Pharmacokinetics and pharmacodynamics of antimicrobials in sepsis

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Sepsis and septic shock are among the important causes of ICU mortality[1]. Early treatment with appropriate antibiotics is important in improving the outcomes in these high-risk patients. However, appropriate dosing strategies are difficult to implement as these patients typically have altered drug clearance and volume of distribution. In addition, there are doubts regarding the similarity of concentrations achieved in plasma and interstitial fluid[2]. Clearly, there is a need for understanding the pharmacokinetics (Pk) and pharmacodynamics (Pd) of antimicrobial agents in critically ill patients.

Pharmacokinetics describes the ways the body acts on the drug through liberation, absorption, distribution, metabolism, and elimination and thus deals with drug concentration changes with time. The main parameter used to quantify pharmacokinetics is the half-life ($t_{1/2}$) which is directly proportional to the ratio of volume of distribution to clearance.

Drug concentrations are measured in the blood, saliva, and skin blister fluid by microdialysis, tissue biopsy, or by nuclear imaging such as Magnetic Resonance Spectroscopy (MRS) and Positron Emission Spectroscopy (PET) or from samples of epithelial lining fluid by techniques such as Broncho-alveolar Lavage (BAL)[3]. It is not clear whether plasma or tissue half-life should be considered meaningful. We don't even know if these are linearly correlated. The disposition of drugs into infected and non-infected tissues is not very clear due to the heterogeneity of studies regarding dosage, routes of administration, and processing of specimens.

Pharmacodynamics, on the other hand, describes the effect of the drug on the body through serum levels and drug response, thus dealing with drug effects as related to drug concentration. The antimicrobial effect of drugs is typically measured by the in vitro measure of Minimum Inhibitory Concentration (MIC). It is easily and speedily performed, as an automated method is available, enhancing reproducibility. However, MIC has some inherent limitations. Minor variations in methodology can result in large variations in the MIC values. For example, prolonged incubation will result in a falsely high MIC, while a lower inoculum concentration will make it falsely low. Interlaboratory comparisons may be difficult. Also, MIC is the inhibition of visible growth. The organisms may not have been killed. Most importantly, MIC is an in vitro measurement and does not account for factors such as tissue penetration[4].

It is now clear that neither pharmacokinetics nor pharmacodynamics are sufficiently useful, when considered individually. An integrated Pk/Pd modeling approach, called pharmacometrics, may be much more useful. This approach links concentration versus time profiles of drugs (Pk) with the intensity of response versus concentration (Pd) to estimate the changes in drug effect over time. Theoretically, Pk-Pd modeling can produce the description of both desired and undesired effects, elucidate causal relationships between drug exposure and response, and may allow the prediction of effect profiles.

Pk-Pd modeling has been successful in the field of anti-infective chemotherapy. It has differentiated different classes of drugs like beta-lactams and aminoglycosides. The outcome predictor for beta-lactams is the time of exposure to drug concentrations above the breakpoint MIC (T>MIC), while it is the peak concentration (C_{max}) above the breakpoint MIC (C_{max}/MIC) for aminoglycosides. In addition to these effects, many antibiotics (e.g., vancomycin and azithromycin) suppress bacterial re-growth after their concentrations have fallen below the MIC. This Post-antibiotic Effect (PAE) is most commonly seen with antibiotics that have nucleic acid or protein synthesis inhibitory activity. PAE has been related to another Pk-Pd measure, the ratio of free drug area under the concentration-time curve (AUC) to MIC over a 24-hour period (AUC: MIC).

These concepts have direct clinical implications. We now think that concentration-dependent drugs such as aminoglycosides are effective with few side effects when administered in large, infrequent doses. On the other hand, time-dependent antibiotics frequently fail to reach adequate concentrations throughout the treatment period and may benefit from being administered as a loading dose followed by a continuous infusion.

However, most of the Pk-Pd modeling studies are in hemodynamically stable, non-critically ill patients. The

pharmacokinetics of antibiotics are affected extensively in the critically ill patient[5]. In sepsis, absorption through the oral route is affected by gastric dysmotility and pH, interaction with feeds, etc. Similarly, subcutaneous and intramuscular routes are affected by changes in the peripheral circulation. These concerns tend to favor the intravenous administration of drugs in critically ill patients.

In general, volume of distribution is greater than normal in critically ill patients. Antimicrobial distribution is changed profoundly through the effects of bacterial endotoxins and inflammatory mediators on vascular endothelium, leading to altered blood flow distribution, increased capillary permeability, and acid/base imbalance. Septic shock, mechanical ventilation, hypoalbuminemia, and possible extracorporeal circuits also contribute to the changes in the volume of distribution (Figure 1).

Drug metabolism and elimination are also affected in sepsis, with increased renal perfusion, creatinine clearance, optimization of non-renal metabolism and elimination of hydrophilic drugs in the absence of organ dysfunction. Later, in the course of the disease, myocardial dysfunction and decreased organ perfusion increase drug half-lives and potential toxicity. Renal support is indicated in critically ill patients with acute renal injury, though currently, there is no consensus on the type of support. Acute renal support during sepsis can lead to subtherapeutic antimicrobials such as vancomycin levels.

Dosing during sepsis is problematic as the drug concentrations alter to a great extent depending on the individual pathophysiology and the course of management. Overall, the risk of suboptimal dosing is greater than that of adverse effects due to overdosing, especially for hydrophilic compounds. Patients with fulminant hepatic failure or those with severely impaired renal function; without renal support are at a high risk of adverse effects when overdosed. However, even in these cases, the adverse effects are mitigated by the increased volume of distribution. Literature shows that underdosing is more common than overdosing[6].

Most Pk-Pd studies in the literature suffer from small sample sizes, variable tissue site sampling, and not measuring the free drug concentrations. In addition, all three Pk-Pd parameters described above depend upon a measure of in vitro susceptibility. The targets are developed based on bacterial killing in animal models. We do not have

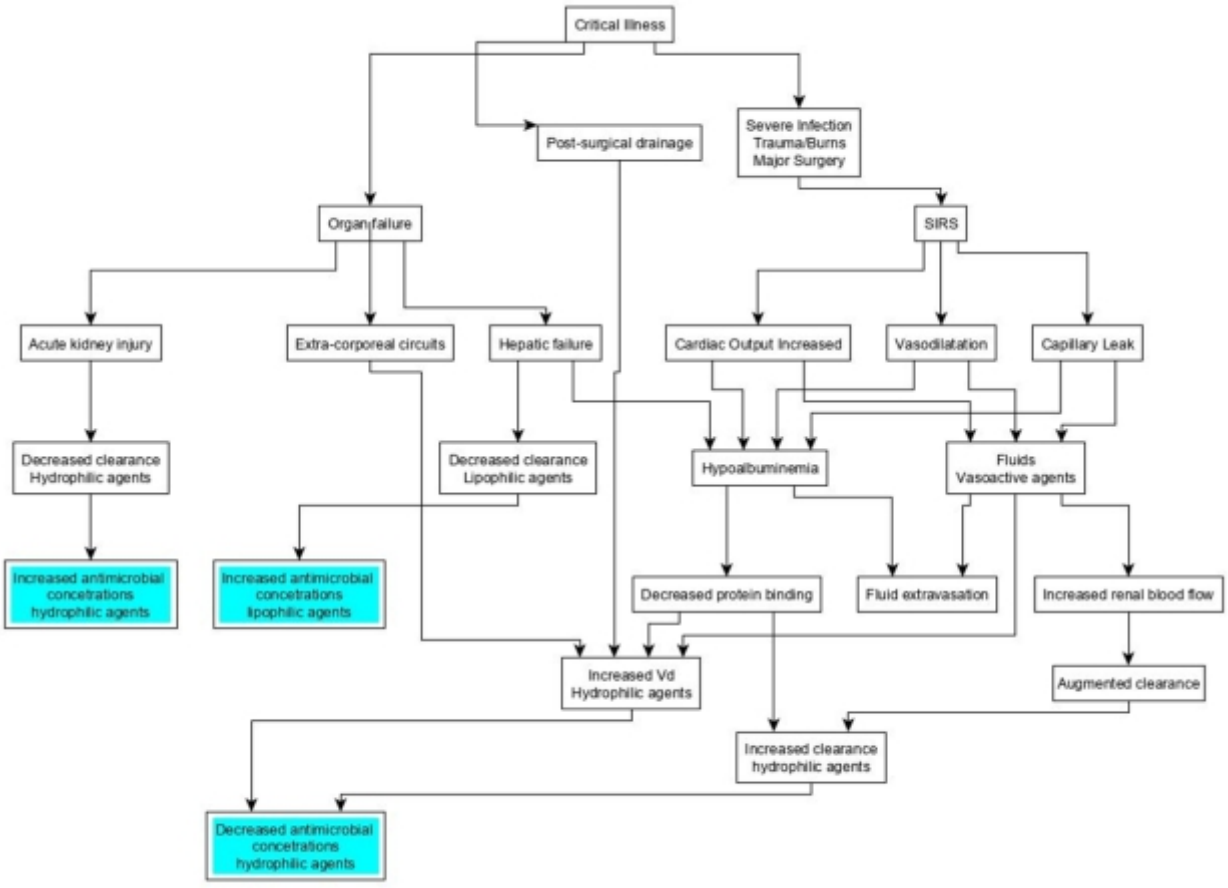

Figure 1: Effect of pathophysiological alterations during critical illness on the pharmacokinetics of antimicrobial agents. (Modified based on Blot et al., 2014)[5].

information on targets required to suppress the emergence of antibiotic resistance, which has become essential in the face of the current pandemic of multidrug-resistant pathogens. Also, these models do not account for cases where multiple antibiotics are used concurrently.

In addition to the development of models addressing these issues, future areas of study include population modeling of pharmacokinetics, development of rapid diagnostic methods to identify the organism, susceptibility, and resistance mechanisms, impact of individual patient characteristics on pharmacokinetics, and widespread availability of plasma and tissue drug level monitoring[7].

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