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.
Graphical Abstract

**TISSUE PHARMACOKINETIC BIOMARKERS IN SEPSIS**

**COAGULOPATHY**
- ADAMTS-13
- Antithrombin
- Protein C
- Protein S
- Protein C3
- Protein S3

**RENAL IMPAIRMENT**
- Creatinine clearance
- GFR output

**ENDOTHELIAL DAMAGE**
- ADAMTS-13
- Angiopoietin-1/2
- Endostatin
- ICAM
- VCAM
- VEGF
- VWF

**PERSONALIZED DRUG DOSE**
- Pathophysiologic variability
- Serum concentration
- Target site concentration
- Biological effect

**BIOMARKERS**
- CRP
- Ferritin
- Haptoglobin
- LBP
- Procalcitonin
- Prothrombin

**CELL MARKERS, RECEPTORS**
- CD40, mHLA
- TLR 2 and 4, sTREM-1
- TNF receptor, soluble

**CYTOKINES, COMPLEMENT**
- IL-1β, IL-2, IL-6, IL-8, TNF-α
- C5a, C5b-9
- MCP-1 and 2
- MIP-1
- MIP-2

**HEPATIC IMPAIRMENT**
- Bilirubin
- ALAT/ASAT
- Albumin
- Acute phase protein
- PT

**ACUTE PHASE REACTANTS**
- SAA
- CRP
- Ferritin
- Hepatidin
- LBP
- Procalcitonin
- Prothrombin

**EXTERNAL FACTORS**
- Fluid resuscitation
- Inotropic drugs
- RRT
- Apheresis
- Immunoadsorption
- Biological response regulators

**BLOOD FLOW**
- CO2
- Blood pressure
- Cardiac output
- Heart rate
- PCO2
- pCO2

**Adis**

**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** 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, **PCO2** partial pressure of carbon dioxide, **PT** prothrombin time, **RRT** renal replacement therapy, **SAPSS III** Simplified Acute Physiology Score-III, **sO2** 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**

Pathophysiologival 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.

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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].

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**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.
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.

### 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, antibiotic pharmacokinetics, critically ill patients, biomarkers, drug and host factors, and pharmacokinetic variability.

### 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

### Table 2 Protein binding of antibiotics

| Pharmacokinetics | 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, lincomamides | [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
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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 pharmacodynamic 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...
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

| Antibiotic                      | Gram+/− | Mechanism of action | PK/PD index | \( V_d \) (L/kg) | \( C_{\text{max}} \) | \( t_\text{1/2} \) (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     | 0.7–1.4         | 90              | 7.5–9           | Renal     | Hydrophilic | [206]      |
| Vancomycin                      | G+      | Bactericidal        | AUC/MIC     | 0.4–1           | 10–50           | 6               | Renal     | Hydrophilic | [207]      |
| **Lipopeptide**                 |         |                     |             |                 |                 |                |           |            |            |
| Daptomycin                      | G+      | Bactericidal        | AUC/MIC     | 0.1             | 90              | 7.5–9           | Renal     | Hydrophilic core lipophilic tail | [208–210] |
| Fosfomycin                      | G+/G−   | Bactericidal        | AUC/MIC     | 1.4–2.4         | 10              | 2.9–8.5         | Renal     | Hydrophilic | [211–213]  |
| **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        | \( C_{\text{max}}/MIC \) | 0.22–0.27       | 0–30            | 1.25            | Renal     | Hydrophilic | [219]      |
| Amikacin                        | G+/G−   | Bactericidal        | \( C_{\text{max}}/MIC \) | 0.22–0.27       | <10             | 2–3             | Renal     | Hydrophilic | [220]      |
| Tobramycin                      | G+/G−   | Bactericidal        | \( C_{\text{max}}/MIC \) | 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 (prod-rug) | Hydrophilic | [225]      |
| **Oxazolidinones**              |         |                     |             |                 |                 |                |           |            |            |
| Linezolid                       | G+      | Bactericidal, bacteriostatic | AUC/MIC | 0.7            | 31              | 4–6             | Hepatic, renal | Lipophilic | [226]      |

\( AUC \) area under the plasma concentration–time curve, \( C_{\text{max}} \) 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, \( t_\text{1/2} \) elimination half-life, \( V_d \) volume of distribution
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
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
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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) | \( t_{1/2} \) | 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 | Neutrophil 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, neutrophil activation | Px | 17.3 | 6 | 1–2 | D | [233] |
| IFNγ | T\(_h\) 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] |
| CSa, 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** | | | | | | | |
| SO₂ % | 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) | Affected drug PK | References |
|------------|--------------|-------|----------|----------|------------------|------------|
| HR         | Heart rate   | Px    | NA       | NA       | NA               | D [289]    |
| ScvO₂      | Central venous oxygen saturation | Px    | NA       | NA       | NA               | D [290]    |
| StO₂       | 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] |
| Fibrinogen | 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** is 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** monocyte 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, **ScvO₂** central venous oxygen saturation, **sCAM** soluble ICAM, **SO₂**% oxygen saturation, **StO₂** tissue oxygen saturation, **sTREM** soluble triggering receptor expressed on myeloid cells 1, **suPAR** soluble urokinase-type plasminogen activator receptor, **sVCAM** soluble VCAM, **t½** elimination half-life, **Th1** 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.

*Presented in h unless otherwise indicated.

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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 CO₂ 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

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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 vasodilation or vasoconstriction that drives changes in drug 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.

### 4.3.5 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.

### 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
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].

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 basis for different drugs.
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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