# Clinical Management of Endotoxemia: Antibiotics

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## 6.1 Introduction

Endotoxemia is commonly caused by infections sustained by Gram-negative bacteria [1] that represent the most common pathogens isolated from critically ill patients with suspected infection [2]. In this setting, adequate antimicrobial therapy is pivotal to reduce pathogen load, in order to mitigate inflammatory dysfunction and tissue damage, with significant benefit on patient outcomes [3]. However, this intervention is challenged by concurrent patient and pathogen characteristics that may limit its efficacy. In this chapter, we will discuss the importance of adequate antibiotic therapy in patients with sepsis and provide an overview of the most recent evidence on antimicrobial therapy in patients with Gram-negative infection.

## 6.2 Timing and Adequacy of Antibiotic Therapy in Septic Shock

The early administration of adequate antimicrobial therapy was demonstrated to effectively improve the outcome of patients with sepsis [4–6] and several studies reported a direct association between timing of adequate antimicrobial administration and mortality [6–8]. For these reasons, the Surviving Sepsis Guideline for

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management of sepsis and septic shock 2021 [3] issued a strong recommendation to administer antimicrobials within 1 h of septic shock recognition, and within 3 h in patients with high likelihood of sepsis. On the contrary, antimicrobials administration should be deferred in patients with a low likelihood of sepsis or septic shock, in order to prevent potential harms like allergic or hypersensitivity reactions, kidney injury, thrombocytopenia, Clostridium difficile infection, and antimicrobial resistance [3]. Accordingly, a stewardship program for antimicrobial administration [9, 10] has been strongly advocated and should account for the epidemiology of pathogens, the suspected source of infection, and the characteristics of the patients. Moreover, the pharmacokinetic (PK) characteristics of the drug and the spectrum of sensitivity to antimicrobials of the pathogen (pharmacodynamic, PD) should be considered, in order to optimize this therapy and allow prompt de-escalation [11]. However, positive microbiological cultures may be retrieved only in 65% of critically ill patients with suspected infection, for whom Gram-negative bacteria are prevalent [2]. In this setting, rapid molecular tests have raised interest to provide pathogen identification, in order to shorten adequate antimicrobial administration [12].

## 6.3 PK-PD Principles to Optimize Antimicrobic Treatment

The optimization of antimicrobial therapy is a key treatment intervention in the management of sepsis, both to maximize therapeutic success and limit the emergence of resistant pathogens [13, 14]. Specifically, critically ill patients with severe infections are at high risk of suboptimal antimicrobial dosing, mostly due to homeostatic changes associated with sepsis [organ dysfunction, increased volume of distribution due to endothelial permeability, fluid overload, and hypoalbuminemia], therapeutic interventions (e.g., extracorporeal organ support therapies), and comorbidities [15–18]. These conditions may influence PK characteristics of antimicrobials and challenge conventional drug dosing [13] (Fig. 6.1). Moreover, antibiotic dose should be targeted to PD, in order to overcome the in vitro minimum concentration of antimicrobic to inhibit (MIC) pathogen growth. Accordingly, antimicrobic dose optimization in critically ill patients is difficult to achieve and requires a personalized approach. In this setting, several strategies have been suggested like unit-level interventions (e.g., prolonged infusions), nomograms based on renal function or body weight and therapeutic drug monitoring (TDM) [15, 19, 20]. The latter involves the measurement of drug concentration at the tissue level (usually, the bloodstream or bronchial secretions) and may help to adjust antimicrobial dosing to overcome the MIC of the pathogen, mitigate the emergence of resistance and limit toxicity [19]. TDM is recommended for many antimicrobials used to treat Gram-negative infections, such as beta-lactams and aminoglycosides, whereas there are not specific recommendations for other classes of antimicrobial like polymyxins and fluoroquinolones [21, 22].

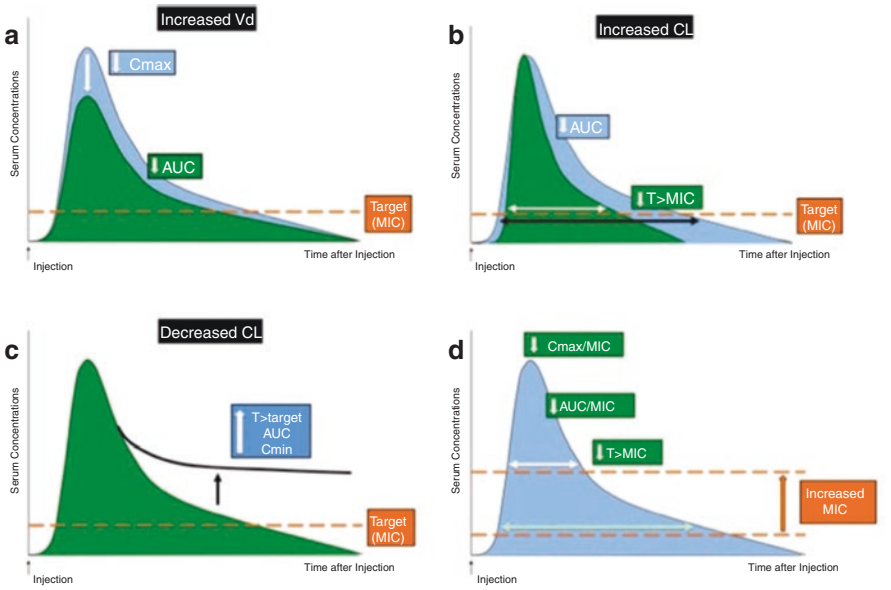


**Fig. 6.1** PK/PD changes for antibiotics in critically ill patients. (**a**) Increased volume of distribution (*Vd*) will decrease the peak concentration (*C*max; relevant for drugs like aminoglycosides) and the area under the curve of drug concentrations over time (AUC; relevant for drugs like quinolones) of the drug in the first dosing interval. (**b**) Increased drug clearance (CL) will reduce the AUC and the time above the minimum inhibitory concentration (T>MIC, relevant for drugs like beta-lactams). (**c**) Decreased CL will increase the AUC, the T>MIC and the minimum drug concentration before the next administration (*C*min). (**d**) Increased MIC of the pathogen will result in decreased PD targets (*C*max/MIC, AUC/MIC and T>MIC). From Roberts et al., Examples of PK/PD changes for antibiotics in critically ill patients, Intensive Care Med. 2016 with permission [18]

## 6.4 The Placement of New Molecules Against Gram-Negative Bacteria

The emergence of multi-drug resistant (MDR) pathogens, characterized by high MIC for the majority of commonly used wide spectrum antimicrobials, challenges the adequate administration of this therapy. Recent evidence [2] showed that critically ill patients are at risk of Gram-negative infections sustained by MDR strains like carbapenem resistant (CR) or extended-spectrum beta-lactamase (ESBL) *Enterobacterales*, *Pseudomonas aeruginosa* (PA), and *Acinetobacter baumannii* (AB). For these reasons, many efforts have been invested to test the effectiveness of new drug with marked antimicrobial properties (Table 6.1) or to improve the use of "old" molecules with narrow therapeutic windows (e.g., polymyxins) [24]. Among the former, Ceftolozane/Tazobactam (TOL/TAZ), a combination of a fourth-generation cephalosporin with a b-lactamase inhibitor, was demonstrated effective to treat infections

**Table 6.1** New drugs with marked antimicrobial properties against Gram-negative bacteria [23]

| Drug | FDA/EMA infection approval | Dosage |
|---|---|---|
| Ceftolozane/ Tazobactam | Complicated intra-abdominal infections<br>Complicated urinary tract infections<br>Ventilator associated pneumonia | 1.5 g q 8 iv in 1 h infusion<br>3 g q 8 iv (ventilator associated pneumonia) |
| Ceftazidime-Avibactam | Complicated intra-abdominal infections<br>Complicated urinary tract infections<br>Ventilator associated pneumonia | 2.5 g q 8 iv in 2 h infusion |
| Meropenem-Vaborbactam | Complicated intra-abdominal infections<br>Complicated urinary tract infections<br>Hospital associated pneumonia<br>Ventilator associated pneumonia<br>Bacteremia | 4 g q 8 iv in 3 h infusion |
| Imipenem/ Relebactam | Complicated urinary tract infections | 1.25 g q 6 in 30 min infusion |
| Cefiderocol | Complicated urinary tract infections | 2 g q 8 iv in 3 h infusion |

Abbreviations: *EMA* European Medicine Agencies, *FDA* Food and Drug Administration

caused by Enterobacterales and MDR Pseudomonas Aeruginosa. For these strains, the time above the MIC (T > MIC) needed to produce bactericidal activity was much lower (approximately 30%) compared with other drugs of the same class [25, 26]. In this setting, a recent trial demonstrated that the efficacy of TOL/TAZ was not inferior to meropenem in patients with ventilator associated pneumonia (VAP) caused by Gram-negative bacteria [27]. On top of that, Ceftazidime-Avibactam (CAZ/AVI), a combination of a third-generation cephalosporin with a b-lactamase inhibitor, was demonstrated effective to treat infections caused by MDR bacteria with ESBL and Class A, C and some D (OXA 48) carbapenemases activities [28]. Moreover, Meropenem-Vaborbactam (MER/VAB) and Imipenem/Relebactam (IMI/REL) were demonstrated effective against Enterobacteriaceae KPC as well as MDR bacteria with class A carbapenemases (MER/VAB) [29, 30] and class A and C b-lactamase (IMI/REL) activities. Furthermore, other antibiotic combinations like aztreonam-avibactam were demonstrated to be effective against Enterobacteriaceae producing β-lactamases, ESBL and AmpC enzymes [31].

Finally, a new generation of cephalosporins, Cefiderocol, was demonstrated effective against KPC, NDM carbapenemases, MDR PA, AB and Stenotrophomonas maltophilia. This molecule has been approved to treat urinary infections, although it may play a role in the management of patients with pneumonia caused by these strains [32, 33].

## 6.5 Polymyxins in the Clinical Practice

Polymyxins are "old" antibiotics that were discovered in Japan in 1947 [34]. This group consists of cationic polypeptides (A–E), among which only Polymyxin B and E (colistin) have been used in clinical practice to treat Gram-negative infections.

Polymyxin B and Colistin are produced by *Bacillus* spp. [35] and consist of cyclic decapeptide molecule, positively charged and linked to a fatty acid chain. They cause lipopolysaccharide disruption and exert concentration-dependent bactericidal activity against many Gram-negative bacteria like *Acinetobacter* spp., *Klebsiella Pneumoniae*, *Escherichia Coli*, *Pseudomonas Aeruginosa*, and *Enterobacter* spp. The systemic use of polymyxin was abandoned after the 1970s, when some reports warned about their neurologic (only Polymyxin B) and renal toxicity. However, the emergence of MDR Gram-negative bacteria has raised interest towards these molecules and systemic administration of colistin is now considered a cornerstone of therapy in this setting, despite its narrow therapeutic window. In the same period, the use of Polymyxin B has been recovered as well and this molecule has been manufactured into cartridges of polystyrene fibers for endotoxin removal via extracorporeal blood purification therapy [36], in order to prevent its toxicity.

## 6.6 Conclusions

Timely and appropriate antibiotic therapy is of paramount importance in the management of patients with endotoxemia and sepsis. In order to optimize this intervention and prevent potential undesirable adverse events, antibiotic therapy should be driven by evidence-based stewardship programs that take into account the severity of organ dysfunction, pharmacokinetic/pharmacodynamic characteristics of the drug, and the emergence of multi-drug resistant pathogens. In this setting, several diagnostic tools and new drugs may help the clinician to overcome these issues and improve patient-related clinical outcomes.

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