Chapter 8
Dose Adjustment and Pharmacodynamic Considerations for Antibiotics in Severe Sepsis and Septic Shock

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8.1 Introduction

Prescription of antibiotics in the critically ill is a complex process. It requires consideration of the likely causative organism/s, an appreciation of the underlying pathophysiological state and how this dynamic process influences drug distribution, metabolism and elimination. Associated organ dysfunction, fluid shifts and altered immune status are common, and each can influence the efficacy of many antimicrobial agents. This chapter will focus on the prescription of antibiotics commonly used in the treatment of critically ill patients with severe sepsis or septic shock. Early appropriate antimicrobial therapy remains the cornerstone of successful treatment in this group (Kollef et al. 1999; Ibrahim et al. 2000; Garnacho-Montero et al. 2003; Valles et al. 2003). Pharmacokinetic and pharmacodynamic principles will be reviewed, with the aim to optimize dosing and improve outcome. There are similar considerations concerning the use of antifungal and possibly antiviral agents in the critically ill; however, a wider discussion of these agents is beyond the scope of this chapter.

8.2 Applied Clinical Pharmacology

Successful treatment of an infection involves optimizing the interaction between the host, the pathogen and the antibiotic (Nicolau 1998). Recommended antibiotic regimens have often been derived from studies on healthy volunteers or non-critically ill patient groups, making extrapolation to dosing in severe sepsis difficult. Key considerations involve a variety of pathophysiological changes associated with sepsis, and their effects on the pharmacokinetic and pharmacodynamic parameters of the chosen antibiotic. This process is dynamic, and ongoing evaluation of illness severity, organ function and the resuscitation status are necessary to allow the timely adjustment of antibiotic dosing.
8.2.1 Pharmacokinetic Considerations

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

- **Volume of distribution (Vd).** Apparent (hypothetical) volume of fluid that contains the total amount of administered drug, at the same concentration as that measured in plasma.
- **Clearance (CL).** Volume of plasma effectively cleared of the drug per unit time. Total clearance is the sum of the clearances for each eliminating organ or tissue.
- **Plasma half-life (T_{1/2}).** Time required to decrease the plasma concentration by one half.
- **C_{max}**. The peak concentration achieved by a single dose.
- **C_{min}**. The lowest concentration during a dosing period.
- **Area under the curve (AUC).** The area under the plasma concentration–time curve.

Antibiotics can be classified by their affinity for water (hydrophilic) or lipids (lipophilic). Where hydrophilic drugs are typically distributed in extracellular water, lipophilic drugs may distribute intracellularly and into body fat, favouring bioaccumulation. Protein binding of antibiotics either to albumin or alpha-1 acid glycoprotein (AAG) effects their distribution throughout the body and their biological effect. More highly bound drugs generally have a longer duration of action and a lower volume of distribution. The free drug concentration is important for clinical effect, and is influenced by plasma protein levels and binding competition from other drugs. Consideration of these basic pharmacokinetic factors can be used to determine whether appropriate concentrations of the antibiotic are being delivered to the target area (Nicolau 2003).

8.2.2 Pharmacodynamic Considerations

The pharmacodynamic (PD) effect of antibiotics refers to the ability of the antibiotic to kill or inhibit the growth of the infective organism. How this is effected by an antibiotic’s PK properties is referred to as “pharmacokinetics-pharmacodynamics or PK–PD characteristics” but will be termed “pharmacodynamics” (PD) here. PD parameters include:

- **T > MIC.** The time for which a drug’s concentration remains above the minimum inhibitory concentration (MIC) for bacterial growth during a given dosing period
- **C_{max}/MIC.** The ratio of the maximum antibiotic concentration (C_{max}) to the MIC of the pathogen
- **AUC_{0-24}/MIC.** The ratio of the area under the concentration time curve during a 24-hour time period to the MIC of the pathogen (see Fig. 8.1)