Intensive Care Med (2023) 49:475–476
https://doi.org/10.1007/s00134-023-06990-4

CORRESPONDENCE

Individualised dosing of antibiotics in ICU patients: timing, target and model selection matter

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Therapeutic drug monitoring (TDM) of antibiotics is recommended and increasingly used in critically ill patients to optimize target attainment and account for inter-patient pharmacokinetic variability [1]. Beyond TDM, critically ill patients could benefit from model-informed precision dosing (MIPD), a newer and not yet extensively employed but promising technology integrating TDM results into mathematical models [2]. We would like to compare and contrast two recently published randomized controlled trials investigating the effect of TDM and MIPD on critically ill patient outcomes.

In 249 enrolled critically ill patients treated with piperacillin Hagel et al. showed that the use of TDM (without MIPD) improved the rate of target attainment (14.6% without TDM vs. 37.3% with TDM) but found no significant difference in mortality and cure rate. However, it should be noted that, in the TDM group, 40% remained overdosed and 24% underdosed, which justifies the investigation of additional benefits of MIPD [3]. Ewoldt et al. analyzed 388 patients with or without MIPD of beta-lactams and ciprofloxacin and found no significant difference in the primary (intensive care unit (ICU) length of stay) and secondary outcomes. Unexpectedly, the use of MIPD also failed to increase the rate of target attainment [4]. A closer look at the study setting might therefore be beneficial for future investigations.

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This comment refers to the articles available online at https://doi.org/10.1007/s00134-021-06609-6 and https://doi.org/10.1007/s00134-022-06921-9

Ewoldt et al. applied the dosing software InsightRx including the therein-implemented models. There is no publicly available information that the models have been verified against external datasets. In the case of meropenem, an external evaluation of the used models [5, 6] showed high bias and/or a low precision [7]. In this context, an assessment of the predictive performance of the models in their cohort could be performed to inform future studies in the field.

All patients received standard doses during the initial treatment course implying that there was effectively no difference between the two groups for the most critical period of sepsis treatment [1]. This group uniformity may have masked an effect of MIPD on the clinical/chemical parameters (mortality, ICU-length of stay, delta Sequential Organ Failure Assessment (SOFA) score, delta C-reactive protein and delta white blood count).

The protocol of the study defined the dosing range strictly (e.g. max. daily dose 18 g piperacillin/tazobactam, 6 g meropenem) preventing presumably required dose adaptions (e.g. MIPD-group T5 40% target non-attainment vs. 13.3% dose adjustments). In contrast, the target range was defined broadly with a high upper threshold ($100\%fT_{>10x\ MIC\ ECOFF}$; e.g. piperacillin ~ 200 mg/L). Hagel et al. [3] demonstrated that mortality increases with concentrations above the upper target range (piperacillin: 96 mg/L). Of note, overexposure was observed in twice as many patients in the intervention arm as compared to the control arm [4].

Taken together, we hypothesize that an optimization of the study setting might help to maximize the benefit of MIPD. In future studies, MIPD could be re-evaluated employing externally evaluated models, using continuous infusion for time-dependent antibiotics, and a timely

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susceptibility testing of pathogens. This could be particularly valuable for patients at increased risk of target non-attainment such as critically ill patients with sepsis, obesity, augmented renal clearance, renal and liver insufficiency, and patients at risk of infections caused by less susceptible pathogens.

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Funding
Open Access funding enabled and organized by Projekt DEAL. This work had no funding support.

Declarations

Conflicts of interest
UL and JB declare no conflict of interest. AB reports lecture fees from MSD Sharp & Dohme GmbH, Pfizer Pharma GmbH, Fresenius Medical Care (FMC), Labor Volkmann (Karlsruhe). OF reports lecture feed from MSD Germany and Fresenius Kabi Germany. SGW reports grants from Boehringer Ingelheim, consulting fees from Medicines for Malaria Venture, Merck KGaA, UTIlity Therapeutics, and lecture fees from GlaxoSmithKline.

Publisher's Note

Accepted: 16 January 2023
Published: 31 January 2023

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