Activity of mecillinam against ESBL producers
in vitro

K. Thomas¹, M. J. Weinbren¹*, M. Warner², N. Woodford²
and D. Livermore²

¹Department of Microbiology, Coventry and Warwickshire
Hospital, University Hospitals of Coventry and Warwickshire,
Stoney Stanton Road, Coventry CV1 4FH, UK; ²Antibiotic
Resistance Monitoring and Reference Laboratory, Centre for
Infections, Health Protection Agency, 61 Colindale Avenue,
London NW9 5HT, UK

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*Corresponding author. Tel: +44-24-76844124; Fax: +44-24-
76220081; E-mail: michael.weinbren@uhcw.nhs.uk

Sir,

Extended-spectrum β-lactamases (ESBLs) have emerged as an
important mechanism of resistance in Gram-negative bacteria, pre-
senting challenges on several fronts. Until recently most ESBL
producers were nosocomial Klebsiella spp. with TEM or SHV
enzyme mutants; but this pattern has now changed, with the spread of
CTX-M ESBLs in community Escherichia coli as well as nosocomial Klebsiella spp.¹ Treatment failures and deaths have occurred when cephalosporins were used against infections caused by ESBL producers that appeared susceptible in vitro, meaning that routine susceptibility tests with individual β-lactams are unreliable and that direct ESBL detection tests are desirable.²

From a clinical perspective, ESBL-producing organisms frequently possess multiple resistance determinants to non-β-lactam antibiotics, including aminoglycosides and fluoroquinolones, leaving an extremely limited range of treatment options.³ The management of community urinary tract infections (UTIs) caused by ESBL pro-
ducers can be particularly difficult, and the paucity of active oral agents (essentially nitrofurantoin and fosfomycin) may necessitate the administration of a parenteral carbapenem.

Mecillinam (aminocillin), an oral penicillin with good in vitro
activity against Enterobacteriaceae, often appears active in vitro
against ESBL producers in standard MIC test conditions, but its ef
cicacy against infections caused by producers is uncertain.¹ To
investigate further, we undertook inoculum effect and synergy
studies using 30 ESBL-producing E. coli and Klebsiella spp.
These were selected to include representatives of current UK out-
break and non-clonal strains with CTX-M-15 enzymes, along with
reference E. coli J62-1 and J53-2 transconjugants with TEM and
SHV ESBLs.¹ Isolates were confirmed as ESBL producers using
cefpodoxime and cefpodoxime plus clavulanic acid discs on
Iso-Sensitest agar according to standard Health Protection Agency
and BSAC methods.³ Four MICs were determined by agar dilution on
Iso-Sensitest agar with or without clavulenate (GlaxoSmithKline,
Brentford, UK) at 2 or 4 mg/L. Inocula were adjusted to
comprise 10⁴ cfu/spot, as in standard BSAC tests, or 10⁵ cfu/
spot. The controls were E. coli NCTC 11954, with a classical
TEM-1 β-lactamase, and E. coli NCTC 12241 (ATCC 25922),
fully susceptible to β-lactams. Plates were incubated and results
recorded in-line with standard BSAC protocols.³

The combined results are summarized in Table 1. Mecillinam
MICs for CTX-M ESBL-positive E. coli and Klebsiella isolates
were 0.125–2 mg/L at an inoculum of 10⁴ cfu/spot, rising to 1–
16 mg/L at 10⁶ cfu/spot; MICs for E. coli with TEM-3, -9, -10
and SHV-2, -4 and -5 ESBLs were 4–64 mg/L at the low inoculum, rising to 64 mg/L at the higher inoculum. The β-lactamase-
negative control displayed no significant inoculum effect (MICs
of 0.125 mg/L and 0.25 mg/L at 10⁴ and 10⁶ cfu/spot, respectively)
whereas an effect was seen with the TEM-1-producing control
(MICs of 0.06 and 0.5 mg/L at 10⁴ and 10⁶ cfu/spot, respectively),
confirming that even classical penicillinas have activity against
mecillinam. The values compared with the BSAC’s urinary break-
points of susceptible, ≤1 mg/L; intermediate, 2 to 8 mg/L; and
resistant, ≥16 mg/L. Addition of clavulanate reduces the MICs
of mecillinam for ESBL producers, bringing the modal value, as
determined with an inoculum of 10⁶ cfu/spot, down from
8–16 mg/L to 0.03–0.06 mg/L, though a few producers remained
more resistant, perhaps owing to production of overwhelming
amounts of enzyme.

The raised mecillinam MICs at the higher inoculum and the MIC
reductions achieved by clavulanate both suggest that the com-
 pound is not stable to ESBLs and should not be used in severe
 infections caused by producers. It may potentially be useful in
 uncomplicated lower UTIs caused by ESBL producers with low
 MICs, because of the high levels of mecillinam achieved in the
 urine, but clinical investigation is needed. While several recent
 reviews of mecillinam’s potential in community UTI have
 appeared, they do not give clear guidance on the agent’s relative
efficacy in infections caused by ampicillin-susceptible and
-resistant E. coli, although its ability to TEM-1 enzyme is well
recognized. One Russian study, with only an abstract in English,
does note that mecillinam was less efficacious against E. coli with
R1 plasmid, which encodes TEM-1 enzyme, than against its
plasmid-free counterpart in a murine septicaemia model.⁷

Although mecillinam can show β-lactamase-independent synergy
with penicillins that bind to penicillin-binding proteins (PBPs) 1
and 3, this seems unlikely to have interfered with the present
interaction studies, both because no synergy was seen with the

Table 1. MIC distributions of mecillinam for 30 ESBL-producing
isolates

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>inoculum 10⁴ cfu/spot</th>
<th>inoculum 10⁵ cfu/spot</th>
<th>inoculum 4 mg/La</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03–0.06</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>0.125–0.25</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>0.5–1</td>
<td>20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2–4</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>8–16</td>
<td>3</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>≥32</td>
<td>2</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

*aOne strain failed to grow.
β-lactamase-negative control and, secondly, because clavulanate, like meccillinam, has primary affinity for PBP-2 of E. coli. The simultaneous administration of oral meccillinam with a compound containing a β-lactamase inhibitor such as co-amoxiclav appears promising, based on the present in vitro data, but cannot be advocated for clinical use without clinical evaluation.

**Transparency declarations**

We have no conflicts to declare.

**References**


**Correspondence**

We have no conflicts to declare.

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We have no conflicts to declare.

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