MIC, ≤8/4 μg/mL, per MicroScan system) and resistant to cefotaxime, ceftriaxone, ceftazidime, ertapenem, ciprofloxacin, and gentamicin. Seven isolates were also resistant to imipenem. The results of analyses of continuous variables are expressed herein as mean ± SD.

Discussion

The cases of acinetobacter meningitis in this study were related to head trauma or neurosurgical procedures, including

### Table 1. Clinical characteristics of the eight patients with nosocomial A. baumannii meningitis, as well as microbiological findings, treatment, and outcome.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)/sex</th>
<th>Underlying condition(s)</th>
<th>Neurosurgical procedure(s)</th>
<th>Sources of other Acinetobacter isolates</th>
<th>Dosage (g/g) of ampicillin/sulbactam</th>
<th>Duration (d) of therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/F</td>
<td>Head trauma, subdural hematoma</td>
<td>Burr holes drilled</td>
<td>Blood, surgical wound</td>
<td>2/1 q6h</td>
<td>8*</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>Intracerebral hemorrhage</td>
<td>External CSF shunt placed</td>
<td>External CSF shunt</td>
<td>2/1 q6h</td>
<td>14</td>
<td>Cured</td>
</tr>
<tr>
<td>3</td>
<td>53/F</td>
<td>Subarachnoid hemorrhage</td>
<td>External CSF shunt placed</td>
<td>None</td>
<td>2/1 q6h</td>
<td>21¹</td>
<td>Cured</td>
</tr>
<tr>
<td>4</td>
<td>40/M</td>
<td>Choroid plexus papilloma</td>
<td>Posterior fossa craniotomy, external CSF shunt</td>
<td>Surgical wounds</td>
<td>2/1 q6h</td>
<td>16²</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>65/M</td>
<td>Intraventricular hemorrhage</td>
<td>External CSF shunt exchanged</td>
<td>Blood, bronchial aspirate</td>
<td>2/1 q6h</td>
<td>21</td>
<td>Cured</td>
</tr>
<tr>
<td>6</td>
<td>43/M</td>
<td>Cerebellar hematoma</td>
<td>External CSF shunt placed</td>
<td>Blood, bronchial aspirate</td>
<td>2/1 q6h</td>
<td>19¹</td>
<td>Cured</td>
</tr>
<tr>
<td>7</td>
<td>30/F</td>
<td>Head trauma, cranial fracture, subdural hematoma</td>
<td>Burr holes drilled, external CSF and VP shunts placed</td>
<td>Bronchial aspirate, VP shunt</td>
<td>2/1 q6h</td>
<td>21</td>
<td>Cured</td>
</tr>
<tr>
<td>8</td>
<td>35/M</td>
<td>Syringomyelia</td>
<td>Posterior fossa craniotomy</td>
<td>Bronchial aspirate</td>
<td>2/1 q6h</td>
<td>5</td>
<td>Died</td>
</tr>
</tbody>
</table>

* He was switched to imipenem therapy on day 8 of treatment (see Results).
¹ Intraventricular netilmicin (15–20 mg qd) also was given during the same time period.
² Intraventricular amikacin (15 mg qd) also was given during the same time period.
³ Ventriculoperitoneal.
placement of external ventricular devices (present for >5 days), factors which have previously been associated with this infection [6–9, 17]. The excessive administration of antimicrobial agents to neurosurgical patients may facilitate the appearance of acinetobacter meningitis [6, 9], as probably occurred in seven of the cases in the present study.

Nosocomial *A. baumannii* infections have a high related mortality, with a case fatality rate of 20%–27% for acinetobacter meningitis [6, 7]. The mortality is related to inappropirate treatment of bacteremias due to *A. baumannii* [3], a finding which stresses the importance of correct empirical treatment.

Many nosocomial *A. baumannii* strains are resistant to a wide variety of antimicrobial agents. Imipenem, tetracycline, ampicillin/sulbactam, polymyxin B, and (according to some studies) cefazidime and ciprofloxacin are among the more active antimicrobial agents against *A. baumannii* [3, 18–20]. However, antimicrobial susceptibility patterns may change from hospital to hospital. Thus, the use of imipenem for acinetobacter infections caused by strains that are only imipenem-susceptible may induce the appearance of imipenem-resistant acinetobacter infections.

Urban et al. [13] referred to an outbreak of acinetobacter infections that necessitated widespread use of cefazidime and later the use of imipenem. Subsequently, they observed *Acinetobacter* strains resistant to all antimicrobial agents tested, including imipenem, cefazidime, and amikacin [13]. We have observed a steady increase in the incidence of multiresistant *A. baumannii* infections in our hospital, including those resistant to imipenem, after extensive use of this antimicrobial agent. For instance, only 43%, 26%, and 38% of *A. baumannii* isolates from the same building of the hospital were susceptible to imipenem in 1993, 1994, and 1995, respectively.

In the treatment of imipenem-resistant acinetobacter infections, ampicillin/sulbactam has been useful for patients with respiratory tract infections and bacteremias [13]. Ampicillin/sulbactam was also useful in the treatment of uncomplicated urinary tract infections [21]. There are few clinical data on the treatment of meningitis with ampicillin/sulbactam. These β-lactam drugs have been effective in the treatment of bacterial meningitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Staphylococcus* species in infants, children, and adults [22–24].

Only one patient with acinetobacter posttraumatic meningitis was treated and cured with ampicillin/sulbactam [22]. Sulbactam penetrates into the CSF of patients with bacterial meningitis in a pattern similar to that of ampicillin [23]. One gram of sulbactam administered intravenously achieved CSF concentrations as high as 32% of serum concentrations (8.5 μg/mL) in patients with meningitis [25] but <1% of those in patients without meningitis [26].

There are data indicating that sulbactam is responsible for the bactericidal effect of ampicillin/sulbactam on *Acinetobacter* species. Sulbactam was more active than cefazidime and clavulanate on *Acinetobacter calcoaceticus*, both in vitro and in vivo, in mice models of intraperitoneal infection [27]. In another study, of 20 *Acinetobacter* strains that were resistant to imipenem and most probably of clonal origin, the MIC90 of sulbactam was ≤4 μg/mL and the MIC90 of ampicillin/sulbactam was ≤8/4 μg/mL, while the MIC90 of ampicillin was >128 μg/mL [13].

The mortality rate in our study (25%) was similar to those previously reported with regard to acinetobacter meningitis [6, 7] and slightly higher than the mortality of 15.4% among 13 cases treated with imipenem [8, 9, 11, 12]. Seven of the patients in the present study had another acinetobacter infection, such as tracheobronchitis or pneumonia and bacteremia, which are associated with high mortality [3–5]. Eradication of *Acinetobacter* species from the CSF in shunt-associated meningitis required complete removal of ventricular devices plus administration of bactericidal antibiotics. In this study, all external or ventriculoperitoneal CSF shunts were removed. There were neither recurrences nor superinfections.

In conclusion, the results of this study suggest that administration of ampicillin/sulbactam may be an effective therapy for meningitis caused by *A. baumannii* resistant to imipenem and other β-lactam drugs.

References


15. Bouvet PJM, Grimont PAD. Taxonomy of the genus *Acinetobacter* with the recognition of *Acinetobacter baumannii* sp. nov., *Acinetobacter haemolyticus* sp. nov., *Acinetobacter johnsonii* sp. nov., and *Acinetobacter junii* sp. nov. and emended descriptions of *Acinetobacter calcoaceticus* and *Acinetobacter lwaffii*. J Syst Bacteriol 1986; 36:228–40.


