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Optimizing ceftolozane-tazobactam dosage in critically ill patients during continuous venovenous hemodiafiltration

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Ceftolozane-tazobactam (C/T), the combination of a new cephalosporin with a classic β-lactamase inhibitor, is currently considered the most active betalactam antibiotic against *P. aeruginosa* [1]. Despite several case reports on C/T pharmacokinetics in critically ill patients during continuous renal replacement therapy (CRRT) [2–4], the optimal dose in this clinical scenario still remains unclear [5].

A 68-year-old patient was admitted to our ICU with septic shock (nosocomial peritonitis) and anuric acute renal failure. Broad-spectrum antimicrobial therapy, including C/T and continuous venovenous hemodiafiltration (CVVHD), was initiated, using a polysulphone hemofilter (Fresenius, Germany) with blood flow, dialysate fluid, and replacement fluid rates of 100 mL/min, 2000 mL/h, and 1000 mL/h. The patient received high C/T doses of C/T 2 g/1 g every 8 h (infused over 1 h) while receiving CVVHD, and became apyrexial 7 days after C/T treatment initiation, remaining fever-free for 14 days without any adverse effects related to this drug.

Pre-filter and post-filter blood and ultradiafiltrate samples were obtained during the 8-h dosing interval after the fourth dose. Drug concentrations were measured by high-performance liquid chromatography. Figure 1 and Table 1 show pre- and post-filter plasma concentrations. Pharmacokinetic parameters were calculated (Table 2). Extraction ratios were high for both ceftolozane and tazobactam (49.3% ± 1.8% and 40.5% ± 4.5%). Mean C/T concentrations in the ultrafiltrate were 40 mg/L and 13.5 mg/L, respectively.

We decided on a 3 g/iv dose every 8 h, taking into account two previous studies [3, 4] and a recent study which showed CRRT to be an independent predictor of clinical failure (OR 4.5, 95% CI 1.18–17.39, $p = 0.02$) when C/T is administered at 1.5 g every 8 h [5].

Ceftolozane and tazobactam are small molecules with low plasma protein binding rates, causing most to be removed during CRRT. Despite the considerable C/T clearance observed in our patients during

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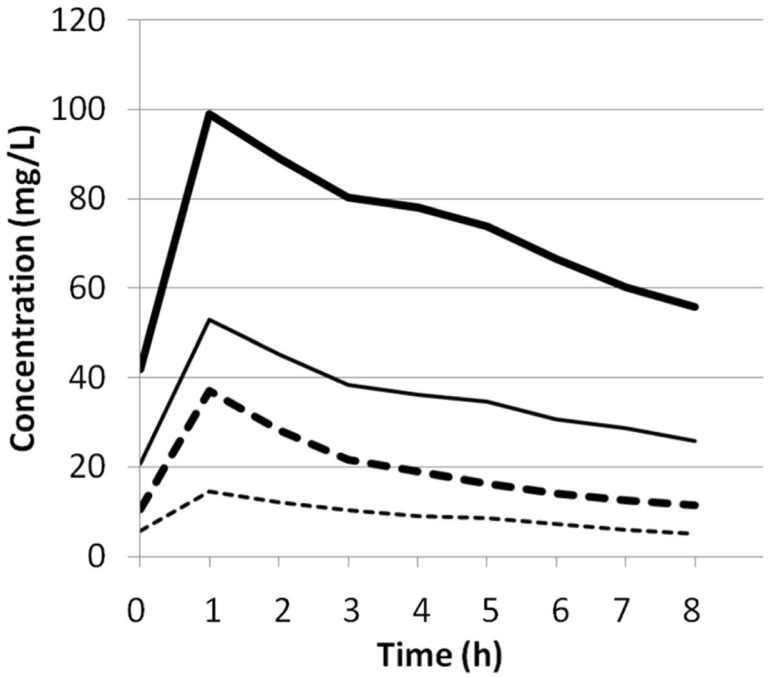

Fig. 1 Simulated plasma concentrations versus time curves for ceftolozane and tazobactam. Pre-filter (thick line) and post-filter (fine line) ceftolozane plasma concentrations and pre-filter (thick dotted line) and post-filter (fine dotted line) tazobactam plasma concentrations. (The figure is original for this article)

CVVHD, however, ceftolozane plasma concentrations remained above the MIC, for MICs of up to 8 μg/mL, throughout the dosing interval, assuming 20% protein binding. Given that C/T exhibits linear, dose-proportional pharmacokinetics, a standard C/T dose of 1 g/0.5 g would be expected to maintain ceftolozane levels above the MIC during the entire dosing interval, although tazobactam concentrations could be insufficient, even taking higher pre-filter rather than lower post-filter levels as representative of therapeutic serum levels.

In conclusion, our data underscore that a dosage of 3 g every 8 h can be used safely to prevent the potential harm of underdosing ceftolozane/tazobactam during CRRT; larger studies are however needed to confirm our findings.

Table 1 Concentrations of ceftolozane and tazobactam in pre-filter and post-filter plasma samples obtained after the fourth dose of 2 g/1 g ceftolozane-tazobactam administered as intravenous 1-h infusion

Sampling time	Ceftolozane (mg/L)		Tazobactam (mg/L)	
	Pre-filter	Post-filter	Pre-filter	Post-filter
0 h (pre dose)	41.9	20.7	10.6	5.8
1.5 h post dose	89.1	45.2	28.3	12.2
2 h post dose	80.3	38.4	21.6	10.3
2.5 h post dose	77.1	36.1	19.0	9.0
3 h post dose	73.8	34.7	16.3	8.2
5 h post dose	66.6	30.6	14.2	7.4
7 h post dose	60.2	28.7	12.7	6.0
8 h post dose	55.8	25.8	11.4	5.1

Table 2 Pharmacokinetic parameters of ceftolozane and tazobactam

Parameter	Ceftolozane		Tazobactam	
	Pre-filter	Post-filter	Pre-filter	Post-filter
Clearance (L/h)	2.1	5.4	6.4	17.4
Volume of distribution (L)	53.9	97.5	108.9	194.2
Half-life (h)	17.9	12.6	11.9	7.8
AUC (h mg/L)	960	373	157	57.6
Maximum concentration (mg/L)	99	53	37	14.5
Minimum concentration (mg/L)	55.9	25.8	11.4	5.1

AUC area under the concentration-time curve

Abbreviations
AUC: Area under the concentration-time curve; C/T: Ceftolozane-tazobactam; CRRT: Continuous renal replacement therapy; CVVHD: Continuous venovenous hemodiafiltration; HPLC: High-performance liquid chromatography

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Availability of data and materials
All relevant data are within the paper and its supporting information files. All data are fully available without restriction.

Authors' contributions
GA conceived the study, participated in its design, and drafted the manuscript. RF participated in the study design and coordination and helped draft the manuscript. CE performed pharmacokinetics analysis and helped revise the manuscript. SMC, EP, JC, and participated in data analysis and interpretation and helped revise the manuscript. DN and MA participated in the study design and coordination and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol (TC-TCRR-2018) was approved by the local ethics committee (INCLIVA Health Research Institute) and written informed consent obtained from the patients or their relatives prior to study inclusion.

Consent for publication
Written informed consent was obtained from the patient or their relatives for publication of their individual details. The consent form is held by the authors' institution and is available for review by the Editor-in-Chief.

Competing interests
GA received financial support for speaking at meetings organized on behalf of Astellas, Gilead, Merck Sharp and Dohme (MSD), and Pfizer, as well as unrestricted research grants from Astellas, MSD, and Pfizer. DN received financial support for speaking at meetings organized on behalf of Astellas, MSD, and Pfizer and received unrestricted research grants from Astellas and Pfizer. All other authors declare that they have no competing interests.

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