strains compared with only 14% of patients infected with non-ESBL-producing strains. Most of the patients received a dose of 200 mg three times daily in accordance with national guidelines. This was in contrast to the study by Jansa˚ker et al., 1 in which 77% of patients received twice this dose (400 mg three times daily), and this is likely to be a factor in the difference in outcomes between these studies.

Our study suggests that mecillinam is a relatively poor substrate for hydrolysis by NDM-1 carbapenemase and most of the isolates (83.9%) possessing this enzyme were susceptible under standard test conditions. The proportion of resistant isolates was much higher for K. pneumoniae (50%) than for E. coli (3.5%). Although there was a substantial increase in mecillinam resistance when the inoculum was increased 100-fold, this is likely to be the case for other antibiotics to which these bacteria are, on occasion, deemed to be susceptible—not least carbapenems.5 Enterobacteriaceae with NDM-1 are common in both hospitals and the community in areas of the Indian subcontinent5 and are isolated with increasing frequency in countries across the world.9 Such isolates frequently have resistance to a wide range of antimicrobials and treatment options may become increasingly limited. In such circumstances, the use of mecillinam alone, or in combination with other agents, may warrant further investigation into its potential in the treatment of uncomplicated UTI.

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Transparency declarations
None to declare.

References
and culture were negative. Approximately 21 days following the initial procedure, a repeat urinalysis showed pyuria with >50 white blood cells and urine culture showed growth of K. pneumoniae. On this occasion, the organism remained susceptible to tigecycline, but with an increased MIC of 2 mg/L. No treatment was initiated since she was asymptomatic and clinically stable. She had no further admissions for urinary tract infection or sepsis.

It is well known that certain microorganisms (e.g., Proteus) can cause stone formation through their ability to degrade urea using the enzyme urease and K. pneumoniae is one of those important urease producers. Complete removal of infected stones is paramount as residual stones can complicate the treatment of urinary tract infections by causing relapse of infection and persistent infection can likewise lead to ongoing stone formation. The successful outcome in this patient is attributed to adequate source control through extraction of her staghorn calculus as well as doubling the usual dose of tigecycline. Other studies have advocated the same (see the accompanying systematic review[7]). In conclusion, high-dose tigecycline may be a reasonable treatment option for multidrug-resistant urinary tract infections when effective source control can be accomplished.

Table 1. Pharmacokinetic parameters after the end of tigecycline infusion

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$C_s^{a,b,c}$ (mg/L)</th>
<th>AUC (mg-h/L)</th>
<th>(AUC (mg-h/L)</th>
<th>AUC/MIC$^{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>2.38</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>6</td>
<td>0.67</td>
<td>5.52</td>
<td>1.16</td>
<td>1.16</td>
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<td>0.4</td>
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<td>1.83</td>
<td>1.83</td>
</tr>
<tr>
<td>24</td>
<td>0.4</td>
<td>13.53</td>
<td>2.84</td>
<td>2.84</td>
</tr>
</tbody>
</table>

$^a$Tigecycline serum concentration ($C_s$) after 2 h infusion of a 200 mg intravenous dose.
$^b$Testing was by a validated HPLC method through the Center for Anti-Infective Research and Development (David P. Nicolau, Pharm.D at Hartford Hospital, Center for Anti-Infective Research).
$^c$The patient received tigecycline for 48 h at 200 mg intravenously daily prior to these samples.
$^d$Tigecycline MIC by Etest $= 1.0$ mg/L.

Follow-up cultures obtained on hospital day 2 were negative. After obtaining susceptibilities on her urine and blood isolates, therapy was changed to tigecycline monotherapy in an effort to avoid nephrotoxic agents. Since tigecycline in traditional doses (100 mg intravenously followed by 50 mg intravenously every 12 h) has low serum and urinary concentrations, we initially used a 200 mg intravenous loading dose followed by 100 mg intravenously every 12 h. The dose of tigecycline was subsequently changed to 200 mg intravenously every 24 h. Tigecycline serum levels were monitored while the patient was receiving 200 mg intravenously every 24 h (Table 1). We calculated the 24 h area under the concentration–time curve (AUC$_{24}$; mg-h/L) using the linear trapezoidal rule (Table 1). Assuming 79% protein binding, the AUC$_{24}$/MIC ratio for our patient was found to be 2.84 at 24 h post-infusion, indicating what should have been an adequate level of tigecycline in the bloodstream.

The patient ultimately developed intractable nausea on 200 mg of tigecycline intravenously every 24 h, so her dose was changed back to 100 mg intravenously every 12 h and the diluent volume was doubled. We also extended the infusion time from 1 to 2 h based on previous work showing that side effects may be lessened with a longer infusion time. With concurrent use of ondansetron, she tolerated this dose without further adverse effects. Repeat urine cultures initially showed persistence of the K. pneumoniae on day 6 of tigecycline treatment. This was not anticipated given the patient’s kidney stone, which presumably served as a nidus of persistent infection. After 15 days of tigecycline, she was taken to the operating room for percutaneous nephrolithotomy, removal of the right ureteral stent and placement of a left ureteral stent. She received two doses of perioperative amikacin. The patient tolerated the procedure well and finished two additional days of tigecycline to complete a 17 day course. She was discharged home in good condition the following day with a markedly improved creatinine of 2.9 mg/dL.

Two weeks following the urological procedure, a repeat urinalysis showed pyuria with >50 white blood cells and urine culture showed growth of K. pneumoniae. On this occasion, the organism remained susceptible to tigecycline, but with an increased MIC of 2 mg/L. No treatment was initiated since she was asymptomatic and clinically stable. She had no further admissions for urinary tract infection or sepsis.

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We acknowledge David P. Nicolau, Pharm D at Hartford Hospital, Center for Anti-Infective Research, for providing tigecycline serum concentrations (Table 1).

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Transparency declarations

None to declare.

References