12.1 General

Prescription of antibiotics in critically ill patients is a complex process that requires ongoing patient health evaluation to account for the dynamic sepsis disease process. Pathophysiological changes such as organ dysfunction, fluid shifts and altered immune status are common, and are able to reduce the efficacy of anti-infective treatments. Throughout this chapter, dosing of antibiotics that are commonly used in critically patients with sepsis or septic shock will be discussed. The importance of knowledge of the pharmacokinetic and pharmacodynamic principles of each class will be discussed, and how to optimise these parameters and therefore augment patient responses.

12.1.1 Sepsis

The older definitions of sepsis [1] (a systemic inflammatory response syndrome (SIRS) triggered by an overwhelming infection) have recently been refined [1, 2]. Severe sepsis occurs upon failure or dysfunction of at least one organ. Septic shock is defined by hypotension in the setting of severe sepsis which is unresponsive to fluid resuscitation. While much research has been directed at cellular targets to limit the associated inflammatory and coagulation cascades including interleukins, cytokines and tumour necrosis factor-alpha (TNF-α) [3], none of these interventions have been found to be as important or effective as optimal antibiotic therapy [3–8]. However, the appropriate prescription of antibiotics requires a detailed knowledge of the pathophysiological and subsequent pharmacokinetic changes that occur throughout the course of sepsis [9, 10].

12.1.1 Pathophysiological Changes in Sepsis That Can Affect Drug Distribution

Brief Pathophysiology of Sepsis Without Organ Dysfunction

The pathogenesis of sepsis appears highly complex [2, 3, 11, 12]. Endotoxins from bacteria or fungi stimulate the production of various endogenous mediators [13]. These mediators may affect the vascular endothelium directly or indirectly, resulting in either vasoconstriction or vasodilatation with maldistribution of blood flow, endothelial damage and increased capillary permeability. This capillary leak syndrome results in fluid shifts from the intravascular compartment to the interstitial space [14, 15] which is known as ‘third spacing’. This would increase the volume of distribution (Vd) of water-soluble drugs which decreases their serum drug concentration.

Increased Creatinine Clearance in Critically Ill Patients Without Renal Dysfunction

Patients often present with hypotension from the inflammatory response associated with sepsis. Standard initial management involves administration of intravenous fluids to elevate blood pressure. If hypotension persists, inotropic agents (some of which may be “inconstrictors”) are prescribed. It is therefore not surprising that patients with sepsis often have higher than normal cardiac indices [11, 16, 17]. In the absence of significant organ dysfunction, often there is an increased renal preload and consequently increased creatinine and drug clearance [18–20].

Previous studies have reported that critically ill patients with normal serum creatinine levels may have high creatinine clearance [21, 22]. This phenomenon is most likely to result from the clinical interventions used to reverse hypotension as described above. The implications of the high creatinine clearance, which is probably related to high renal (and hepatic) blood flow, will result in supranormal clearance of renally cleared drugs. This increase in clearance is the major reason for the different dosing requirements between ICU and
non-ICU patients [23, 24]. A similar scenario probably occurs for hepatically cleared antibiotics.

**Pathophysiology of Sepsis Causing Organ Dysfunction**

As sepsis progresses, significant myocardial depression can occur which leads to a decrease in organ perfusion [16]. Myocardial insufficiency and abnormalities of the macrovascular circulation are compounded by failure of the microcirculation. This induces end-organ microvascular alterations which may progress to multiple organ dysfunction syndrome (MODS) [25]. This often includes renal and/or hepatic dysfunction. There is a consequent decrease in antibiotic clearance, which prolongs elimination half-life and may increase antibiotic concentrations and/or lead to the accumulation of metabolites [26].

Figure 12.1 schematically identifies the pharmacokinetic changes that can occur due to the altered pathophysiology during sepsis.

**Determining Renal Function in Critically Ill Patients with Sepsis**

Accurate knowledge of renal function is a critical factor in drug and antibiotic dosing as most antibiotics are primarily eliminated by this means. If renal dysfunction occurs in a critically ill patient with sepsis, calculation of the efficiency of the kidney can be problematic. Accepted norms for calculating creatinine clearance (as a marker of renal function) in ‘normal’ ward patients such as the Cockroft-Gault method [27] and the Modified Diet in Renal Disease (MDRD) study [28] have been reported to lose their accuracy in critically ill patients [29]. As such, the most effective way to calculate renal function remains using either an 8-, 12- or 24-h creatinine clearance collection [30–32]. If acute renal failure occurs such that the patient needs intermittent haemodialysis or continuous renal replacement therapy (CRRT), a new variable is introduced. Chapter 13 discusses the altered dosing of antibiotics that is necessary in these patients.

**12.1.2 Applied Clinical Pharmacology**

To achieve ‘ideal’ treatment of an infection, it is necessary to optimise the possible interactions between the host, the pathogen, and the antibiotic [33]. This task becomes more difficult in critically ill patients, where recommended antibiotic regimens have been derived from volunteer studies or other patient groups who were not critically ill. Therefore, consideration of the effect of the pathophysiological changes, caused by sepsis, on the pharmacokinetic and pharmacodynamic parameters of the antibiotic is necessary. Further, since the physiology of these patients may change over a relatively short period of time, ongoing evaluations of sickness severity are indicated to allow timely adjustment of antibiotic dosing.

**12.1.2.1 Pharmacokinetic Considerations**

Pharmacokinetics (PK) refers to the study of concentration changes of a drug over a given time period. The primary PK parameters of importance to antibiotics include:

- Volume of distribution ($V_d$)
- Clearance ($CL$)
- Half-life ($T_{1/2}$)
- The peak serum concentration achieved by a single dose ($C_{max}$)
- The lowest concentration during a dosing period ($C_{min}$)
- The area under the serum concentration time curve (AUC).