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CASE REPORT

Ceftolozane/tazobactam for febrile UTI due to multidrug-resistant *Pseudomonas aeruginosa* in a patient with neurogenic bladder

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INTRODUCTION: Urinary tract infections (UTI) are a major public health problem among spinal cord injury (SCI) patients. They frequently involve multidrug-resistant (MDR) bacteria. Ceftolozane/tazobactam (C/T) is a novel antibiotic combination approved for complicated intra-abdominal and UTI caused by Gram-positive and Gram-negative organisms, including some MDR strains. Little is known about the use of this agent for complicated febrile UTI occurring among SCI patients with neurogenic bladder due to MDR *Pseudomonas aeruginosa* (PSA).

CASE PRESENTATION: We describe the case of a 35-year-old man with SCI due to multiple sclerosis, with a neurogenic bladder necessitating a bilateral nephrostomy and double J catheter, who developed a febrile UTI due to a MDR PSA, which was susceptible only to amikacin and colistin. Because of this MDR phenotype and the underlying kidney disease, a 1000 mg (1000 mg per 500 mg) dose of C/T was given as monotherapy every 8 h for 7 days, after 3 days of colistin and amikacin. Thanks to this treatment, the patient had a favorable outcome with no clinical signs of UTI or positive urine culture up to 1 month after diagnosis.

DISCUSSION: C/T seems to be an effective and safe therapeutic option for febrile UTI due to MDR PSA in SCI patients with neurogenic bladder, even when administered in monotherapy for 10 days.

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INTRODUCTION

Infections caused by multidrug-resistant (MDR) bacteria are an increasing challenge, especially among spinal cord injury (SCI) patients. Ceftolozane/tazobactam (C/T) is a new antimicrobial drug combining a cephalosporin and a β-lactamase inhibitor.[1,2] C/T is currently approved by the United States Food and Drug Administration for the treatment of complicated urinary tract infections (UTI), including pyelonephritis and complicated intra-abdominal infections.[1] The drug was recently approved in France for these infections. One of the most promising applications of C/T is the treatment of infections caused by *Pseudomonas aeruginosa* (PSA). However, as published clinical data are still scarce, we are in critical need for more knowledge and experience in the treatment of MDR infections in general, and MDR PSA especially. MDR PSA could be involved in febrile UTI occurring among SCI patients.[3] Also, little is known about the use of this agent for urosepsis treatment due to MDR PSA among patients with neurogenic bladder, and its efficacy during 10 days of monotherapy.

CASE PRESENTATION

We describe the case of a tetraplegic 35-year-old man, with a history of advanced multiple sclerosis rapidly progressing, and with neurogenic bladder. He weighed 44 kg, with a height of 172 cm (body mass index = 15), and was malnourished (albumin level = 27 g l^{-1}). He had recurrent nephrolithiasis, bilateral nephrostomy, a double J catheter and a tracheostomy. A percutaneous endoscopic gastrostomy tube was placed 4 days before hospitalization.

He was admitted to our infectious disease unit with complaints of fever and chills for the last 3 days. He had no alteration of mental status, dyspnea, cough or digestive trouble. No venous thrombosis or pressure sore was noted. At admission, he presented low blood pressure (systolic pressure = 90 mm Hg) with tachycardia (pulse = 124 min^{-1}).

Laboratory tests showed serum creatinine level at 48 µmol l^{-1}; chemistry panel and liver enzyme levels were normal; hemogram showed leukocytosis (11.5×10^9 l^{-1}) and thrombocytosis (233×10^9 l^{-1}); and C-reactive protein level was high (80 mg l^{-1}).

Full body CT scan found moderately dilated pyelocaliceal cavities, compatible with acute pyelonephritis, multiple bilateral nephrolithiasis and no signs of pneumonia (Figure 1).

Blood cultures prepared at admission were sterile. Urinalysis was found positive for a MDR PSA with a concentration of 1×10^5CFU ml^{-1}, only susceptible to amikacin and colistin (colistin minimum inhibitory concentration (MIC) at 0.125 mg l^{-1}). Analysis of this strain's resistance mechanisms by the French National Reference Center for Antibiotic Resistance (University Hospital of Besançon) showed overproduction of intrinsic cephalosporinase AmpC associated with an alteration of carbapenem-specific porin

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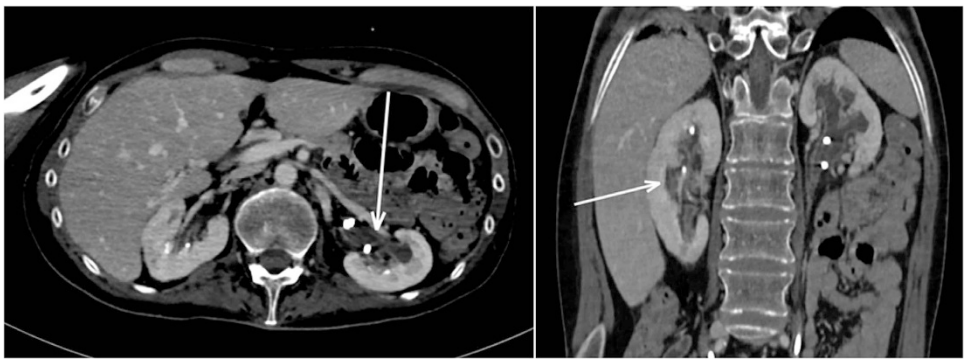

Figure 1. CT scan revealing dilated pyelocaliceal cavities, with infiltrative lesion of the parenchyma (white arrows) compatible with acute pyelonephritis, multiple bilateral nephrolithiasis and double J catheter.

OprD and overexpression of efflux system MexAB-OprM. C/T MIC being 4 per 4 mg l^{-1}, the strain was categorized as susceptible to the drug combination (lower breakpoint = 4 per 4 mg l^{-1}).

For the first 48 h, the patient was treated with sodium colistimethate (3 million international units (MIU) every 8 h, with discontinued perfusion of 1 hour) and amikacin (15 mg kg^{-1} once a day with a 30 min perfusion), and by hyperhydratation (1500 ml per 24 h).

Because of the MDR phenotype and the potential nephrotoxicity of colistin and amikacin, the antibiotic treatment was switched to C/T monotherapy at 1 g per 500 mg tid for 7 days. This switch was performed despite any evidence of renal impairment, but was justified by the presence of urinary lithiasis and the difficulties in evaluating renal function among patients with severe malnutrition, amyotrophia and nephrostomia.

Evolution was rapidly favorable, with apyrexia reached at day 2. The double J catheter was switched at day 5; three blood cultures from after the procedure were found negative. No relapse was detected at day 28 after the end of antimicrobial treatment. Urinalysis remained negative throughout the follow-up period. A second CT scan was performed 17 days after the end of treatment, and it showed regression of pyelonephritis lesions.

DISCUSSION

C/T is a new antibiotic combination, which contains a new cephalosporin (ceftolozane) and a beta-lactamase inhibitor (tazobactam).[1] Ceftolozane displays activity against common Gram-negative pathogens, and the addition of tazobactam extends its activity to most extended-spectrum beta-lactamase producers.[2] Ceftolozane also demonstrates a potent activity against PSA compared to ceftazidime and cefepime.[2] C/T was shown to be effective against 310 MDR PSA isolates resistant to most antimicrobial classes, and it retained activity against PSA strains resistant to ceftazidime and/or meropenem.[4] C/T efficacy has been evaluated in two randomized controlled trials including patients with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).[5,6]

However, data on infections due to multidrug-resistant PSA treated by C/T are scarce. In the cUTI-ASPECT trial, the noninferiority of C/T was demonstrated in comparison to levofloxacin, but only few PSA infections were involved.[6] C/T resulted in microbiological eradication in 85.7% (six out of seven) of PSA cases, but due to this small sample size, no statistical conclusions could be drawn.[6] Although patients with indwelling catheter were included in this study, none had neurogenic bladder. Data in literature showed that UTI among patients with neurogenic bladder have a lower cure rate than those among general population.[3] Furthermore, although these Phase 3 studies seemed to show clinical and microbiological efficacy of C/T against PSA isolates, no patient included presented with combined neurogenic bladder with urinary foreign device and an infection due to MDR PSA.

Published clinical data concerning the treatment of infections due to MDR PSA are still rare, and randomized controlled trials are hardly feasible because of their low prevalence.[7] Hence, in a bayesian approach, every experience that could add some evidence of efficient treatment is of interest.

In the study from Wagenlehner *et al.*[6] on C/T and UTI, 23 PSA were involved but their antimicrobial susceptibilities are unknown. Miller *et al.*[8] studied cIAI due to PSA; among them 26 MDR PSA were involved and treated by CT with a cure rate of 93%. Also, Castón *et al.*[7] found that CT as salvage therapy for pneumonia due to MDR PSA was effective.

Nevertheless, data on MDR PSA during UTI are not available.

In our report, C/T was clinically efficient against an MDR PSA strain from a urinary source. It was found to be safe and provided a favorable outcome even in monotherapy during 10 days in a patient with neurogenic bladder and foreign device.

Incidence of infections due to MDR PSA is increasing worldwide. They are associated with high mortality and health-care costs. Their management remains a clinical challenge especially among patients with neurogenic bladder.[9–12]

Moreover, the indication of dual therapy for infections due to PSA is still under debate. Combination therapy with two antipseudomonal agents is often empirically started to avoid initial inappropriate empirical antibiotic therapy, which is an independent risk factor for mortality.[13–18]

Few successful regimens for MDR PSA infections are described in literature, and no clinical trials are available. The main regimens used have included continuous-infusion meropenem with parenteral colistin therapy. Some colleagues have used combination therapy with antipseudomonal beta-lactams plus aminoglycosides.[13,15,19] Double antipseudomonal beta-lactam therapy has shown *in vitro* synergistic effects.[20,21]

Furthermore, data on management of febrile UTI among patients with neurogenic bladder are limited.[3] Diagnosis of UTI among patients with neurogenic bladder is a challenge. Indeed, bacteriuria is frequent in this population and clinical signs are not specific, although the first cause of fever in this population. Absence of other source of infection and indirect signs found on CT scan (usually kidney infiltrations, even without contrast) tend to confirm the diagnosis.

Usual dual therapy and prolonged treatment have been advocated as the gold standard. Nevertheless, recent data showed effectiveness of short-course regimen and monotherapy.[3] Meanwhile, data on MDR PSA are lacking. The 10-day treatment duration we used is the lower threshold of usual Infectious Diseases Society of America guidelines (10 − 14 days), and in our case a MDR PSA is involved.[22] Still, our case report supports that this attitude is effective. It should limit toxicity and the emergence

of MDR organisms in a specific population already overexposed to antimicrobials with a high rate of MDR carriers.[3,9]

Therefore, we report the first case of severe pyelonephritis due to MDR PSA in a SCI patient with neurogenic bladder and foreign device successfully treated with short-course C/T monotherapy. These results should be confirmed by controlled studies, ideally a randomized double-blinded control trial.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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