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Antimicrobial Exposure: Do Not Forget the Patient's Condition Beneath the Extracorporeal Membrane Oxygenation Support!



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To the Editor:

We read with great interest the large multicenter study recently published in the *Journal* by Shekar and colleagues (1). The study brings a valuable description of the pharmacokinetics (PK) of antimicrobials in critically ill adult patients receiving extracorporeal membrane oxygenation (ECMO) and evaluates the effective exposure of current antimicrobial dosing regimens. Interestingly, large variations in all PK parameters were observed for all antimicrobials, and only 56% of concentration profiles achieved the predefined target concentration. These data are crucial for daily patient management with ECMO support. However, because of methodological issues, it is unclear if ECMO impacts antimicrobial exposure or if the chosen target concentrations are relevant in this setting.

The first methodological issue is the disproportion between the number of antimicrobial drugs evaluated ($n = 11$) and the small sample size. Although the authors should be congratulated for their ambitious work, only 85 patients were finally enrolled.

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Accordingly, only 124 concentration profiles were available for analysis, with a wide disparity for each drug (from only 1 profile for voriconazole to 27 profiles for piperacillin). As a consequence, the authors could not perform population pharmacokinetic modeling. Indeed, the same authors stated elsewhere that when the sample size used remains small (approximately 10–20 patients), it is likely that PK variability is insufficiently captured by these models (2). Accordingly, a noncompartmental PK-analyzing series of concentration values at different time points, which is a valuable alternative, was preferred by the authors. However, such analysis prohibits any exploration of ECMO as a covariate.

We can also regret the lack of a control group, which did not allow a conclusion regarding the impact of ECMO support. Herein, a prospective study remains the best design for assessing the impact of ECMO on PK, with a comparison of patients with and without ECMO support. Indeed, a patient's related organ dysfunction modifies PK parameters more strongly than ECMO itself. For example, when Kim and colleagues affirmed that piperacillin exposure is lower among patients with ECMO support, differences in baseline characteristics such as glomerular filtration or severity scores precluded firm conclusions (3). Conversely, when patients with ECMO support were matched with control patients on the basis of SOFA (Sequential Organ Failure Assessment) score and glomerular filtration rate, there was no impact of ECMO on PK parameters or piperacillin exposure (4). This is in line with our experiments on *ex-vivo* ECMO devices, as we found no significant sequestration of the hydrophilic drug β -lactam in the ECMO circuit (5). When the authors stated that antimicrobial dosing in patients with ECMO support should generally align with the recommended dosing strategies for critically ill patients without ECMO support, one should not forget the associated patient's condition beneath ECMO support that likely impacts PK.

Finally, readers should be aware that the study focusing on β -lactam target nonattainment mostly relies on European Committee on Antimicrobial Susceptibility Testing (EUCAST) Epidemiological cut-off value (ECOFF) or EUCAST breakpoint. Consequently, they do not take into account the specific situation in its specific environment. When actual minimal inhibitor concentration (MIC) is applied, target attainment was observed in nearly 90% of patients treated with β -lactam in ICUs (6). Although some experts support the use of antibiotic concentrations at four times the MIC, others recommend only one time the MIC. To date, the appropriate antimicrobial target concentration for patients with sepsis is unclear and should be better defined before further studies in this field.

In conclusion, we should congratulate the authors for this large work, but studies assessing the real impact of ECMO support on pharmacological drugs are still needed. We agree with the authors that therapeutic drug monitoring appears essential nowadays, but it should be analyzed in accordance with contextual MIC. ■

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