Case Report

Successful treatment of pan-resistant *Klebsiella pneumoniae* pneumonia and bacteraemia with a combination of high-dose tigecycline and colistin

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The spread of antimicrobial resistance among members of the *Enterobacteriaceae* is a significant clinical threat. We report the treatment of pan-resistant *Klebsiella pneumoniae* bacteraemia with combination tigecycline and colistin in a 49-year-old male and review available therapeutic options. Despite a poor prognosis, the patient recovered, but remains colonized with the pan-resistant isolate.

Case report

A 49-year-old previously healthy male presented to an outside hospital with myalgias, fevers and shortness of breath and was diagnosed with novel H1N1 influenza and treated with oseltamivir. The patient developed acute respiratory distress syndrome requiring intubation. On hospital day 27, the patient's sputum cultures grew *Klebsiella pneumoniae*, which was resistant to all β-lactams, including carbapenems, aminoglycosides and fluoroquinolones (Table 1), and had intermediate susceptibility to amikacin and tigecycline. The patient's ongoing fevers, increased respiratory secretions and radiographic evidence of multilobar pneumonia on chest X-ray were consistent with hospital-acquired pneumonia. *K. pneumoniae* was persistently isolated from the patient's secretions despite prolonged imipenem (500 mg four times daily for 59 days), tigecycline (50 mg i.v. twice daily for 28 days) and minocycline (200 mg orally twice daily for 59 days) treatment. *K. pneumoniae* bacteraemia thought to be associated with the peripheral inserted central catheter (PICC) incited removal of this catheter. Following tracheostomy, the patient was transferred to our facility for a higher level of care after 72 days of hospitalization.

At the time of transfer, the patient's white blood cell count was 16 400 cells mm^{-3} with 87.4 % neutrophils and the presence of bands. Computed tomography of the chest revealed interstitial fibrosis. Three sets of BacT/Alert (bioMérieux) blood bottles, one drawn from the PICC,

grew *K. pneumoniae*. *K. pneumoniae* was also isolated from sputum cultures. Antibiotic susceptibilities were determined (Table 1) using a Clinical and Laboratory Standards Institute reference broth microdilution method (CLSI, 2009) or disc diffusion (fosfomycin). The isolate was resistant to carbapenems (Table 1), and carbapenemase production was confirmed by a positive Modified Hodge Test and PCR detection of the bla_{KPC} gene. Sequence analysis of the bla_{KPC} gene revealed a 100 % match to *K. pneumoniae* carbapenemase (KPC) type 2 sequence (NCBI GenBank accession no. GU086225).

The isolate was resistant to all other conventional antibiotics tested (summarized in Table 1), with the exception of tigecycline (MIC 2 µg ml^{-1}), fosfomycin (using the *Escherichia coli* urinary tract infection breakpoint of $\geqslant 16$ mm zone of growth inhibition surrounding the disc) and amikacin (MIC 32 µg ml^{-1}, intermediate resistance). The isolate was subsequently cultured from the patient's sputum throughout his hospital stay at our facility.

End point chequerboard antibiotic synergy tests were performed on the isolate, as described by Isenberg (1992). The combinations of tigecycline plus amikacin and tigecycline plus colistin were tested. The fractional inhibitory concentration [FIC (MIC of antibiotic in combination)/ (MIC of antibiotic alone)] was determined for each antibiotic agent in the combination, and these FICs were summed to determine the FIC index. Both combinations exhibited indifference (0.5 < ΣFIC < 4; Table 1).

The patient was thought to have bloodstream infection related to an infected venous catheter (PICC line). The line was removed and the patient was treated with i.v. (350 mg

Table 1. Select MICs of antibiotics tested for the *Klebsiella pneumoniae* isolate

MBC, Minimum bactericidal concentration; R, resistant; I, intermediately susceptible; S, susceptible; ND, not done; FIC, fractional inhibitory concentration.

Antibiotic	MIC	MIC interpretation	MBC
Ampicillin	>32	R	ND
Ampicillin/sulbactam	>32	R	ND
Piperacillin/tazobactam	512	R	ND
Cefazolin	>32	R	ND
Ceftriaxone	>32	R	ND
Meropenem	>16	R	ND
Ertapenem	>16	R	ND
Imipenem	>16	R	ND
Amikacin	32	I	ND
Gentamicin	>10	R	ND
Tobramycin	>10	R	ND
Ciprofloxacin	>2	R	ND
Trimethoprim/ sulfamethoxazole	>4/80	R	ND
Colistin	>8	R	ND
Tigecycline	2	S	>128
Fosfomycin*	26 mm	S	ND

Antibiotic combinations	FIC index†	Interpretation
Tigecycline + amikacin	1.25	Indifference
Tigecycline + colistin	0.56	Indifference

*Fosfomycin was tested by disc diffusion.
†FIC index was determined by Σ (MIC of the agents in combination/MIC of the agent alone).

daily) and inhaled (75 mg twice daily) colistin, high-dose tigecycline (200 mg i.v. daily) and i.v. amikacin (500 mg every 12 h for 10 days) and his bacteraemia resolved on hospital day 75. No bacteria were recovered from culture of the PICC tip. The patient was transferred to a long-term acute care hospital for ventilator weaning following improvement in respiratory status on hospital day 95. Despite a poor prognosis, the patient was successfully weaned from the ventilator following 185 hospital days. Rectal swab surveillance cultures from the patient at that time revealed the pan-resistant *K. pneumoniae*, as did sputum cultures. The identity of these isolates was confirmed by PFGE, using a standard protocol on *Xba*I-digested genomic DNA. This revealed identical banding patterns between all *K. pneumoniae* isolates from this patient throughout his hospital course (not shown). PFGE was also performed by the Centers for Disease Control and Prevention, where it was determined that the isolate shared >80 % similarity with other multilocus sequence type 258 (ST 258) *K. pneumoniae* isolates. ST 258 is the dominant strain of KPC-producing *K. pneumoniae* seen in the United States.

Discussion

Literature following the H1N1 epidemic has identified *Streptococcus pneumoniae* infection as a significant correlate to disease severity in some patients (Palacios *et al.*, 2009). *K. pneumoniae*, *Acinetobacter baumannii* and meticillin-resistant *Staphylococcus aureus* superinfections have also been documented, but all were associated with mild disease. In our patient, H1N1 disease likely set the stage for pneumonia and sepsis due to multidrug-resistant *K. pneumoniae*, an organism he remained colonized with at the time of his discharge.

The increasing spread of antimicrobial drug resistance among members of the *Enterobacteriaceae* poses a significant clinical problem due to limited treatment options. Of particular importance is the production of plasmid-encoded carbapenemases by these pathogens. KPC-producing isolates, in addition to being resistant *in vitro* to all β-lactams and carbapenems, are also frequently resistant to quinolones and aminoglycosides, leaving the therapeutic options limited to tigecycline or colistin (Nordmann *et al.*, 2009). However, in the New York City area, reports of colistin- and tigecycline-resistant isolates have emerged (Elemam *et al.*, 2009); these isolates are commonly referred to as pan-resistant, owing to their resistance to all routine antibiotics. To the best of our knowledge, this is the first report of pan-resistant *K. pneumoniae* on the western coast of the United States.

While well established on the eastern coast of the USA, KPC-producing *K. pneumoniae* isolates have only recently been documented in southern California (Kitchel *et al.*, 2009; Le *et al.*, 2010). The isolate's tigecycline MIC (1 µg ml^{-1}) is classified as susceptible by the Food and Drug Administration (FDA) criteria, which suggest a breakpoint of 2 µg ml^{-1}. However, significant concern exists regarding the effectiveness of tigecycline for the treatment of bloodstream infections caused by pathogens with such elevated MICs (Scheetz *et al.*, 2007), as only 1 mg l^{-1} can be achieved in serum using recommended dosing (100 mg i.v. followed by 50 mg i.v. twice daily). Some success has been noted using high-dose tigecycline for the treatment of bacteraemia (Cunha, 2009), with evidence that high-dose tigecycline allows serum concentrations of up to 12 mg l^{-1} (Agwuh & MacGowan, 2006). Reports of treatment-emergent tigecycline resistance exist; however, a large multi-centre study that documented the outcomes of long-term tigecycline treatment found no increase in tigecycline resistance in multiple Gram-negative organisms (Vasilev *et al.*, 2008). Recently, tigecycline (Kelesidis *et al.*, 2008) has been suggested as a valuable option for the treatment of KPC-producing *K. pneumoniae*, as 91.2 % of isolates (*n*=2627 isolates) remained susceptible. In our case, bacteraemia was successfully treated after removal of the PICC line and combination treatment of high-dose tigecycline, colistin and amikacin. The relative role of each of these interventions in the resolution of the patient's bacteraemia is unknown, but we feel that removal of the line was perhaps the most significant intervention. It is difficult to

ascertain the effect of the combination of tigecycline, colistin and amikacin *in vivo*, in light of indifferent synergy results obtained *in vitro*. Regardless, left with no other therapeutic options, the combination of tigecycline (high-dose regimen) and colistin was used, based on evidence that higher serum concentrations may be obtained for tigecycline *in vivo* with high dosage. It is also important to note that we observed no change in tigecycline MICs between the original *K. pneumoniae* isolate and those isolated at the time of the patient's discharge home, despite 5 months of continual tigecycline treatment.

The *K. pneumoniae* isolate was also resistant to colistin, which we defined using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria of 2 μg ml^{-1}, in the absence of Clinical and Laboratory Standards Institute or FDA interpretive criteria. Interestingly, while our patient was treated at both the outside hospital and at our facility with tigecycline, colistin treatment only commenced upon transfer to our facility, and following isolation of the colistin-resistant *K. pneumoniae*.

Intravenous fosfomycin has been proposed as a treatment option for serious infections caused by pan-resistant *K. pneumoniae* (Falagas *et al.*, 2010); all *K. pneumoniae* isolates from our patient were susceptible to fosfomycin *in vitro* (Table 1). No intravenous formulation of fosfomycin is approved by the FDA.

Of concern from an infection control perspective is the continued carriage of a pan-resistant *K. pneumoniae* strain by our patient at the time of discharge home. Similarly, Elemam *et al.* (2009) reported continued colonization of a 70-year-old woman by pan-resistant *K. pneumoniae* following a urinary tract infection. In a more extensive study, Perez *et al.* (2010) documented outcomes for 13 patients infected with carbapenem-resistant *K. pneumoniae* isolates. Of the 13 patients, 4 expired from their infections, 5 remained colonized with the carbapenem-resistant *K. pneumoniae* and 2 obtained microbiological clearance of the organism (Perez *et al.*, 2010). Like our patient, all but one persistently colonized patient was discharged to a long-term care facility, which are well-known for the spread and maintenance of multidrug-resistant organisms. Surveillance cultures of other patients at the ventilator facility did not indicate the spread of the isolate through this patient population. Spread at our institution is unlikely, with appropriate infection control practices, as all rooms are single bed. Furthermore, no other pan-resistant or carbapenem-resistant *K. pneumoniae* have since been isolated from patients at our institution. The potential to spread of KPC-producing and pan-resistant *K. pneumoniae* in hospital settings is clearly present nonetheless. In an attempt to stop the spread of these organisms, some have proposed targeted surveillance to identify patients with gastrointestinal colonization. Such measures, when combined with intensified infection control practices, have garnered success in reducing the incidence of KPC-producing *K. pneumoniae* at one facility (Kochar *et al.*, 2009), and would likely be an effective strategy to prevent the spread of pan-resistant isolates.

Clinicians are left with few therapeutic options for the treatment of pan-resistant *K. pneumoniae* infection, an organism associated with significant mortality. We present, to our knowledge, the first report of a pan-resistant *K. pneumoniae* isolate in the western United States. This case illustrates that the combination of colistin and high-dose tigecycline may be useful in the treatment of these infections. While our patient was able to recover from his infection, the spread of pan-resistant *K. pneumoniae* in acute care facilities could lead to significant morbidity and mortality.

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