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EDITORIAL

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Antibiotic dosing in the critically ill: asking the same questions but expecting different answers

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The approach of severe sepsis and septic shock has three fundamental steps: early recognition, hemodynamic resuscitation and early empiric antibiotic therapy with focus control if appropriate. Empiric antibiotic therapy involves two decisions: the choice of antibiotics, which depends on the presumed focus and pathogens, and dosing of antibiotics, which should be appropriate along with a correct route and mode of administration [1].

In a recent issue of *Intensive Care Medicine*, Jan De Waele et al. [2] presented data from the Defining Antibiotic Levels in Intensive care unit patients (DALI) study looking at patient characteristics predictive of non-attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets, namely $fT >$ MIC of the suspected pathogen for at least 50 and 100 % of the dosing interval, in intensive care unit (ICU) patients receiving eight different β-lactams. The DALI project [3] is an international prospective, multicentre, pharmacokinetic point prevalence study involving 68 hospitals, ten countries, with a total of 343 patients, of whom 259 had infection. In the present study, 57 % of patients received penicillins, 27 % carbapenems, and 16 % cephalosporins. Dosing was at the discretion of the treating clinician.

In the present study, antibiotics were given for treatment of infection in 75.5 % of patients; however, there was no information on the rate of microbiological documentation or on the bacterial antibiotic susceptibility. The aim of the study was to evaluate target non-attainment neither for the actual infection nor for the microbiological agents, but envisioning an empirical situation where the least susceptible organism was potentially causing the infection. To overcome this weakness, recognized by the authors, they assume that the concentrations obtained in the DALI study were also the concentrations that would be reached during empirical dosing. Accordingly, the authors calculate the non-attainment of PK/PD targets using the highest European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC90 data breakpoint for the administered antibiotic among all potential pathogens. The rationale for this choice was that empiric antibiotic dose selection is based on the 'worst-case' scenario in terms of bacterial susceptibility.

The authors showed that free antibiotic concentrations remained below the least susceptible MIC during 50 and 100 % of the dosing interval in 66 (19.2 %) and 142 (41.4 %) patients, respectively. By multivariate analysis, they found that intermittent infusion (vs. extended or

continuous infusion) was significantly associated with target non-attainment (either 50 or 100 % $fT > \text{MIC}$), and that high creatinine clearance (CL_{CR}), measured with the Cockcroft–Gault formula, was only associated with 100 % $fT > \text{MIC}$ non-attainment.

The use of the Cockcroft–Gault formula to estimate CL_{CR} raises several concerns since it has been repeatedly shown to be inaccurate in the critical care setting, in particular in patients showing augmented renal clearance [4]. Only measured CL_{CR} should be used to accurately guide drug dosing [5].

The authors also showed that, in patients treated with intermittent infusion, antibiotics for prophylaxis was the only identified risk factor for not achieving a 50 % $fT > \text{MIC}$. This finding is difficult to explain since we could assume that patients under antibiotic prophylaxis were less severely ill, since at least some could have been subjected to elective surgery, and as a result should have normal or near normal volume of distribution (Vd); however, on the other hand, they could present high CL_{CR} that could be the reason for target PK/PD non-attainment since surgery has been repeatedly shown to be a risk factor for augmented renal clearance. Concerning the target 100 % $fT > \text{MIC}$, the identified risk factors of non-attainment were high CL_{CR}, recent surgery and the first days of therapy. All these factors are expected to influence PK as they markedly influence antibiotic clearance and Vd [6].

Target non-attainment was also assessed in a subanalysis looking into the three most frequently administered antibiotics, i.e. piperacillin, meropenem and amoxicillin. Interestingly, the risk of target non-attainment was very high with amoxicillin used in conventional doses; almost 90 % of patients did not attain the 100 % $fT > \text{MIC}$. However, more worrisome was that in more than 50 % of patients treated with conventional doses of amoxicillin, 50 % $fT > \text{MIC}$ was not attained! This is in contrast to meropenem; when used in conventional doses and regardless of the method of administration, almost all patients reach 50 % $fT > \text{MIC}$ of the dosing interval and less than 30 % did not attain 100 % $fT > \text{MIC}$. These findings, not discussed by the authors, should be carefully scrutinized in the light of the accepted PK/PD targets for the treatment of bacterial infections for cephalosporins and penicillins $fT > \text{MIC} \geq 50$ % and for carbapenems $fT > \text{MIC} \geq 40$ % [7]. Consequently, the data from the present study points to the fact that, at least for meropenem, the proposed conventional dose attains the PK/PD target in almost all patients irrespective of the mode of administration, raising questions when looking into the contrasting results of the recently published randomised controlled trials [8, 9]. On the other hand, the very high frequency of non-attainment of PK/PD target with amoxicillin raises the issue of underdosing encountered with the widely used conventional dosing.

Besides underdosing, the issues of antibiotic accumulation and neurologic toxicity of β-lactams, not been evaluated in this study, have been well documented [10, 11] in particular in patients with renal and/or hepatic dysfunction.

One of the main messages of the present study is that with extended or continuous infusion of β-lactams the risk of non-attainment of target PK/PD decreases markedly. In spite of the well-known PK benefits of this strategy, studies have repeatedly failed to show a significant impact on mortality [12, 13]. As a result further clinical studies are needed to assess the impact of this strategy, continuous infusion of β-lactams, on patient outcomes.

Therapeutic drug monitoring (TDM) would help clinicians in the safe adjustment of the dose, especially when cheap, reliable and timely documentation of antibiotic concentrations becomes widely available. However, we are not there yet as PK/PD targets (especially in ICU patients), the effect of TDM on clinical cure and ICU mortality, are still all matter of debate. Meanwhile, studies elucidating antibiotic underdosing in ICU patients, such as the one conducted by De Waele et al., are warmly welcomed.

Conflicts of interest The authors have no conflicts of interest related to this topic.

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