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REVIEW ARTICLE

Biomarkers Predicting Tissue Pharmacokinetics of Antimicrobials in Sepsis: A Review

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Abstract

The pathophysiology of sepsis alters drug pharmacokinetics, resulting in inadequate drug exposure and target-site concentration. Suboptimal exposure leads to treatment failure and the development of antimicrobial resistance. Therefore, we seek to optimize antimicrobial therapy in sepsis by selecting the right drug and the correct dosage. A prerequisite for achieving this goal is characterization and understanding of the mechanisms of pharmacokinetic alterations. However, most infections take place not in blood but in different body compartments. Since tissue pharmacokinetic assessment is not feasible in daily practice, we need to tailor antibiotic treatment according to the specific patient's pathophysiological processes. The complex pathophysiology of sepsis and the ineffectiveness of current targeted therapies suggest that treatments guided by biomarkers predicting target-site concentration could provide a new therapeutic strategy. Inflammation, endothelial and coagulation activation markers, and blood flow parameters might be indicators of impaired tissue distribution. Moreover, hepatic and renal dysfunction biomarkers can predict not only drug metabolism and clearance but also drug distribution. Identification of the right biomarkers can direct drug dosing and provide timely feedback on its effectiveness. Therefore, this might decrease antibiotic resistance and the mortality of critically ill patients. This article fills the literature gap by characterizing patient biomarkers that might be used to predict unbound plasma-to-tissue drug distribution in critically ill patients. Although all biomarkers must be clinically evaluated with the ultimate goal of combining them in a clinically feasible scoring system, we support the concept that the appropriate biomarkers could be used to direct targeted antibiotic dosing.

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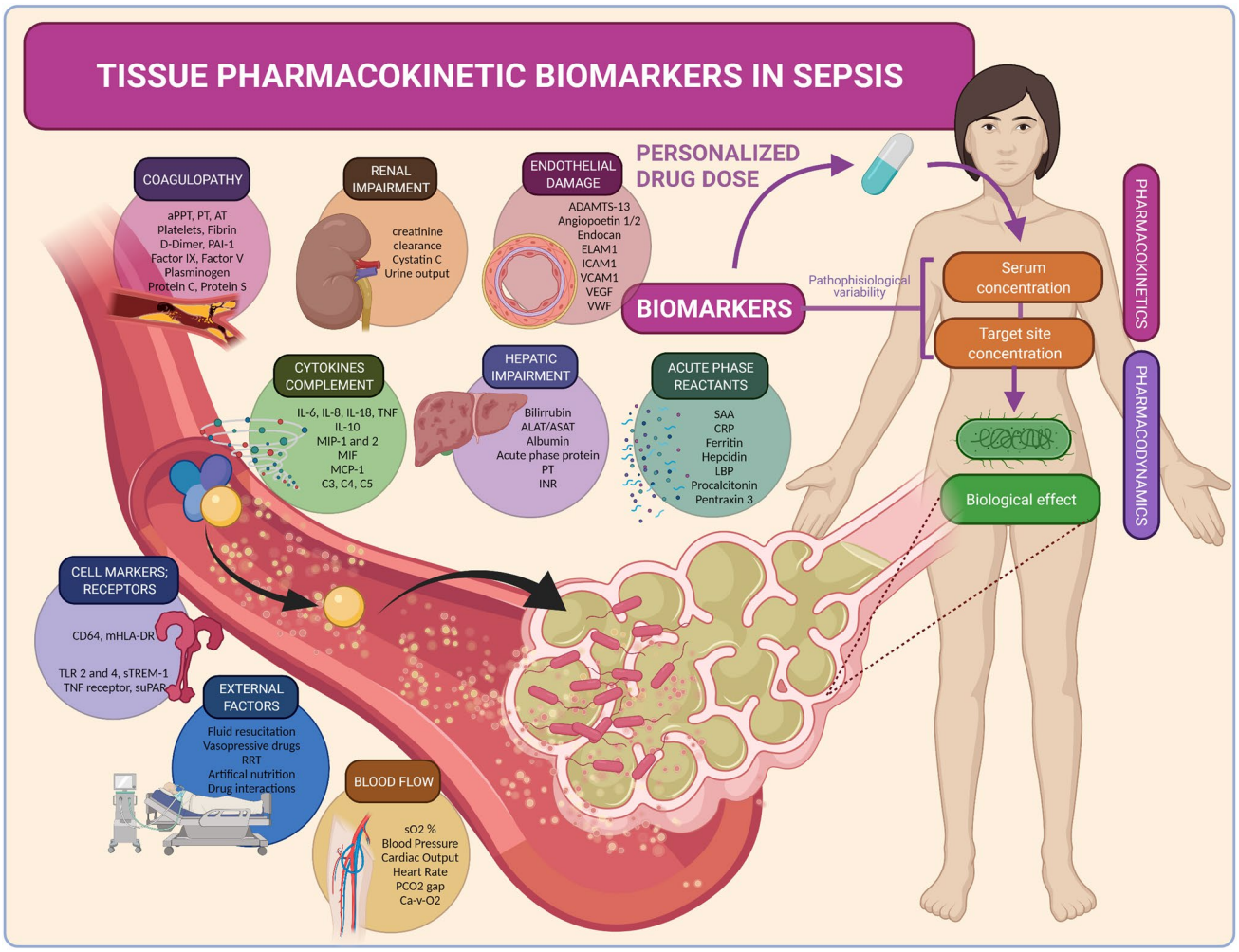
Graphical Abstract



ADAMTS-13 a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13, *ALAT* alanine amino transferase, *APACHE IV* Acute Physiology and Chronic Health Evaluation-IV, *aPPT* activated partial thromboplastin time, *ASAT* aspartate amino transferase, *AT* antithrombin, *Ca-V-O_2* oxygen content difference, arterial-venous,*CRP* C-reactive protein, *ELAM* endothelial leukocyte adhesion molecule, *ICAM* intercellular adhesion molecule, *IL* interleukin, *INR* international normalized ratio, *LBP* lipopolysaccharide-binding protein, *MCP* monocyte chemoattractant protein, *mHLA* monocytic human leukocyte antigen, *MIF* migration inhibitory factor, *MIP* macrophage inflammatory protein, *PAI* plasminogen activator inhibitor, *PCO_2* partial pressure of carbon dioxide, *PT* prothrombin time, *RRT* renal replacement therapy, *SAPSS III* Simplified Acute Physiology Score-III, *sO_2* oxygen saturation, *SOFA* Sequential [Sepsis-related] Organ Failure Assessment, *sTREM* soluble triggering receptor expressed on myeloid cells 1, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *VCAM* vascular cell adhesion molecule, *VEGF* vascular endothelial growth factor, *vWf* von Willebrand factor

Key Points

Pathophysiological changes in sepsis lead to pharmacokinetic variability and altered antibiotic infection site concentrations.

Biomarkers reflecting drug pharmacokinetics might help optimize antimicrobial dosing.

According to the pathophysiology of sepsis, the following host factors might be suitable to predict antibiotic target-site exposure in critically ill patients: inflammation, endotheliopathy, blood flow, coagulation, and hepatic and renal dysfunction. Prospective pharmacokinetic studies are needed.

1 Introduction

Sepsis is a life-threatening organ dysfunction resulting from a deregulated host response to infection (Fig. 1) [1]. The World Health Organization considers sepsis a global health emergency because 11 million sepsis-related deaths worldwide occur every year [2]. Thus, there is a call for global action to improve prevention, diagnostic, and treatment tools [3–5]. Part of this high mortality in critically ill patients has been linked to antibiotic treatment failure [6].

Several factors might lead to this treatment failure, including inadequate penetration of the antimicrobial to the target site [7–9], since site drug levels may substantially vary from the corresponding plasma drug concentrations [15]. Suboptimal antibiotic doses in the site of infection may also result in adverse reactions, toxicity, resistance, and higher costs [10]. Critically ill patient pathophysiology leads to highly variable systemic pharmacokinetics and altered tissue penetration of antibiotics [11]. Therefore, standardized doses might not fit patients in the intensive care unit (ICU), who have an increased risk of not receiving target-site therapeutic concentrations [10].

Various strategies have been proposed to improve antibiotic use, such as antibiotic stewardship [12, 13], therapeutic drug monitoring (TDM), and precision dosing [14–16]. Dose adjustments have recently shown promising evidence for improved outcomes and reduction of antimicrobial resistance [17]. In recent years, dosing nomograms and population-pharmacokinetic dosing software have appeared to optimize antibiotic use [18, 19]. However, these techniques have a significant limitation: they predict the drug concentration in plasma, and rarely in the site of infection [20].

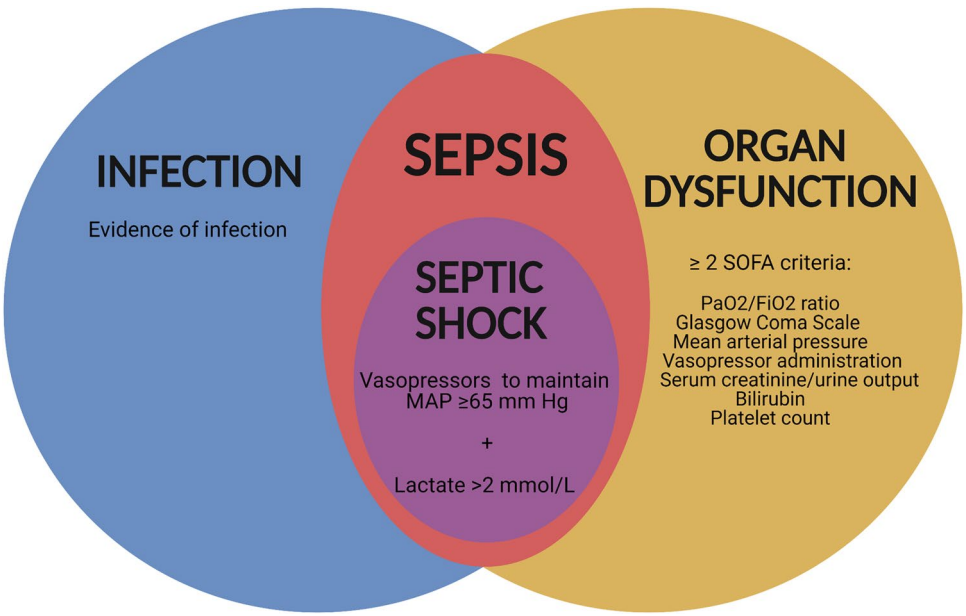


Fig. 1 The Sepsis-3 criteria. "Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [suspected or confirmed]" [192]. The SOFA (Sequential [Sepsis-related] Organ Failure Assessment) score can be used to determine organ dysfunction. Organ dysfunction representing sepsis is defined as an increase in the SOFA score of ≥ 2 points. The SOFA score rates the functioning of six organ systems from 0 to 4. A subtype of sepsis is septic shock, which requires a vasopressor to preserve a mean blood pressure of ≥ 65 mmHg, and by a serum lactate level > 2 mmol/L (> 18 mg/dL) without hypovolemia. *MAP* mean arterial pressure, *PaO2/FiO2* ratio of arterial oxygen partial pressure to fractional inspired oxygen

Table 1 Physiological antibiotic properties and implications for pharmacokinetics in critical illness

Pharmacokinetics	Lipid solubility	
	Hydrophilic antibiotics	Lipophilic antibiotics
General	↓ V_d; ↑ C_{max}, ↓ intracellular penetration; renal clearance	↑ V_d; ↓ C_{max}; ↑ intracellular penetration; hepatic clearance
In critically ill	↑ V_d; ↑/↓ renal clearance; dependent on renal function and PB	Unchanged V_d; ↑/↓ hepatic clearance; dependent on hepatic function and PB
Examples	β-lactams, aminoglycosides, glycopeptides	Fluoroquinolones, macrolides, rifampicin, linezolid

C_{max} maximum plasma drug concentration, *PB* protein binding, V_d volume of distribution, ↑ and ↓ indicate increase and decrease, respectively

Determining the concentration at the infection site for individual patients is challenging, so biomarkers that might predict target-site concentrations are needed. Sepsis biomarkers have already been used to prove infection and help confirm a sepsis suspicion [21, 22], and procalcitonin-guided antibiotic therapy is already a reality [23]. A retrospective study examined the accuracy of different markers and scoring systems for predicting tissue penetration of antimicrobials and found that oxygen saturation, serum lactate concentration, and the dose per unit time of norepinephrine administered were best correlated with tissue penetration [24]. Nevertheless, a gap remains in the literature linking such time-varying host biomarkers to target-site concentration and antibiotic exposure. Such knowledge would enable the stratification of patients with increased risk of treatment failure and individualize antibiotic treatment.

This review aims to characterize biomarkers that predict antibiotic pharmacokinetics in critically ill patients. Our objective is to summarize the effect of pathophysiological changes in critically ill patients on pharmacokinetics and how biomarkers might predict them. First, we give an overview of drug and host factors influencing pharmacokinetic changes. Then we propose and classify biomarkers that can predict this pharmacokinetic variability and thus the antibiotic concentration at the infection site.

2 Methods

We conducted a literature review in the MEDLINE, Google Scholar, and ISI Web of Science databases. We also identified references from relevant articles and from searches of the authors' extensive files. Search terms used were sepsis,

Table 2 Protein binding of antibiotics

Pharmacokinetics	Protein binding	
	High	Low
General	↓ Diffusion, ↓ tissue penetration, ↓ antimicrobial activity	↑ Diffusion, ↑ tissue penetration, ↑ antimicrobial activity
In the critically ill	↑ Diffusion, ↑ tissue penetration, ↑ antimicrobial activity	Unchanged
Examples	Ceftriaxone, doxycycline, ertapenem	Fluoroquinolones, fosfomycin, meropenem

↑ and ↓ indicate increase and decrease, respectively

Table 3 PK/PD index predictors of efficacy in antibiotics

PK/PD index predictor	PK/PD	Objective	Antibiotics	References
C_{max}/MIC	Concentration dependent	Maximize the concentration	Aminoglycosides, fluoroquinolones, ketolides, metronidazole, polymyxin	[29]
T>MIC	Time dependent	Maximize duration of exposure	β-lactams, erythromycin, clarithromycin, linezolid, lincosamides	[30]
AUC_{0-24}/MIC	Concentration dependent with time dependence	Maximize the amount of drug exposure	Azithromycin, clindamycin, linezolid, tetracyclines, daptomycin, fluoroquinolones, aminoglycosides, tigecycline, vancomycin	[31, 32]

AUC_{0-24} area under the plasma concentration–time curve from time zero to 24 h, C_{max} maximum plasma drug concentration, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetics/pharmacodynamics, *T>MIC* time above MIC

critically ill, pharmacokinetics, pharmacodynamics, biomarkers, and individual dosing. After the initial revision, we conducted individual searches for each relevant biomarker. We only reviewed English language articles. No date restrictions were set in these searches.

3 Antibiotic Factors

Antibiotics can be classed according to their physicochemical properties and pharmacodynamic characteristics (Tables 1, 2 and 3).

3.1 Antibiotic Characteristics According to Physicochemistry

The physicochemical properties of antibiotics play a significant role in achieving target-site concentration by affecting the volume of distribution (V_d), unbound concentrations, and clearance [25].

3.2 Lipid Solubility

Compounds with higher lipid solubility penetrate more easily into lipid membranes and, therefore, can be distributed intracellularly and in adipose tissues. On the other hand, hydrophilic antibiotics have a lower V_d and are predominantly distributed in the intravascular and interstitial space. Lipophilic drugs tend to have higher protein binding than hydrophilic drugs and usually need to be metabolized before being excreted [26].

3.2.1 Protein Binding

Changes in protein binding (PB) might influence pharmacokinetic parameters. Since only the nonbonded drug can diffuse into the extracellular space, PB has a significant effect on the V_d, so a reduction of PB could lead to higher target exposure. On the other hand, only the unbound drug can be metabolized and excreted [27]. As such, reduced PB might lead to an increase of the unbound ratio (unbound/bound drug), increasing the amount of drug available for clearance. Since this complex interaction is difficult to predict and might differ between antibiotics, it is important to measure both total and free drug in pharmacological studies. Usually this is not feasible for clinical TDM.

3.3 Antibiotic Characteristics According to Pharmacokinetic/Pharmacodynamic Index

Antibiotics are also classified with the pharmacokinetic/pharmacodynamic (PK/PD) index using the minimum inhibitory concentration (MIC) to measure the potency of drug–microorganism interaction. Once the PK/PD ratio has been determined, it is possible to tailor the pharmacodynamics target linked to the highest bactericidal activity. PK/PD ratios have benefited clinical practice and have been included in the development and approval of new antibiotics [28]. Antibiotics are classified as follows.

3.3.1 Time-Dependent Antibiotics

Time-dependent antibiotics are most effective if their concentration is maintained for as long as possible above the MIC (the lowest concentration should be at least four times the MIC) [29].

3.3.2 Concentration-Dependent Antibiotics

Concentration-dependent antibiotics require high concentration peaks as bacterial clearance depends on concentration rather than duration of exposure [30].

3.3.3 Concentration- and Time-Dependent Antibiotics

The area under the plasma concentration–time curve for 24 h for the MIC is the PK/PD index used to characterize antimicrobial efficacy. Dose optimization of these drugs aims to maximize overall exposure [31, 32].

3.4 Antibiotic Use in the Intensive Care Unit

Inadequate antimicrobial therapy correlates with reduced survival in critically ill patients [33]. The most used antibiotics in European ICUs are β-lactams, glycopeptides, and quinolones, with other antibiotics reserved for severe bacterial infections with antibiotic resistance [34]. Table 4 provides the characteristics of the most commonly used antibiotics in the ICU. Most of these antibiotics are hydrophilic, renally cleared, and time dependent. Therefore, their limited tissue distribution and the fluctuations of renal function in the critically ill make these antibiotics very susceptible to pharmacokinetic variability and target attainment failure [35, 36].

4 Host Factors

4.1 Sepsis Pathophysiology

Sepsis is caused by a dysregulated immune response (Fig. 2). An increase in the production of proinflammatory cytokines by the innate immune system can result in a "cytokine storm." This inflammatory state results in endothelial damage and coagulation alterations [37]. Blood flow is impaired, leading to heterogeneous organ perfusion, mitochondrial dysfunction, cellular hypoxia, and organ dysfunction and

Table 4 PK/PD characteristics of common antibiotics used in intensive care units

Antibiotic	Gram+/−	Mechanism of action	PK/PD index	V_d (L/kg)	PB (%)	$t_{½}$ (h)	Clearance	Solubility	References
β-lactam									
Meropenem	G+/G−	Bactericidal	T>MIC	0.25	2	1	Renal	Hydrophilic	[193, 194]
Cefuroxime	G+/G−	Bactericidal	T>MIC	6.4–9.1	33–50	1.1	Renal	Hydrophilic	[195]
Cefazolin	G+/G−	Bactericidal	T>MIC	0.14	80–90	1.8	Renal	Hydrophilic	[196, 197]
Piperacillin/tazobactam	G+/G−	Bactericidal	T>MIC	0.38/0.31	25/30	1.14/0.92	Renal	Hydrophilic	[198, 199]
Ampicillin/sulbactam	G+/G−	Bactericidal	T>MIC	0.16/0.1	28/38	1/1	Renal	Hydrophilic	[200–202]
Ceftolozane/tazobactam	G+/G−	Bactericidal	T>MIC	0.19/0.31	21/30	2.77/0.92	Renal	Hydrophilic	[203–205]
Glycopeptide									
Teicoplanin	G+	Bacteriostatic	AUC/MIC T>MIC	0.7–1.4	90	70–100	Renal	Hydrophilic	[206]
Vancomycin	G+	Bactericidal	AUC/MIC T>MIC	0.4–1	10–50	6	Renal	Hydrophilic	[207]
Lipopeptide									
Daptomycin	G+	Bactericidal	AUC/MIC C_{max}/MIC	0.1	90	7.5–9	Renal	Hydrophilic core lipophilic tail	[208–210]
Fosfomycin	G+/G−	Bactericidal	T>MIC	1.4–2.4	10	2.9–8.5	Renal	Hydrophilic	[211–213]
Glycylcycline									
Tigecycline	G+/G−	Bacteriostatic	AUC/MIC	7–10	71–89	37–67	Hepatic	Lipophilic	[214, 215]
Fluoroquinolone									
Ciprofloxacin	G+/G−	Bactericidal	AUC/MIC	1.74–5	20–30	3–4	Hepatic	Lipophilic	[216]
Moxifloxacin	G+/G−	Bactericidal	AUC/MIC	1.65	30–50	12	Hepatic	Lipophilic	[217]
Metronidazole									
Metronidazole	Anaerobic	Bactericidal	AUC/MIC	0.51–1.1	<20	6–10	Renal	Hydrophilic	[218]
Aminoglycosides									
Gentamicin	G+/G−	Bactericidal	C_{max}/MIC AUC/MIC	0.22–0.27	0–30	1.25	Renal	Hydrophilic	[219]
Amikacin	G+/G−	Bactericidal	C_{max}/MIC AUC/MIC	0.22–0.27	<10	2–3	Renal	Hydrophilic	[220]
Tobramycin	G+/G−	Bactericidal	C_{max}/MIC AUC/MIC	0.25	–	2.2–2.4	Renal	Hydrophilic	[221]
Macrolides									
Azithromycin	G+/G−	Bacteriostatic	AUC/MIC	0.35–0.5	<50	11–14	Hepatic	Lipophilic	[222, 223]
Erythromycin	G+/G−	Bacteriostatic	AUC/MIC	0.6–1.1	80–90	1.4–2.8	Hepatic	Lipophilic	[224]
Polymyxins									
Colistin	G−	Bactericidal	AUC/MIC	0.2	>50	0.5	Renal (prodrug)	Hydrophilic	[225]
Oxazolidinones									
Linezolid	G+	Bactericidal, bacteriostatic	AUC/MIC T>MIC	0.7	31	4–6	Hepatic, renal	Lipophilic	[226]

AUC area under the plasma concentration–time curve, C_{max} maximum plasma drug concentration, *G+/G−* Gram positive/negative, *MIC* minimum inhibitory concentration, *PB* protein binding, *PK/PD* pharmacokinetics/pharmacodynamics, *T>MIC* time above MIC, $t_{½}$ elimination half-life, V_d volume of distribution

failure. Consequently, there is an increased capillary leak, resulting in hypotension associated with a hyperdynamic cardiovascular state. Moreover, body fluid increases, especially after resuscitation [38]. Following, there might be an immunosuppression phase that fails to control the infection [39]. Such inflammatory and immunosuppressive states are thought to be overlapping, which further complicates the monitoring of the disease [40]. Ultimately, inflammation and

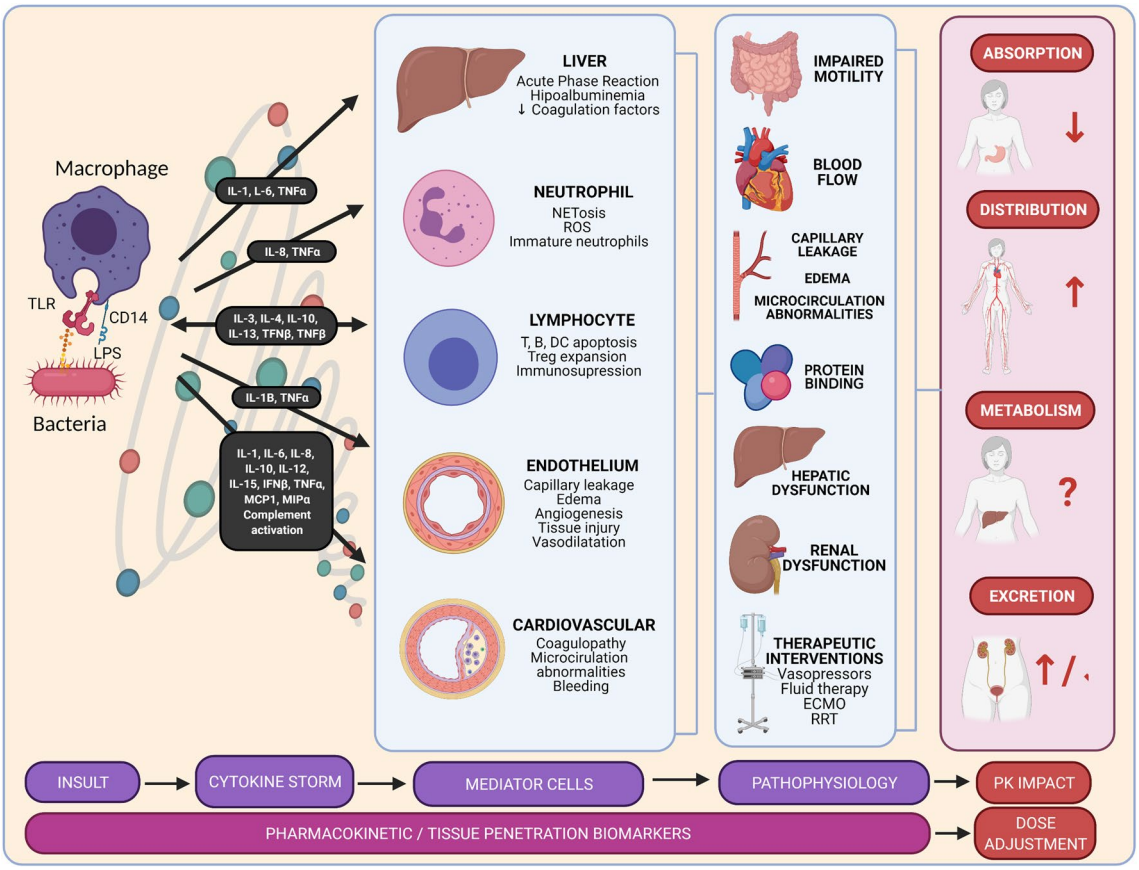


Fig. 2 Sepsis pathophysiology and its implications in pharmacokinetics. Sepsis occurs when there is a dysregulated immune response. During infections, pathogen-associated molecular patterns, such as LPS or peptidoglycan, bind to pattern-recognizing receptors, such as TLRs, potentiated by the CD14 receptors. As a result, the immune system might respond with an exaggerated, uncontrolled, and massive release of proinflammatory cytokines. This cytokine storm results in the continuous activation and expansion of immune cells, lymphocytes, and macrophages from the circulation to the infection, with destructive effects on human tissue. Consequently, endothelial cell interactions destabilize vascular barrier damages and there is multiorgan failure. The overwhelming systemic response causes an increase in cardiac output, fluid extravasation, a decrease in protein binding, and hepatic and renal dysfunction. Together with the aggressive therapeutic interventions in the critically ill, these pathophysiological changes might lead to variability in pharmacokinetics (absorption, distribution, metabolism, and excretion). *DC* dendritic cell, *ECMO* extracorporeal membrane oxygenation, *IFN* interferon, *IL* interleukin, *LPS* lipopolysaccharide, *MCP* monocyte chemoattractant protein, *MIP* macrophage inflammatory protein, *PK* pharmacokinetics, *ROS* reactive oxygen species, *RRT* renal replacement therapy, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *Treg* T-regulatory cells

coagulopathy cause the vascular and organ damage characteristic of severe sepsis and septic shock and, lastly, cause organ failure and death.

4.2 Pharmacokinetic Alterations in Septic Patients

The unique pathophysiology of sepsis alters the components of pharmacokinetics. Figure 2 provides an overview of how the sepsis pathogenesis drives pharmacokinetic alterations.

4.2.1 Absorption

Critically ill patients have unpredictable oral bioavailability because of their delayed and impaired absorption. Gut motility is reduced, so gastric emptying is delayed and splanchnic blood flow reduced. The delay in gastric emptying prolongs the time for the antibiotic to reach the maximum concentration. An impaired peripheral blood flow also compromises absorption from subcutaneous and intramuscular injection. Because of these alterations, antibiotics in the ICU are usually initially administered intravenously [41].

4.2.2 Distribution

The proinflammatory state of sepsis induces endothelial damage and increases capillary permeability [42]. This results in capillary leak syndrome, which causes fluid extravasation and increases the V_d of hydrophilic antibiotics [11]. Therapeutic interventions (e.g., fluid resuscitation, extracorporeal circuits, drainages) can also increase the

V_d [43, 44]. Hypalbuminemia is also common in patients with sepsis, resulting in lower PB and higher unbound drug concentrations subject to increased clearance. These higher unbound drug concentrations may influence the V_d, leading to subtherapeutic antibiotic concentrations and ineffective microbial clearance [45–47]. Inadequate tissue perfusion and tissue hypoxia are typical of critically ill patients, with both low and high oxygenation and perfusion areas [48].

4.2.3 Metabolism

Decreased hepatic blood flow, hepatic dysfunction, and altered enzyme activity impair metabolism in critically ill patients [49]. Tissue metabolism is also impaired by the decreased tissue blood flow and hypothermia [50]. Lipophilic antimicrobials may require dose adjustment in patients with hepatic failure since they are usually highly metabolized [47].

4.2.4 Excretion

The elimination process can be disturbed during critical illness, as renal clearance can be either enhanced or impaired. Biliary excretion is usually less impaired but can be affected by biliary stasis and a decreased gut transit leading to recirculation. Some critically ill patients have vasodilatation followed by a hyperdynamic cardiovascular state and therefore develop an augmented glomerular filtration rate (GFR), enhanced by the use of resuscitation fluid and vasopressors. This augmented renal clearance leads to increased elimination of hydrophilic drugs [51, 52]. This may lead to underdosage, as demonstrated in a study with β-lactams [53]. On the other hand, some critically ill patients have acute kidney injury (AKI) and need renal replacement therapy (RRT) [54, 55]. This will result in decreased antimicrobial clearance of hydrophilic antibiotics, prolonged half-life, and potential toxicity [53]. Therefore, when AKI or RRT are present, dose adjustments should be considered.

4.3 Sepsis Biomarkers

Given the complexity of the host response in sepsis, some biomarkers may or may not predict these pharmacokinetic changes in the critically ill (Fig. 3). A biomarker is a quantifiable biological parameter that indicates a biological, pathogenic, or pharmacological response to exposure or therapeutic intervention. The ideal biomarker must be specific, sensitive, predictive, fast, cost effective, stable in vivo and in vitro, noninvasive, and sufficiently preclinically and clinically relevant [56]. Biomarkers are valuable because they generally occur earlier than clinical outcomes and are measured by objective methods [57]. Patient-specific response biomarkers to infections represent an opportunity to monitor treatment response and predict alterations in drug target-site exposure and clinical outcomes.

Sepsis biomarkers can predict the severity of sepsis and the development of organ failure, differentiate the type or prognosis of infection, and assess the response to treatment. However, the role of biomarkers in guiding antibiotic dosing has not yet been deeply evaluated [58]. Research on procalcitonin stewardship has been conducted, but other biomarkers may outperform it [59, 60]. We have classified the potential biomarker predictors of pharmacokinetics according to pathophysiology: inflammation, endotheliopathy, coagulation, blood flow, and hepatic and renal function (Table 5). The diagnostic, prognostic, or therapeutic value of some of these biomarkers has been demonstrated, whereas the impact on drug pharmacokinetics is insufficiently understood. Table 5 displays the important biomarker characteristics. Knowledge of the biomarker's molecular weight (MW) is important to determine their reliability during extracorporeal therapies [61]. Comprehension of biomarker kinetics is essential because pathophysiological processes are continuously changing, and delayed dynamics may lead to delayed clinical decisions.

4.3.1 Inflammation Biomarkers

Sepsis is a "cytokine storm" syndrome. During infections, pathogen-associated molecular patterns such as lipopolysaccharide or peptidoglycan bind to pattern-recognizing receptors (PRRs) such as toll-like receptors, potentiated by the CD14 receptors. The immune system might respond to the pathogen with an exaggerated, uncontrolled, and massive release of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-18; interferon, and tumor necrosis factor-α [42]. This increase in cytokines results in the continuous activation and expansion of immune cells from circulation to the infection. Proinflammatory cytokines also mediate the production of acute-phase reactants (APRs) by the liver [62, 63]. Some crucial APRs, such as C-reactive protein or procalcitonin, are routinely available for the identification and monitoring of inflammatory states [64, 65]. Conversely, the negative APRs, such as albumin and transferrin, decrease in response to inflammation [66].

This overwhelming inflammatory response correlates with capillary leakage, tissue edema, organ failure, and shock that causes the pharmacokinetic variability and changed plasma-to-tissue equilibration in sepsis. For example, IL-6, presepsin (sCD14 subtype), proadrenomedullin, and soluble triggering expressed receptor on myeloid cells (sTREM) have proven to be helpful biomarkers for the early diagnosis and prognosis of sepsis [67–71]. Some of these innovative biomarkers seem to be superior to the routinely used procalcitonin or C-reactive protein [72–74], so combinations of biomarkers have been proposed to increase

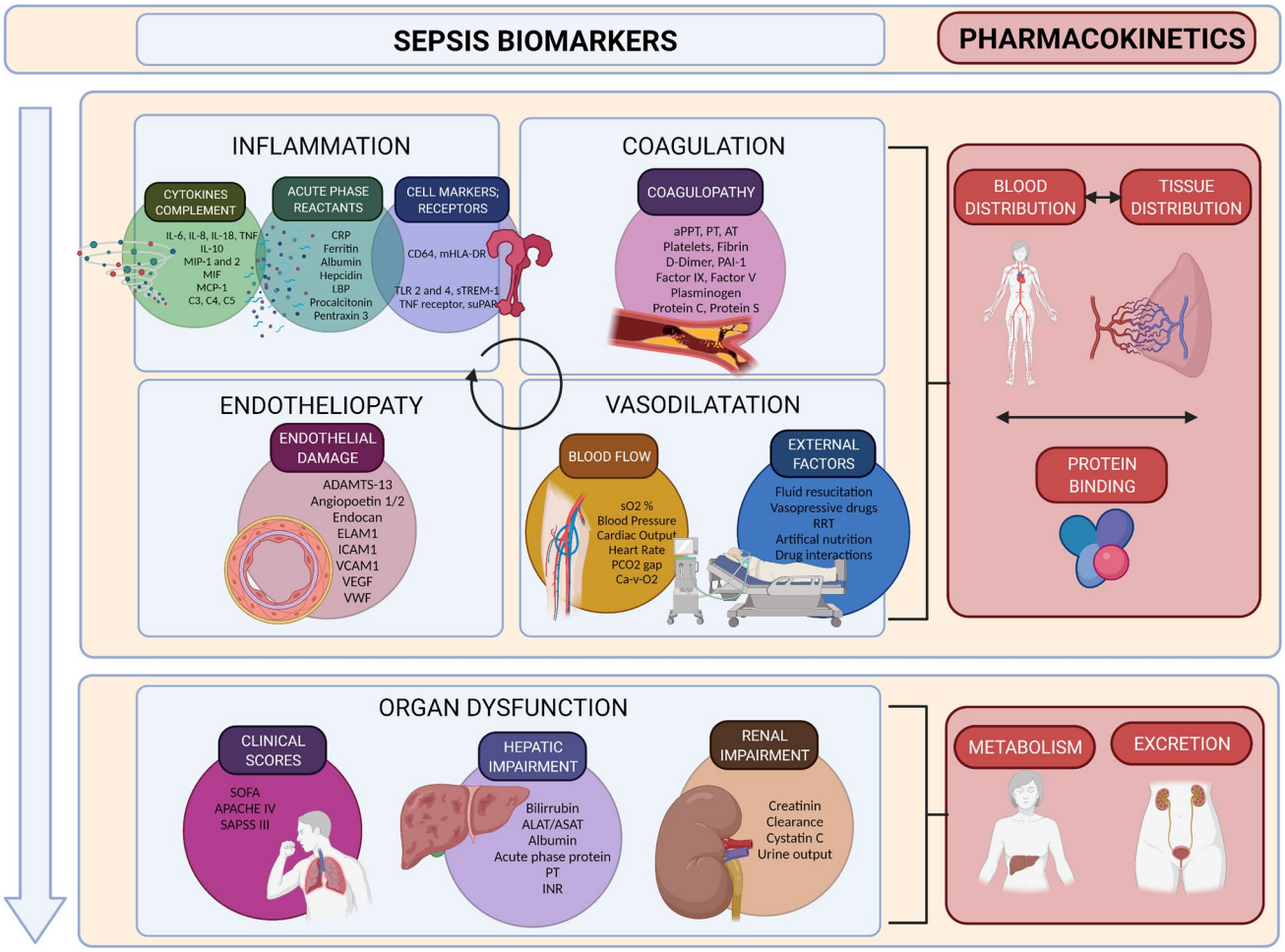


Fig. 3 Biomarkers that predict tissue pharmacokinetics in sepsis. The potential biomarkers and host factor predictors of pharmacokinetics are classified according to the different systems activated in sepsis: Changes in distribution (blood and tissue), metabolism, and excretion. Biomarkers representing each type of pathophysiological alteration might be able to predict the inter and intra-pharmacokinetic variability. *ADAMTS-13* a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13, *ALAT* alanine amino transferase, *APACHE IV* Acute Physiology and Chronic Health Evaluation-IV, *aPPT* activated partial thromboplastin time, *ASAT* aspartate amino transferase, *AT* antithrombin, *Ca-V-O_2* oxygen content difference, arterial-venous, *CRP* C-reactive protein, *ELAM* endothelial leukocyte adhesion molecule, *ICAM* intercellular adhesion molecule, *IL* interleukin, *INR* international normalized ratio, *LBP* lipopolysaccharide-binding protein, *MCP* monocyte chemoattractant protein, *mHLA* monocytic human leukocyte antigen, *MIF* migration inhibitory factor, *MIP* macrophage inflammatory protein, *PAI* plasminogen activator inhibitor, *PCO_2* partial pressure of carbon dioxide, *PT* prothrombin time, *RRT* renal replacement therapy, *SAPSS III* Simplified Acute Physiology Score-III, *sO_2* oxygen saturation, *SOFA* Sequential [Sepsis-related] Organ Failure Assessment, sTREM soluble triggering receptor expressed on myeloid cells 1, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *VCAM* vascular cell adhesion molecule, *VEGF* vascular endothelial growth factor, *vWf* von Willebrand factor

sensitivity and specificity [75, 76]. Immunological biomarkers have been found to be indicative of effective antimicrobial therapy [77]. They are also promoters of the pathophysiological changes leading to pharmacokinetic variability in critically ill patients [78]. Accordingly, the immunological cells, cytokines, cell markers, and APRs may be potential biomarkers for predicting the tissue penetration and pharmacokinetics of antibiotics. The extent to which these inflammation molecules alter the PK/PD of antibiotics is unclear [79], but some of these molecules have already been successfully used to guide antibiotic treatment [59].

4.3.2 Endothelial Biomarkers

Inflammation, complement activation, and coagulation in sepsis induce severe impairment of endothelial functions. Endothelial cells are essential for hemostasis regulation, vasomotor control, and immune functions and form the vascular barrier for solute transport and osmotic balance [80–82]. Sepsis is associated with glycocalyx degradation and severe endothelial cell dysfunction, leading to dysregulation of hemostasis and vascular reactivity, as well as tissue edema [83]. This endotheliopathy results in excessive

Table 5 Selected biomarkers for predicting antibiotic pharmacokinetics

Biomarkers	Pathogenesis	Value	MW (kDa)	Peak (h)	$t_{½}$[a]	Affected drug PK	References
Inflammation biomarkers							
Cytokines/chemokines							
IL-1β	Proinflammatory cytokine	Px	18–25	4	2	D	[227]
IL-6	Proinflammatory cytokine	Dx, Px	21	6	2–4	D	[228, 229]
IL-8	Neutrophilic inflammation cytokine	Dx, Px	8.4	4–8	4	D	[230, 231]
IL-10	Regulatory cytokine	Dx, Px	18	12–24	2–4	D	[232]
TNFα	Proinflammatory cytokine, neutrophilic activation	Px	17.3	6	1–2	D	[233]
IFNγ	Th_1 immune response	–	17	6	2	D	[234, 235]
MIP-1, -2	Neutrophil, leukocyte activation	Px	440	2	2.5	D	[236, 237]
MCP-1	Monocyte chemoattractant protein	Px					[238]
Cell markers/soluble receptors							
Presepsin	N-terminal fragment of sCD14 (LPS receptor)	Dx, Px, Tx	13	3	4–5	D	[239–241]
CD64	Binds Fc fraction of IgG, induces phagocytosis	Dx, Tx	43	4–6	5–17	D	[242–244]
mHLA-DR	Expressed on APC, activation of T-cells	Px	–	24	3–22	D	[245, 246]
TLR2, TLR4	Recognition of bacterial peptidoglycan (TLR2) or LPS (TLR4)	Dx	–	–	3	D	[247–249]
sTREM-1	TREM-1 secreted by phagocytes	Dx, Px	23.8	6	1.5	D	[250–252]
SuPAR	Recruitment of neutrophils and monocytes	Dx, Px	–	4 (d)	10 (d)	D	[253–255]
Acute-phase reactants							
CRP	Complement activation, proinflammatory effects	Px	20–25	24–48	19	D	[256, 257]
PCT	Prohormone stimulated by IL-1, IL-6, TNFα	Dx, Px, Tx	14.5	6–24	20–36	D	[258, 259]
LBP	Connects CD14 to bacteria LPS	Dx, Px	50	12	12–24	D	[260]
Pro-ADM	Precursor of adrenomedullin, induces vasodilatation	Px	4–5.5	4	2	D	[261–263]
Pentraxin 3	Pathogen recognition and removal	Dx, Px	35	–	4	D	[264–266]
C5a, C3a	Neutrophil migration, coagulopathy	Dx, Px	190	–	4	D	[267, 268]
Albumin	Increased vascular permeability	Px	66.5	NA	21 (d)	D, M	[269–271]
Endotheliopathy biomarkers							
Syndecans	Glycocalyx component indicates damage	Px	30	NA	0.06	D	[272]
Heparan sulfate	Polysaccharide	Px	30	NA	3–4	D	[273]
Endocan	Soluble endothelial peptidoglycan, increases microvascular permeability	Px	50	NA	–	D	[94, 274, 275]
Ang-2/Ang-1	Vascular integrity, Ang-2 is Ang-1 antagonist	Px	1	NA	30 (s)	D	[99, 254, 276, 277]
sVCAM-1	Adhesion protein expressed by endothelial cells, which binds to lymphocytes	Px	102	NA	4	D	[278, 279]
sICAM-1	Intercellular adhesion molecules	Dx, Px	76–114	NA	–	D	[278–281]
E-selectin	Glycoprotein expressed in activated endothelial cells	Px	115	NA	1.9	D	[279, 281, 282]
P-selectin	Adhesion receptor expressed in platelets and endothelial cell	Px	140	NA	2.3	D	[283]
VEGF	Endothelial cells proliferation factor	Px	23	NA	0.5–1	D	[284]
Blood flow biomarkers							
SO_2 %	Oxygen saturation	Px	NA	NA	NA	D	[285]
MAP	Main global perfusion index	Px	NA	NA	NA	D	[286, 287]
CO	Cardiac output	Px	NA	NA	NA	D	[288]

Table 5 (continued)

Biomarkers	Pathogenesis	Value	MW (kDa)	Peak (h)	$t_{½}$[a]	Affected drug PK	References
HR	Heart rate	Px	NA	NA	NA	D	[289]
$ScvO_2$	Central venous oxygen saturation	Px	NA	NA	NA	D	[290]
StO_2	Tissue oxygen saturation	Px	NA	NA	NA	D	[291]
Lactate	Anaerobic glycolysis end product	Px	0.08	–	20 (m)	D	[286]
Coagulation biomarkers							
vWf Ag	Platelet adhesion and accumulation	Px	5000–10,000	NA	4–26	D, M	[292]
ADAMTS-13 activity	vWf cleaving protease	Px	154	NA	48–72	D, M	[293–295]
F ibrinogen	Low activation of secondary fibrinolysis	Px	340	NA	100	D, M	[296, 297]
PT	Consumption, depletion of endogenous haemostasis factors	Px	NA	NA	–	D, M	[298, 299]
aPPT	Indicative of CRP activity	Dx	NA	NA	–	D, M	[300–303]
AT activity	Coagulation inhibition and anti-inflammation	Px	58	NA	72	D, M	[296]
PF-4	Protein secreted by activated platelets	Px	29	NA		D	[304–306]
D-Dimer	Fibrinogen, fibrin breakdown, excessive coagulation	Px	180	NA	8	D, M	[304]
PAI-1	Fibrinolysis inhibition	Px	43	NA	2	D	[304, 307]
Protein C	Antithrombotic action	Dx, Px	62	NA	8	D, M	[308–310]
Thrombomodulin	Endothelial cells glycoprotein, protein C pathway	Px	74	NA	20	D, M	[311–313]
Hepatic function biomarkers							
Bilirubin	Product of heme catabolism	Px	548.67	NA	2–4	M	[314–316]
ALT	Transaminase enzyme, indicates liver function	–	110	NA	8	M	[316, 317]
AST	Transaminase enzyme, indicates liver function	–	90	NA	16	M	[316, 317]
Ceruloplasmin	Increases as part of acute-phase response	Px	115	-	15	M	[318]
Hyaluronic acid	Indicates liver dysfunction	Px	1000–8000	NA	4 (m)	D, M	[319]
Renal function biomarkers							
Creatinine	Estimate GFR	Px	0.113	NA	3.85	E	[320]
Cystatin C	Estimate GFR	Px	13.3	NA	2	E	[320]
BUN	Urea nitrogen in blood, indicative of renal function	Px	NA	NA	NA	M, E	[321–323]
NGAL	Indicative of kidney injury	Px	25	6–12	15	E	[320, 324]
KIM-1	Injured kidney epithelial cells	Px	60–90	12–24	6	E	[320]

The proposed biomarkers are classified according to the pathophysiological processes. We provide some important characteristics: pathogenesis, proved value, MW, biology (peak concentration, half-life), and the proposed pharmacokinetic process affected

ADAMTS-13 a disintegrin-like and metalloprotease with thrombospondin type 1 motif no, 13, *ALT* alanine transaminase, *Ang* angiotensin, *APC* activated protein C, *aPPT* activated partial thromboplastin time, *AST* aspartate transaminase, *AT* antithrombin, *BUN* blood urea nitrogen, *CO* cardiac output, *CRP* C-reactive protein, *d* days, *D* distribution, *Dx* diagnostic, *E* excretion, *GFR* glomerular filtration rate, *HR* heart rate, *ICAM* intercellular adhesion molecule 1, *IFN* interferon, *IgG* immunoglobulin, *IL* interleukin , *KIM-1* kidney injury molecule-1, *LBP* lipopolysaccharide-binding protein, *LPS* lipopolysaccharide, *M* metabolism, *m* minutes, *MAP* mean arterial pressure, *MCP* monocyte chemoattractant protein, *mHLA* monocytic human leukocyte antigen, *MIP* macrophage inflammatory protein, *MW* molecular weight, *NA* not applicable, *NGAL* Neutrophil Gelatinase-Associated Lipocalin, *PAI-1* plasminogen activator inhibitor-1, *PCT* procalcitonin, *PF-4* platelet factor 4, *PK* pharmacokinetics, *Pro-ADM* proadrenomedullin, *PT* prothrombin time, *Px* prognostic, *s* seconds, *sCD14* soluble cluster of differentiation 14, $ScvO_2$ central venous oxygen saturation, *sICAM* soluble ICAM, SO_2% oxygen saturation, StO_2 tissue oxygen saturation, *sTREM* soluble triggering receptor expressed on myeloid cells 1, *suPAR* soluble urokinase-type plasminogen activator receptor, *sVCAM* soluble VCAM, $t_{½}$ elimination half-life, Th_1 T helper type 1, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *Tx* therapeutic, *VCAM* vascular cell adhesion molecule, *VEGF* vascular endothelial growth factor, *vWf* von Willebrand factor

[a] $t_{½}$ presented in h unless otherwise indicated

microvascular permeability to the extravascular space, leading to interstitial edema [84–86].

Glycocalyx degradation releases components such as syndecan-1 [87–89], heparan sulfate [90], and hyaluronan [91, 92] into the plasma. Endocan is expressed in human endothelial cells in response to proinflammatory cytokines and increases microvascular permeability [93–95]. These endothelial glycocalyx biomarkers have already been presented as predictors of death and/or organ dysfunction during sepsis. The angiopoietin protein family has been investigated as a critical mediator of glycocalyx degradation since angiopoietin-2-activated endothelial cells increase the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 [96, 97]. As a result, endothelial cell–cell junctions alter, resulting in microvascular leak. The angiopoietin-2/1 ratio has been found to be a good predictor of 28-day mortality in patients with sepsis [98–100]. Serum vascular endothelial growth factor and its receptor stimulate endothelial growth, proliferation, and permeability. Higher levels can be found in sepsis and so can be used for prognosis [101]. Therefore, these endotheliopathy biomarkers are predictors of the capillary leakage that drives the pharmacokinetic variability in tissues of patients with sepsis, yet the extent of the relevance needs to be established for the individual markers.

4.3.3 Coagulation Biomarkers

Coagulopathy and disseminated intravascular coagulation (DIC) are common defense mechanisms in critically ill patients [102]. Coagulopathy consists of microvascular thrombosis and consumption of platelets and coagulation proteins, eventually causing bleeding [103]. DIC is a microvascular thrombosis leading to bleeding and organ dysfunction, leading to amplified coagulopathy. Although the formation of microthrombi might prevent microorganisms from accessing tissue, it also further enhances tissue ischemia and organ damage, contributing to decreased antibiotic distribution [103]. However, it can also lead to capillary leakage, promoting an increase in tissue permeability [104]. Coagulopathy is also the hallmark of liver failure, an organ with a central role in clotting [105]. Different coagulation phenotypes in sepsis have been described, with two sepsis subgroups showing severe disease and coagulopathy [106].

Various significant players drive the pathogenesis of coagulopathy in sepsis: platelets, the coagulation system, the endothelium, and the immune system [107]. In sepsis, procoagulant mechanisms are upregulated while natural anticoagulants are simultaneously downregulated. Tissue factor activates the coagulation cascade (including Factor VII, Factor X, thrombin, and fibrin) and is amplified by proinflammatory cytokines. Sepsis inflammation response also activates platelet activating factor and thrombin-induced exocytosis of P-selectin and von Willebrand factor (vWf). As a result, platelets adhere, activate, and aggregate, leading to microvascular obstruction. Cell receptors and adhesive proteins, such as vWf and fibrinogen, mediate this interaction between platelets and the vessel wall [108]. Thrombogenesis is accelerated when the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-13 protease is consumed and cannot cleave the excessive amount of large vWf polymers [109], and the microthrombosis leads to thrombocytopenia. The inflammatory response impairs the three central anticoagulant mechanisms: tissue factor pathway inhibitor, antithrombin, and activated protein C. Tissue factor pathway inhibitor is decreased in sepsis because of degradation by proteolytic enzymes produced by the host, such as plasmin [110]. Another essential anticoagulant protein is antithrombin. Most of these coagulation biomarkers have been related to a worse prognosis: thrombomodulin [111, 112], plasminogen activator inhibitor 1 [113], vWf [114–116], ADAMTS-13 [116–118], and thrombocytopenia [119, 120]. A prolonged coagulation time is frequent in critically ill patients, and prothrombin time and activated partial thromboplastin time have been found to be predictors of sepsis and mortality [107, 121]. Hemolysis (free hemoglobin) [122] and D-dimers (excessive coagulation activation) [107, 123] have also been demonstrated as survival predictors. Scoring systems such as sepsis-induced coagulopathy [124] and Overt-DIC scoring systems [125] have been described to predict coagulopathy in patients with associated disorders. A capillary leakage index using albumin and polymerase chain reaction has also been described as a prognosis marker [126]. Coagulation host factors indicative of tissue penetration may indicate changes in antibiotic tissue penetration. Therefore, both conventional and new molecular markers may be used to determine coagulopathy and optimize antibiotic dosing.

4.3.4 Blood Flow Biomarkers

Sepsis has variable effects on macro/microvascular blood flow, which might lead to simultaneous observation of vasoconstriction and vasodilatation [127]. Septic shock is characterized by derangement in global hemodynamic parameters, such as blood pressure (BP), cardiac output, and heart rate. Despite increased cardiac output, the tissues cannot utilize oxygen, as evidenced by high lactate levels, deranged acid-base balance, and increased CO_2 levels [128]. This indicates that macrovascular tissue perfusion in severe sepsis is often uncoupled from systemic circulation [129]. This discrepancy between macro- and microcirculation of internal organs impedes effective hemodynamic monitoring of patients with sepsis [130].

The determination of macro/microvascular dysfunction can be a prognostic parameter and can guide therapeutic

measures in patients with septic shock. We can use some objective markers of tissue perfusion to predict global tissue distribution. The main global perfusion index is mean arterial pressure, preferably systolic, as it better reflects organ perfusion. Oxygen saturation of mixed venous blood is another routinely used indicator of the balance between oxygen transport and consumption, since its decrease reflects a reduction in cardiac output [131]. Although tissue oxygen saturation, measured by tissue spectroscopy, is not routinely used, it has been found to correlate with central venous saturation [132] and cardiac index in patients with septic shock [133]. In addition, the need for vasopressors to maintain BP has indicated inadequate antibiotic penetration [24]. Hyperlactatemia is a common condition in patients with sepsis and may be indicative of changes in microvascular flow. Lactate is the anaerobic glycolysis product, and its blood levels increase significantly in hypoperfusion or hypoxia cases [134]. Lactate levels have been used to guide resuscitation, predict in-hospital mortality, and stratify patient risk [135, 136]. Moreover, lactate is one of the criteria for diagnosing septic shock, as indicated by Sepsis-3 criteria [137]. However, septic hyperlactatemia is not a straightforward indication of inadequate oxygen delivery [138]. Lactate overproduction is also a protective response to stress to allow cellular energy production to continue when tissue oxygen supply is inadequate for aerobic metabolism [139], and elevated levels of lactate can also be caused by a decreased clearance by the liver [139, 140]. It is suggested that initially elevated lactate can indicate an adaptive response to a hypermetabolic state during sepsis [139]. Therefore, when assessing tissue perfusion, lactate should be combined with other markers. Finally, regional perfusion can also be assessed using indices of organ function, such as the SOFA (Sequential [Sepsis-related] Organ Failure Assessment) score. Other nonobjective indicators of tissue hypoperfusion are oliguria, impaired sensorium, delayed capillary refill, and skin coldness. All these blood flow markers might predict the vasodilatation or vasoconstriction that drives changes in drug V_d, especially affecting hydrophilic antibiotics.

4.3.5 Hepatic Function Biomarkers

The liver has a significant role in sepsis response through clearance of pathogenic microorganisms, APRs, and release of liver-derived cytokines, inflammatory mediators, and coagulation cascade components. Of course, it also has a central role in all metabolic processes in the body [141, 142]. Remarkably, liver dysfunction is common in patients in the ICU and is found in at least one-third of patients with sepsis [143]. Hepatic malfunction results in impaired detoxification of drugs that are typically excreted in the bile because of phase I and II enzyme deficiency [144, 145]. It also contributes to stress hyperglycemia through increased hepatic output of glucose, decreased clearance of lactate, and increased metabolism of lipids, but cholesterol synthesis and turnover are impaired.

Deficiencies in fibrinolytic proteins, anticoagulant proteins, procoagulation factors, and protein synthesis, such as albumin, are often present in liver failure, in part due to failure of the synthesis and consumption. Hypoalbuminemia leads to alterations in PB, which may increase the unbound drug fraction in high-PB drugs [146] as described in Sect. 4.1. However, ascites are typical of advanced liver disease and increase the V_d of hydrophilic antibiotics. Therefore, hepatic dysfunction may affect not only the metabolism of drugs but also their PB and V_d, modifying antibiotic concentrations in the site of infection. These pharmacokinetic changes have been found in critically ill patients receiving meropenem, which required dosing modifications to reach target attainment [147].

Various liver dysfunction markers may serve as biomarkers for predicting pharmacokinetic variability. Bilirubin is the standard parameter for assessing hepatic failure, has been confirmed as an independent predictor of sepsis mortality [148], and is routinely checked with the SOFA score. The antimicrobial proteins, inflammatory mediators, and coagulation factors produced by the liver during acute-phase response might also be considered as indicators of pharmacokinetic changes. Although these biomarkers lack the specificity for liver damage, they may be indicators of pathophysiological changes in drug metabolism, distribution, and clearance, which affects the penetration of antibiotics [149–152]. Recently, hyaluronic acid was proposed as an indicator of early liver impairment in critically ill patients and was identified as a particular risk for mortality in patients with infections [153]. The Child–Pugh score categorizes patients according to the severity of liver function impairment by incorporating five variables: serum bilirubin, serum albumin, prothrombin time, the presence of encephalopathy, and the presence of ascites. It is frequently used to assess the severity of liver function impairment but lacks the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs [151]. Moreover, in patients in the ICU, the Child–Pugh score may be strongly influenced by hypoalbuminemia and thus not be optimal to identify hepatic impairment. However, it can be useful to identify pharmacokinetic changes, since hypoalbuminemia is relevant for altered pharmacokinetics (PB). The liver plays a central role in pharmacokinetic processes, so liver biomarker-guided dosing may be essential to identify at-risk patients and optimize treatment.

4.3.6 Renal Function Biomarkers

Renal injury is typical in the ICU and can be caused by ischemia, cellular hypoxia, inflammation, or toxic injury

[54, 55]. Many antibiotics are renally cleared or nephrotoxic; therefore, kidney disease or augmented renal clearance further complicate sepsis treatment as explained in Sect. 4.2.4. Alterations in renal function require careful consideration of drug dosing. Diagnosis of renal function usually relies on biomarkers determining the GFR, which is also used for monitoring and calculating drug dosage. The determination of GFR is based on the concept of clearance: renal clearance. If the marker has no extrarenal elimination, tubular reabsorption, or secretion, clearance is given by the formula GFR = UV/P, where U is the concentration of the marker in urine, V is the urine flow rate, and P is the concentration in plasma. Classic biomarkers to determine renal function are blood urea nitrogen, urine output, serum creatinine (sCr), and urinary albumin [154–156]. sCr is the most common marker of renal function and has been used as a significant covariate in pharmacokinetic models for critically ill patients [157–159]. However, sCr is prone to error in patients with low muscle mass or fluid overload, which is a limitation. Furthermore, sCr or blood urea nitrogen levels change late after injury since there is a functional reserve. To overcome these limitations, novel biomarkers have been proposed. The correlation of cystatin C with GFR is superior to that of sCr and is not influenced by changes in muscle mass, which is important in hospitalization-associated myopathy [160–162]. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 are innovative biomarkers specific to renal ischemia, which leads to renal failure [163, 164]. Moreover, NGAL appears to correlate with sepsis severity [165]. GFR is already used for individualized dosage adjustments since antimicrobial concentrations depend on the extent of renal function impairment. Hypoalbuminemia and altered renal clearance are pathophysiological processes that have a high prevalence in critically ill patients and lead to pharmacokinetic-related changes. Yet, the potential impact on tissue pharmacokinetics is yet to be established.

4.3.7 Other Factors

Other factors, including specific treatments, influence the underlying pathophysiological mechanisms and, therefore, pharmacokinetics.

Need for fluid resuscitation During sepsis, the body needs extra fluids to help keep the BP from dropping dangerously low and causing shock [166, 167]. However, it increases the V_d, therefore affecting pharmacokinetics. Moreover, fluid resuscitation may significantly affect glycocalyx integrity via atrial natriuretic peptide release, leading to capillary leakage and drug distribution changes [168, 169].

Need for vasopressive drugs Vasopressor agents are used to increase BP and improve tissue perfusion. However, they may also impair cardiac output and preferentially vasoconstrict some vascular beds, particularly the skin and splanchnic area [170, 171]. Therefore, drug distribution and clearance might be impaired.

RRT Extracorporeal support is often necessary for the critically ill population. However, this exchange of substances between the blood and other fluid via a semipermeable membrane alters V_d and PB and the excretion of the drug [172–175]. RRT leads to high pharmacokinetic variability [176], probably because of the residual organ function and the changes in dialysate flow rates. Therefore, dose adjustment may be indicated [175].

Obesity Lipophilicity is a significant determinant of a drug's V_d. Patients with obesity have more lipophilic tissue than those included in standardized studies. Lipophilic drugs are associated with a higher V_d in patients with obesity, but the weight-related V_d of lipophilic drugs can be higher or lower in patients with obesity than in those without [177]. Therefore, adjustment of dose needs to be considered on a case-by-case base for different drugs.

5 Biomarker-Guided Dosing

Critically ill patients experience a range of these alterations in varying degrees of severity, which in turn, also varies over time. This results in intra- and interpatient variability in antibiotic concentration at the site of infection [7, 8]. A wide range of methods might be used to assess penetration at the target site in critically ill patients [178, 179], although they cannot be used routinely. Instead, we could strengthen antibiotic dosing strategies with biomarkers that correlate with pharmacokinetic alterations, since they might predict target-site concentrations (Fig. 4). With model-informed precision dosing, clinical and microbiological elements might be used in pharmacometric models to optimize dosing in critically ill patients [180–183]. The identified biomarkers can be added to model-informed precision dosing [58] as covariates.

5.1 Testing Methods

An ideal biomarker should have a fast, widely available, and reliable determination method. However, it is challenging to obtain pure reference standards for specific biomarkers and also complex to validate analytical methods because of their heterogeneity. Some of the biomarkers proposed are routinely available, whereas some of the promising new ones might be more difficult to perform and validate. Recently, some of these new biomarkers have been tested in multiplex tests [184]. These tests simultaneously measure various biomarkers from the same biological sample with low sample volumes. Obviously, we need to harmonize and standardize the immunoassays before incorporating these biomarkers into clinical practice [185, 186].

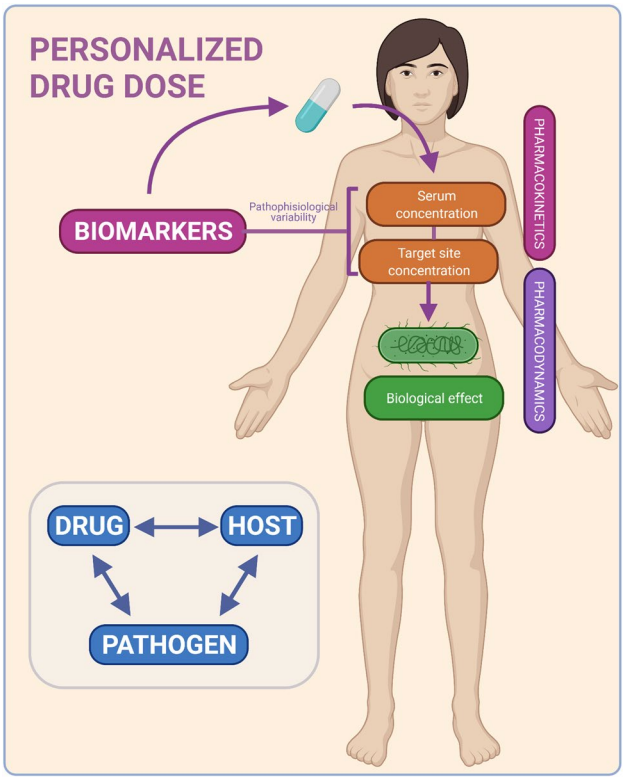


Fig. 4 Personalized antibiotic dosing. Antibiotic dosing strategies taken by physicians might be strengthened by the levels of biomarkers that reflect the drug pharmacokinetics

5.2 Kinetics of Biomarkers

In addition, sepsis is a rapidly changing condition. The precise time during which a biomarker is useful varies because of the substantial differences in their kinetics. An ideal biomarker should rapidly and specifically increase in sepsis, rapidly decrease after effective therapy, and have a short half life. None of the current biomarkers includes all of these specifications. Moreover, in most studies, biomarkers have not been measured repeatedly, and static threshold concentrations have been used to make clinical decisions [187]. This limits their use in antibiotic optimization as the variability must be assessed and controlled.

5.3 Molecular Weight

An increase in the use of extracorporeal therapies makes us consider whether RRT may remove these biomarkers. If so, we would need to consider the extent of this, depending on the biomarker MW and cut-off value of the membrane and RRT technique used [61].

5.4 Combination of Biomarkers

Sepsis is complex and heterogeneous, so no ideal single sepsis biomarker exists. The most effective way to optimize the treatment of sepsis is the combination of various sepsis biomarkers [188]. Over 258 biomarkers have been assessed for their use in sepsis [189], but none has shown sufficient specificity and sensitivity for routine use in clinical practice. Combining these biomarkers will reflect different aspects of the host response and help overcome the limitations of a single biomolecule for the prediction of the plasma and tissue pharmacokinetics of antibiotics [190].

5.5 Missing Evidence

Several biomarkers have been linked to diagnosis or prognosis, but few studies have evaluated their role in antibiotic stewardship. Therefore, prospective studies investigating the potential role of the expanding field of sepsis biomarkers for antimicrobial dose optimization are needed. Moreover, clinic-economic data to recommend its introduction into clinical practice effectively are lacking.

5.6 Therapeutic Drug Monitoring

TDM allows adjustment of the antibiotic dose based on the concentration measured in plasma. This tool can help with personalization and optimization of antibiotic doses [191]. However, it should be noted that no studies have yet demonstrated clinical improvements with TDM. Because the antibiotic concentration in the plasma is not always the same as that at the target site, the proposed biomarkers could be applied in TDM based on antibiotic concentrations at the site of infection, rather than in plasma.

6 Critical Discussion

Current evidence on biomarkers and pharmacokinetic optimization of antibiotics in the critically ill population is limited. There is evidence to demonstrate the failure of optimal PK/PD exposure in critically ill patients. However, robust data on how to predict a therapeutic effect based on antimicrobial exposure and how precision dosing improves patient outcomes are lacking. In recent years, many new sepsis biomarkers have emerged to improve and guide treatment. However, most of the biomarker studies have limited evidence, and their clinical significance has yet to be proven. The weak evidence of current studies may be due to the study design, sample size, risk of bias, and lack of validation. A biomarker must be able to guide treatment to be useful in clinical practice. Moreover, critically ill patients are a

very heterogeneous population. Based on current knowledge and evidence, it is difficult to design a personalized dosing regimen.

With this review, we proposed and discussed how pharmacokinetic biomarker-guided therapy can optimize antibiotic exposure in critically ill patients. The association between hepatic and renal biomarkers and pharmacokinetics is clear. We now also propose inflammation, endothelial, coagulation, and blood flow markers to characterize this pharmacokinetic variability in critically ill patients. We link biomarkers and pharmacokinetic changes based on extrapolation of patient physiological changes during sepsis that lead to this pharmacokinetic variability. However, their association with altered pharmacokinetics and their clinical relevance still needs to be characterized. We therefore propose potential biomarkers to define antibiotic pharmacokinetics in sepsis as a research perspective to improve antibiotic treatment in the ICU.

7 Conclusion

Adequate antimicrobial dosing to achieve PK/PD targets in patients with sepsis remains a challenge because of changes in V_d, clearance, and PB. On top of changes in systemic plasma, exposure to the tissue-to-plasma ratio might differ from that in a healthier population. This review aimed to characterize sepsis biomarkers and propose how they can predict the target-site concentrations of antibiotics. We categorized the main drivers of altered tissue pharmacokinetics into inflammation, coagulopathy, endotheliopathy, and organ failure. These sepsis biomarkers might predict pharmacokinetic changes and target-site concentrations. However, clinical evidence, standardization, and threshold definitions for these biomarkers are currently lacking. We propose biomarker-based drug monitoring for dose optimization and encourage new lines of research in this direction. Future research should focus on the determination of in vivo plasma/tissue distribution, the study of sepsis biomarkers, and their correlation and clinical application.

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