animals, humans may have high-risk factors for infection with such bacteria.

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Transparency declarations
None to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References

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Kinetics of the interaction between avibactam and the CHE-1 class C ß-lactamase
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Keywords: CHE ß-lactamase, P99 ß-lactamase, inhibitors

Sir,
Avibactam is a non-ß-lactam inhibitor of class A, class C and some class D active-site serine ß-lactamases.1–3 On the basis of the

Table 1. Phenotypic and genotypic features of the P. aeruginosa and A. baumannii isolates

<table>
<thead>
<tr>
<th>Isolate no.</th>
<th>Source</th>
<th>Imipenem MIC (mg/L)</th>
<th>Hodge test result</th>
<th>MALDI-TOF MS Ultraflex essay</th>
<th>EDTA result</th>
<th>CarbAcineto result</th>
<th>CarbApénemase gene(s) detected</th>
<th>ST</th>
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<tr>
<td>PA_269</td>
<td>cattle</td>
<td>&gt;32</td>
<td>+</td>
<td>+</td>
<td>++ +</td>
<td>blaVIM-2</td>
<td>++</td>
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<td>++</td>
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</tr>
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<td>++ +</td>
<td>blaVIM-2</td>
<td>++</td>
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<td>++</td>
<td>ST1762</td>
</tr>
<tr>
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<td>&gt;32</td>
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<td>+</td>
<td>++ +</td>
<td>blaOXA-23</td>
<td>++</td>
<td>ST2</td>
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<tr>
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<td>pig</td>
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<td>+</td>
<td>++ +</td>
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<td>++</td>
<td>ST491</td>
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<td>fowl</td>
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<tr>
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<td>+</td>
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<td>blaOXA-23, blaOXA-58</td>
<td>++</td>
<td>ST20</td>
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<tr>
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<td>+</td>
<td>++ +</td>
<td>blaOXA-23</td>
<td>++</td>
<td>ST492</td>
</tr>
</tbody>
</table>

PA, P. aeruginosa; AB, A. baumannii.
structural analysis of the avibactam binding mode in class C enzymes and MIC determinations, Lahiri et al. suggested, in a recent paper, that the Enterobacter cloacae CHE β-lactamase was less sensitive to inhibition by avibactam than the P99 enzyme, from which it differs mainly by a six-residue deletion in the H-10 helix in addition to four other mutations, which did not appear to be involved in the sensitivity differences.

In this letter we present direct measurements of the interaction between avibactam and the CHE enzyme that confirm the decreased sensitivity suggested by Lahiri et al.

The production and purification of the enzyme will be described elsewhere. The analysis of the kinetic results was based on the two-step model:

\[
K_{\text{eq}} = \frac{k_{+2}}{k_{-2}}
\]

where \(E\) is the enzyme, \(A\) is avibactam, \(EA\) is a non-covalent complex (dissociation constant \(K\)), \(EA^*\) is the covalent adduct and \(k_{+2}\) and \(k_{-2}\) are first-order rate constants.

Unless otherwise stated, all experiments were performed at 30°C in 100 mM HEPES, pH 7.5, containing 0.2 M NaCl and 50 μg/mL BSA when the enzyme was diluted to <2.5 μM. The pseudo-first-order rate constants for inactivation (\(k_i\), see below) were determined by mixing the enzyme (6 nM) with avibactam (60–140 μM) and nitrocefin (58 μM). Hydrolysis of the reporter substrate (nitrocefin) was monitored at 482 nm for 40 min. The \(k_i\) values were deduced from the hydrolysis curves as described by De Meester et al. At the highest avibactam concentration, the \(k_i\) value was \(1.5 \times 10^{-3}\) s\(^{-1}\) and the residual activity at the end of the run was <2%, indicating a \(k_{-2}\) value <3 \times 10^{-5} \text{ s}^{-1}. The \(k_i\) values ranged from 1.00 to 1.5 \times 10^{-3} \text{ s}^{-1} and were thus not proportional to the avibactam concentrations. In consequence, a Hanes-type plot ([A]/\(k_i\) versus [A]) was utilized to determine the \(k_{+2}\) and \(K'\) values (Figure 1). Note that the general expression for \(k_i\) is:

\[
k_i = k_{-2} + k_{+2} \frac{[A]}{(K' + [A])}
\]

Figure 1. Determination of the \(k_{+2}\) and \(K'\) parameters. The slope of the line gives \(1/k_{+2}\) and the intercept with the ordinate \(K'/k_{+2}\). SD values were <15%.

To our knowledge, the CHE enzyme, which is considered to be an extended-spectrum AmpC (ESAC) β-lactamase, has only been observed once. Other ESAC enzymes, which do not present the six-residue deletion, seem to have retained full sensitivity to avibactam. One can only hope that the CHE-type deletion will remain rare and that the clinical utilization of avibactam will not result in the selection of mutants exhibiting a decreased sensitivity to this inactivator due to the same or similar mutations in the same region of the protein.
Acknowledgements
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Transparency declarations
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References

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Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis
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Key words: cephalosporins, CNS, MRSA

Sir,
Ceftaroline is a cephalosporin antibiotic indicated for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Ceftaroline has been used for non-FDA-approved indications, including osteomyelitis, endocarditis, bacteraemia and epidural abscesses. Data on use for meningitis are limited to two rabbit models, showing penetration into CSF of 14%–15% in inflamed meninges and 3% in uninfammned meninges. The distribution of drugs into the CSF is dependent upon multiple factors, including their lipophilicity, plasma protein binding and molecular size, and the affinity of active transport mechanisms to remove them from the CNS. Ceftaroline has low protein binding, is hydrophilic and has a similar volume of distribution to other cephalosporins. Cephalosporins distribute into the CSF relatively poorly, averaging AUCCSF/AUCserum ratios of 0.007–0.1 for uninfamed or mildly inflamed meninges and 0.15 for strongly inflamed meninges. However, due to their potency, many cephalosporins achieve therapeutic CSF concentrations.

We report a case of ceftaroline for the treatment of MRSA meningitis related to an infected ventriculoperitoneal (VP) shunt. This case report was reviewed and approved by our Institutional Review Board.

A patient presented with altered mental status and lethargy for 24 h. The patient had a history of hydrocephalus with chronic VP shunt placement and 1 month prior had undergone shunt replacement due to infection with methicillin-resistant Staphylococcus epidermidis, which was treated with vancomycin.

On presentation, vitals were stable. However, the patient suddenly desaturated to 40% oxygen on room air and was intubated. The white blood cell count was 23.6/mm³ with 93% segmented neutrophils and 4% bands. Arterial blood gas results were pH 7.55, pCO₂ 29 mmHg, pO₂ 216 mmHg and HCO₃⁻ 25.4 mmol/L. Serum creatinine was 0.5 mg/dL, which remained stable with an estimated creatinine clearance of >100 mL/min throughout admission. A CT scan showed new prominent dilatation of the lateral ventricles. The patient was diagnosed with obstructive hydrocephalus and taken to the operating room. Cefazolin was administered for surgical prophylaxis and a proximal shunt malfunction was addressed with insertion of a new proximal catheter. CSF was drawn from the shunt and sent for culture. The patient was transferred to the ICU.

On day 1 of admission, the CSF Gram stain report showed Gram-positive cocci in pairs and clusters. Fluid count was not completed. Infectious diseases consultation was requested for meningitis. On day 2, the patient became febrile at 39.1 °C and was taken to the operating room for removal of the shunt and placement of an external ventricular drain. A repeat CSF culture and the VP shunt tip were sent for analysis. The patient was started on linezolid, ceftriaxone and nafcillin and then switched to 600 mg of ceftaroline intravenously every 8 h on day 3. Vancomycin was avoided given recent use and concern for treatment failure. The CSF culture from day 1 was finalized as MRSA with a ceftaroline MIC = 1.0 mg/L by Etest. The CSF culture from day 2 was finalized as negative, while the shunt tip grew MRSA. By the time of finalization, the patient had been started on cefaroline and had additional repeat CSF cultures that were negative so ceftaroline was continued. Due to the lack of data on the use of ceftaroline for meningitis, samples of

Keywords: cephalosporins, CNS, MRSA