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Ceftolozane–tazobactam for the treatment of osteomyelitis caused by multidrug-resistant pathogens: a case series

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Abstract: Ceftolozane–tazobactam (CT) is a recently approved novel cephalosporin and β-lactamase inhibitor combination agent with *in vitro* activity against various Gram-positive and Gram-negative pathogens, including several multidrug-resistant (MDR) Gram-negative organisms. CT is currently approved by the US Food and Drug Administration for the treatment of complicated intrabdominal infection and complicated urinary tract infection at a dose of 1.5 g intravenously every 8 h. This agent is an attractive option for MDR osteomyelitis (OM) treatment, but clinical data is limited to case reports and series. Here we report a series of five patients with MDR OM who were treated with CT. Pathogens involved in these infections were MDR *Acinetobacter baumannii* (two isolates) and MDR *Pseudomonas aeruginosa* (four isolates). Two patients were disease free 6 months after therapy was discontinued, one required an additional curative surgical procedure, and two (both on high-dose therapy) developed adverse reactions likely related to CT that necessitated early antibiotic discontinuation.

Keywords: ceftolozane/tazobactam, osteomyelitis, *Pseudomonas aeruginosa*

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Introduction

Ceftolozane–tazobactam (CT) is a recently approved novel cephalosporin and β-lactamase inhibitor combination agent with *in vitro* activity against various Gram-positive and Gram-negative pathogens.[1–3] CT has also demonstrated *in vitro* activity against multidrug-resistant (MDR), or strains resistant to at least three classes of antimicrobials, *Pseudomonas aeruginosa*, and some strains of *Acinetobacter*.[1–3] In 2014, the US Food and Drug Administration (FDA) approved CT for treatment of complicated urinary tract infections (cUTIs) as monotherapy and complicated intraabdominal infections (cIAIs) in combination with metronidazole at a dose of 1.5 g every 8 h.[4]

To date, much of the use of CT has been for non-FDA approved indications, including MDR organism treatment, pneumonias, blood-stream infections, and even osteomyelitis (OM); for some of these treatments, doses above the approved 1.5 g every 8 h are routinely being used.[5] OM in diabetic patients is a complicated, polymicrobial infection in which Gram-negative organisms, even MDR organisms, play a significant role.[6] CT is an attractive option for OM treatment, but clinical data is limited to case reports and series.[7–12] Here we report the largest case series of patients with complicated OM owing to MDR pathogens treated with CT, including four who received high-dose (3 g every 8 h) therapy.

The Institutional Review Board at the VA St. Louis Health Care System does not require review or approval of case series and, because of the retrospective, noninterventional nature, in conjunction with the fact that it is often not feasible, informed consent is waived.

Patient cases

Patient #1

A 67-year-old patient with T5 paraplegia and chronic pelvic OM on suppressive antibiotics [sulfamethoxazole/trimethoprim (TMP-SMX) and

ciprofloxacin] for 8 years presented for evaluation of a new groin wound. The surgical team elected not to operate on the groin, but planned to debride an existing gluteal wound in 3 weeks; ceftriaxone and metronidazole were initiated while awaiting debridement.

Tissue cultures obtained during the debridement grew *Acinetobacter baumannii*, *P. aeruginosa*, and *Morganella morganii* (see Table 1). All isolates identified were MDR and the patient's antimicrobial regimen was changed to CT 1.5 g intravenously (IV) every 8 h.

The patient was treated with CT for 6 weeks and tolerated it well. No additional intervention was required in the 6 months after completing therapy.

Patient #2

A 67-year-old man with a new C7 tetraplegia and a stage IV sacral pressure had recently completed a 6 week course of vancomycin and meropenem for OM.

The surgical service did not believe the bone had adequately healed and obtained another biopsy, which grew *Streptococcus agalactiae*, methicillin-susceptible *Staphylococcus aureus* (MSSA), and MDR *P. aeruginosa* (see Table 1). Antimicrobials were initially held, but within 2 weeks the patient was observed to have fever and hypoxia, and was believed to have developed pneumonia. Respiratory cultures grew the same MDR *P. aeruginosa* and the patient was initiated on CT 3 g IV every 8 h and amikacin 1000 mg IV every day. CT was continued for 6 weeks (to treat OM and the pneumonia) and amikacin was continued for 4 weeks.

The patient tolerated therapy well and required no additional antibiotic therapy or surgical intervention 6 months after completion of treatment.

Patient #3

A 64-year-old man with multiple toe amputations and revascularization procedures presented for a planned left below knee amputation (BKA) due to nonhealing wounds on his left foot. The patient ultimately refused the procedure and the surgical service debrided the area of the first to third digits on the left foot. Tissue samples obtained in the operating room grew *P. aeruginosa* and *Corynebacterium striatum*.

The *P. aeruginosa* was identified as an MDR pathogen (see Table 1) and the infectious diseases service recommended to initiate vancomycin 1.25 g every 12 h and CT 3 g IV every 8 h and continue both for 6 weeks.

Seven weeks after completing therapy the patient presented with more erythema, swelling, and foul-smelling discharge from the left foot wound. Within 2 days the patient underwent a left BKA.

Patient #4

A 76-year-old man with T4 tetraplegia and chronic ulcers on his right ischium and heel recently completed 6 weeks of therapy with ceftriaxone, IV TMP-SMX, and metronidazole for OM involving *Acinetobacter baumannii*. New imaging demonstrated right proximal femur and right acetabulum destruction, likely from new OM. The infectious diseases service recommended to re-treat the patient, but, owing to previous hyperkalemia with IV TMP-SMX, change the regimen and treat with high doses of tigecycline and CT 100 mg every 12 h and 3 g every 8 h, respectively, even though the isolate was intermediate to both (see Table 1).

Twelve days later the patient's aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased (see Table 1). Tigecycline was decreased to traditional dose (50 mg IV every 12 h) and the AST and ALT began to trend downward, though never normalized. Two days later the patient had developed thrombocytopenia (see Table 1).

Owing to multiple adverse reactions, both antibiotics were discontinued approximately 2 weeks prior to the planned stop date. The patient was transitioned to hospice care because of multiple comorbidities and failure to thrive and expired 12 weeks after the CT was discontinued.

Patient #5

A 64-year-old man with T6 paraplegia and bilateral ischial and sacral pressures ulcers who had undergone multiple debridements and courses of antibiotics presented a week after finishing a course of ceftriaxone and metronidazole for additional debridement. Cultures from the procedure grew *Enterococcus faecalis*, *Staphylococcus epidermidis*, and MDR *P. aeruginosa* (see Table 1).

Table 1. Patient data.

Patient	Pertinent past medical history	Culture data	CT dose	Additional concomitant antibiotic therapy	Pertinent lab values at CT initiation	Pertinent lab values on therapy or at the end of treatment	Duration of therapy (days)	Result of treatment
1	T5 paraplegia Neurogenic bowel and bladder Chronic pelvic OM Diabetes Depression	Tissue cultures (left gluteal) *Acinetobacter baumannii* S: amikacin, CT (MIC = 8)[a] I: imipenem, meropenem R: gentamicin, cefepime, ceftriaxone, ciprofloxacin, p/t, TMP-SMX, aztreonam *Pseudomonas aeruginosa* S: amikacin, CT (MIC = 1.5)[a], meropenem I: ceftazidime, imipenem R: gentamicin, tobramycin, p/t, cefepime, ciprofloxacin *Morganella morganii* S: ertapenem, imipenem, cefepime, I: gentamicin R: a/s, cefazolin, ceftriaxone, ciprofloxacin, TMP-SMX, ampicillin	1.5 g every 8 h	No	SCr: 0.56 WBC: 4600 ESR: 68 CRP: 6.4	ESR: 14 CRP: 3.2	42	Intervention free 6 months after therapy
2	C7 tetraplegia Neurogenic bowel and bladder Stage IV sacral ulcers OM Diabetes Coronary artery disease	Tissue culture (sacrum) *Streptococcus agalactiae* S: ceftriaxone, vancomycin, clindamycin, erythromycin, penicillin *Staphylococcus aureus* S: ciprofloxacin, oxacillin, TMP-SMX, vancomycin, clindamycin, erythromycin *P. aeruginosa* S: amikacin, gentamicin, tobramycin, CT (MIC = 1.5)[b], colistin (MIC = 0.75)[a] R: p/t, imipenem, meropenem, cefepime, ceftazidime, c/a[a], ciprofloxacin	3 g every 8 h	Amikacin 1000 mg daily	SCr: 0.53 WBC: 8900 ESR: 106 CRP: 9.1	ESR: 57 CRP: 1.1	42 (CT) 28 (amikacin)	Intervention free 6 months after therapy
3	Diabetes Coronary artery disease Bipolar disorder Obesity Alcohol abuse Atrial fibrillation Peripheral vascular disease OM	Bone culture (left foot) *P. aeruginosa* S: amikacin, gentamicin, tobramycin, CT (MIC = 4)[a] R: p/t, imipenem, meropenem, cefepime, ceftazidime, c/a (MIC = 16)[a], ciprofloxacin *Corynebacterium* sp., not tested for susceptibilities	3 g every 8 h	Vancomycin 1.25 g every 12 h	SCr: 0.76 WBC: 7100 ESR: 1 CRP: 3.1	WBC: 5800 ESR: 2 CRP: 1.3	42	7 weeks after therapy required a left BKA

(Continued)

Table 1. (Continued)

Patient	Pertinent past medical history	Culture data	CT dose	Additional concomitant antibiotic therapy	Pertinent lab values at CT initiation	Pertinent lab values on therapy or at the end of treatment	Duration of therapy (days)	Result of treatment
4	T4 paraplegia Neurogenic bowel and bladder Decubitis ulcers OM Diverting colostomy Peripheral vascular disease	Bone culture (right ischium) *Acinetobacter baumannii* S: TMP-SMX I: a/s, imipenem, tigecycline, CT (MIC = 4)[a] R: gentamicin, p/t, ceftazidime, ceftriaxone, ciprofloxacin, minocycline	3 g every 8 h	Tigecycline 100 mg every 12 h (initially); then Tigecycline 50 mg every 12 h	SCr: 0.65 WBC: 12,200 Platelets: 226,000 AST/ALT: 44/35	ESR: 109 CRP: 15.6 WBC: 12,000 AST/ALT: 159/98 Platelets: 45,000	28	Developed AST/ALT elevation and thrombocytopenia possible due to antibiotics: therapy stopped 2 week prior to planned stop date. Transitioned to hospice care and expired 12 weeks after CT was stopped.
5	T6 paraplegia Neurogenic bowel and bladder Decubitis ulcer OM Coronary artery disease Depression	Bone culture (sacrum) *Enterococcus faecalis* S: vancomycin, ampicillin, streptomycin, daptomycin R: gentamicin synergy, tetracycline *Staphylococcus epidermidis* S: TMP-SMX, vancomycin R: gentamicin, oxacillin, clindamycin, erythromycin, moxifloxacin *P. aeruginosa* S: amikacin, tobramycin, c/a (MIC = 2)[a], CT (MIC = 0.75)[a] I: gentamicin, cefepime, ceftazidime R: imipenem, meropenem, ciprofloxacin	3 g every 8 h	Vancomycin 1 g every 12 h	SCr: 0.71 WBC: 5000 Eosinophils: 7.1%	WBC: 4900 Eosinophils: 6.8%	35	Developed rash, possibly due to CT, and therapy was stopped 1 week prior to planned stop date. No additional antimicrobial therapy or surgical intervention was required in the 6 months after CT was stopped.

Unless otherwise noted, all susceptibilities were obtained using the VITEK® II system (bioMerieux, Inc.).
ALT, alanine aminotransferase; a/s, ampicillin–sulbactam; AST, aspartate aminotransferase; BKA, below the knee amputation; c/a, ceftazidime–avibactam; CRP, C-reactive protein; CT, ceftolozane–tazobactam; ESR, erythrocyte sedimentation rate; MIC, minimum inhibitory concentration; OM, osteomyelitis; p/t, piperacillin–tazobactam; SCr, serum creatinine; TMP-SMX, trimethoprim–sulfamethoxazole; WBC, white blood cell count.
[a]MIC determined *via* Epsilometer® Test (E-test).
[b]MIC determined at a reference laboratory *via* broth microdilution.

CT 3 g IV every 8 h and vancomycin 1 g IV every 12 h were started with a plan to treat for 6 weeks.

The patient presented to the emergency department approximately 3 weeks later with complaints of a red rash on his face and chest. The patient had been infusing his vancomycin faster than prescribed and was counseled to infuse over at least 2 h.

About 10 days later the patient presented again with worsening rash on his trunk and arms (this patient had no known drug allergies at the beginning of treatment). The infectious diseases service believed the patient was reacting to the CT and therapy was stopped 1 week prior to the stated goal. The patient did not require any additional antimicrobial therapy or surgical intervention within the 6 months after CT was discontinued.

Discussion

In our series of five complicated OM patients the majority (four) had spinal cord injuries, and four received high-dose CT to improve bone penetration. Pathogens that were targeted with CT were MDR *A. baumannii* (2) and MDR *P. aeruginosa* (3). Two patients were disease free 6 months after therapy was discontinued, one required an additional curative surgical procedure, and two (both on high-dose therapy) developed adverse drug reactions (ADRs) likely related to CT that necessitated early antibiotic discontinuation.

Clinical evidence for the use of CT in OM is limited to case reports and series. Jolliff *et al.*[7] described a case of post-surgical OM with *Streptococcus anginosus, Granulicatella adiacens*, and MDR *Stenotrophomonas maltophilia* in which the patient was successfully treated with CT 1.5 g every 8 h plus metronidazole for 6 weeks.[7] Another report published by Kurtzhalts *et al.*[8] detailed a case of pubic symphysis OM with *P. aeruginosa*, only susceptible to colistin and aminoglycosides, that was effectively treated with CT 1.5 g IV every 8 h for 6 weeks.[8] Gentile *et al.*[9] also reported a case of MDR *P. aeruginosa*, sensitive only to colistin, OM in the femur. The patient developed tubulopathy while receiving colistin and completed an 8-week treatment course with CT, adjusted for renal function. The patient was infection free at a 3-month follow up.[9] Hassan *et al.*[10] detailed a patient with a right humeral shaft fracture with open reduction and internal fixation (ORIF) who developed a post-surgical infection with two MDR *P. aeruginosa* isolates. The patient failed an initial 8-week course of cefepime and ciprofloxacin and was transitioned to CT 1.5 g every 8 h for 8-weeks with hardware removal; the patient tolerated therapy well and did not require further antibiotics.[10] Unlike the patients in our series, none of the above cases used high-dose CT treatment, and all report positive outcomes at follow up. In addition, there were no reported ADRs in these other cases; two patients in our series appeared not to tolerate higher doses of CT.

A case series reported by Dietl *et al.*[11] included patients four with OM caused by MDR *P. aeruginosa*. Median duration of therapy was 48 days and no patients received high-dose therapy. One of the four developed infection recurrence and one was re-infected with *S. aureus*. The authors reported no significant ADRs associated with CT.[11]

Finally, a case series by Escola-Verge *et al.*[12] included four patients treated for OM with CT for MDR *P.* aeruginosa; ~60% of patients were treated with high-dose CT. The authors only report the specific treatment outcome (persistent infection) for one OM patient. Overall, 50% (13/26) of all patients treated with high-dose CT achieved clinical cure at 90 days.[12]

In the patients outlined here, high-dose CT was chosen to improve bone penetration in the setting of OM with MDR pathogens. Rationale for high-dose CT is based on proposed dosing for pneumonia. A pharmacokinetic/pharmacodynamic model has demonstrated that plasma-to-epithelial lining fluid (ELF) ratio for CT is only 50%. The model determined that, to achieve a similar or better antibacterial effect as previously observed the dose of CT would need to be doubled.[13] Unfortunately, owing to a lack of published bone penetration data in human subjects and larger-scale clinical evaluations, the optimal dosing for CT in OM is not known. Unpublished animal data from the manufacturer, reported in Jolliff *et al.*,[7] does report bone:serum concentration ratios of up to 9% for bone and 17.5% for marrow in a rabbit model, and 27% for bone and 40% for marrow in a rat model (1 g every 8 h, and 20 mg/kg were utilized in the models, respectively).[7] It is not unreasonable to evaluate this limited animal model data, and what has been observed in human lungs and assume that, if CT

is used to treat OM, higher-dose therapy may offer the best chance of achieving adequate drug concentration at the site.

Traditionally, treatment for MDR *Acinetobacter* and *Pseudomonas* have involved combination therapy, occasionally featuring a polymyxin antibiotic. Polymyxins have proven useful, historically, in managing MDR infections, but are associated with significant rates of nephrotoxicity. The exact rates of nephrotoxicity vary in the literature depending upon which polymyxin is used (colistimethate or polymyxin B) and the definition of acute kidney injury (AKI), but rates are generally between 31% and 50%.[14] CT, in addition to maintaining activity against many of these MDR isolates, is better tolerated than the polymyxins. In the ASPECT-cUTI and ASPECT-cIAI trials no patients were reported to have developed AKI; the most common ADR in the cUTI trial was headache (5.8%; 31/533) and nausea in the cIAI trial (7.9%; 38/482). Serious ADRs occurred in only 2.8% (15/533) of patients in ASPECT-cUTI and 8.1% (39/482) of ASPECT-cIAI patients.[15,16]

In conclusion, we report the largest case series to-date of patients treated with CT for OM, with a majority (4/5) receiving high-dose therapy. These patients are complex, and we believe reflect the real-world population who require broad Gram-negative therapy and may not always be candidates for curative surgical procedures. Two patients did not require additional therapy or develop any ADRs in the 6 months after initial therapy was discontinued, and two of four receiving high-dose treatment with CT developed possible ADRs. This small case series is limited, but may bring to light that patients receiving higher doses of CT for longer periods may not tolerate therapy as well; however, ADRs in these patients did not include AKI, which could be common in other therapies for MDR Gram-negative pathogens (i.e. polymixins) CT remains an attractive option for OM, but more studies, including those reporting plasma-to-bone penetration and clinical outcomes, need to be conducted to help determine safe and efficacious dosing.

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Conflict of interest statement

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