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EDITORIAL

Advancing precision-based antimicrobial dosing in critically ill patients

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Treatment of infections among critically ill patients remains problematic, with ongoing challenges in antimicrobial dosing optimisation. Strategies, such as model-informed precision dosing (MIPD), may be effective solutions but as yet without documented clinical benefit.

In a paper published in the December issue of Intensive Care Medicine, Ewoldt and colleagues conducted the DOLPHIN trial to evaluate whether a MIPD intervention (therapeutic drug monitoring [TDM] and use of dosing software) in critically ill patients prescribed beta-lactam antimicrobials and ciprofloxacin decreased length of stay (LOS) in the intensive care unit (ICU) when compared to standard dosing alone [1]. The investigators should be commended for the first ever multicentre trial evaluating the potential benefits of MIPD in critically ill patients. The organisational aspects of conducting a multicentre study with essentially two interventions (TDM and dosing software) are challenging.

Included in the primary analysis of the trial were 388 patients (MIPD group; $n=189$, standard dosing group; $n=199$). Contrary to their hypothesis, the investigators found a similar median LOS among both groups, with the MIPD group having a non-significant increase of 2 days on average compared to the standard dosing group (10 days vs 8 days, respectively). In addition, pharmacodynamic (PD) target attainment in the MIPD group remained low, ranging from 55.6 to 71.4%.

Do these recent findings mark the beginning of the end to evaluating MIPD as a clinically relevant dose optimisation strategy in critically ill patients? In our opinion, no. We believe that there were some limitations with the study which should be addressed in future studies that test the benefits associated with precision-based antimicrobial dosing.

Early application of dosing interventions

Given the mortality benefits associated with using early effective antimicrobial therapy in sepsis [2], studies should ideally research dose personalisation as part of the first dose. To allow for subsequent dosing refinement to be timely, a turn-around time for reporting TDM results should ideally be within a few hours [3].

Consenting for 'ongoing' patient participation [4], rather than incurring the delays associated with obtaining informed consent prior to participation, would enable testing of early dosing interventions on clinical outcomes. This is especially relevant given that antimicrobial courses can often be of short duration, as evidenced by the DOLPHIN trial (median duration of therapy: 4 days in MIPD group vs 3.5 in standard dosing group) [1]. If dosing interventions are delayed, as noted in the trial where there were delays of up to 36 h in performing the initial dose adjustment, the opportunity for these to have an effect is severely handicapped.

Inclusion of critically ill sub-groups likely to benefit from a targeted dosing approach

Certain sub-groups of critically ill patients may benefit from the use of adaptive dosing adjustments that account for the bacterial kill characteristics of the antimicrobial (i.e. a pharmacokinetic–pharmacodynamic [PK–PD] based approach). An example of using PK–PD principles to inform dosing is use of prolonged infusions in patients prescribed time-dependent antimicrobials, such as the beta-lactam class of antimicrobials. Sub-groups where this approach may be of benefit include those with ventilator-associated pneumonia (VAP) [5], high severity of disease [6], and pathogens with decreased susceptibility

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Table 1 Ideal characteristics of MIPD software in the ICU

Software information	Availability to support a priori dosing (empiric dosing recommendations) and a posteriori dosing (dosing recommendations taking into consideration measured drug concentrations) Ability to adjust pharmacodynamic (PD) targets Externally validated and clinically appropriate population PK models that underpin dosing software recommendations Ability to archive and retrieve previous dosing data and recommendations
Software interface	Ability to use as computer- and smart phone-based applications Cross-platform integration with local electronic health records (EHR) and clinical information systems (CIS) Assessed for acceptance and usability using industry-validated tools such as Technology Acceptance Model 2 (TAM2) and Post-study System Usability Questionnaire (PSSUQ), respectively Flexibility of inputting dosing information (e.g. as either dosing schedules or exact administration times) Outputs are easy for clinicians to understand (e.g. exposure plots of predicted concentrations) and automated to generate reports for clinical notes

(i.e. those with a higher minimum inhibitory concentration (MIC) but still within the ranges that are responsive to the chosen antimicrobial therapy) [7, 8].

Traditional 'restrictive dose adjustments' (i.e. a maximal cutoff to either a dose increase or decrease in between sampling periods) together with an absolute maximum in the daily dose (e.g. a maximum cumulative dose of 16–2 g of piperacillin–tazobactam) [1] may reduce the likelihood of PD target attainment in these patient sub-groups.

Future interventional studies should endeavour to enrich for these sub-groups of patients and allow for more targeted dose optimisation approaches so that challenges associated with attaining PD targets can be overcome.

Selection of MIPD software and validation of population PK models

Choice of MIPD software is a key consideration when designing clinical trials evaluating this approach (Table 1) [9]. Importantly, software usability must also be considered to ensure appropriate use so that the likelihood of PD target attainment is maximised. Likewise, integration of clinically applicable PK models into the MIPD software that are validated in local critical care settings should occur prior to software evaluation. Choice of a PK model that is not appropriate in a population where the dosing intervention is being targeted may reduce the effectiveness of the software. For example, the use of a PK model that only uses total concentrations of a highly protein bound antimicrobial is unlikely to be accurate in estimating the unbound fraction of that antimicrobial (i.e. the fraction that is pharmacologically active) [10]. This in turn will reduce the capacity of MIPD in designing dosing regimens that can achieve PD targets.

Exclusion of resistant pathogens from final analysis

Given the often limited a priori data available when planning interventional studies, there are inherent challenges in ensuring clinical trials are adequately powered to test relevant outcomes. This is especially true for interventional studies conducted in populations where actual infections may be difficult to identify, such as those with a provisional diagnosis of sepsis. Despite these challenges, patients with infections caused by pathogens not susceptible to the study drug should be excluded from the intention-to-treat analysis.

The concept of dose optimisation strategies, such as MIPD interventions, remains of great interest, albeit currently not well supported. Recent clinical trial evidence shows no favourable impact and is hampered by low rates of PD target attainment.

Nevertheless, dose optimisation strategies such as MIPD are still likely to be important in ensuring effective antimicrobial therapy. Testing these interventions requires careful planning and should consider early application with efficient feedback mechanisms to inform dose adjustments, inclusion of sub-groups that are at high risk of therapeutic failure due to sub-optimal antimicrobial exposure and use of adaptive dosing strategies based on PK–PD principles of the chosen antimicrobial. In the case of interventions specifically using dosing software, selection of an appropriate MIPD application and integration of PK models that are validated in the targeted patient population are important to consider prior to conducting a trial that evaluates their impact on health system- and patient-centred outcomes.

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Data availability
These data that support the information within this Editorial are available from the corresponding authors upon reasonable request.

Declarations

Conflicts of interest
The authors declare that they have no conflict of interest.

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