of the *first-pass effect*—the process by which drugs are absorbed in the small intestine through the portal circulation and then directly transported to the liver for metabolism.

Distribution *Distribution* describes the process by which a drug transfers reversibly between the general circulation and the tissues. After absorption into the general circulation and the central compartment (the extensively perfused organs), the drug will also distribute into the peripheral compartment (less well-perfused tissues). The volume of distribution (Vd) is a pharmacokinetic parameter that describes the amount of drug in the body at a given time relative to the measured serum concentration. Properties such as the drug's lipophilicity, partition coefficient within different body tissues, and protein binding; blood flow; and pH can affect the volume of distribution. Drugs with a small volume of distribution are limited to certain areas within the body (typically extracellular fluid), whereas those with a higher volume of distribution penetrate extensively into tissues throughout the body. Antibacterial drugs can bind to serum proteins, and a given drug is usually described as either poorly or highly protein bound. Only the unbound (free) drug is active and available to exert antibacterial effects. For example, because tigecycline is highly protein bound and also has a large volume of distribution, concentrations of free drug in the serum are low.

Metabolism *Metabolism* is the chemical transformation of a drug by the body. This modification can occur within several areas; the liver is the organ most commonly involved. Drugs are metabolized by enzymes, but enzyme systems have a finite capacity to metabolize a substrate drug. If a drug is given in a dose at which the concentration does not exceed the rate of metabolism, then the metabolic process is generally linear. If the dose exceeds the amount that can be metabolized, drug accumulation and potential toxicity may occur. Drugs are metabolized through phase I or phase II reactions. In phase I reactions, the drug is made more polar through dealkylation, hydroxylation, oxidation, and deamination. Polarity facilitates drug removal from the body. Phase II reactions, which include glucuronidation, sulfation, and acetylation, result in compounds larger and more polar than the parent drug. Both phases usually inactivate the parent drug, but some drugs are rendered more active. The cytochrome P450 (CYP) enzyme system is responsible for phase I reactions and is generally found in the liver. CYP3A4 is a common subfamily within this system that is responsible for the majority of drug metabolism. Antibacterial drugs can be substrates, inhibitors, or inducers of a particular CYP enzyme. Inducers, such as rifampin, can increase the production of CYP enzymes and consequently increase the metabolism of other drugs. Inhibitors, such as quinupristin-dalfopristin, cause a decrease in enzyme activity (or competition for CYP substrate) and therefore an increase in the concentration of the interacting drug.

Excretion *Excretion* describes the body's mechanisms of drug elimination. Drugs can be eliminated through more than one mechanism. Renal clearance is the most common route and includes elimination through glomerular filtration, tubular secretion, and/or passive diffusion. Some agents have nonrenal clearance and rely on the biliary tree or the intestine for excretion. Excretion affects the half-life of a drug—i.e., the time it takes for the blood concentration of a drug to decrease by one-half. This value can range from minutes to days. Approximately five to seven half-lives are required for a drug to reach steady state when multiple doses are given in a time frame shorter than the half-life itself. Drug half-life and overall clearance can be extended if the organ responsible for clearance is impaired. Patients with renal or hepatic impairment may require dose adjustments that take delayed clearance into account and prevent toxicities from drug accumulation. For example, imipenem is cleared predominantly through glomerular filtration, and in the presence of renal impairment the dosing interval is typically increased to account for the increased half-life.

PHARMACODYNAMICS

The term *pharmacodynamics* describes the relationship between the serum concentrations that determine the efficacy of the drug and the serum concentrations that produce the toxic effects of the drug. For an antibacterial agent, the pharmacodynamic focus is the type of drug exposure needed for optimal antibacterial effect in relation to the minimal inhibitory concentration (MIC)—the lowest drug concentration that inhibits the visible growth of a microorganism under standardized laboratory conditions. Antibacterial effect usually correlates with one of the following parameters: (1) ratio of peak serum concentration to the MIC (C_{max}/MIC), (2) ratio of the area under the concentration–time curve to the MIC (AUC/MIC), or (3) duration of concentrations above the MIC (T>MIC) (Fig. 170-2).

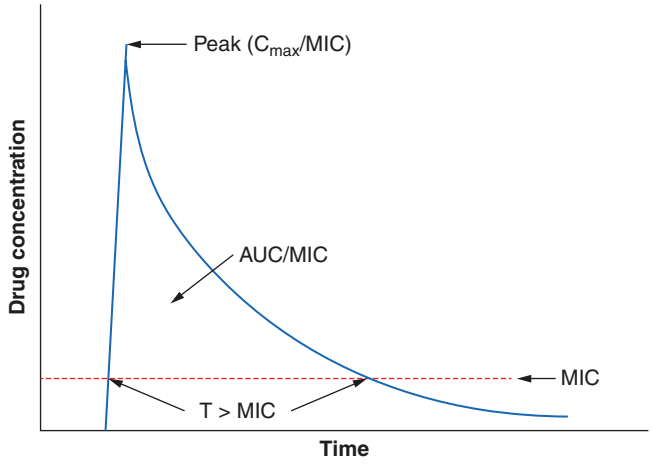

FIGURE 170-2 Pharmacokinetic and pharmacodynamic model predicting efficacy of antibacterial drugs. AUC, area under the time–concentration curve; C_{max}, peak serum concentration of drug; MIC, minimal inhibitory concentration; T>MIC, duration of drug concentrations above the MIC.

For *concentration-dependent* killing agents, as the designation implies, the higher the drug concentration, the higher the rate and extent of bacterial killing. Aminoglycosides fit into the C_{max}/MIC model of pharmacodynamics activity, and a particular peak serum concentration is often targeted to achieve optimal killing. Fluoroquinolones exemplify antibacterial agents for which the AUC/MIC is a predictor of efficacy. For example, studies have found that an AUC/MIC ratio of >30 will maximize killing of *S. pneumoniae* by fluoroquinolones. In contrast, *time-dependent* killing agents reach a ceiling at which higher concentrations do not result in increased effect. Instead, these agents are active against bacteria only when the drug concentration is above the MIC. The T>MIC predicts clinical efficacy for all β-lactams. The longer the concentration of the β-lactam remains above the MIC for an infecting pathogen during the dosing interval, the greater the killing effect. For some drug classes, such as aminoglycosides, a *postantibiotic effect*—the delayed regrowth of surviving bacteria after exposure to an antibiotic—supports less frequent dosing.

APPROACH TO THERAPY

The approach to antibiotic therapy is driven by host factors, site of infection, and local resistance profiles of suspected or known pathogens. Further, national and local drug shortages and formulary restrictions can affect available therapies. Regular monitoring of the patient and collection of laboratory data should be undertaken to streamline antibacterial therapy as appropriate and to investigate the possibility of treatment failure if the patient fails to respond appropriately.

EMPIRICAL AND DIRECTED THERAPY

Therapy is considered *empirical* when the causative agent has yet to be determined and therapeutic decisions are based on the severity of illness and the clinician's assessment of likely pathogens in light of the clinical syndrome, the patient's medical conditions and prior therapy, and relevant epidemiologic factors. For patients with severe illness, empirical therapy often takes the form of an antibacterial combination that provides broad coverage of diverse agents and thus ensures adequate treatment of possible pathogens while additional data are being collected. *Directed* therapy is predicated on identification of the