Carbapenemase-producing *Klebsiella pneumoniae*: a major clinical challenge

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Clinical record

A 59-year-old man from rural Victoria, with no hospital contact for 15 years or recent history of international travel, presented to his local hospital with severe acute pancreatitis secondary to gallstones. He was transferred to a metropolitan hospital for further management, including intermittent admissions to the intensive care unit (ICU) for haemodynamic support. On Day 4 of admission, empirical antibiotics were prescribed for severe pancreatitis and concurrent nosocomial pneumonia, according to hospital guidelines and advice from the infectious diseases team; initially ceftriaxone, later changed to piperacillin–tazobactam and then meropenem, due to clinical deterioration. Diagnostic microbiology did not reveal any significant pathogens.

Serial computed tomography demonstrated persistent peri-pancreatic fluid collections despite repeated percutaneous drainage and broad-spectrum antibiotics. One month into admission, vancomycin-resistant *Enterococcus faecium*, *Candida albicans* and *Stenotrophomonas maltophilia* were identified in peri-pancreatic fluid. Contact precautions were implemented, and an infectious diseases physician recommended piperacillin–tazobactam, fluconazole, co-trimoxazole and linezolid (later changed to teicoplanin) to cover these organisms. Teicoplanin, co-trimoxazole and fluconazole were ceased after 8 weeks of treatment.

Pancreatic debridement performed 2 months into admission due to persistent pancreatic infection identified carbapenem-resistant *Klebsiella pneumoniae* in the pancreatic tissue. Testing by polymerase chain reaction detected the bla_{KPC-2} gene. Antimicrobial-susceptibility results are shown in the Box. Surrounding patients were screened.

Owing to limited antibiotic options, gentamicin combined with dual carbapenems (high-dose prolonged meropenem infusion three times a day combined with daily ertapenem) was prescribed for the *K. pneumoniae*. Gentamicin was continued for 3 weeks in conjunction with repeated pancreatic debridements in an attempt to control infection. Oliguric renal failure and sepsis developed, requiring ICU transfer, renal replacement therapy and cessation of gentamicin.

Three months into admission, following further attempted pancreatic debridement, multiple blood cultures grew bla_{KPC-2}-producing *K. pneumoniae* that now demonstrated intermediate gentamicin susceptibility (minimum inhibitory concentration, 8 µg/L). Renal replacement therapy continued, all intravenous lines were replaced, two doses of gentamicin were administered and intravenous doxycycline was added to meropenem, ertapenem and fluconazole. Repeat blood cultures were negative. Application for compassionate access to ceftazidime–avibactam was made (to which the isolate was susceptible) and it was supplied 1 week later.

Because of further deterioration and isolation of doxycycline-resistant *K. pneumoniae* from abdominal fluid, antibiotics were changed to ceftazidime–avibactam (adjusted for renal function), metronidazole and teicoplanin. Over the next 3 weeks while receiving these agents, the patient had resolution of fever, a decrease in serum inflammatory markers, reduction in vasopressor requirements and radiological improvement of the peri-pancreatic collections. No side effects were reported from ceftazidime–avibactam.

During the fifth month, a laparotomy was performed in a final attempt to control pancreatic infection, but was unsuccessful due to the compromised state of pancreatic and peri-pancreatic tissues. Intra-abdominal drain tube fluid continued to grow bla_{KPC-2}-producing *K. pneumoniae* that was susceptible to ceftazidime–avibactam. Shortly after this, and following discussion with the patient, family and treating teams, the patient was discharged home for palliation and died soon after. ◆

Initial *Klebsiella pneumoniae* antimicrobial-susceptibility results*

Antibiotic	Resistance	MIC (µg/mL)
Amoxycillin-clavulanic acid	R	≥ 32
Piperacillin–tazobactam	R	≥ 128
Ceftriaxone	R	≥ 64
Cefepime	R	≥ 64
Cefoxitin	R	≥ 64
Ciprofloxacin	R	≥ 4
Meropenem	R	≥ 16
Amikacin	R	≥ 64
Tobramycin	R	≥ 16
Gentamicin	S	4
Co-trimoxazole	R	≥ 320
Nitrofurantoin	R	≥ 512
Colistin†	R	4
Fosfomycin†	R	≥ 1024
Tigecycline†	R	4
Tetracycline–doxycycline	S	4

MIC = minimum inhibitory concentration. R = resistant. S = susceptible. * Using Vitek 2 gram-negative antibiotic susceptibility cards (bioMérieux) according to Clinical and Laboratory Standards Institute (CLSI) interpretative criteria, unless otherwise indicated. † Etest (bioMérieux), according to European Committee on Antimicrobial Susceptibility Testing interpretative criteria (CLSI interpretative criteria not available). ◆

Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacteriaceae have been responsible for nosocomial outbreaks worldwide and have become endemic in several countries. These organisms provide immense challenges for healthcare systems, health care providers and patients. Reports of KPC-producing organisms in Australia have been uncommon, with most cases found to be imported

from endemic countries.[1] Genes responsible for KPC production (eg, bla_{KPC-2}) are acquired via transferable plasmids and, when expressed, result in enzymatic hydrolysis of all β-lactams including carbapenems.[2] Additional antimicrobial resistance genes frequently accompany carbapenem-resistance mechanisms, limiting the choice of effective antimicrobials.[2]

Multiple risk factors have been associated with carbapenem-resistant Enterobacteriaceae (CRE) acquisition. These include prolonged duration of hospital stay, receipt of broad-spectrum antibiotics, presence of invasive devices, use of mechanical ventilation, total parental nutrition or nasogastric feeds, and colonisation pressure.[3]

Such infections pose management challenges given their propensity for causing severe sepsis in patients with multiple comorbidities. Many remaining active antibiotics have limitations in terms of efficacy (eg, tigecycline is not ideal for bacteraemia or urinary tract infections) and toxicity (eg, colistin can have significant nephrotoxicity).

There is a paucity of evidence to guide management decisions, and optimal antibiotic treatment is unknown.[4,5] Current expert recommendations are largely based on retrospective observational data. These suggest that combination therapy with two or three active agents should be used. Antibiotic classes including fluoroquinolones and sulphonamides are usually inactive against these organisms. Despite the inherent presence of carbapenemases, inclusion of meropenem (usually high-dose extended infusions) in treatment regimens is usually recommended.[4,5] However, more recent studies have suggested that a benefit may be restricted to isolates with only low-level carbapenem resistance (minimum inhibitory concentration, ≤ 8 μg/mL).[4] At the time of this case, a small number of reports used dual carbapenems as salvage therapy for pandrug-resistant *K. pneumoniae*, which informed the decision to use combination ertapenem and meropenem. However, the clinical value of this practice remains uncertain.[6,7]

Ceftazidime–avibactam plus metronidazole has been shown in Phase II studies to have similar efficacy in complicated intra-abdominal infections when compared with meropenem,[8] and has been approved for this indication in the United States by the Food and Drug Administration. Avibactam is a new β-lactamase inhibitor in the diazabicyclooctane class and, in combination with ceftazidime, retains activity against some KPC-producing Enterobacteriaceae in vitro.[9] There is a paucity of clinical data relating specifically to its efficacy in infections caused by KPC-producing Enterobacteriaceae. Our patient demonstrated a clinical, biochemical and radiological response after administration of ceftazidime–avibactam, metronidazole and teicoplanin, with no development of in vitro resistance after 6 weeks of treatment. However, microbiological clearance was not achieved. Given that early treatment may be effective in managing CRE infections, timely access to antibiotics such as ceftazidime–avibactam and associated antibiotic susceptibility testing in Australia is crucial.

CRE infections are an increasing problem that Australian hospitals are facing; now in both local residents and returned travellers.[10] Combination strategies and newer agents under investigation, such as ceftazidime–avibactam, are potential treatment options.

Lessons from practice

- Carbapenem-resistant Enterobacteriaceae (CRE) infections pose a clinical challenge for management with limited effective antibiotics available.
- New strategies, and new antibiotics, will be required to manage the increasing threat of CRE.
- Ceftazidime–avibactam, a novel antimicrobial combination with activity against many CRE, may be a future option for treating such infections. ◆

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