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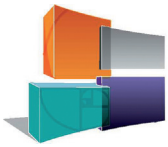

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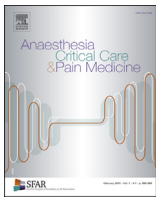

Letter to the Editor

Preliminary therapeutic drug monitoring data of β-lactams in critically ill patients with SARS-CoV-2 infection

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Dear Editor,

Among the treatment strategies recommended for the management of SARS-CoV-2 critically ill patients, early administration of antibiotics is suggested [1]. In the intensive care unit (ICU), β-lactam antibiotic therapy remains the first choice and can be optimised by a continuous infusion combined with therapeutic drug monitoring (TDM) [2,3]. However, in the context of COVID-19 disease outbreak, the feasibility of routine TDM could be challenged by the work overload associated with the surge of patients.

Herein, we present pooled routine TDM data obtained from the first days of β-lactam therapy in 20 critically ill patients with a confirmed SARS CoV-2 viral infection. Our local stewardship program included systematic invasive respiratory samples before the start of antibiotics (β-lactams administered continuously after intravenous bolus dose in association with spiramycin), blood sampling for TDM of β-lactams after 24 hours and reassessment of the treatment at 48 hours.

The clinical patient characteristics and TDM data are reported in Tables 1A and 1B. None of the patients presented with septic shock. All the patients were managed using protective mechanical ventilation, early use of prone positioning and conservative fluid management.

Overall, unbound β-lactam concentrations were above 4 × MIC when considering bacteria commonly involved in community acquired pneumonia (namely *Streptococcus*, *Staphylococcus aureus* and Enterobacteriaceae). Cefotaxime (6 g/24 h) was the most used antibiotic. Piperacillin/tazobactam and cefepime were used for patient with previous antibiotic exposure within the last 3 months. No initial severe acute renal failure was observed. Within the first 24 hours, serum albumin concentrations were low despite conservative fluid management, which may increase unbound fraction of antibiotics. Interestingly, all patients manifested neurological dysfunction (confusion or delirium after first cessation of sedative drugs. Although several confounding factors may explain or contribute to the observed neurological state (advanced age, severe hypoxemia, sedative drugs, SARS-Cov-2 related encephalopathy), β-lactam neurotoxicity as contributing factor could not be excluded. Considering the high risk for healthcare workers to be contaminated, electro-encephalograms were not performed. Trough cefepime concentrations were consistently above the thresholds associated with toxicity [4]. Thus, this cephalosporin should be used with extreme cautious in these patients. Concerning cefotaxime and piperacillin, the concentrations were below the published range of neurotoxicity [5,6].

As previously described, few patients presented early bacterial coinfection [7]. Herein, only one patient presented a documented pneumonia due to *Streptococcus pneumoniae* and *Staphylococcus aureus*.

To conclude, the low prevalence of early bacterial coinfection and the peculiarities of β-lactam pharmacokinetics during the early phase of SARS CoV-2 infection should be considered for antibiotic stewardship. Indeed, since a high interindividual variability of β-lactam concentrations was observed despite apparent similarities in clinical features, β-lactam TDM should be advised. Moreover, as many patients will require long duration

Table 1A
Population baseline and therapeutic drug monitoring data.

Characteristics	n = 20
Sex ratio M/F	14/6
Age (years old)	65 [62–72]
Total body weight (kg)	84 [75–95]
Ideal body weight (kg)	66 [62–71]
Body mass index (kg/m^2)	28.5 [26–31]
Comorbidities	
Hypertension	12 (60)
Diabetes	8 (40)
Ischemic heart disease	3 (15)
COPD	4 (20)
Obstructive sleep apnoea	6 (30)
Chronic kidney disease[a]	1 (5)
ICU data	
SOFA score[d] at admission	7 [5–8]
SAPS II[e]	37 [33–48]
PaO_2/FiO_2 at admission	97 [81–127]
Albumin level (g/L)	23.4 [21.1–27.2]
Acute renal failure KDIGO 1	5 (25%)
Measured renal clearance (mL/min)[b]	98 [68–120]
Fluid balance (mL)[c]	−465 [−823; +165]

Data are presented as: *n* (%), median [Q1–Q3].
[a] Chronic kidney disease was defined as a creatinine renal clearance < 60 mL/min/m^2.
[b] Renal clearance was measured using the ($Urine_{Creatinine}$ × volume)/$P_{Creatinine}$ formula.
[c] Fluid balance was calculated the day of the dosage of β-lactam concentration.
[d] Sequential Organ Failure Assessment Score.
[e] Simplified Acute Physiology Score.

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Table 1B
Population baseline and therapeutic drug monitoring data.

β lactam	*n* (%)	Total concentration[a] (mg/L)	Unbound concentration[a] (mg/L)	FC > 4 × MIC[b]
Cefotaxime (6 g/24 h)	13 (63)	23 [17–26]	18.4 [13.6–20.8]	100%
Cefepime (6 g/24 h)	3 (16)	29 [29–81.2]	23 [23–65]	100%
Piperacillin/tazobactam (12 g/24 h)	4 (21)	42 [34–67]	33.6 [25.3–53.6]	100%

Plasma concentrations of β-lactams were measured directly using a validated and previously published HPLC assay.
[a] Total concentration and free concentration (FC) (estimated using previous published data regarding the percentage of unbound fraction: 80% for each β-lactam) were obtained after 24 hours of continuous administration, at steady state.
[b] Adequation of FC > 4 × MIC was based on the EUCAST highest epidemiological cut-off (ECOFF) values. The species taken into account in community-acquired pneumonia were *Staphylococus aureus*, Enterobacteriaceae and *Streptococcus pneumoniae*.

of invasive mechanical ventilation [8] exposing them to a high risk of ventilator-associated pneumonia, these patients should not be exposed to inadequate antibiotics drug dosing. However, since the prevalence of augmented renal clearance was low, the risk of β-lactam underdosage is probably low and conventional doses of β-lactams should be sufficient. Finally, clinicians should be aware of a shifted risk of overdosage after the first days of admission, when approaching the period of weaning from mechanical ventilation. In view of the apparently high prevalence of neurological disorder that affects patients suffering from SARS-CoV-2, TDM should be performed, at least to screen possible β-lactam overexposure.

Author contributions

E.N. and J.S.B. participated equally in this work. ICU performed the statistical analysis and takes responsibility for the integrity of the data and the accuracy of the data analysis. E.N. and P.G. collected ICU data. J.S.B. performed the β-lactam measures. E.N., J.S.B., C.R. and P.G. contributed substantially to the study design, data interpretation and the writing of the manuscript.

Ethics consideration

TDM of β-lactams is performed routinely in our ICU. Approval to analyse these data was granted by the local ethic committee. The need for informed consent was waived in view of the retrospective nature of the study.

Disclosure of interest

The authors declare that they have no competing interest.

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