



Editorial

Augmented renal clearance and therapeutic monitoring of β -lactams

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ABSTRACT

Successful application of antibacterial therapy in the critically ill requires an appreciation of the complex interaction between the host, the causative pathogen and the chosen pharmaceutical. A pathophysiological change in the intensive care unit (ICU) patient challenging the 'one dose fits all' concept includes augmented renal clearance (ARC), defined as a creatinine clearance (CL_{Cr}) of ≥ 130 mL/min. Ideally, CL_{Cr} values should be obtained by a timed measured collection of urine, with plasma and urine creatinine levels. Increased renal clearance of antibiotics also occurs in the ICU patient and therefore β -lactam antibiotic exposure in the critically ill could easily lead to trough drug concentrations below therapeutic ranges. One way to document and alter drug levels is via therapeutic drug monitoring (TDM). The interactions of ARC and β -lactam TDM are further explored in this article in specific reference to a concomitant article in this issue of the journal.

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Successful application of antibacterial therapy in the critically ill requires an appreciation of the complex interaction between the host, the causative pathogen and the chosen pharmaceutical [1]. The prescriber's principal desire is to achieve therapeutic drug concentrations at the site of infection, ensuring rapid bacterial killing and the prevention of infection-related organ and tissue damage. Timely recognition of sepsis and the administration of an appropriate antimicrobial agent (with a suitable spectrum of cover) remains the cornerstone of effective management [2], but what is more uncertain is the impact of variable antibacterial exposure, beyond simple susceptibility patterns. In this fashion, the host response as well as ancillary interventions provided can have marked effects on the pharmacokinetics of these agents, leading to highly variable drug concentrations following standard dosing [3–16].

Huttner et al. in this issue of *International Journal of Antimicrobial Agents* report their findings from a single-centre observational study of β -lactam antibiotic concentrations and clinical outcomes in a cohort of critically ill patients with presumed severe infection [17]. In total, 100 patients were enrolled, with the majority (64%) manifesting augmented renal clearance (ARC) on study inclusion [Cockcroft–Gault-estimated creatinine clearance ($CG\ CL_{Cr}$) ≥ 130 mL/min]. Plasma imipenem, meropenem, piperacillin and cefepime concentrations were measured on Days 1–3 and 5 and were correlated against European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. Subthreshold and undetectable trough concentrations were common (71% and 20%, respectively) and were strongly associated with ARC. Clinical failure was documented in 18 of 98 evaluable patients at Day 28. Of note, no association with ARC or subthreshold drug levels was identified in regression modelling [17].

Although these data confirm findings from previous work [18,19] that a simple 'one dose fits all' approach to β -lactam antibiotic dosing in the intensive care unit (ICU) is significantly flawed, important issues remain regarding the diagnosis of ARC. Furthermore, the impact of ARC on any clinical outcome remains unclear, as this study could not show a survival disadvantage for ARC patients.

ARC occurs in approximately two-thirds of patients who are admitted to the ICU with a normal serum creatinine [20]. The impact of ARC on β -lactam antibiotic concentrations is now well established, and is not surprising given the pharmacokinetic (PK) profile of these agents that are primarily cleared renally. Conil et al. illustrated this in their single-centre, prospective, observational study involving 72 critically ill patients receiving piperacillin [21]. Subthreshold levels were frequently observed, with a strong inverse relationship between measured 24-h CL_{Cr} values and trough piperacillin concentrations. Udy et al. observed similar findings in their analysis of β -lactam therapeutic drug monitoring (TDM) in the critically ill [18]. More recently, Carlier et al. explored the impact of ARC on β -lactam target attainment in patients receiving meropenem and piperacillin by extended infusion [19]. In regression analysis, higher CL_{Cr} was identified as an independent predictor of failing to achieve the required level of drug exposure. These data reinforce the influence of ARC in distorting the pharmacokinetics of renally eliminated β -lactams, in turn predisposing to subthreshold trough plasma concentrations. However, despite the clear PK disadvantage, the clinical implications of this phenomenon remain uncertain, as was also evident from the analysis by Huttner et al. [17].

One of the key elements in determining the role of ARC is the diagnosis of ARC itself. In the analysis by Huttner et al. [17],

glomerular filtration rate (GFR) was estimated (eGFR) based on the Cockcroft–Gault method. Several recent studies have compared different measures of GFR in critically ill patients, and eGFR methods have consistently been demonstrated to be not very accurate for this; moreover, recent data using inulin clearance show that eGFR is particularly poor at estimating kidney function when GFR is high [22]. Measured CL_{Cr} probably is the most convenient way to calculate GFR with an acceptable accuracy [15].

ARC is often evaluated using a cut-off value, but physiologically, GFR is a continuum with higher clearances associated with lower concentrations. It can be expected that the impact on antibiotic concentrations is higher when GFR is >200 mL/min. If we want to study the impact of GFR, it should be studied as a continuous variable and not as a cut-off. Apart from this, ARC is also a dynamic phenomenon, and GFR may fluctuate considerably during antibiotic therapy resulting in variable antibiotic concentrations [23].

It would be naïve to expect that higher concentrations are effective in improving outcome in all patients, without considering actual susceptibility and other pathogen-related issues. When assessing the impact of antibiotic concentrations, the minimum inhibitory concentration (MIC) of each pathogen should be known, rather than inferred from population estimates. In this fashion, use of susceptibility breakpoints can grossly inflate the frequency of subthreshold levels, when in fact drug concentrations are entirely adequate owing to the 'true' MIC being substantially lower. Also, in clinical reality, many patients will continue to receive antibacterial therapy despite being culture-negative [24], and newer molecular techniques should hopefully enhance both diagnostic and therapeutic decision-making [25]. In future, some measure of bacterial load should also be incorporated into this assessment, as a higher burden will infer an increasing reliance on chemotherapy to ensure clinical success [26]. As such, the adequacy of antibacterial exposure cannot be viewed in isolation from the host immune response.

At this point it is not clear how to overcome or prevent the PK changes associated with ARC. Increased dosing or dose optimisation using prolonged infusion could offer increased antibiotic exposure. Numerous retrospective analyses have reported the merits of a strategy using prolonged infusions [27–29], particularly with difficult-to-treat organisms and higher illness severity [30]. No study, however, has focused specifically on patients with ARC, and some studies suggest that prolonged infusion may not be enough, particularly if one wants to aim for higher pharmacokinetic/pharmacodynamic targets such as $100\% fT_{>MIC}$ [31]. TDM-guided therapy with dose adaptation could be a solution to reach adequate plasma concentrations, or patient-tailored therapy using software that incorporates actual GFR [3,4].

As suggested by the authors, the wider ecological implications of subthreshold β -lactam levels require substantially greater study, and the implications in terms of drug resistance are significant [32]. Indeed, less susceptible pathogens are more frequently isolated in the ICU [33], which could potentially be a reflection of the widespread application of 'underpowered' antibacterial therapy. In an era where fewer therapeutic options are entering clinical practice, it remains imperative that clinicians consider the wider implications of individual antibacterial treatment decisions possible with the help of TDM.

In conclusion, Huttner et al. provide further data on the impact of kidney function on β -lactam antibiotic exposure in the critically ill, reinforcing that in patients manifesting ARC, trough drug concentrations are unlikely to be therapeutic. Unfortunately, the principle measure of kidney function was $CG\ CL_{Cr}$, methodology that is poorly suited to the critical care environment. In addition, accurate MIC data were available for less than one-half of the cohort, confounding clinical outcome analysis. Nevertheless, their results raise interesting questions as to the interaction between infection, drug exposure and kidney function. Future research should now focus

on more accurately quantifying both changes in kidney function and the burden of infection, in order to more reliably identify the implications for clinical outcomes in this group. Equally, the ecological consequences of subthreshold concentrations in terms of drug resistance requires substantial investment so that future critical care physicians are not faced with an ever-decreasing number of therapeutic antibacterial options.

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