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Principles of Antimicrobial Use

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The emergence of antimicrobial resistance (AMR) and its linkage to misuse of antimicrobial agents, highlights the need to better understand the key features of their action and use. These principles apply equally to human, animal, and agricultural settings because it is clear that antimicrobial use has increased dramatically in all sectors over the past decades (WHO, 2012; WHO, 2015; Van Boeckel *et al.*, 2014; Van Boeckel *et al.*, 2015; O'Neill, 2016). This chapter will focus primarily on human antimicrobial use, and nonhuman use is discussed elsewhere (see Chapter 2, Use of Critically Important Antimicrobials in Food Production).

The key principles of antimicrobial use include choosing the correct drug for the indication, at the correct dose for the individual conditions (site of infection, patient age and organ [renal, hepatic] function, drug interactions) and for the appropriate duration (based on site and severity of infection). Some national guidelines have expanded these principles to the simple acronym MIND ME (Table 1.1) (Antibiotic Expert Group, 2014). However, this does not fully address all the variables that should be considered when prescribing antimicrobials, with issues such as prophylaxis vs. therapeutic use and empiric vs. directed therapy also being important (Antibiotic Expert Group, 2014). In fact, it is often a misunderstanding of these latter issues that is commonly associated with inappropriate prescribing and excess drug usage (WHO, 2001; WHO, 2012; Pulcini *et al.* 2012; Davies, 2013; Laxminarayan *et al.*, 2013).

Improved knowledge regarding the key pharmacokinetic (PK) and pharmacodynamic (PD) indices of antimicrobials has made a significant difference to our understanding of drug efficacy in various body sites and the potential to develop resistance among key pathogens. This is particularly true for antibiotics, antifungals and some antivirals for which drug penetration into certain so-called sanctuary sites, such as the brain, eye, prostate, and bone, is variable, depending on the drug's structure and the impact of the host inflammatory response on drug permeability (Antibiotic Expert Group, 2014). Furthermore, improved understanding of a drug's key PK-PD features helps define the optimal means of dosing. The obvious example is the aminoglycosides, for which it is recognized that efficacy is associated with the area-under-the-concentration-time curve (AUC) rather than time above the minimum inhibitory concentration (MIC) (time-dependent activity) and that this feature allows for effective once-daily aminoglycoside therapy, while minimizing renal- and ototoxicity. Similarly, beta-lactams are increasingly being administered as a prolonged or continuous infusion because their efficacy is time dependent. The search for PK-PD relationships to reduce emergence of resistance is still in its infancy, but it is increasingly evident that the duration of treatment as well as suboptimal dosing are correlated to emergence of resistance (Mouton *et al.*, 2011). However, a clear understanding of the PK-PD features for many commonly used drugs, particularly older agents that

Table 1.1. Appropriate prescribing acronym MIND ME

M	Microbiology guides therapy wherever possible.
I	Indications should be evidence based.
N	Narrowest spectrum therapy preferred.
D	Dosage individualized to the patient and appropriate to the site and type of infection.
M	Minimize duration of therapy.
E	Ensure oral therapy is used when clinically appropriate.

Source: Modified from Antibiotic Expert Group (2014), with permission.