

Letter to the Editor

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Postoperative soft-tissue infection due to multidrug-resistant *Pseudomonas aeruginosa*: usefulness of ceftolozane-tazobactam

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Sir,

Ceftolozane-tazobactam (CT) is a combination that contains a novel cephalosporin, ceftolozane, with activity against Gram-negative drug-resistant pathogens including *Pseudomonas aeruginosa* and Enterobacteriaceae, and tazobactam, an inhibitor of different beta-lactamases produced by some Gram-negative bacilli. This drug has been approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections [1], however its use is increasingly described in medical literature in other indications [2-4].

We report on a case of successful use of CT in a patient with a postoperative soft-tissue infection with repeated isolation of multi-resistant *P. aeruginosa*. Due to a lengthy course of therapy with colistin and tobramycin the patient developed acute kidney failure that required continuous renal replacement therapy and intensive care unit (ICU) admission.

The patient was a 52-year-old man with an history of heavy smoking, alcoholism, hypertension, dyslipemia and dilated cardiomyopathy. He was admitted to our hospital after suffering a traffic accident and was diagnosed of a comminute tibial and peroneal open fracture involving its middle third. Antibiotic prophylactic therapy with intravenous cefazolin and gentamycin was initiated and maintained during five days. Nail osteosynthesis surgery was then performed with good postoperative evolution so he was discharged six days later. Three weeks later, he was transferred from outpatient traumatology consultations to the emergency department for hospital admission due to skin necrosis with an eschar on the anterior side of the right leg with serohematic fluid discharge from which two samples for culture were positive for *P. aeruginosa* with susceptibility to all antimicrobial categories. Lab tests showed

an increase in C-reactive protein (9.55 mg/dL) and globular sedimentation rate (98 mm). Treatment with intravenous ceftazidime (1 g t.i.d.) and tobramycin (100 mg t.i.d.) was started and maintained for two weeks. Daily cures were performed in the ward and in the surgery room, where the devitalized anterior tibial muscle was cleaned and the eschar and one bone fragment were removed. Subsequently, ceftazidime was replaced by imipenem (1 g t.i.d.) due to repeated isolation on wound cultures of a new strain of *P. aeruginosa* with resistance to aztreonam, cefepime, ceftazidime and piperacillin-tazobactam and susceptibility to quinolones, colistin, imipenem and tobramycin. Tobramycin was also withdrawn and ciprofloxacin was added but treatment with the latter was stopped due to the suspicion of an allergic reaction. In the following three weeks, a new isolate of *P. aeruginosa* appeared with resistance to imipenem so antimicrobial therapy was changed to intravenous tobramycin (300 mg in a once-daily dose) and colistin (2 million IU t.i.d.). At this time, susceptibility to CT of this *P. aeruginosa* strain was tested by the Etest method, on agar plates incubated at 35°C for 18 hours. MIC₉₀ was determined to be 0.50 mg/L, which is considered susceptible based on the EUCAST guidelines. After a prolonged therapy with intravenous tobramycin and colistin, the patient experienced sudden dyspnea followed by a respiratory arrest requiring advanced cardiopulmonary reanimation, orotracheal intubation and Intensive Care Unit (ICU) admission. Laboratory workup revealed acute kidney failure with high blood levels of creatinine (10.4 mg/dL) and urea (102 mg/dL), severe metabolic acidosis and hyperlactatemia (6.6 mmol/L). Supportive treatment was started with mechanical ventilation, vasoactive drugs for vasodilation and cardiogenic shock, and renal replacement therapy with continuous venovenous hemodiafiltration (CVVHDF). Given the situation of acute kidney failure, repeated isolation on wound cultures of multidrug-resistant *P. aeruginosa* and susceptibility to CT, treatment was started with this antibiotic at doses of 0.5/0.25 g t.i.d. with an infusion time of 1 h. The patient's clinical condition improved, allowing extubation and withdrawal of

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renal support and vasoactive drugs. Microbiological response was also favourable without any side effects of CT and negative results of wound and surveillance samples during ICU stay, so the antimicrobial treatment was withdrawn after seven days. He was discharged of ICU after 12 days and transferred to a conventional ward and then to a Plastic Surgery Service of our referral hospital with good evolution of the wound of his leg.

CT is considered the beta-lactam antibiotic most active against *P. aeruginosa* [5-6] due to its stability in the presence of AmpC beta-lactamases, higher affinity for penicillin-binding proteins, resistance to active efflux pumps and is not affected by the loss of outer membrane porins. The experience on its use, both in off-label indications and in critically ill patients is scarce. We conducted a search in MEDLINE (PubMed) using the Mesh terms "ceftolozane-tazobactam" and "soft-tissue infections" with no results. In addition to pneumonia [3,4], there are only some successful reports of its off-label use in bone and joint infections due to multidrug-resistant *P. aeruginosa*: two patients with osteomyelitis, one secondary to a vesical fistula [7] and other with multiple isolation in blood, lung and sternum [8]; and in a prosthetic hip joint infection [9]. Given the low inoculum after drainage and prescribing drug information in patients with impaired renal function we used a reduced dosage of CT. There are limited data evidence about CT dosing in critically ill patients under continuous renal replacement therapies, but data obtained in previous investigations suggest a decreased CT clearance with increased area under the plasma concentration-time curve and low extraction ratio by the CVVHDF filter, so a lower total daily dose might be utilized and continuous or extended-time infusions may not be necessary [8,9].

In conclusion, CT is a safe and highly effective therapy in multidrug-resistant *P. aeruginosa*. It could also be an alternative to other antibiotics in cases of infections by these bacteria or other Gram-negative bacilli with kidney failure or at high risk of nephrotoxicity. It remains to establish the optimal dosing in critically ill patients under continuous extrarenal clearance techniques, although reduced dosage could be used without extended-time infusions, other factors such as the type of infection, bacterial load, MIC of the causative agent or the ultrafiltration dose might cause us to modify these approximate guidelines in the future.

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None to declare

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

REFERENCES

1. EPAR de Zerbaxa® disponible en: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report_human/003772/EC500194598.pdf
2. Hernández-Tejedor A, Merino-Vega CD, Martín-Vivas A, Ruiz de Luna-González R, Delgado-Iribarren A, Gabán-Diez A, et al. Successful treatment of multidrug-resistant *Pseudomonas aeruginosa* breakthrough bacteremia with ceftolozane-tazobactam. *Infection*. 2017; 45:115-7. PMID:27670678.
3. Gelfand MS, Cleveland KO. Ceftolozane/Tazobactam therapy of respiratory infections due to multidrug-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2015; 61:853-5. PMID:26021991.
4. Álvarez Lerma F, Muñoz Bermúdez R, Grau S, Gracia Arnillas MP, Sorti L, Recasens L, et al. Ceftolozane-tazobactam for the treatment of ventilator-associated infections by colistin-resistant *Pseudomonas aeruginosa*. *Rev Esp Quimioter* 2017; 30:224-8. PMID:28361526.
5. Farrell DJ, Sader HS, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against gram-negative bacterial isolates from hospitalized patients with pneumonia in US and European medical centres (2012). *Int J Antimicrob Agents* 2014;43:533-9. PMID:24856078.
6. Tato M, García-Castillo M, Bofarull AM, Cantón R, CENIT Study Group. In vitro activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* and Enterobacteriaceae recovers in Spanish medical centres: Results of the CENIT study. *Int J Antimicrob Agents* 2015;46:502-10. PMID:26315199.
7. Kurtzhals KE, Mergenhagen KA, Manohar A, Berenson CS. Successful treatment of multidrug-resistant *Pseudomonas aeruginosa* pubic symphysis osteomyelitis with ceftolozane/tazobactam. *BMJ Case Rep* 2017; PMID:28363945. DOI: 10.1136/bcr-2016-217005.
8. Bremmer DN, Nicolau DP, Burcham P, Chunduri A, Shidham G, Bauer KA. Ceftolozane/tazobactam Pharmacokinetics in a Critically Ill Adult Receiving Continuous Renal Replacement Therapy. *Pharmacotherapy* 2016;36:e30-e33. PMID:27012450. DOI: 10.1002/phar.1744.
9. Oliver WD, Heil EL, Gonzales JP, Mehrotra S, Robinett K, Saleeb P, et al. Ceftolozane-Tazobactam Pharmacokinetics in a Critically Ill Patient on Continuous Venovenous Hemofiltration. *Antimicrob Agents Chemother* 2015; 28:1899-901. PMID:26711770.