Clinical Experience with Ceftolozane/Tazobactam at a London Teaching Hospital

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Introduction

Ceftolozane/Tazobactam (Zerbaxa ™), a novel cephalosporin combined with a well-known beta-lactamase inhibitor, is a novel antimicrobial agent licensed in 2015 for the treatment of complicated intra-abdominal infections and urinary tract infections. Ceftolozane alone demonstrates activity against common gram-negative pathogens, and the addition of tazobactam provides stability against several beta-lactamases including extended spectrum beta-lactamase producers. This combination has activity against carbapenem-resistant, non-carbapenemase producing pathogens and therefore offers a therapeutic option against a variety of multi-resistant Gram negative pathogens, including *Pseudomonas aeruginosa*.

Aims

To describe the clinical and microbiological aspects of the application of this novel agent at a large London teaching hospital.

Materials & Methods

The clinical records of all patients treated with ceftolozane/tazobactam were studied retrospectively. Data were collected using a specific proforma. Statistical analyses were performed using Microsoft Excel™.

Results

Six patients over two years (November 2015 – November 2017) have been treated with ceftolozane/tazobactam. Patients were predominantly male (n=5, 83%) and their median age was 36. The indications in all cases were healthcare associated infections – 4/6 (67%) treatments were for pneumonia; the remaining 2 (33%) were for cholangitis. All isolates were multidrug resistant *P. aeruginosa* isolated from blood cultures (17%), sputum (33%), blood cultures and sputum (33%) and drain fluid (17%) with only 1 isolate being a carbapenemase producing organism (discovered later by PCR). Median duration of treatment was 12 days. One patient suffered an undesirable effect leading to discontinuation of the medication. Five (83%) patients experienced resolution of symptoms, but 4 (67%) remained culture positive post treatment. At 30 days post-treatment, one patient had died.

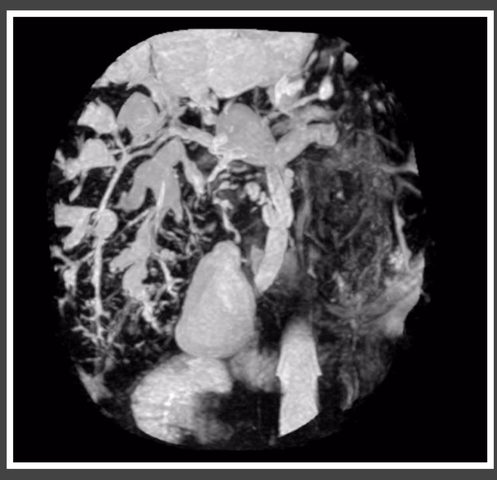
Patient 1:
29 year old male with recurrent cholangitis.

Clinical History:
This patient suffered from recurrent biliary sepsis secondary to Caroli's syndrome. During episodes of sepsis, *P. aeruginosa* was isolated in his blood cultures. He responded well to antimicrobial treatment but repeatedly relapsed swiftly upon cessation of treatment. He was ultimately listed for a liver transplant. He was treated with continuous ceftazidime up until his admission, and post-transplant was treated with ceftolozane/tazobactam 1.5g TDS IV for ten days.

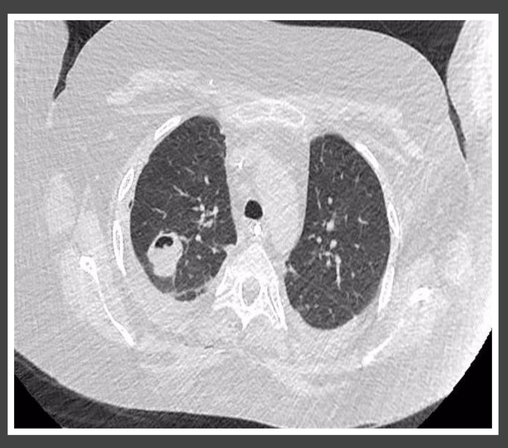
Isolate:
P. aeruginosa
CTZ/TZP MIC < 0.25

R Ciprofloxacin, Levofloxacin, Tazocin, Meropenem, Imipenem
S Gentamicin, Amikacin, Ceftolozane/tazobactam, Ceftazidime

Outcome:
This patient achieved full clinical and microbiological cure. He has had no relapses of infection in the 12 months since transplant.



MRCP of Patient 1: The radiologist report describes; "Cystic dilatation of the intrahepatic ducts with multiple intrahepatic calculi ….consistent with known Caroli's disease.



CT Thorax of Patient 2: The radiologist report describes; "within the ….. right lung there are multiple cavitating lung nodules measuring up to 3 cm in diameter with more confluent consolidation at the right lung base."

Patient 2:
24 year old female with hospital acquired pneumonia.

Clinical History:
This patient suffered from familial erythromelalgia and was admitted for treatment of ulceration of her extremities. She was known to be colonised with *P. aeruginosa.* During her admission she became acutely unwell with fever and hypoxia. A CT of her chest revealed pleural effusions and right sided cavitating nodules. Blood and urine cultures isolated *P. aeruginosa.* She was commenced on ceftolozane/tazobactam 3g TDS IV for six weeks duration.

Isolate:
Pseudomonas aeruginosa.

R	S
Aztreonam	Amikacin
Cefepime	Gentamicin
Ceftazidime	Colistin
Ciprofloxacin	Tobramycin
Tazocin	CTZ/TZP (MIC 0.5)
Levofloxacin	
Meropenem	
Imipenem	

Outcome: This patient achieved clinical cure. However a urine sample several months later during a separate admission cultured *P. aeruginosa* with the same antibiogram.

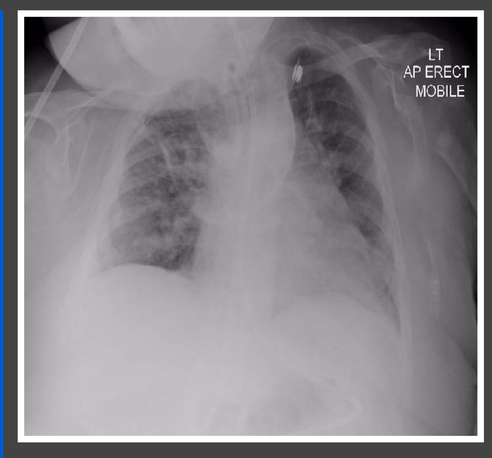
Isolate:
Pseudomonas aeruginosa.

R	S
Aztreonam (I)	Amikacin
Cefepime	Colistin
Ceftazidime	Tobramycin
Ciprofloxacin	
Tazocin	
Levofloxacin	
Meropenem	
Imipenem	

Patient 3: 30 year old male with hospital acquired pneumonia.

Clinical History: This patient with a previous renal transplant had been transferred from Kuwait for ongoing care of new onset seizures. Initially managed in ITU, he had a tracheostomy in situ. He was known to be colonised with a multidrug resistant P. aeruginosa cultured in his urine, stool, tracheostomy site and rectal swabs. During his admission he developed tachypnoea, fever and desaturation. His chest X-Ray revealed right sided consolidation. Blood and sputum cultures grew *P. aeruginosa*. He was treated with 34 days of ceftolozane/tazobactam 3g TDS IV. His isolate was sent to the reference laboratory where PCR detected blaIMP metallo-carbapenemase.

Outcome: This patient achieved clinical cure. However, repeated stool, urine and sputum cultures continued to isolate the carbapenemase producing multidrug resistant *P. aeruginosa*.



Chest X-Ray of Patient 3: The radiologist report describes; "There is patchy shadowing seen in the right lower zone suggesting possible infective change."

Patient 4: 42 year old male with recurrent intra-abdominal sepsis and peri-hepatic collections.

Clinical History: This patient with ischaemic cholangiopathy had a resection of an accessory lobe of his liver followed by years of liver instrumentation and recurrent infection. He had recurrent peri-hepatic collections over a period of two years. He was known to be colonised with multi-drug resistant *Pseudomonas aeruginosa* cultured from abdominal drain fluid and rectal swabs. A CT scan revealed a large peri-hepatic collection superior to the right lobe of the liver. He had a peri-hepatic drain placed and was planned for 6 weeks of ceftolozane/tazobactam IV 1.5g TDS. However, after 15 days of therapy, ceftolozane/tazobactam had to be discontinued due to the development of an itchy widespread macular rash.

Isolate:
P. Aeruginosa
CTZ/TZP MIC 0.5

R Aztreonam, Ceftazidime, Levofloxacin, Ciprofloxacin (I), Meropenem, Tazocin
S Amikacin, Colistin, Gentamicin, Tobramycin, Ceftolozane/tazobactam

Outcome: This patient achieved clinical cure from the episode of intra-abdominal infection. He went on to have a liver transplant to treat his underlying cholangiopathy.

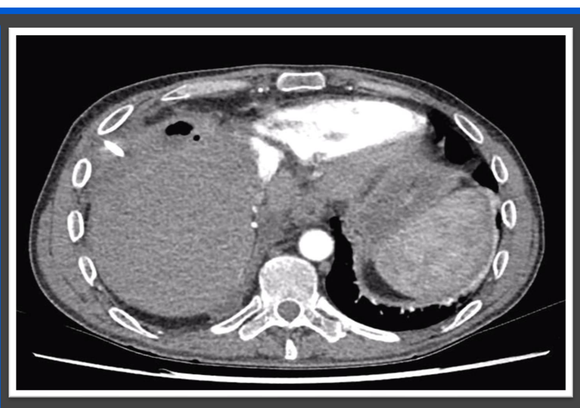
Patient 5: 76 year old male with severe hospital acquired pneumonia

Clinical history: This patient had a background of lymphoma, myasthenia gravis and recently treated disseminated tuberculosis. He was admitted to hospital in septic shock and was managed in ITU for a severe hospital acquired pneumonia. He was known to be colonised with multi-drug resistant *Pseudomonas aeruginosa* in his sputum from a previous year-long admission and cultured it again in sputum. He was treated with 9 days of ceftolozane/tazobactam 3g TDS IV

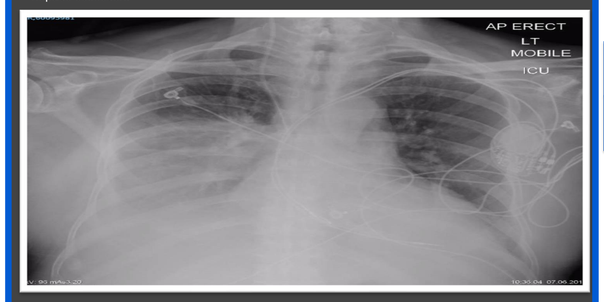
Isolate:
Pseudomonas aeruginosa
Ceftolozane/Tazobactam MIC 0.5
The reference laboratory report stated, 'the intermediate resistance to meropenem is consistent with upregulated efflux'.

R Aztreonam, Levofloxacin, Tazocin, Meropenem (I)
S Amikacin, Ceftazidime, Ciprofloxacin, Gentamicin, Tobramycin, Imipenem, Ceftolozane/Tazobactam

Outcome: This patient continued to deteriorate despite optimal organ support in an intensive care setting and died due to hospital acquired pneumonia 9 days after admission.



CT Abdomen of Patient 4 – The abdominal drain is shown in connection with the right sided peri-hepatic collection.



Chest X-ray of Patient 5 – There is dense right sided basal consolidation suggestive of infection.

Patient 6: 70 year old male with hospital acquired pneumonia.
Clinical history: This patient with a previous renal transplant had been an inpatient for more than 3 years with multiple episodes of healthcare-associated infections and ITU admissions. He was known to be heavily colonised with multi-drug resistant *Pseudomonas aeruginosa* in sputum, urine, rectal screen and tracheostomy swabs. He had 6 days of ceftolozane/tazobactam 3g TDS IV for hospital acquired pneumonia.
Isolate:
Pseudomonas aeruginosa, CTZ/TZP MIC 1

R Aztreonam, Ceftazidime, Ciprofloxacin (I), Levofloxacin, Meropenem, Tazocin, Imipenem
S Amikacin, Colistin, Gentamicin, Tobramycin, Ceftolozane/Tazobactam

Outcome: This patient achieved clinical cure of the infective episode. However, he remains heavily colonised with *Pseudomonas* and the isolate has now developed resistance with CTZ/TZP MIC 256.

Discussion

Treatment of *P. aeruginosa* infection is complicated by its ability to develop antimicrobial resistance (via multiple pathways including; porin deletion, upregulation of efflux pumps and derepressed AmpC production) and to generate biofilm. Treatments used after resistance to beta-lactams and quinolones has developed include aminoglycosides and colistin which both confer a risk of nephrotoxicity. In our study, all isolates were highly resistant strains. The UK reference laboratory examined the susceptibility of 1099 *P. aeruginosa* isolates to ceftolozane/tazobactam and found 99.8% of isolates were susceptible.[1] *In vitro* studies also demonstrate ceftolozane/tazobactam mean inhibitory concentration for *P. aeruginosa* four to eightfold lower than those for ceftazidime.[1] High level resistance to ceftolozane/tazobactam is noted in metallo beta-lactamases or VEB type extended spectrum beta-lactamases; 96.8-100% of these isolates were found resistant by the UK reference laboratory.[1] This is potentially due to tazobactam acting as a poor permeant or good efflux substrate for *P. aeruginosa.* In our study, one patient had a carbapenamase producing *Pseudomonas*. He responded clinically to treatment, but it was noted repeated isolates continued to grow a resistant *P. aeruginosa.* Ceftolozane/tazobactam is currently not licensed for the treatment of chest infections. The higher dosage regimen chosen for our patients with pneumonia was based on data from Monte-Carlo simulation studies.- a trial is underway to further evidence this.[2, 3] In our case series, the medication was not associated with any serious adverse events; one patient developed an itchy rash which led to discontinuation of the medicine. One patient developed resistance to ceftolozane/tazobactam.

Conclusions

- Ceftolozane/Tazobactam has an important role to play in the management of multi-drug resistant Gram negative hospital associated infections.
- The majority of our experience was with pneumonia, for which CTZ/TZP remains off-license.
- Careful and select use is important.
- Hypersensitivity reactions, treatment failure and the development of resistance are all very real risks.
- A valuable addition to the antibiotic arsenal.

References [1] Livermore D, Mushtaq S, Meunier D. (2017) Activity of Ceftolozane/Tazobactam against surveillance and 'problem' Enterobacteriaceae, pseudomonas aeruginosa and non-fermenters from the British Isles. Journal of antimicrobial chemotherapy 72: 2278-2289. [2] Xiao A, Caro L, Popejoy M. (2017) PK/PD Target Attainment with Cetfolozane/Tazobactam Using Monte Carlo Simulation in Patients with various degrees of renal function. Infect Dis Ther. 2017 Mar; 6(1): 137 – 148. [3] ClinicalTrials.gov, NCT02070757