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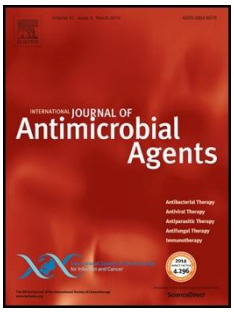

Title: Evidence of clinical response and stability of Ceftolozane/Tazobactam used to treat A carbapenem-resistant *Pseudomonas aeruginosa* lung abscess on an outpatient antimicrobial program

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EVIDENCE OF CLINICAL RESPONSE AND STABILITY OF CEFTOLOZANE/TAZOBACTAM USED TO TREAT A CARBAPENEM-RESISTANT *PSEUDOMONAS AERUGINOSA* LUNG ABSCESS ON AN OUTPATIENT ANTIMICROBIAL PROGRAM

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Sir,

Ceftolozane/Tazobactam (C/T) is a cephalosporin and β-lactamase inhibitor with potent activity against *Pseudomonas aeruginosa* [1]. There is limited experience with C/T as a continuous infusion, and as such, to ensure attainment of pharmacodynamic targets, therapeutic drug monitoring (TDM) should be undertaken. It is unknown whether temperature or other deviations that occur when the infusion is run in the community affect overall drug stability and exposure. Here we report a case of a patient who received C/T where drug concentrations were measured in the hospital and then later in the community.

A 58 year-old male with a renal transplant was admitted to a tertiary referral hospital following subacute fevers. No prior infections were noted. On admission, computed tomography of his chest revealed a four-centimetre cavitating lung lesion within the right upper lobe of the lung. A pan-susceptible *Pseudomonas aeruginosa* was isolated via bronchoscopy and initial therapy of meropenem 1g IV three times daily was commenced. His clinical condition worsened and he required inotropic support in the intensive care unit (ICU). He developed acute kidney injury with a serum creatinine rise to 231 μmol/L (baseline serum creatinine 96 μmol/L), however, did not require renal replacement therapy. He was discharged to a medical ward and went on to complete a total of fourteen days of meropenem. Five days after cessation of antibiotic therapy the patient became febrile. Repeat imaging of his chest revealed progression of the cavitating lung abscess. An induced sputum sample taken revealed a *P. aeruginosa* isolate resistant to meropenem, ciprofloxacin and ceftazidime. The C/T MIC was determined by E-Test as 2 mg/L (susceptible) and the patient was

commenced on a 3/1.5g per 24-hour continuous C/T infusion. The infusion composition was C/T 3g/1.5g in (final volume) 300mL 0.9% sodium chloride and administered via a CADD pump. Following clinical and biochemical improvement (C-reactive protein <2mg/L), he was planned for discharge to his home in via an Outpatient Parenteral Antibiotic Therapy (OPAT) service. Repeat imaging of his chest after 42 days of C/T therapy revealed a significant reduction in size of the cavitating lung lesion.

Three blood samples were taken at pharmacokinetic steady state (after 24-hours of ceftolozane continuous infusion therapy), initially while the patient was an inpatient, then two weeks later whilst on the OPAT program. This occurred during April 2017 (local reported temperatures ranged from 13.0-29.0 degrees Celsius [2]) with samples separated by at least 4-hours. Drug concentrations of ceftolozane and tazobactam in plasma were measured by a validated UHPLC-MS/MS method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer**.** The mean $\pm$ SD drug concentrations in the hospital and community were 37.3 $\pm$ 1.4 versus 34.8 $\pm$ 0.2 for ceftolozane and 6.57 $\pm$ 1.78 versus 7.66 $\pm$ 0.79 mg/L for tazobactam respectively. The individual patient concentrations are shown in Figure 1a and 1b.

This is the first known report of C/T continuous infusion therapy used to treat a multi-drug resistant *Pseudomonas aeruginosa* pulmonary infection. This report outlines the successful use of a long course of C/T in an immunosuppressed patient delivered through an OPAT service. There did not appear to be a significant difference in unbound drug concentrations measured in the hospital as compared with the

community setting, as well as between designated time points throughout the day (minimum 4-hour gap between samples).

There have been only two reports of the successful use of C/T as a continuous infusion [3]. C/T is known to be stable for at least 24 hours at room temperature making it a suitable candidate for continuous infusion [3]. A study evaluating the stability of C/T in elastomeric pumps determined physical and chemical stability of at least 7 days with greater than 93% drug recovery at this time [4].

Recommended dosing of C/T in patients with a creatinine clearance of >50ml/min is 1.5g, over a 1-hour infusion, every 8 hours [4]. The decision to use the standard dose (3g/1.5g) in this patient was due to his low body weight (approx. 65kg), creatinine clearance of 55 mL/min and that the patient was not critically unwell at the time of treatment initiation. The unbound ceftolozane concentrations in plasma were well above the 4-5 times the MIC value that is associated with maximal bacterial killing. The mean penetration of ceftolozane into epithelial lining fluid is suggested to be 50% of plasma concentrations [5]. Using this figure, the concentrations were likely to be greater than 4-5 times the MIC at the site of infection for the full dosing interval.

C/T as a continuous infusion administered in the community setting was found to be effective in the treatment of a carbapenem-resistant *P. aeruginosa* lung abscess. More investigations are required to characterise the pharmacokinetics of C/T in different patient populations as well as its stability in different clinical scenarios to further optimise its use.

Declarations

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Competing Interests: No conflicts of interest

Ethical Approval: Not required

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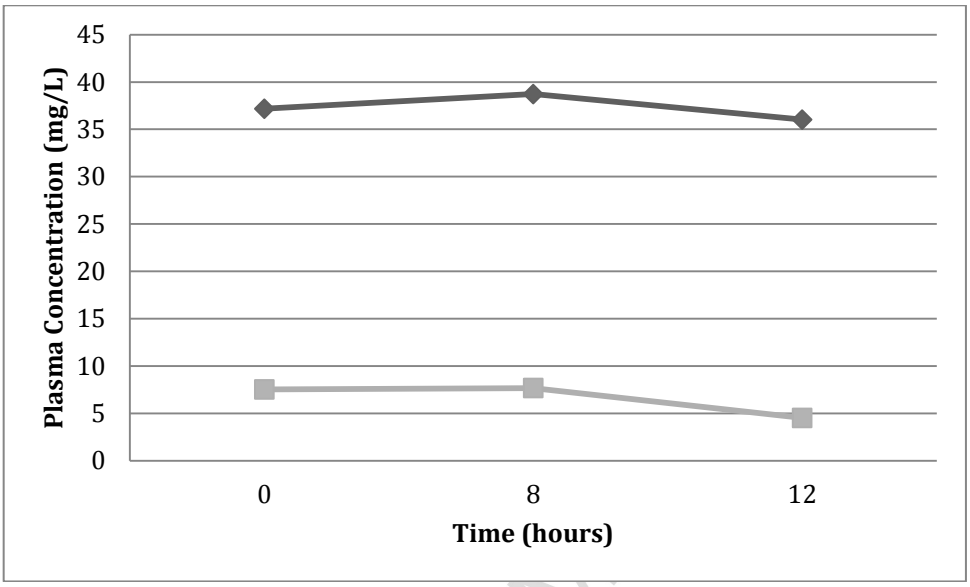
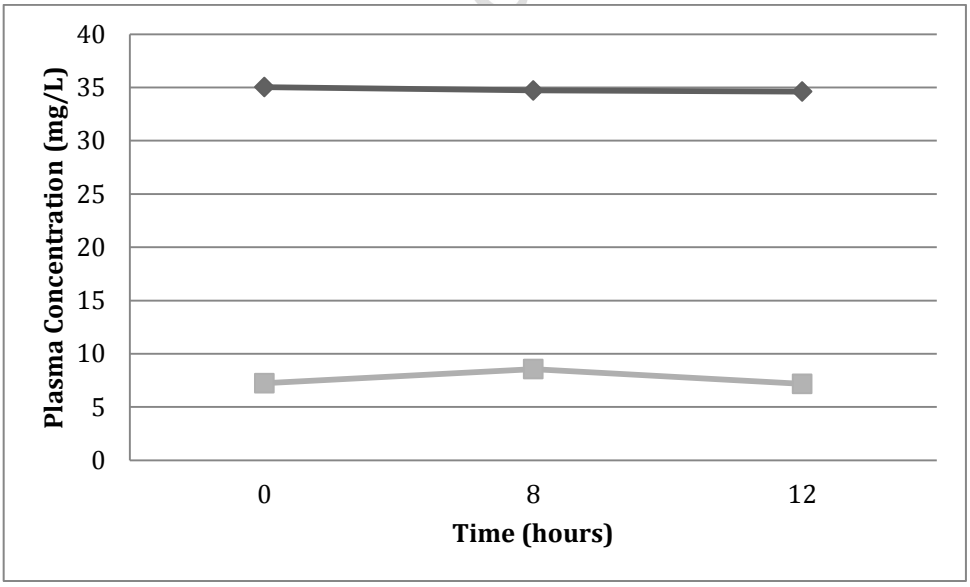
FIGURES

1. Unbound Ceftolozane/Tazobactam plasma concentrations (mg/L) in both hospital and community settings using a continuous infusion of 3/1.5g over twenty-four hours (samples taken two weeks apart)

1a. Hospital



1b. Community



Ceftolozane (mg/L)

Tazobactam (mg/L)