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Ceftolozane-Tazobactam Pharmacokinetics during Extracorporeal Membrane Oxygenation in a Lung Transplant Recipient

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Ceftolozane-tazobactam (C/T) pharmacokinetics during extracorporeal membrane oxygenation (ECMO) has not been previously studied. In this work, we report on the C/T plasmatic levels in a lung transplant (LTX) recipient during ECMO who was treated with C/T (intravenous [i.v.], 2 g ceftolozane and 1 g tazobactam, every 8 h]) for a *Pseudomonas aeruginosa* pulmonary infection.

The patient was a 42-year-old female (weight, 65 kg; body surface area, 1.72 m^2) with a history of sarcoidosis with pulmonary fibrosis (stage IV) and pulmonary emphysema with alpha-1 antitrypsin deficiency, admitted to the hospital due to acute respiratory failure. Upon admission, a chest X-ray showed bilateral infiltrates, and empirical antibiotic therapy was started with vancomycin and meropenem. Two days after admission, following worsening of respiratory conditions, a veno-venous ECMO (vvECMO) support was started according to the ELSO guidelines (www.elso.org). A permanent life support (PLS) circuit system (Maquet Holding B.V. & Co. KG., Rastatt, DE) with a preconnected PLS-i oxygenator and a centrifugal pump (Rotaflow) was used. Blood and gas flows were adapted to maintain a partial pressure of oxygen (PaO_2) of >90 mm Hg, partial pressure of carbon dioxide (PCO_2) of <40 mm Hg, and pH 7.4, under protective ventilation.

At the same time, the antimicrobial therapy was modified to vancomycin, amikacin, and ciprofloxacin, since the tracheal aspirate culture grew a carbapenem-resistant *Pseudomonas aeruginosa* strain (Table 1). On day 10, the culture of the tracheal aspirate was still positive for *P. aeruginosa* at $>1 \times 10^6$ CFU/ml. On day 13, the patient was subjected to bilateral LTX. During surgery, the extracorporeal support was switched from veno-venous to veno-arterial ECMO (vaECMO).

Immediately after surgery, the antibiotic therapy was modified to C/T (2 g/1 g) every 8 h over a 1-h infusion, 400 mg ciprofloxacin every 8 h, and vancomycin in continuous infusion (the vancomycin dose was adjusted to obtain target trough levels between 15 and 20 μg/ml). The patient had a normal renal function with creatinine clearance (estimated using the Cockcroft-Gault formula) (Fig. 1).

C/T plasma concentrations obtained in the first 96 h after LTX were retrospectively determined using a validated high-performance liquid chromatography (HPLC) method (1) (maximum concentration of drug in serum [C_{max}], ½ h after the end of infusion; minimum concentration of drug in serum [C_{min}], immediately before the beginning of the following dose). Written patient consent was obtained for collection and publication of these data.

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TABLE 1 Susceptibility profile of the *Pseudomonas aeruginosa* isolate obtained from tracheal aspirate culture

Antibiotic	MIC (μg/ml)	Categorization[a]
Amikacin	4	Susceptible
Aztreonam	16	Resistant
Ceftazidime	2	Susceptible
Ciprofloxacin	0.5	Susceptible
Colistin	0.5	Susceptible
Gentamicin	1	Susceptible
Imipenem	16	Resistant
Meropenem	16	Resistant
Piperacillin-tazobactam[b]	32	Resistant
Ceftolozane-tazobactam[b]	4	Susceptible

[a]Interpretation according to EUCAST clinical breakpoints v_8.1 (8). Susceptibility testing was performed according to a reference broth microdilution method (9).
[b]The concentration of tazobactam was fixed at 4 μg/ml.

During this period, ceftolozane levels remained above the ceftolozane MIC (4 μg/ml). In the first 48 h, the ceftolozane C_{max} was above 100 μg/ml. Later, from 48 to 96 h, there was a decline in C_{max} and C_{min}, which, however, remained above 60 and 20 μg/ml, respectively. Tazobactam concentrations followed the same trend, remaining at above 1.9 μg/ml for the whole period (Fig. 1).

vaECMO was halted on day 8 after LTX. The patient's condition eventually improved, and on day 15 after LTX, the antimicrobial therapy was discontinued. Four consecutive tracheal aspirate cultural exams, performed in the last day of treatment and 3, 4, and 7 days after the discontinuation of antibiotics, did not grow any pathogen.

In conclusion, we report the success of C/T treatment (in association with ciprofloxacin) for a case of a carbapenem-resistant *P. aeruginosa* low respiratory tract infection in an LTX recipient subjected to vaECMO support. Retrospective assessment of C/T plasmatic levels revealed that good drug exposure was achieved with a free drug concentration that exceeds the MIC ($fT_{>MIC}$) of 100% (60% $fT_{>MIC}$ is commonly considered predictive of cephalosporin microbiological success in pneumonia and CFU reduction against Gram-negative bacteria) (2–4).

During the monitored period, we observed a decrease in C/T C_{min} and C_{max} that could be probably attributed to the increase in the patient's creatinine clearance. In fact, it has been previously demonstrated that C/T clearance is highly correlated with renal function, with creatinine clearance significantly influencing exposure. However, alterations in the volume of distribution (*V*) (very frequent in critical patients) and the

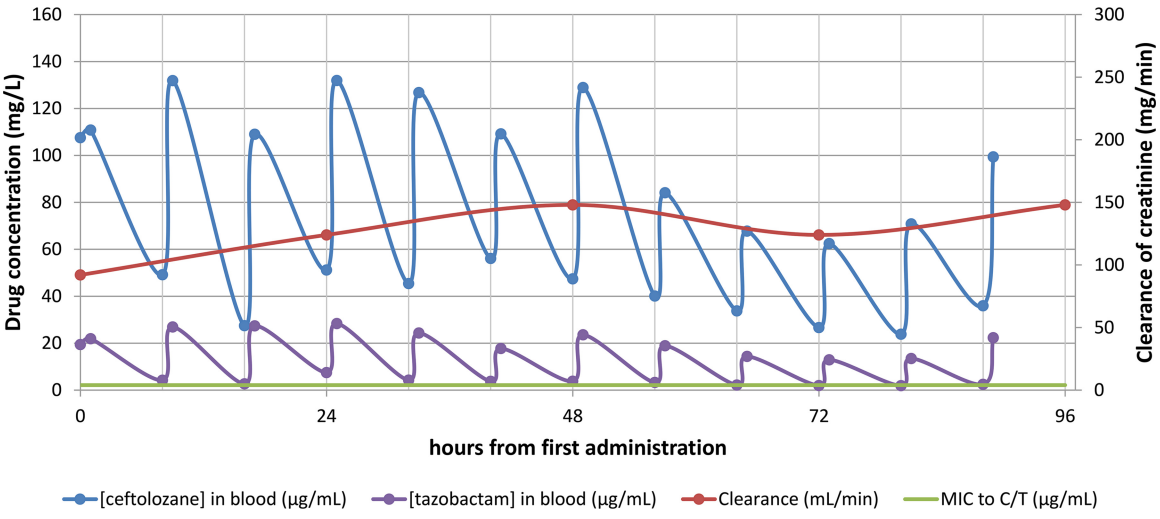

FIG 1 Ceftolozane-tazobactam plasmatic concentrations in the 96 h following LTX.

possible increase in *V* related to ECMO can cause variations in C/T concentrations (5–7). In our patient, in the period 48 to 96 h after LTX, a positive body fluid balance was recorded (≈2,000 ml input excess). This could have also partially contributed to the observed decrease in C/T plasmatic levels in this period.

Our findings suggest that optimal ceftolozane-tazobactam C/T PK parameters can be achieved in severely ill patients with normal renal function requiring ECMO, without the need for dose or infusion time adjustment.

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