



Case report

Successful treatment of multidrug resistant *Klebsiella pneumoniae* using dual carbapenem regimen in immunocompromised patient



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ABSTRACT

This report describes a longitudinal case of immunocompromised patient post kidney transplant who was admitted to our institution repeatedly for treatment of various infections caused by multi-drug resistant *Klebsiella pneumoniae*. The patient was successfully treated with a combination of ertapenem/meropenem on multiple occasions despite the elevated MICs. Our observations corroborate previous preclinical studies and case reports showing the efficacy of double carbapenem regimens against resistant Enterobacteriaceae.

Introduction

Infections caused by Enterobacteriaceae that exhibit resistance to major antibiotic classes including carbapenems, represent a therapeutic dilemma and innovative approaches are warranted [1]. In this context, *in vitro* studies [2,3] suggested the potential synergy of double carbapenem therapy and animal studies [4,5] substantiated the evidence of combination efficacy *in vivo*. In the absence of clinical trial data to support this approach, we are reporting a longitudinal case study describing repeatedly successful treatment of an immunocompromised patient infected with carbapenemase-producing *Klebsiella pneumoniae* (KP).

Case report

The patient is a 62-year-old Caucasian female weighing 84 kg, BMI 34, with multiple admissions secondary to repeated KP infections at various sites. The patient's medical history is significant for reno-vascular hypertension, type 2 diabetes, dyslipidemia, non-STEMI and end stage renal disease for which she underwent kidney transplant 4 years prior to first admission and was maintained on immunosuppressive regimen consisting of mycophenolate 500 mg twice daily, tacrolimus 3 mg twice daily and prednisolone 5 mg daily.

First admission (December 2015), the patient was transferred to our institution for the treatment of acute pancreatitis with pseudocyst formation attributed potentially to the use of tigecycline [6] for a

recurrent urinary tract infection caused by carbapenem-resistant KP. Tigecycline was chosen in the transferring institution prior to admission subsequent to culture and sensitivity results showing sensitivity to tigecycline but fosfomycin was not tested. The patient was given 1 dose of fosfomycin 3 g PO initially. On day 6, the patient developed fever and leukocytosis. Urine culture was positive for KP sensitive to fosfomycin (resistant to colistin, aminoglycosides and carbapenems). Meropenem 1 g q8 h (14 days for the treatment of pancreatitis) and fosfomycin PO 3 g × 2 doses were prescribed. Initial Improvement was noted and repeated urine culture was negative on day 8. Patient continued to have abdominal pain and the possibility of hemorrhagic pancreatic pseudocyst was considered. On day 29, the patient underwent endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) and fine needle aspiration (FNA) of the pseudocyst. Post-procedure course was complicated by presumed sepsis and she was transferred to Intensive Care Unit (ICU) where empiric treatment with vancomycin, ciprofloxacin, amikacin and caspofungin was initiated, additionally tacrolimus and mycophenolate were temporarily halted. Microbiological cultures demonstrated growth of coagulase-negative Staphylococci from blood and catheter tip. On day33, ciprofloxacin was replaced by meropenem and amikacin was discontinued the following day. A treatment period of 4 weeks was planned for meropenem and caspofungin. A rectal swab revealed colonization with carbapenem-resistant Enterobacteriaceae (CRE) KP demonstrating the same previous phenotype. On day 42, the clinical course was complicated by gastrointestinal bleeding. Hypoxia and lung consolidation

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Table 1
Susceptibility results of the isolated *Klebsiella pneumoniae*.

Antibiotic	Phenotype	MIC µg/mL Microscan
Amikacin	R	≥ 64
Ampicillin/Sulbactam	R	≥ 32
Cefepime	R	≥ 64
Cefoxitin	R	≥ 64
Ceftazidime-Avibactam	R	> 256
Ceftolozane/Tazobactam	R	> 256
Ceftriaxone	R	≥ 64
Ciprofloxacin	R	≥ 4
Colistin	R	≥ 16
Ertapenem	R	≥ 8
Fosfomycin	R, I	No clear points
Gentamicin	R	≥ 16
Minocycline	R	≥ 16
Piperacillin/Tazobactam	R	≥ 128
Tigecycline	S	0.25
Tobramycin	R	≥ 16
Trimethoprim/Sulfa	R	≥ 320

developed on day 47. The culture of bronchoalveolar lavage (BAL) done on day 49 grew KP resistant to the antibiotics listed earlier in addition to fosfomycin and ceftazidime/avibactam. The patient was not previously exposed to ceftazidime/avibactam due to recent commercial availability in United Arab Emirates, this antibiotic was added to the tested panel in an attempt to seek other therapeutic options for the patient. On day 51 blood cultures grew same organism plus *Enterococcus faecium*. Consequently, vancomycin was added empirically to the antibiotic regimen. Abdominal CT scan detected a pancreatic-pseudocyst-related soft tissue inflammatory changes raising the possibility of necrotic abscess. On day 62, the patient was resuscitated following a cardiac arrest and a combination of ertapenem 1 g q24 h and meropenem 1 g q8 h replaced all antibiotics as a salvage therapy. On day 71, our patient underwent cyst drainage which grew KP with the same resistance profile. Necrosectomy for source control was performed on day 77. *Candida parapsilosis* fungemia was detected and treated with fluconazole. Abdominal fluid cultures grew KP again with the same resistance profile. Combination therapy was continued for 4 weeks with a good clinical response. Nine days following cessation of antibiotics, patient spiked a fever and grew a resistant KP from urine. Combination ertapenem and meropenem was re-administered for 7 days with resolution of symptoms and microbiological clearance. The patient was discharged after a total of 105 days of hospitalization. Colonization screening through rectal swab showed KP producing carbapenemases (NDM and OXA) as evidenced by PCR. Whole genome sequencing to explore the complete set of resistance genes was not done but KPC production was excluded by PCR. Surprisingly, despite using low immunosuppression (tacrolimus with levels of 4–6 ng/dL and 5 mg of prednisolone), the kidney function continued to be stable throughout the course of the infections except for temporary worsening due to sepsis episodes and severe pneumonia.

Second admission, the patient was admitted 19 days later through outpatient clinic with dysuria and left costovertebral angle tenderness. Urine culture grew KP (the same as previous phenotype) resistant to the tested antibiotic panel (including fosfomycin and ceftazidime/avibactam) except tigecycline Table 1. The patient was prescribed the ertapenem and meropenem combination, repeat urine culture 6 days later was negative. The patient completed 10-day treatment course with the resultant resolution of symptoms.

Third admission (day 63 post latest discharge) due to 1 day history of fever and chills. She was noted to have an abscess on the right buttock that was drained and grew *Streptococcus* sp, *E. Coli*, and susceptible *K. oxytoca*. In addition, blood cultures grew KP resistant to all antibiotics except colistin and tigecycline. The double carbapenem regimen (ertapenem and meropenem) was given for 2 weeks following

which the patient was discharged with good clinical response.

Fourth admission (day 56 post latest discharge) was secondary to fever and respiratory symptoms. Chest X-ray and computed tomography scan were suggestive of right lower lobe necrotizing pneumonia for which ertapenem and meropenem. A sputum culture grew methicillin-sensitive *Staphylococcus aureus* (MSSA) and KP of the same phenotype. The carbapenem combination was continued for 4 weeks with favorable clinical and microbiological response, after which she was discharged. The screening rectal swab remained positive for carbapenemase producing KP.

By the end of 2016 (day 58 post latest discharge), the patient was admitted for the fifth time with fever, thigh abscess and urinary symptoms. The abscess was drained, both fluid and urine culture grew KP with same phenotype. Combination therapy with ertapenem and meropenem was reinstated for 2 weeks with good clinical and microbiological response. She was subsequently discharged with no further complication up to the time of writing this report (recent urine culture March 2017 is negative).

Several publications have described the use of double carbapenem regimens in the treatment of multi-drug resistant Enterobacteriaceae. Oliva et al. reported eradicating 3 blood stream infections caused by KPC (serine-type carbapenemase) producing KP, using a combination of meropenem and ertapenem [7]. Similarly, Giamarellou et al. reported the efficacy of ertapenem plus either meropenem or doripenem against KPC producing KP in bacteremia and urinary tract infection (UTI) [8]. Moreover, Cecarrel et al. delineated the treatment of ventilator associated pneumonia caused by KPC producing KP with ertapenem/doripenem regimen [9]. Recently, a blood stream infection caused by KPC producing *Escherichia coli* was treated with ertapenem/meropenem combination in a renal transplant patient [10].

Herein, in our case, we are reporting the consistent activity of meropenem and ertapenem combination against a strain of MDR KP in eradicating infections from different organs. Our observations reflect approximately 2 years of maintained contact with the patient revealing the utility of repeated use of this regimen without loss of efficacy, the ability of the combination therapy to combat different infection types and importantly the efficacy against distinct resistance genotype manifested by the combination of NDM and OXA carbapenemases (metallo and serine – β -lactamases).

Of note, the 2 carbapenems were prescribed in conventional doses administered in intermittent fashion with adjustment for renal function based on creatinine clearance if warranted and no adverse drug events leading to discontinuation of therapy were reported. Additionally, as it is not a standard clinical practice, genotypic sequencing to investigate the clone of the isolated strains was not performed but nearly identical phenotypic profiles were observed. Finally, combination of ceftazidime/avibactam plus aztreonam could have been other possibility to consider for this patient [11].

While case reports may provide preliminary insights for the treatment of these recalcitrant infections, the place of double carbapenem regimens in therapy remains to be defined in randomized clinical trials.

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Declaration of transparency

All the authors declare no conflict of interest.

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