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 Jansåker et al., 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 carbapenemases. Enterobacteriaceae with NDM-1 are common in both hospitals and the community in areas of the Indian subcontinent and are isolated with increasing frequency in countries across the world. 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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Favourable outcome in the treatment of carbapenem-resistant Enterobacteriaceae urinary tract infection with high-dose tigecycline

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Sir,
We report the case of a middle-aged woman with a history of insulin-dependent diabetes mellitus, chronic kidney disease and bilateral nephrolithiasis admitted to our hospital for weakness, falls and a 2 day history of diffuse abdominal pain. Admission vital signs showed a temperature of 96.4°F, a pulse of 94 bpm and blood pressure of 142/80 mmHg. Her examination showed a non-toxic appearing female with a diffusely tender abdomen. She had no rebound, guarding or flank tenderness. CT imaging of the abdomen revealed a small right-sided non-obstructing renal calculus, a previously placed right double-J ureteral stent and a large left staghorn calculus. Admission laboratory data included a white blood cell count of 26.3×109/L (89% neutrophils), haemoglobin 9.6 g/dL, platelets 352×109/L, blood urea nitrogen 69 mg/dL and creatinine 5.9 mg/dL (baseline creatinine 1.7 mg/dL). Using the Cockcroft and Gault method, the estimated creatinine clearance was ~20 mL/min.1 Urinalysis showed pyuria with >50 white blood cells and many bacteria. The patient was empirically treated with vancomycin and piperacillin/tazobactam. Her urine culture grew >100 000 cfu/mL of Klebsiella pneumoniae. Two sets of blood cultures drawn at the time of admission also grew K. pneumoniae. All isolates were a carbapenem-resistant K. pneumoniae susceptible to amikacin, colistin and tigecycline only. No molecular typing was performed. Susceptibility testing was performed initially using a Microscan Gram Negative Combo Panel 41 (Siemens Healthcare Diagnostics Inc., West Sacramento, CA, USA). Carbapenemase production was confirmed by the modified Hodge test performed in accordance with CLSI document M100-S20.2 For both blood and
urine isolates, an Etest was performed showing a tigecycline MIC of 1.0 mg/L, indicating susceptibility as defined by the FDA.3

Follow-up blood 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 intravenous load 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 ($\text{AUC}_{24}$; mg .h/L) using the linear trapezoidal rule (Table 1). Assuming 79% protein binding, the $\text{AUC}_{24}/\text{MIC}$ 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.4

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.5 With concurrent use of ondansetron, she tolerated this dose without further adverse effects. Repeat urine cultures initially showed persistence of the $\text{K. pneumoniae}$ 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 15,000 cfu/mL of $\text{K. pneumoniae}$. 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. $\text{Proteus}$) can cause stone formation through their ability to degrade urea using the enzyme urease and $\text{K. pneumoniae}$ is one of those important urease producers.6 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 review7). In conclusion, high-dose tigecycline may be a reasonable treatment option for multidrug-resistant urinary tract infections when effective source control can be accomplished.

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