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684 SECTION 8 Infectious diseases patients, measures including nursing them in single rooms and taking great care to avoid nosocomial acquisition of infection from staff, visitors, or other patients is simple but effective. Chemoprophylaxis for a wide range of bacterial, viral, and fungal pathogens has had a major impact (Table 8.2.4.5). Guidelines regarding immunization in immunocompromised hosts have been drawn up by the Infectious Diseases Society of America (see Further reading). In addition, routine screening of transplant recipients and donors should include serological tests for cytomegalovirus, hepatitis B, and HIV. FURTHER READING Baker TM, et al. (2016). The Growing Threat of Multidrug-Resistant Gram-Negative Infections in Patients with Hematologic Malignancies. *Leuk & Lymph*, 57, 2245–58. Davies JM, Barnes R, Milligan D (2002). Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Clin Med*, 2, 440–3. Heinz WJ, et al. (2017). Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol*, 96, 1775–92. Jaksic B, et al. (2006). β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ*, 326, 1111–19. Kalil AC, et al. (2018). Severe infections in critically ill solid organ transplant recipients. *Clin Microbiol Infect*, <https://doi.org/10.1016/j.cmi.2018.04.022> Mikulska M, et al. (2018). Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect*, 76, 20–37. Pappas PG, et al. (2016). Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*, 62, e1–e50. Patterson TF, et al. (2016). Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*, 63, e1–e60. Rubin LG, et al. (2014). 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*, 58, 309–18. 8.2.5 Antimicrobial chemotherapy Maha Albur, Alasdair MacGowan, and Roger G. Finch ESSENTIALS The practice of medicine changed dramatically with the availability of effective antimicrobial agents. Often fatal diseases, such as infective endocarditis, became treatable; much minor community infectious morbidity became readily controlled; for example,

urinary tract infection; many surgical procedures became much safer, and developments in solid organ and bone marrow transplantation became possible. However, the very success of antimicrobial chemotherapy has led to anti-infective overuse and misuse. In some countries, antibiotics are freely available to the public for purchase 'over the counter', with few controls or guidance to ensure their safe and effective use. In many others there are poorly developed antimicrobial stewardship programmes. The emergence and spread of antimicrobial resistance worldwide and the decline in development and licensing of new antimicrobials over the last 30 years has threatened the future successful treatment of bacterial infections.

Antimicrobial drugs Pharmacological characteristics and antimicrobial spectrum—antibacterial drugs can be divided according to their mode of action into those that (1) inhibit cell wall synthesis (e.g. β -lactams such as penicillins, cephalosporins, carbapenems, and monobactams); (2) interfere with protein synthesis (e.g. tetracyclines, aminoglycosides); (3) inhibit bacterial nucleic acid synthesis (e.g. fluoroquinolones); and (4) act on metabolic pathways (e.g. sulphonamides and trimethoprim). The antimicrobial spectrum of a drug is determined by the mode of action and ability to reach the relevant bacterial target site. Antibiotics active against a few particular bacteria species are considered narrow spectrum (e.g. benzylpenicillin), while others are active against many species and are labelled broad spectrum (e.g. meropenem). Some antimicrobials are only active against anaerobically dividing bacteria (e.g. metronidazole). Clinical effectiveness—to be effective clinically, sufficient drug must reach the infection site and show antibacterial activity. The pharmacokinetic characteristics of absorption, distribution, metabolism, and excretion are critical to defining dose, efficacy and, often, safety. Poorly absorbed agents are often administered parenterally, some topically. Hydrophobicity and hydrophilicity are important in defining tissue and extracellular fluid concentrations, as are factors such as molecular size and pH. Highly protein-bound drugs such as flucloxacillin achieve lower tissue concentrations in selected body sites. The pharmacodynamic properties with drug pharmacokinetics determine microbiological efficacy. Pharmacodynamics describes the antibacterial effect of a drug at various concentrations and is assessed by measurement such as minimum inhibitory concentration, persistent antibiotic effects, whether a drug kills or inhibits bacteria, as well as the risk of emergence of resistance. Excretion, metabolism, and drug monitoring—many drugs are metabolically degraded in the liver and/or excreted by the kidney via glomerular filtration or tubular secretion. It should therefore be anticipated that dose modification might be necessary to avoid adverse events and preserve microbiological efficacy in patients with compromised hepatic or renal function. Therapeutic drug monitoring is important in ensuring therapeutic and nontoxic concentrations of some drugs (e.g. aminoglycosides and glycopeptides) but is not restricted to these drugs or patients with poor excretory organ function. Antiviral, antifungal, and antiparasitic drugs—the availability of drugs to treat herpesvirus infections (herpes simplex, varicella-zoster and cytomegalovirus), and the development of new drugs active against influenza, hepatitis viruses, influenza viruses, and HIV have revolutionized the management of viral infections. Advances in the

8.2.5 Antimicrobial chemotherapy 685 management of invasive fungal disease have seen the reliance on polyenes (e.g. amphotericin), eclipsed with the availability of several azoles and triazoles and echinocandins. In the case of many parasitic diseases, advances have been extremely slow, but the importance of malaria has led to new compounds being developed (e.g. the artemisinin derivatives), also new ways of using established drugs in combination. Resistance to antimicrobial drugs Resistance mechanisms—loss of efficacy through acquisition of resistance mechanisms is unique to antimicrobial drugs. There are four main types: (1) drug inactivation or

destruction, (2) target site alteration, (3) reduced cell wall permeability (porin mutation) or increased removal from the cell (efflux resistance); and (4) inhibition as a result of metabolic bypass. Individual drugs can be subject to one or more mechanisms of resistance, which may vary by infecting microorganism. Spread of resistance—genetic mutations that confer resistance do not just affect the target pathogen in the treated individual. They can disseminate both horizontally and vertically as a result of person-to-person or indirect spread of the pathogen. Spread through genetic mechanisms via plasmids, transposons, integrons, and phages between bacteria of the same and different species are common, as is spread between genera. Likewise, resistance mechanisms can spread to organisms making up the normal flora of the gut and skin. Clinical impact—antibiotic resistance is of considerable medical and public concern, and affects all aspects of medicine. Infections become unresponsive to initial therapy, sometimes with fatal consequences in the seriously ill. In others, reassessment and alternative therapy with agents that are often more toxic and more expensive are required, leading to increased morbidity and increased costs through prolonged hospitalization. The spread of resistant pathogens within hospitals, nursing homes, and the community is a very significant concern. Increasing rates of multidrug-resistant *E. coli* and *Klebsiella* species infections are present in many countries, including those in North America, Europe, and Asia. Public concern has led to major government initiatives in the United Kingdom, European Union, United States of America, and many other countries in efforts to contain resistant pathogens. Prescribing of antimicrobial drugs A set of principles has emerged to support safe and effective prescribing, covering issues of choice of drug, dose and route of administration, duration of therapy, strategies to minimize adverse reactions, and what factors need to be considered should initial treatment fail. The complexity of modern therapeutics has led to the development of formularies and practice guidelines, the latter increasingly being evidence based, with the goals of minimizing the risks of emergence of antibiotic resistance, ensuring effective and safe therapy, and supporting cost-effective treatment. These principles are often supported by active steps in both hospital and the community to manage antibiotic use via routine monitoring, specific audits, clinical feedback, drug restriction, and educational initiatives. These activities make up antibiotic stewardship programmes, which are now increasingly common worldwide.

Introduction The discovery and clinical application of antimicrobial chemotherapeutic agents is one of the major achievements in medicine. Life-threatening infections such as infective endocarditis and typhoid fever are now treatable, whereas before they were generally fatal. Likewise, the morbidity associated with many infectious diseases of a less life-threatening nature, such as urinary tract infections, skin and soft tissue infections, and bone and joint sepsis, has been substantially reduced. Major advances in medicine, such as solid organ and especially bone marrow transplantation, as well as the use of cancer chemotherapy, have become safer because of the availability of effective antimicrobial agents. In the field of surgery, perioperative prophylactic use of antibiotics has reduced the risk of infections complicating procedures such as large bowel and gall bladder surgery, vaginal hysterectomy, caesarean section, and implant surgery such as the insertion of prosthetic heart valves, joints, and neurosurgical shunting devices. Antimicrobial chemotherapy is the use of antibiotics and chemotherapeutic substances to control infectious disease. The term 'antibiotic' was coined by Waksman to describe a substance derived from naturally occurring microorganisms and possessing antimicrobial activity in high dilution. The latter characteristic is essential in defining its selective toxicity to other microorganisms. True antibiotics include penicillin, derived from the mould *Penicillium notatum*, streptomycin from *Streptomyces griseus*, and the cephalosporins from *Cephalosporium* spp. Many chemotherapeutic substances with antimicrobial activity have been artificially synthesized, such as the

sulphonamides, quinolones, oxazolidinones, and isoniazid. However, the term 'antibiotic' is loosely applied to both the true antibiotics and other antimicrobial agents. Anti-infectives are among the most widely prescribed drugs, accounting for a projected international expenditure of \$190 billion by 2025. In the United Kingdom, around 80% of all prescribing is in the community where the emphasis is largely on oral agents; the remainder are used in hospitals where there is a greater emphasis on injectable drugs. More than 125 different antibiotics are available, but a relatively small number are necessary to deal with most prescribing needs. It is important that clinicians who prescribe these drugs are familiar with the principles of antimicrobial chemotherapy and that they adopt a continuous learning approach throughout their professional lives to ensure safe and effective prescribing. Table 8.2.5.1 summarizes the agents available for the treatment of bacterial, mycobacterial, fungal, viral, protozoal, and helminthic infections. More agents have been developed for the treatment of viral infections, but globally viral, fungal, and parasitic infections predominate. In recent years, there have been major advances in the availability of antiviral drugs, particularly for the treatment of the influenza, herpes viruses, and HIV. Likewise, safe and effective systemic antifungal agents have resulted from the discovery of azoles, triazoles, and echinocandins. The very success of antimicrobial chemotherapy has led to widespread and often excessive use, particularly in community practice where prescribing is largely empirical and clinical distinction between viral and bacterial infections is difficult. Antibiotics are used extensively in animal husbandry both for the treatment and prevention of infectious disease. This has raised concerns about the

686 SECTION 8 Infectious diseases emergence and spread of antibiotic resistance, which affects many classes of antibiotic, may be intrinsic to a particular pathogen, or may result from genetic mutation. Resistance can be caused by enzymatic inactivation (β -lactamase), failure of drug penetration into the bacterial cell (porin mutation), alteration of the target binding site (e.g. penicillin-binding protein alteration in penicillin-resistant *Streptococcus pneumoniae*), or from efflux resistance whereby the drug is extruded from the bacterial cell (e.g. chloroquine-resistant *Plasmodium falciparum*). Organisms can also develop alternative metabolic pathways which bypass drug inactivation. Resistance may be transferable between the same species or genera but may also spread between genera. Coding for multiple antibiotic resistance has been increasingly observed and results from several mechanisms, in particular plasmid transfer. Despite the advances in antimicrobial chemotherapy, fresh challenges remain. These include the treatment of viral causes of enteric infection, hepatitis A and E, and viral meningitis, all of which are still without effective chemotherapy. Tuberculosis and malaria are among the world's major infectious disease killers and here problems of antibiotic resistance have escalated. In the case of tuberculosis, the continuing reliance on lengthy and complex regimens continue to frustrate disease management as a result of cost, toxicity, and patient compliance with these regimens. Recent advances include the development and licensing of new agents with novel mechanisms of action: for tuberculosis, bedaquiline, which blocks adenosine S-triphosphate synthesis; and delamanid, which blocks manufacture of mycolic acids and destabilize the bacterial cell wall. Among the more worrying trends in antibiotic resistance is the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, and multidrug-resistant Gram-negative species such as extended-spectrum β -lactamases or Delhi metallo- β -lactamase (NDM)-producing *E. coli*, KPC-producing *Klebsiella* sp., and IMP- or VIM-producing *P. aeruginosa*. *Streptococcus pneumoniae* is another community pathogen which has rapidly become less sensitive to penicillins, macrolides, and fluoroquinolones causing clinical failures when causing meningitis or otitis media.

Internationally, multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, and multidrug-resistant salmonellae, including *Salmonella typhi*, are also of major concern. Resistance is not confined to bacteria. Fungal resistance is increasing (e.g. *Candida albicans* and *C. krusei* to fluconazole). Resistance of the HIV to the nucleoside, nonnucleoside, and protease inhibitors is rapidly emerging with many treatment-naïve patients acquiring virus resistance to one or more agents. Antiviral resistance resulting in virological treatment failure is now a major factor responsible for progression of HIV disease.

Table 8.2.5.1 Antimicrobial agents available by class or indication effective against bacterial, fungal, viral, protozoal, and helminthic infection (indicative number of agents available)

Class	Number of agents
Antibacterial	78
Antifungal	10
Antiviral	52
Antiprotozoal	
Anthelmintics	15
Penicillins	
Polyenes	
Hepatitis B & C agents	
Antimalarials	
Anticutaneous larva migrans	
Cephalosporins	
Triazoles	
Herpes virus agents	
Amoebicides	
Antihydatid agents	
Carbapenems	
Echinocandins	
HIV nucleoside analogues	
Trichomonacides	
Antistrongyloidiasis	
Monobactams	
Tetracyclines	
Triazoles	
HIV nonnucleoside agents	
Antigiardiasis	
Antithreadworm/hookworm	
Aminoglycosides	
Flucytosine	
HIV protease inhibitors	
Leishmaniacides	
Ascaricides	
Macrolides	
HIV fusion entry inhibitor	
Trypanocides	
Filaricides	
Ketolides	
HIV integrase inhibitors	
Lincosamides	
Triazoles	
Ribavirin	
Antipneumocystis agents	
Schistosomicides	
Chloramphenicol	
Terbinafine	
Amantadine/rimantadine	
Taeniocides	
Sodium fusidate	
Foscarnet	
Glycopeptides	
cidofovir	
Daptomycin	
Linezolid	
Neuraminidase inhibitors	
Quinupristin/dalfopristin	
Colistin	
Sulphonamides	
Trimethoprim	
Antituberculous	
Antileprotic	
Nitroimidazoles	
Quinolones	
Urinary antiseptics	

a Based on agents listed in the British National Formulary (<https://www.bnf.org>).

8.2.5 Antimicrobial chemotherapy 687 Pharmacology Mode of action Knowledge of the pharmacological mode of action of an antimicrobial agent permits an understanding of the diverse mechanisms of microbial inhibition and the opportunities for drug resistance. This is best established for antibacterial and antiviral agents. In the case of antifungal and, especially, antiparasitic agents the modes of action are less well defined. This reflects the process of drug discovery whereby an understanding of the biochemical and molecular action of agents derived from natural or chemical sources has not always been a priority in establishing efficacy and safety, especially with regard to older agents.

Antibacterial drugs Antibacterial agents may affect cell wall or protein synthesis, nucleic acid formation, or may act on critical metabolic pathways (Table 8.2.5.2). The β -lactams (penicillins, cephalosporins, carbapenems, and monobactams) and the glycopeptides (vancomycin, teicoplanin, telavancin, oritavancin, dalbavancin), inhibit cell wall synthesis. The β -lactams, which share the common β -lactam ring, act on cell wall transpeptidases to inhibit cross-linking of peptidoglycan. The glycopeptide antibiotics act at an earlier stage of cell wall synthesis by binding to acyl-d-alanyl-d-alanine. Despite both being cell wall active, the glycopeptides, such as vancomycin, are less bactericidal agents than the β -lactams, such as flucloxacillin, against *Staphylococcus aureus*.

Inhibitors of protein synthesis Antibacterial agents that inhibit protein synthesis act on the 30S ribosomal subunit responsible for binding mRNA, or the 50S subunit which binds aminoacyl tRNA. The aminoglycosides, tetracyclines, and macrolide antibiotics are the most widely used inhibitors of protein synthesis. Chloramphenicol, clindamycin, and the recently introduced oxazolidinones (linezolid, tedizolid) also act at this site.

Inhibitors of nucleic acid synthesis Nucleic acid synthesis is targeted by quinolones, metronidazole, and rifampicin. The bacterial DNA gyrase is essential for the supercoiling of bacterial DNA. This, together with the enzyme topoisomerase IV, are the major targets for the quinolones. These enzymes are absent in humans, explaining the selective activity of these drugs. Rifampicin and other rifamycins interfere with DNA-dependent RNA polymerase, preventing chain initiation.

Table 8.2.5.2 Microbial site

of action and targets for selected antibacterial drugs

Site of action	Drugs	Target
Cell wall	peptidoglycan	Penicillins
	Transpeptidase	Cephalosporins
	Transpeptidase	Vancomycin
	Acyl-d-alanyl-d-alanine	Teicoplanin
	Acyl-d-alanyl-d-alanine	Telavancin
Binds late stage peptidoglycan precursors and disrupts bacterial membrane	Oritavancin	Inhibits transglycosylation and transpeptidation and disrupts bacterial membranes
	Dalbavancin	D-alanyl-D-alanine
	Fosfomycin	UDP-N-acetylglucosamine 3 enolpyruvyl transferase
	Daptomycin	Binds to bacterial membranes
	Colistin	Binds to bacterial membranes
	Ribosome	Chloramphenicol
	Peptidyl transferase of 50S subunit	Pleuromutilins
	Peptidyl transferase of 50S subunit	Clindamycin
	50S ribosomal subunit	transpeptidation
	Linezolid	Blocks initiation phase
	Tedizolid	Blocks initiation phase
	Macrolides	50S ribosomal subunit
	Tetracyclines	Ribosomal A site
	Aminoglycosides	Initiation complex and translation
	Mupirocin	Isoleucyl-transfer RNA synthetase
	Fusidic acid	Elongation factor G
	Nucleic acid	Fluoroquinolones
	DNA gyrase	Metronidazole
	DNA strands	Rifampicin
	RNA polymerase	Folic acid synthesis
	Sulphonamides	Pteronic acid synthetase
	Trimethoprim	Dihydrofolate reductase

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Metabolic inhibitors

The best known metabolic inhibitors are the sulphonamides and tri- methoprim which interfere with folic acid synthesis by sequentially inhibiting the enzymes dihydropteroic acid synthetase (EC 2.5.1.15) and dihydrofolate reductase (EC 1.5.1.3). The two drugs act sequen- tially on the metabolic pathway, resulting in a combined antibiotic effect. The selective activity of these compounds is dependent on the fact that humans are unable to synthesize folic acid and require pre- formed folic acid in their diet.

Antiviral agents

Viruses live and replicate within the host cell. Antiviral chemo- therapy therefore presents a particular challenge if it is to be selectively toxic. The cycle of viral replication provides several op- portunities for therapeutic intervention. Most available antiviral agents are nucleoside analogues, largely used in the treatment of HIV or herpesvirus infections (Table 8.2.5.3). The growth in num- bers of antiviral agents has greatly benefited from HIV-related re- search through the identification of new drug targets (Fig. 8.2.5.1).

Table 8.2.5.3 Mode of action of selected antiviral drugs

Drug	Target virus	Antiviral activity
Aciclovir	HSV, VZV	Nucleoside analogue
Cidofovir	HSV and CMV	Nucleoside analogue
Famciclovir	VZV	Nucleoside analogue
Foscarnet	CMV	Inhibits DNA polymerase
Ganciclovir	CMV	Nucleoside analogue
Valaciclovir	HSV, VZV	Valyl ester of aciclovir
Valganciclovir	CMV	Valyl ester of ganciclovir
Interferon	HBV, HCV	Induce interferon stimulated genes and block viral protein synthesis
Adefovir	HBV	Nucleotide reverse transcriptase inhibitor
Entecavir	HBV	Nucleoside analogue
Telbivudine	HBV	Nucleoside analogue
Ribavirin	HCV, RSV	Inhibits replication of DNA and RNA viruses, inhibits initiation and elongation of RNA fragments
Boceprevir	HCV	Binds to NS3 serine protease of HCV
Telaprevir	HCV	Binds to NS3 serine protease of HCV
Oseltamivir	Influenza A and B	Inhibits viral neuraminidase
Zanamivir	Influenza A and B	Inhibits viral neuraminidase
Amantadine	Influenza A	Uncoating and assembly
Rimantadine	Influenza A	Uncoating and assembly
Abacavir	HIV	Nucleoside reverse transcriptase inhibitor
Didanosine	HIV	Nucleoside reverse transcriptase inhibitor
Emtricitabine	HIV	Nucleoside reverse transcriptase inhibitor
Lamivudine	HIV, HBV	Nucleoside reverse transcriptase inhibitor
Stavudine	HIV	Nucleoside reverse transcriptase inhibitor
Tenofovir	HIV	Nucleoside reverse transcriptase inhibitor
Zalcitabine	HIV	Nucleoside reverse transcriptase inhibitor
Zidovudine	HIV	Nucleoside reverse transcriptase inhibitor
Delavirdine	HIV	Nonnucleoside reverse transcriptase inhibitor
Efavirenz	HIV	Nonnucleoside reverse transcriptase inhibitor
Etravirine	HIV	Nonnucleoside reverse transcriptase inhibitor
Nevirapine	HIV	Nonnucleoside reverse transcriptase inhibitor
Rilpivirine	HIV	Nonnucleoside reverse transcriptase inhibitor
Amprenavir	HIV	Protease inhibitor
Atazanavir	HIV	Protease inhibitor
Darunavir	HIV	Protease inhibitor
Fosamprenavir	HIV	Protease inhibitor
Indinavir	HIV	Protease inhibitor

8.2.5 Antimicrobial chemotherapy 689 Interference with cell surface attachment through ligand blockade of surface receptors provides a theoretical, but so far unfulfilled, target. Penetration into the host cell may be through a process of trans- location or direct fusion between the outer lipid membrane of the virus and the cell membrane, before uncoating and release of viral nucleic acid. Replication differs among viruses, thereby providing several therapeutic options. Viral mRNA becomes translated into multiple copies of viral proteins encoded by the viral genome either as a result of virus-specific enzymes or by co-opting host-derived protein. For example, HIV employs its own reverse transcriptase to convert RNA to DNA before integration into the host cell chromo- some. Transcription and translation follow. Before the virus can be released, new viral particles must be assembled for which host cell proteins and mechanisms of phosphorylation and glycosylation may be recruited. The protease inhibitors act at this stage and have been particularly successful. Virus release is the result of either transpor- tation and budding or host cell lysis.

Antifungal agents The polyene antifungals (amphotericin B and nystatin) act on er- gosterol within the fungal cell membrane. Ergosterol is largely absent from bacteria and humans, explaining the selective tox- icity of these agents. The azole antifungals include the imidazoles (e.g. clotrimazole, miconazole, and ketoconazole) and the tri- azoles (fluconazole, itraconazole, voriconazole and posaconazole) which bind preferentially to fungal cytochrome P450 to inhibit Drug Target virus

Antiviral activity Lopinavir HIV Protease inhibitor Fosamprenavir HIV Protease inhibitor Nelfinavir HIV Protease inhibitor Ritonavir HIV Protease inhibitor Saquinavir HIV Protease inhibitor Tipranavir HIV Protease inhibitor Enfuvirtide HIV Fusion entry inhibitor Raltegravir HIV Integrase inhibitor Dolutegravir HIV Integrase inhibitor Elvitegravir HIV Integrase inhibitor Maraviroc HIV CCR5 antagonist CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus Table 8.2.5.3 Continued Fusion inhibitor: enfuvirtide Penetration Uncoating Reverse transcription Integration Transcription Translation Assembly and release Complete HIV peptide Glycoprotein Glycosylation and cleavage Host chromosome Proviral DNA Viral mRNA Unintegrated dsDNA Genomic RNA cDNA HIV virion Receptor/ Coreceptor Building particle Nucleosides: abacavir, didanosine, emtricitabine lamivudine, stavudine, tenofovir, zalcitabine, zidovudine Nonnucleosides: efavirenz, nevirapine Protease inhibitors: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir Fig. 8.2.5.1 Sites of inhibition of HIV replication by current antiretroviral drugs.

690 SECTION 8 Infectious diseases 14- α -methylsterol demethylation to ergosterol. The echinocandins (e.g. caspofungin, micafungin, and anidulafungin) act on fungal cell wall β (1-3) d- glycan to inhibit growth. Antiparasitic agents The mechanism of action of many antiparasitic drugs is only par- tially known. Among the antimalarials, chloroquine interferes with the metabolism and utilization of haemoglobin by malaria parasites. It also concentrates within parasite acid vesicles and raises internal pH, inhibiting parasite growth. Amodiaquine is similar in structure to chloroquine and there is cross-resistance between the two drugs. Quinine acts by depressing oxygen uptake and carbohydrate metabolism and by intercalating into DNA, disrupting para- site replication and transcription. Mefloquine is a quinolone methanol compound structurally similar to quinine. Primaquine disrupts mitochondria, disrupts DNA, and eliminates the tissue exoerythrocytic forms of *Plasmodium falciparum*. The exact mech- anism of action of lumefantrine is unknown but it may inhibit the formation of β -haematin by complexing with haemin. Sulfadoxine-pyrimethamine

inhibits tetrahydrofolate synthesis. Atovaquone inhibits parasite electron transport in mitochondria, resulting in inhibition of adenosine triphosphate (ATP) and nucleic acid synthesis. Proguanil inhibits dihydrofolate reductase. Together, atovaquone and proguanil affect the erythrocytic and exoerythrocytic stages of parasite development. Artemisinin derivatives include artemether, arteether, dihydroartemisinin, and artesunate. They appear to act by binding iron, breaking down peroxide bridges leading to the generation of free radicals that damage parasite proteins. They kill all blood stages of *Plasmodium* spp. and have the fastest parasite clearance times of any antimalarial. Metronidazole is active against several protozoa such as *Entamoeba histolytica* and *Giardia lamblia* as well as anaerobic bacteria. It acts as an electron sink, by reduction of its 5-nitro group activated by nitroreductase within the target pathogen, thus interrupting DNA synthesis. Among the anthelmintic drugs, piperazine and praziquantel act by selectively inducing muscle paralysis in the target helminth. Others, such as thiabendazole, inhibit parasitic ATP synthesis and energy production.

Antimicrobial spectrum of activity The antimicrobial spectrum of an agent is dependent on target site susceptibility among pathogenic organisms at clinically achievable drug concentrations. Some microorganisms are intrinsically resistant to certain antibiotics. For example, the aminoglycosides are inactive against anaerobic bacteria because cell entry is an energy-dependent process relying on respiratory quinones, which are absent in anaerobic bacteria. The antimicrobial spectrum of a drug in part dictates its clinical indications. While information on this spectrum is more easily determined in vitro, in vivo efficacy can only be confirmed through clinical use, which can be supported by preclinical model data during drug development. For example, in vitro, *Salmonella typhi* is susceptible to gentamicin, but the drug is not effective clinically.

Narrow-spectrum and broad-spectrum agents There are few truly narrow-spectrum agents. Fusidic acid, the glycopeptides (vancomycin and teicoplanin), daptomycin, and linezolid target specific Gram-positive pathogens and are mainly used to treat microbiologically confirmed infections. Broad-spectrum agents, such as the fluoroquinolone antibiotics and the parenteral cephalosporins such as cefotaxime or ceftriaxone, are active against many Gram-positive and Gram-negative species of pathogens. Metronidazole has activity against many anaerobic bacteria and, because of this restricted activity, is considered to have a narrow spectrum. The aminoglycosides, although active against staphylococci and aerobic Gram-negative bacilli, are inactive against streptococci and anaerobes and are, therefore, frequently prescribed in combination. The carbapenems (imipenem, meropenem, doripenem, and ertapenem) possess the broadest spectrum of activity which includes most aerobic and anaerobic bacterial pathogens. Ertapenem differs from the other carbapenems in its lack of activity against *Pseudomonas aeruginosa*. Broad-spectrum agents are often used empirically in the initial management of severe infection. However, they frequently affect the normal flora so that superinfection with *Clostridium difficile* and yeasts are more likely to arise. Narrow-spectrum drugs are used as definitive therapy, that is, after a microbiological diagnosis is reached but are also used in combination as empiric therapy.

Susceptibility testing Antibiotic susceptibility testing of clinical isolates is important for appropriate prescribing and for gathering epidemiological data on the burden of antimicrobial resistance. It is determined in vitro by using either broth-based or agar-based methods. Pathogens are exposed to known concentrations of an antibiotic and their degree of inhibition compared to a standard control. Disc susceptibility testing is a widely used method. Zones of inhibition around the antibiotic-containing disc are measured, compared to a standard, and the pathogen designated sensitive, resistant, or of intermediate susceptibility to the drug. Currently, such methods require the isolate to be tested in pure culture. It is, therefore, difficult to obtain information on the susceptibility of a pathogen in less than 36–48 h from sample collection. The minimum inhibitory

concentration (MIC) in milligrams per litre (L) provides more precise in vitro information on the activity of a drug against a bacterial pathogen. It is more time consuming and costly to determine, although automated systems and commercial strip tests are available (Fig. 8.2.5.2). Defining susceptibility by MIC determination permits greater predictive benefit in the treatment of certain infections such as gonorrhoea, bacterial endocarditis, and pneumococcal meningitis. Knowledge of the in vitro susceptibility of common pathogens to antimicrobial agents (Fig. 8.2.5.3) is helpful in selecting drug therapy but is only relevant to the achievable drug concentrations, which is important in predicting performance as discussed next. Combined drug therapy In hospital practice, it is common to combine agents when dealing with mixed infections or where initial broad-spectrum empirical therapy is required. Another important reason for combining

8.2.5 Antimicrobial chemotherapy 691 drugs is to prevent the emergence of antibiotic resistance, such as in the treatment of tuberculosis, HIV, and malaria. Antituberculosis regimens have been developed to ensure that naturally occurring minority populations of *Mycobacterium tuberculosis* resistant to isoniazid or rifampicin do not emerge during therapy. By combining isoniazid and rifampicin with pyrazinamide and ethambutol for the initial phase of therapy (2 months), resistance is usually avoided. Therapy can be restricted to isoniazid and rifampicin for the continuation phase (4 months). The regimen is extended in those patients unable to tolerate pyrazinamide and in the treatment of tuberculous meningitis (Box 8.2.5.1). HIV infection is treated with multidrug regimens. The success of highly active antiretroviral therapy, in which nucleoside analogues and protease inhibitors are combined in a three-drug regimen, is not only based on greater efficacy of the combined regimen but also on its ability to slow the emergence of drug-resistant mutants. The nonnucleoside reverse transcriptase inhibitors, such as efavirenz, appear to be equally effective in combination with nucleoside Fig. 8.2.5.2 *Staph. aureus* resistant to penicillin (MIC 8 mg/litre) on the left and sensitive to vancomycin (MIC 1.0 mg/litre) on the right, as demonstrated by a commercial antibiotic gradient strip test. Penicillin Ampicillin/amoxicillin Amoxicillin/clavulanate Flucloxacillin Cefuroxime Cefotaxime Ceftazidime Erythromycin Clindamycin Tetracyclines Vancomycin/teicoplanin Linezolid Gentamicin/tobramycin/ netilmicin/amikacin Co-trimoxazole Trimethoprim Ciprofloxacin *Staph. aureus* (penicillin-resistant) *Staph. aureus* (meticillin-resistant) *Strep. pneumoniae* *Strep. pyogenes* *Enterococcus faecalis* *Neisseria gonorrhoeae* *N. meningitidis* *Haemophilus influenzae* *E. coli* *Klebsiella* spp. *Proteus mirabilis* *Serratia* spp. *P. aeruginosa* *Bacteroides fragilis* Sensitive Resistant Sensitive but not appropriate therapy Some strains resistant Fig. 8.2.5.3 Sensitivity of selected pathogenic bacteria to some common antibacterial agents.

692 SECTION 8 Infectious diseases analogues but have a lower barrier to resistance. The options for treating HIV infection are summarized in Box 8.2.5.2 (see also Chapter 8.5.23). Occasionally, drugs are combined for the purpose of achieving a synergistic effect based on evidence that the in vitro activity of the combination is shown to be greater than the sum of the activity of the individual agents. Most drugs in combination will simply be additive in effect. One of the more frequently prescribed synergistic combinations is that of penicillin (or ampicillin) and streptomycin (or gentamicin) in the treatment of endocarditis caused by *Enterococcus* spp. The aminoglycoside alone is generally inactive against enterococci but in combination with ampicillin achieves synergistic killing (Fig. 8.2.5.4). A similar effect is employed in the treatment of viridans streptococcal endocarditis with this combination. Another widely used example of synergistic inhibition is the combined effects of an antipseudomonal β -lactam, such as ceftazidime or piperacillin, and an aminoglycoside, such as gentamicin, tobramycin, or amikacin. This

combination can be used to treat documented or suspected *P. aeruginosa* infections occurring in neutropenic states complicating bone marrow transplantation, cytotoxic chemotherapy, and burn wound infections. Antibiotic resistance General considerations Antibiotic resistance has been recognized since the introduction of effective antibiotics. For example, penicillin-resistant strains of *S. aureus* became widespread shortly after the introduction of this agent; penicillin-sensitive strains are now uncommon. Resistant strains of Gram-negative bacteria, such as *E. coli*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, and *Pseudomonas aeruginosa* are commonly found in high-dependency and other hospital units where they may cause outbreaks. Conventional approaches to controlling these infections may be unsuccessful, leading to contagion through out the healthcare system. The emergence of extended-spectrum β -lactamase-producing *E. coli* and *Klebsiella* in the last 15 years in hospital and community practice has led to an increase in the use of carbapenem antibiotics which may, in turn, be a driver for the emergence and spread of carbapenemase (NDM, KPC, and OXA-48) producing *Klebsiella* and *E. coli*. Other problems include the emergence of penicillin-resistant pneumococci, β -lactamase-producing *Haemophilus influenza*, and multidrug-resistant gonococci. At present, there is great international concern among professionals, politicians and, increasingly, the public about antibiotic resistance. In the United Kingdom there is a 5-year strategy to address antimicrobial resistance. This led to several initiatives including: (1) reducing the use of antibiotics, particularly in the treatment of minor upper respiratory tract infections in the community; Box 8.2.5.1 Tuberculosis treatment regimens for pulmonary and extrapulmonary tuberculosis infection caused by *Mycobacterium tuberculosis* Initial phase (2 months) • Isoniazid (with pyridoxine) • Rifampicin • Pyrazinamide • Ethambutol Continuation phase (4 months) • Isoniazid • Rifampicin a Central nervous system infection should be treated with isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for 2 months then isoniazid and rifampicin for 10 months. Tuberculosis, NICE Guideline—13 Jan 2016 (nice.org.UK/guidance/fig33). Box 8.2.5.2 HIV infection: Initial treatment regimens for antiretroviral-naïve patients a Two nucleoside reverse transcriptase inhibitors b Plus Boosted protease inhibitor c Or Nonnucleoside reverse transcriptase inhibitor d Or Integrase inhibitor e a See Table 8.2.5.3 for agents available. b The recommended NRTI backbone is tenofovir + emtricitabine. Alternative NRTI backbone is abacavir + lamivudine. c The recommended boosted PI combinations are atazanavir + ritonavir or darunavir + ritonavir. d The recommended NNRTI is rilpivirine (provided the viral load <100 000). Alternative agent is efavirenz. e Any one of the licensed integrase inhibitor (dolutegravir, elvitegravir, or raltegravir). 0 0 Log₁₀ number colony-forming units/ml 10¹⁰ 10⁸ 10⁶ 10⁴ 10² 4 8 Gentamicin 2 mg/litre Control Ampicillin 0.5 mg/litre Ampicillin 0.5 mg/litre + gentamicin 2 mg/litre 12 Time (h) 16 20 24 Fig. 8.2.5.4 Effects of ampicillin (0.5 mg/litre) and gentamicin (2 mg/litre) alone and in combination on a strain of *Enterococcus faecalis* from a patient with infective endocarditis. A synergistic effect is observed with the combined agents.

8.2.5 Antimicrobial chemotherapy 693 (2) education strategies for prescribers and the public; (3) better enforcement of infection control policies; (4) improved antibiotic stewardship for hospitals; (5) monitoring and feedback of drug use in community practice; (6) introduction of infection control and antibiotic stewardship targets for state funded healthcare providers with linked financial incentives or penalties. Within the European Union, similar measures have been proposed. However, antibiotic resistance is a global problem. An increasing number of multidrug-resistant infections caused by *Salmonella* and *Mycobacterium tuberculosis* are being imported from developing countries where the availability and prescribing of antibiotics is less controlled.

The recent emergence of extensively drug-resistant tuberculosis (XDR- TB) and multidrug-resistant gonococci is a major cause for concern. Antibiotic resistance drives changes in patterns of prescribing and is a major impetus to the pharmaceutical industry in its search for new therapies. Microorganisms differ in their ability to develop resistance, which may affect a particular drug, a class, or multiple classes of antibiotics. Genetic mutations select for antibiotic resistance, which frequently occurs under the influence of antibiotic pressure. The major mechanisms of resistance are summarized in Table 8.2.5.4. Resistance to single or multiple antibiotics can be either chromosomally or plasmid mediated, or both. In turn, genes might code for resistance to a single or to multiple antibiotics. In addition to plasmid-mediated resistance, other transposable genetic elements (transposons) and insertion sequences (integrons) incapable of self-replication might exist within a chromosome, plasmid, or rarely bacteriophage. Resistance genes are most frequently transferred between organisms by conjugation. This occurs between the same or different species of bacteria and also between different genera. Other mechanisms of transferring resistance are transformation in which naked DNA released during cell lysis is taken up by other bacteria or very rarely transduction via a bacteriophage. Transposon-mediated resistance reflects transfer of discrete sequences of DNA between chromosomes or plasmids whereby individual or groups of genes can be inserted into the host bacterial cell. Integrons may contain one or more gene cassettes which carry determinants of combinations of resistance genes within the bacterial chromosome, plasmid, or transposons. The antibiotic resistance genes are bound on each side by conserved segments of DNA. These individual resistance genes can be inserted or removed between the conserved structures and act as expression vectors for antibiotic resistance genes. The molecular mechanisms of antibiotic resistance are legion and the ability of drug-resistant microorganisms to survive, disseminate, and cause disease varies widely. In many instances, antibiotic resistance might give a survival advantage only in the presence of continued antibiotic exposure to such agents. This is reflected in the occurrence of epidemic infections in high-dependency units such as intensive care facilities where antibiotic usage is often high. However, it is also clear that once the genetic mechanism for evading antimicrobial activity has been acquired, it is rarely lost and adds to the continuously expanding genetic memory that has steadily eroded the efficacy of many antimicrobial drugs. Enzymatic inactivation

Aminoglycoside-modifying enzymes include adenylating, acetylating, and phosphorylating enzymes. Gentamicin is the most susceptible and amikacin the least susceptible to such inactivation. However, the largest group of inactivating enzymes are the β -lactamases (EC 3.5.2.6) which hydrolyse the β -lactam ring common to all penicillins, cephalosporins, carbapenems, and monobactams. Penicillinase was the first β -lactamase to be identified and is the reason why most strains of *S. aureus* are resistant to this drug. Another important β -lactamase is TEM-1, which is responsible for resistance to ampicillin by *Haemophilus influenzae* or *E. coli*. The major impetus to the development of the broad-spectrum penicillins and cephalosporins was to extend their activity by resisting inactivation by β -lactamases present in many aerobic Gram-negative bacilli. However, new inactivating enzymes continue to emerge, including the extended-spectrum β -lactamases, which are now limiting the clinical utility of third-generation cephalosporins. A further example is the carbapenemase group of β -lactamases which hydrolyse imipenem, meropenem, doripenem, and ertapenem, as well as other β -lactams.

Impermeability resistance Drug uptake of antibiotics such as the β -lactams, tetracyclines, and fluoroquinolone antibiotics by bacteria is through protein channels (porins) which cross the outer membrane. Alterations in the permeability of the outer membrane of Gram-negative bacteria is an increasingly important mechanism of drug resistance. Mutations in porin structure are responsible for resistance among pathogens such as *P. aeruginosa* and Enterobacteriaceae.

Alterations in target site Another important mechanism of resistance is mutational modification of drug binding sites. This affects susceptibility to β -lactams, erythromycin, chloramphenicol, fluoroquinolones, and rifampicin. Erythromycin and chloramphenicol bind to the bacterial 50S ribosomal subunit which is subject to genetic mutation. In contrast, the quinolones target DNA gyrase which is subject to subunit structure alteration resulting in one variety of resistance to drugs such as ciprofloxacin. The increasing resistance to penicillin among *Strep. pneumoniae* is the result of reduced binding of penicillin to several binding proteins (PBP2a and PBP2x). *Staph. aureus* resistance

Table 8.2.5.4 Examples of resistance mechanisms for selected antibiotics

Enzymatic/inactivation	Altered target site	Altered permeability	Efflux	Metabolic bypass
Aminoglycosides	Erythromycin	β -Lactams	Tetracycline	Sulphonamides
β -Lactams	Chloramphenicol	Quinolones	Quinolones	Trimethoprim
Chloramphenicol	Fusidic acid	β -Lactams	Colistin	β -lactams

694 SECTION 8 Infectious diseases to methicillin is due to the presence of penicillin-binding protein (PBP2a) which has reduced affinity for methicillin and other β -lactams and is encoded by the *mecA* gene. The problem of vancomycin-resistant enterococci, which largely affects *Enterococcus faecium*, is the result of the production of enzymes (ligases) which permit continued cell wall synthesis despite the presence of vancomycin. To date, five different genes have been found responsible for this phenomenon (*vanA* to *vanE*) which result in different phenotypic patterns of resistance to the glycopeptides vancomycin and teicoplanin. The transfer of the *vanA* gene from *E. faecium* to *S. aureus* has resulted in the emergence of vancomycin-resistant *S. aureus* (VRSA), but very few clinical cases have been reported in the last decade. Metabolic bypass resistance Bacteria must synthesize folic acid from the precursor p-aminobenzoic acid. The sulphonamide antibiotics competitively inhibit the enzyme dihydropteroate synthetase. Trimethoprim acts on the same metabolic pathway by inhibiting dihydrofolate reductase. The sequential inhibitory effects of trimethoprim and sulfamethoxazole (co-trimoxazole) result in synergistic bactericidal activity against many pathogens. Resistant organisms are able to synthesize their own enzymes thereby evading such competitive inhibition. Surveillance of antibiotic resistance Information on the susceptibility of pathogenic microorganisms is important. Such data can provide information on the relative frequency of pathogens and the pattern of susceptibility to prescribed agents. Surveillance, therefore, has a role in guiding prescribing, in developing prescribing policies, and in identifying and monitoring organisms that are subject to infection control measures. On a broader front, surveillance is also of value in alerting industry, public-private partnerships, researchers, and healthcare planners to the need for new drug and vaccine strategies for disease control. To be of maximum benefit, surveillance needs to be linked to a defined geographical base, which might simply reflect the catchment area of specimens submitted to a particular laboratory, providing information on the trends in community and hospital isolates. Within hospitals, more specific information can be provided about susceptibility patterns in high-dependency units, where antibiotic consumption is often greater, and more resistant pathogens such as *Klebsiella*, *Serratia*, *Enterobacter*, and *Acinetobacter* spp. and *P. aeruginosa* are found. Among Gram-positive pathogens, enterococci, and *Staph. aureus* present the main challenges to prescribing and infection control practice. National networks of surveillance often vary in their focus and include data on Gram-negative pathogens such as *Escherichia coli* and *P. aeruginosa*, *Staph. aureus*, penicillin resistance among pneumococci, and, more recently, vancomycin-resistant enterococci. There are important international networks which collect information on such pathogens as *Legionella pneumophila* and *Mycobacterium tuberculosis*. Drug-resistant tuberculosis is increasingly prevalent in the United Kingdom and elsewhere. Antimicrobial surveillance, based on

specimens referred to laboratories for clinical diagnostic purposes, can be limited if, for example, very few specimens are sent (i.e. otitis media), laboratory networks are poorly developed (i.e. in some middle-income countries) or data extraction is difficult. In these cases, special arrangements may be necessary to collect isolates and perform testing just for surveillance purposes.

Surveillance of resistance to antiviral agents is largely confined to HIV in a few countries. Patient-specific data are increasingly sought in those with HIV infection to assess drug failure, guide change in management, and direct primary therapy in selected cases of person-to-person and mother-to-infant transmission. Determination of phenotypic resistance is still costly and time consuming, and most data relate to genotypic patterns of resistance to antiretroviral drugs among HIV isolates.

Pharmacokinetics To be effective, antimicrobial agents must achieve therapeutic concentrations at the site of the target infection. This might be localized to a single anatomical site, such as the bladder or the cerebrospinal fluid, or involve major organs, such as the lung. Infections can also be generalized and affect many body sites. Drug selection must also take into consideration the fact that pathogens such as *Mycobacterium tuberculosis*, *Legionella pneumophila*, *Listeria monocytogenes*, and *Salmonella typhi* replicate intracellularly. Antimicrobial drugs can be administered parenterally, orally, or topically to the skin, oral and genital mucosae, external auditory meatus, conjunctiva, and by intraocular or intravesical application. In the case of systemically active agents, the effective drug concentrations are determined by the standard pharmacokinetic parameters of absorption, distribution, metabolism, and elimination. Since selective toxicity is crucial to safe prescribing, the dose regimen for each agent aims to avoid concentrations toxic to the host but inhibitory to the microorganism. This 'therapeutic window' varies by drug.

Bioavailability The rate and degree of absorption from the gastrointestinal tract is not only important for plasma concentrations reflected in the pharmacokinetic parameters of C_{max} and T_{max} of a drug, but also for potential adverse effects on the bowel (Table 8.2.5.5). For example, ampicillin, the first of the aminopenicillins, commonly caused gastrointestinal side effects, most notably diarrhoea. These effects have been reduced by increasing the bioavailability of the active drug through the introduction of hydroxyampicillin (amoxicillin) and various esters and prodrugs of ampicillin. Some agents such as cephalexin, doxycycline, linezolid, and quinolone antibiotics are extremely well absorbed, achieving 80–100% bioavailability. In the case of some quinolones, the excellent bioavailability has raised the possibility of treating with oral antibiotics some severely ill patients who might normally require parenteral therapy. In contrast, drugs which are poorly bioavailable, such as cefixime and cefuroxime axetil, not only have a higher incidence of gastrointestinal side effects, but also are more likely (although not uniquely) to select for *C. difficile*-associated disease.

Distribution Most drugs are distributed in the blood via the plasma before gaining access to the extracellular fluid. Tissue concentrations of a particular agent are affected by pH, drug ionizability, lipid solubility, and the presence of an inflammatory reaction whereby the capillary

8.2.5 Antimicrobial chemotherapy 695 fenestrations are increased in size. In the case of agents administered intravenously by infusion or by bolus injection, the distribution phase is rapid in comparison with orally, rectally, or intramuscularly administered drugs. Drugs which are poorly lipophilic, such as the β -lactams and aminoglycosides, achieve low concentrations in tissues such as the brain. However, the β -lactams achieve therapeutic concentrations in the cerebrospinal fluid as a result of the inflammatory reaction which accompanies meningitis. Drugs can also be taken up intracellularly, as in the case of macrolides and quinolones, resulting in a large volume of distribution compared to drugs confined to the extracellular space, such as the β -lactams and

aminoglycosides. This is important in relation to the treatment of intracellular pathogens such as *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Mycobacterium tuberculosis*, which can only be effectively treated by drugs that are concentrated and remain biologically active within the cell. The plasma half-life ($T_{1/2}$), which is the time required for the concentration of a drug in the plasma to fall by one-half, is affected initially by drug distribution and its rate of elimination as a result of metabolism and excretion. This in turn affects the time taken to reach steady state. In the treatment of life-threatening infections, it is important that steady state kinetics are achieved rapidly and the administration of a loading dose may be required. This applies to the use of agents such as intravenous quinine in the case of life-threatening malaria and colistin for the treatment of serious Gram-negative infections where the pharmacokinetic behaviour can be altered by the severity of the disease in comparison with healthy subjects (Fig. 8.2.5.5). Drugs are commonly distributed in the blood and tissues bound to plasma proteins, mostly albumin, and they vary in their degree of protein binding. With agents such as flucloxacillin and ceftriaxone it exceeds 95%. The importance of protein binding lies in the fact that the active moiety is the unbound drug. Dissociation from the bound to the unbound state is usually rapid, but this equilibrium may affect drug performance at certain sites such as the joints. The relationship between protein binding and drug performance has been emphasized from studies of the pharmacodynamics of drug activity (see next). Metabolism Antibiotics, like other drugs, are degraded at various sites in the body but predominantly within the liver. Degradation involves conjugation, hydrolysis, oxidation, glucuronidation, or dealkylation, according to the particular drug. Members of the hepatic cytochrome P450 group of enzymes play a dominant role in this process. Drug metabolites are usually, but not always, biologically inactive. For example, cefotaxime is degraded to desacetylcefotaxime and clarithromycin to hydroxylclarithromycin, both of which are Table 8.2.5.5 Bioavailability and intestinal elimination of some commonly prescribed antibacterial drugs after oral administration

Drug	Bioavailability (%)	Intestinal elimination
Penicillins		
Amoxicillin	80–90	Concentrated up to 10-fold in bile
Ampicillin	50	Concentrated up to 10-fold in bile
Flucloxacillin	80–90	Negligible
Cephalosporins		
Cefalexin	80–100	Concentrated up to 3-fold in bile
Cefixime	40–50	Concentrated up to 50-fold in bile
Cefuroxime axetil	30–40	Bile concentrations of up to 80% of serum
Quinolones		
Ciprofloxacin	70–85	Concentrated up to 10-fold in bile
Levofloxacin	99–100	<5% dose found in bile
Moxifloxacin	90	60% dose, concentrated 2–6-fold in bile
Nalidixic acid	90–100	Biliary concentrations similar to serum
Other antibacterials		
Linezolid	100	1–5 concentrations in bile
Erythromycin	18–45	Concentrated up to 300-fold in bile
Clarithromycin	50–70	
Metronidazole	80–95	Concentrations in bile similar to serum
Rifampicin	90–100	Concentrated up to 1000-fold in bile
Sulfamethoxazole	70–90	Concentrations in bile 40–70% of serum
Tetracycline	75	Concentrated up to 10–30-fold in bile
Doxycycline	95	Concentration in bile 10–30-fold serum
Trimethoprim	80–90	Concentrated up to 2-fold in bile

Note that drugs which are well absorbed may still achieve high concentrations in the faeces because of secretion into bile or other enteral secretions.

696 SECTION 8 Infectious diseases biologically active and contribute to the overall antibacterial activity of these agents. Excretion Most drugs are excreted in the urine by glomerular filtration, tubular secretion, or a combination of these mechanisms. Thus, high concentrations of drug will often be present in the urine; this has therapeutic importance in the treatment of urinary tract infections. Urinary pH affects the biological activity of many drugs (e.g. the activity of ciprofloxacin is markedly reduced at pH 5.5). Tubular excretion can be blocked by probenecid. This was formerly used to ensure higher plasma concentrations of penicillin and is still recommended in alternative treatment regimens for gonorrhoea when single doses of amoxicillin

are prescribed. It is also important to note that any reduction in glomerular filtration rate will affect not only urinary concentrations of drug but also the plasma half-life and, in turn, serum concentrations of drugs which are primarily excreted by this route. In the case of antibiotics such as the aminoglycosides and vancomycin, the dose must be reduced in renal failure. Biliary excretion is another important route for drug elimination either as the active compound or as a microbiologically active or inactive metabolite. Reabsorption from the gastrointestinal tract can result in enterohepatic recirculation, which in turn may affect plasma half-life. Drugs which achieve high concentrations in the bile are effective in the treatment of infections at this site such as cholecystitis. However, biliary obstruction or hepatic impairment can reduce therapeutic efficacy and require dose reduction to avoid toxic effects. Examples include clindamycin, efavirenz, mefloquine, and tetracyclines. Therapeutic drug monitoring of some antibiotics is essential in order to ensure therapeutic yet nontoxic concentrations. This applies particularly to aminoglycosides which have a relatively narrow therapeutic index. Trough concentrations of gentamicin in excess of 1 mg/litre, indicate reduced rates of renal elimination with the subsequent increased risk of accumulation in kidney and inner ear which are associated with nephrotoxicity and ototoxicity. Vancomycin is also frequently monitored, particularly in patients with impaired renal function. Therapeutic drug monitoring is also increasingly used with other drug classes to optimize efficacy especially as it has been increasingly recognized patients with severe sepsis may well have highly variable pharmacokinetics. Pharmacodynamics Pharmacodynamics describes the effect of changes in drug concentration on antimicrobial effect or toxicological effect. However, the interrelationship between drug, microorganism, and the infected host creates the microbiological outcome dynamic. Antibiotics are unique in therapeutics in that they are targeted at an invading microorganism which may be present at a particular site or be more widely distributed in the body. The host's response to infection might modify the pharmacokinetic handling of a drug. Many antibiotics have a measurable effect on a variety of bacterial and host cell functions, even at subinhibitory concentrations. It is difficult to establish the exact role that these factors play clinically, but they are likely to contribute to the overall effect of an antibiotic. Macrolides, such as erythromycin, illustrate this point since they affect a variety of virulence characteristics (Table 8.2.5.6) as well as affecting the host's response to infection. Exposure of microorganisms to sublethal concentrations of an antibiotic may temporarily inhibit growth which recommences following removal of the drug. The time to recovery is known as the persistent antibiotic effect. This varies with the drug and the microorganism; for example, the quinolones have a longer postantibiotic effect than β -lactams (Table 8.2.5.7). The relevance of this observation to the in vivo situation, where plasma drug concentrations

Concentrations (mg/litre)	Time (h)	Severe malaria IV	IM	Uncomplicated malaria	Healthy subjects
0	0	0	0	0	0
5	5	5	5	5	5
10	10	10	10	10	10
15	15	15	15	15	15
20	20	20	20	20	20
25	25	25	25	25	25
30	30	30	30	30	30
35	35	35	35	35	35
40	40	40	40	40	40
45	45	45	45	45	45
50	50	50	50	50	50
55	55	55	55	55	55
60	60	60	60	60	60
65	65	65	65	65	65
70	70	70	70	70	70
75	75	75	75	75	75
80	80	80	80	80	80
85	85	85	85	85	85
90	90	90	90	90	90
95	95	95	95	95	95
100	100	100	100	100	100

Fig. 8.2.5.5 Average plasma quinine concentrations following administration of a loading dose of 20 mg (salt)/kg to patients with severe and uncomplicated malaria, compared with those predicted to occur in normal subjects. From White NJ (1992). Antimalarial pharmacokinetics and treatment regimens.

Br J Clin Pharmacol, 34, 1-10, with permission. © 1992 The British Pharmacological Society.

Table 8.2.5.6 Effect of macrolides on bacterial virulence at subinhibitory concentrations

Factor	Effect
Adhesins (pili, fimbriae)	↓
Exoenzyme production: Fibronectin binding	↓
Elastase	↓
Alginate production	↓
Protease	↓
Exotoxin A production	↓
DNAse	↓
β -Haemolysin activity	↓
Coagulase	↓
Serum susceptibility	↑
Leukocidin	↓
Flagellar function	↓

From Shyrock TR, Mortensen JE, Baumholtz M (1998). The effects of macrolides on the expression of bacterial virulence mechanisms. J Antimicrob Chemother, 41, 505-12.

8.2.5 Antimicrobial chemotherapy 697 are often well above the inhibitory concentration and are sustained through repeat doses, remains uncertain. It may have greater relevance to tissue concentrations, which tend to be lower than plasma concentrations. The persistent antibiotic effect certainly contributes to the effects of agents that are administered once daily, such as gentamicin. The relationship between the pharmacokinetic characteristics of a drug and bacterial inhibition is critical to therapeutic outcome (Table 8.2.5.8). In the case of agents such as penicillins and cephalosporins, the time that drug concentrations are maintained above the MIC predicts the response. This contrasts with agents such as the quinolones and aminoglycosides, where it is more important to achieve high C_{max} to MIC ratios or area under the concentration curve (AUC) to MIC ratios. Modelling the MIC of a particular organism against the dose response curve for a drug (Fig. 8.2.5.6) has established several important pharmacodynamic parameters, which have been supported by studies in preclinical models and man. For example, dosage regimens of quinolones such as ciprofloxacin, levofloxacin, and moxifloxacin have been based on pharmacodynamic data. The ratio of AUC to MIC was defined in preclinical studies and was used to predict effect in man against *S. pneumoniae* or aerobic Gram-negative rods. This was also predictive of outcome in human studies. The importance of protein binding for drug performance has also emerged as an important modifying factor in this modelling. The AUC to MIC ratio of the free drug is the most useful predictor of response. The manner in which these ratios differ for selected quinolones is shown in Table 8.2.5.9. Principles of use In comparison with many other classes of drugs, antimicrobial agents are usually prescribed in short courses ranging from a single dose to a few days. Prolonged therapy is required for certain infections such as tuberculosis and bone and joint infections, and for HIV infection treatment is lifelong. Most antibiotic prescribing, especially within community practice, is empirical. Even among patients in hospital, where there are greater opportunities for diagnostic precision based on laboratory investigations, the exact nature of the infection is established in only a minority of cases. Most therapeutic prescribing requires a presumptive clinical diagnosis that, in turn, is linked to a presumptive microbiological diagnosis based on knowledge of the usual microbial causes of such infections. Among the most widely treated infections are those affecting the upper and lower respiratory tracts, the urinary tract, and skin and soft tissues for which the likely microbial aetiology is restricted. For example, urinary tract infections arising in the community are usually caused by *E. coli* and other Gram-negative enteric pathogens and, less commonly, by enterococci or *Staphylococcus saprophyticus*. Local knowledge of the susceptibility of these pathogens to commonly used agents such as trimethoprim, ampicillin, and a quinolone such as ciprofloxacin is Table 8.2.5.7

Postantibiotic effects (h) of selected drugs against *Staph. aureus*, *E. coli*, and *P. aeruginosa*

Drug	<i>Staph. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
Ampicillin	1.7	0.1	NT
Cefotaxime	1.4	0.2	0.3
Ciprofloxacin	2.0	2.1	2.4
Erythromycin	3.1	NT	NT
Gentamicin	2.0	1.8	2.2
Imipenem	2.6	0.5	1.5
Rifampicin	2.8	4.2	NT
Vancomycin	2.2	NT	NT

NT, not tested.

Table 8.2.5.8 Summary of major pharmacodynamic differences between aminoglycosides and β -lactams

Pharmacodynamic measurement	Aminoglycosides	β -Lactam
Rate of bacterial killing	Rapid and dose related	Slower with little or no increase at higher doses
Number of bacteria killed per dose administered	Concentration-dependent over a wide concentration range	Little increase in degree or rate of killing at concentrations above 4–5 $\times$ MIC
Postantibiotic effect	Concentration-dependent over a wide concentration range	for Gram-positive and Gram-negative pathogens Unpredictable in Gram-negative bacteria, always short with little or no increase related to concentration
Experimental models	Large, infrequent doses more effective than smaller, more frequent doses	which supports once-daily dosing
	Frequent (hourly) injection or constant infusion most effective	Ambrose et al., 2007 Clinical trials C _{max} /MIC

ratios linked to clinical outcomes $T > MIC$ linked to clinical outcomes Clinical trials with amikacin, gentamicin, and netilmicin have shown single daily dosing to be effective as multidosing Increased use of prolonged or continuous infusion dosing regimen in critical care settings Ambrose et al., 2007. Peak (c max) Area under the curve (AUC) exceeding MIC Minimum inhibitory concentration (MIC) Time Time above MIC Drug concentration Fig. 8.2.5.6 Relationship between the minimum inhibitory concentration (MIC) of a drug and its pharmacokinetic profile. Mouton et al., 2005.

698 SECTION 8 Infectious diseases helpful in recommending initial empirical antibiotic management. (Table 8.2.7.10). In more severe infections, such as community-acquired pneumonia, prompt empirical therapy is essential. Although the range of possible pathogens is more extensive (Table 8.2.5.11), *Strep. pneumoniae* predominates and must always be targeted. Assessment of severity, based on validated criteria, assists in defining the initial empirical antibiotic regimen. This is illustrated by the British Thoracic Society's recommendations for the initial empirical antibiotic management of community-acquired pneumonia (Table 8.2.5.12). The use of empirical therapy depends on the ease with which a clinical diagnosis can be made, as well as disease severity and drug toxicity. In the case of herpesvirus infections, the empirical use of aciclovir for the treatment of mucocutaneous herpes simplex infections or of shingles in older people is now common. However, it would be inappropriate to start treatment for HIV or cytomegalovirus infections without laboratory support for these diagnoses in view of the toxicity and cost of the antiviral agents used to treat these infections. Antibiotic prophylaxis Antibiotics are used widely in the prevention of infection, in association with surgery, and in a range of medical conditions (see earlier). Antibiotic prophylaxis is used for selected surgical procedures where the risk of infection, although relatively low, is of serious import should it occur. Examples include prosthetic joint implantation and cardiac surgery in which prosthetic valves and intracardiac patches are inserted. The principles of antibiotic prophylaxis are based on the selection of an agent active against the known potential target pathogen(s). The drug should be present in high concentrations at the site and time of surgery and be relatively free from adverse reactions. One dose is generally effective but further doses may be needed depending on the length of the procedure. No regimen can be effective against all potential pathogens, hence the importance of postoperative follow-up. Medical reasons for prophylaxis are also important; for example, prophylaxis is the use of low-dose suppressive therapy to prevent *Pneumocystis jirovecii* pneumonia in those with advanced HIV infection. Co-trimoxazole is the preferred agent; dapsone, atovaquone, or inhaled pentamidine are also used. Anatomical or functional asplenia is associated with a 12.6-fold increased incidence of severe sepsis compared with the general population. This risk is related to the patient's age and, in those after splenectomy, the reason for surgery and the period of time that has elapsed. Young children are particularly at risk, but this declines substantially after the age of 16 years. Hence the recommendation that immunization be supplemented with prophylactic oral penicillin (erythromycin for the intolerant) to prevent fulminant pneumococcal sepsis which predominates. Other recommended vaccines include *Haemophilus influenzae* type b (Hib) and meningococcal vaccination. Apart from good evidence for the benefit of prophylaxis in children with sickle cell disease, there is poor support Table 8.2.5.9 Pharmacokinetic and pharmacodynamic parameters of some recent quinolone antibacterial drugs

Drug (dose mg)	Protein binding (%)	MIC ₉₀ <i>Strep. pneumoniae</i>	AUC total (mg/h per L)	AUC free (mg/h per litre)	AUC/MIC

(total drug) AUC/MIC (free drug) Gatifloxacin (400) 20 0.5 51.3 41.0 102.6 82 Levofloxacin (500) 25 2.0 72.5 54.4 36.2 27.2 Moxifloxacin (400) 48 0.25 26.9 14.0 107.6 56.0 AUC, area under the concentration curve; AUC, AUC to MIC ratio or area under the inhibitory concentration of total and free (unbound) drugs; MIC90, minimum inhibitory concentration active against 90% of isolates tested. Table 8.2.5.10 Prevalence of antibiotic resistance in 193 E. coli isolate from urine samples referred by general practice in North Bristol MIC (mg/litre) %Sensitive Range MIC50 MIC90 Amoxicillin 0.5->128 8

128 52.9 (45.9-59.9) Co-amoxiclav 0.5->128 4 64 65.3 (58.6-72.0) Ciprofloxacin 0.008->128 0.03 32 82.3 (76.9-87.7) Nitrofurantoin 1->128 8 16 98.6 (96.9-100) Cefradine 4->128 8 16 91.7 (87.8-95.6) Trimethoprim 0.12->128 0.5 128 58.0 (51.0-65.0) Co-trimoxazole 0.015->32 0.12 32 63.7 (56.9-70.5) Fosfomycin 0.25-32 0.5 1 100 Cefixime 0.008-64 0.25 1 93.7 (90.3-97.1) Doxycycline 0.5->128 2 32 — Mecillinam 0.12->128 0.05 16 85.7 (80.8-90.6) From Chin TL, et al. (2015). Prevalence of antibiotic resistance in *Escherichia coli* isolated from urine samples routinely referred by general practitioners in a large urban centre in South-West England. *J Antimicrob Chemother*, 70(7), 2167-2169, by permission of Oxford University Press.

8.2.5 Antimicrobial chemotherapy 699 Table 8.2.5.11 Microbiological aetiology (%) of adult community-acquired pneumonia in the United Kingdom Pathogens Community (n = 236) Hospital (n = 1137) ICU (n = 185) *Strep. pneumoniae* 36.0 39.0 21.6 *Haemophilus influenzae* 10.2 5.2 3.8 *Legionella* spp. 0.4 3.6 17.8 *Staph. aureus* 0.8 1.9 8.7 *Moraxella catarrhalis* ? 1.9 ? Enterobacteriaceae 1.3 1.0 1.6 *Mycoplasma pneumoniae* 1.3 10.8 2.7 *Chlamydophila pneumoniae* ? 13.1 ? *Chlamydophila psittaci* 1.3 2.6 2.2 *Coxiella burnetii* 0 1.2 0 Viruses 13.1 12.8 9.7 Influenza A and B 8.1 10.7 5.4 Mixed 11.0 14.2 6.0 Other 1.7 2.0 4.9 None 45.3 30.8 4.0 ICU, intensive care unit. Reproduced from Lim WS, et al. (2009). The British Thoracic Society guidelines for the management of community-acquired pneumonia in adults. *Thorax*, 64 Suppl III, 1-61, and Lim WS, et al., 2015. Annotated BTS Guideline for the management of CAP in adults (2009). Summary of recommendations (www.brit-thoracic.org.uk). Copyright © 2009, BMJ Publishing Group Ltd and the British Thoracic Society, with permission from BMJ Publishing Group Ltd. Table 8.2.5.12 Preferred and alternative initial empirical treatment regimens for community-acquired pneumonia as recommended by the British Thoracic Society (2009 and 2015) Pneumonia severity (based on clinical judgement supported by CURB65 severity score) Treatment site Preferred treatment Alternative treatment Low severity (e.g. CURB65 = 0-1 or CRB65 score = 0, <3% mortality) Home Amoxicillin 500 mg tds orally Doxycycline 200 mg loading dose then 100 mg orally or clarithromycin 500 mg bd orally Low severity (e.g. CURB65 = 0-1, <3% mortality) but admission indicated for reasons other than pneumonia severity (e.g. social reasons/unstable comorbid illness) Hospital Amoxicillin 500 mg tds orally If oral administration not possible: amoxicillin 500 mg tds IV Doxycycline 200 mg loading dose then 100 mg od orally or clarithromycin 500 mg bd orally Moderate severity (e.g. CURB65 = 2, 9% mortality) Hospital Amoxicillin 500 mg-1.0 g tds orally plus clarithromycin 500 mg bd orally If oral administration not possible: amoxicillin 500 mg tds IV or benzylpenicillin 1.2 g qds IV plus clarithromycin 500 mg bd IV Doxycycline 200 mg loading dose then 100 mg orally or levofloxacin 500 mg od orally or moxifloxacin 400 mg od orally High

severity (e.g. CURB65 = 3–5, 15–40% mortality) Hospital (consider critical care review) Antibiotics given as soon as possible Co-amoxiclav 1.2 g tds IV plus clarithromycin 500 mg bd IV (If Legionella is strongly suspected, consider adding levofloxacin) Benzylpenicillin 1.2 g qds IV plus either levofloxacin 500 mg bd IV or ciprofloxacin 400 mg bd IV OR Cefuroxime 1.5 g tds IV or cefotaxime 1 g tds IV or ceftriaxone 2 g od IV, plus clarithromycin 500 mg bd IV (If Legionella is strongly suspected, consider adding levofloxacin) bd, twice daily; IV, intravenous; od, once daily; qds, four times daily; tds, three times daily. a Following reports of an increased risk of adverse hepatic reactions associated with oral moxifloxacin, in October 2008 the European Medicines Agency (EMA) recommended that moxifloxacin 'should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection'. b Caution – risk of QT prolongation with macrolide-quinolone combination. Reproduced from Lim WS, et al. (2009). The British Thoracic Society guidelines for the management of community-acquired pneumonia in adults. Thorax, 64 Suppl III, 1–61, and Lim WS et al., 2015. Annotated BTS Guideline for the management of CAP in adults (2009). Summary of recommendations (www.brit-thoracic.org.uk). Copyright © 2009, BMJ Publishing Group Ltd and the British Thoracic Society, with permission from BMJ Publishing Group Ltd.

700 SECTION 8 Infectious diseases for efficacy in other populations of asplenic patients. There remain, therefore, differences of opinion about the recommendation for the continued use of chemoprophylaxis in adults, although some recommend that a period of two years is appropriate. Issues of cost, compliance, and drug-resistant pathogens add further fuel to the debate. What is clear is that the patient or legal guardian(s) should be educated concerning this risk. Dose selection Few antibacterial drugs are specific to a single pathogen, or site of infection, hence the dosage regimen must capture a range of susceptibilities of the various target microorganisms as well as likely concentration in different body sites to ensure a successful response. The dosage regimen for new antibiotics is determined initially by pharmacokinetic studies in healthy volunteers combined with pre-clinical pharmacodynamic studies to determine the dominant pharmacodynamic index (C_{max}/MIC, AUC/MIC, T>MIC) and the size of this index for antibacterial effect. This is supplemented by information from standardized animal models that simulate infections such as lung infection, peritonitis, endocarditis, meningitis, otitis media, and sepsis-complicating neutropenia. In man, information on drug penetration into the lung extracellular lining fluid, urine, cerebrospinal fluid, and other tissue spaces are needed. Dosing regimens ultimately need to be validated in clinical trials to measure safety and efficacy and confirm the preclinical pharmacokinetic-dynamic findings. Bactericidal versus bacteriostatic agents In the treatment of many common community infections which are usually of mild or moderate severity, the choice of either a bacteriostatic or a bactericidal antibiotic is of limited importance. However, in patients with severe infection, particularly when complicating an immunocompromised state, a bactericidal agent must be used. This applies particularly to those with severe neutropenia which is a common accompaniment of cytotoxic chemotherapy, especially in the treatment of haematological malignancies and following haematopoietic stem cell transplantation. Another important indication for selecting a bactericidal regimen is in the treatment of infective endocarditis; although the infected vegetations are in the bloodstream, they are relatively protected from host phagocytic control. Effective penetration into the fibrin-platelet mass requires high concentrations of a bactericidal drug to sterilize the infected vegetations. Duration of treatment The duration of therapy for many common infections has not been rigorously determined. The treatment of many common conditions is based on custom and practice and often varies internationally. The trend

over the last 25–30 years has been to shorten duration of therapy, where possible, and this is likely to continue in the future. The duration of treatment has been more thoroughly determined in the following cases:

- Gonococcal urethritis responds promptly to single-dose treatment with agents such as ceftriaxone, azithromycin, or a quinolone antibiotic such as ciprofloxacin or ofloxacin.
- Uncomplicated urinary tract infection, particularly when affecting women of childbearing years, responds promptly to selected agents such as nitrofurantoin and fluoroquinolones. Although bacteriuria can be eliminated with a single dose, the symptoms of dysuria and frequency take longer to subside, hence a 3-day course is preferred.
- Pharyngitis caused by *Streptococcus pyogenes* improves symptomatically within a few days of antibiotics such as penicillin, but eradication of the infecting organism from the throat often takes up to 10 days. It is acknowledged that this presents major difficulties with regard to drug compliance.
- For pulmonary tuberculosis the current recommendation of an initial 2-month treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol (reducing to isoniazid and rifampicin for a further 4 months provided the isolate is confirmed to be susceptible) is based on extensive clinical trials (Box 8.2.5.1).
- In cases of bacterial endocarditis, knowledge of the *in vitro* susceptibility of the infecting organism is crucial in determining dose, duration, and outcome of therapy. Highly penicillin-sensitive strains ($\text{MIC} \leq 0.1 \text{ mg/litre}$) of viridans streptococci are treated effectively with a 2-week regimen of parenteral penicillin and gentamicin or 4–6 weeks of parenteral penicillin alone. Less sensitive strains should be treated with parenteral penicillin for a total of 4–6 weeks, plus 2 weeks IV gentamicin. If the infecting organism is an enterococcus, a minimum of 6 weeks' treatment with parenteral penicillin (or ampicillin) and aminoglycoside is essential. Infections caused by *Staph. aureus* are a particular challenge since the severity is highly variable and yet the potential for metastatic infection and chronicity, as in the case of osteomyelitis, must be kept in mind. The isoxazolyl penicillins such as flucloxacillin are preferred, with the use of combination therapy still largely unproven. Clindamycin is a useful alternative agent. Many *Staph. aureus* infections of the skin and soft tissues respond promptly to 7 day oral therapy and no antibiotics are needed if surgery is used to drain cutaneous abscesses. Where there is a severe systemic response to infection, parenteral therapy is appropriate initially. Where there is evidence of blood stream infection and dissemination, treatment should be extended for periods of up to 4–6 weeks. In the case of septic arthritis, antibiotics should be given promptly and joint aspiration carried out, sometimes repeatedly, to avoid damage to the articular cartilage. The duration of therapy has not been rigorously determined. Most infections will resolve in 2–3 weeks. One of the most challenging infections is staphylococcal osteomyelitis. To avoid chronicity, it is customary to treat for 4–6 weeks. Treatment is generally administered parenterally, at least initially; outpatient intravenous antibiotic therapy is also widely used in the treatment of bone and joint infection employing agents such as ceftriaxone, teicoplanin which can be administered once daily. However, the role of outpatient intravenous antibiotic therapy compared to oral step-down therapy remains controversial and subject to ongoing clinical trials. For most infections, the duration of therapy remains uncertain. However, many mild to moderate uncomplicated infections will defervesce within a 3- to 5-day period suggesting that 5–7 days of treatment is usually adequate. There is little evidence to suggest that treatment periods of 10–14 days, or longer, are any more effective. They are also likely to be associated with an increased risk of side effects, superinfection, and the selection of antibiotic-resistant organisms, as well as being more costly.

8.2.5 Antimicrobial chemotherapy 701 The parenteral administration of antibiotics is appropriate in the management of severe life-threatening infections and when oral therapy is contraindicated,

such as in the postoperative period, if the patient is vomiting, or where gastrointestinal absorption cannot be relied on. However, the need for continued parenteral therapy should be reviewed regularly. In the treatment of many common infections, the acute features of infection such as temperature, tachycardia, and an elevated circulating neutrophil count usually improve within a period of 48 to 72 h. Provided there is no contraindication to oral therapy, this should be considered early in the course of patient management. The advantages are not just in the reduced cost of medication; the risk of intravenous line associated complications, such as infection, is also eliminated, discharge from hospital may be hastened and the need to deliver outpatient intravenous therapy removed. Adverse drug reactions Overall, antimicrobial agents have an outstanding record of safety. Nonetheless, no drug is without the potential for side effects. The risk varies by agent and sometimes by dose, while host genetic factors and pathophysiological status can also be important. Oral antibiotics are largely used in the community where they are generally well tolerated and used in the treatment of minor infections in large populations. Injectable agents selected for short-course perioperative prophylaxis have a well-established safety record. However, agents such as the antiviral drugs and amphotericin B carry a higher risk of more serious adverse drug reactions, which must be balanced against the life-threatening nature of their target infections. While drug safety is assessed during drug development, the full repertoire of adverse reactions becomes apparent only during widespread clinical use, hence, the importance of adverse drug reaction reporting systems. In the United Kingdom, the 'yellow card' system has been very successful and relies on voluntary reporting of possible adverse drug events to the Medicines & Healthcare Products Regulatory Agency (<http://www.mhra.gov.uk>) by doctors, dentists, coroners, pharmacists, nurses (including midwives and health visitors), radiographers, optometrists, and, most recently, patients. It is important to distinguish between adverse event reporting and adverse drug reaction reporting. The latter is more difficult to establish with certainty and may require rechallenge, which raises medical and ethical concerns. It is essential to enquire about previous drug reactions as well as other forms of drug toxicities before prescribing. The relationship to a previously prescribed drug requires careful assessment. Hypersensitivity is among the more common of drug reactions and, in the case of β -lactam drugs, appears to be more a function of the five-membered thiazolidine ring (Fig. 8.2.5.7) of the penicillin molecule, since hypersensitivity reactions are less common with the cephalosporins which have a six-membered dihydrothiazine ring. The monobactam aztreonam has no ring structure and hypersensitivity reactions appear to be rare. However, it is important to note that accelerated systemic hypersensitivity reactions (anaphylaxis) can be life-threatening, such that any previous association with a β -lactam drug is an absolute contraindication to the use of all β -lactams. Some drug toxicities are genetically determined. For example, people who are genetically slow acetylators of isoniazid are more at risk of side effects such as peripheral neuropathy. Those genetically deficient in the enzyme glucose-6-phosphate dehydrogenase (EC 1.1.1.49) are at risk of drug-induced haemolysis. This risk is more common in those of African, Mediterranean, or Far Eastern descent. Hence, it is important to screen for this red cell enzyme deficiency before the administration of oxidant drugs such as primaquine. Adverse drug reactions may not always be acute in their presentation but reveal themselves after prolonged drug exposure. Oral flucloxacillin and co-amoxiclav when administered for several weeks, particularly in older patients, are more likely to induce drug-associated hepatotoxicity. Likewise, parenteral formulations of selected drugs may be more toxic than their oral formulation, as is the case with fusidic acid where prolonged parenteral administration frequently gives rise to hepatotoxicity. Concentration-dependent adverse reactions (Table 8.2.5.13) are more likely to occur in the presence of organ system failure. Penicillins O

COOH O -Lactam ring Thiazolidine ring C R NH S Cephalosporins O O R' COOH -Lactam ring Dihydrothiazine ring C R NH S β β carbapenems R O N COOH R lactam β Monobactams O O N SO₃H -Lactam ring C R NH β Fig. 8.2.5.7 Chemical structure of the β -lactam antibiotics (penicillins, cephalosporins, and monobactams) identifying the common β -lactam ring component which is subject to hydrolysis by β -lactamases.

702 SECTION 8 Infectious diseases Aminoglycoside toxicity is more common in older people, in those with pre-existing renal failure, and after repeated aminoglycoside doses or other nephrotoxic drugs. Concentration-dependent bone marrow suppression characterizes the use of chloramphenicol whereby pancytopenia arises when plasma concentrations are in excess of 25 mg/litre. This is to be distinguished from the idiopathic aplastic anaemia that is a rare accompaniment of chloramphenicol use, but unfortunately is rarely reversible. Much has been learned about the structure-activity determinants of drug toxicity. For example, the quinolone antibiotics as a class have the potential to induce phototoxicity, arthrotoxicity, central nervous system toxicity, cardiotoxicity, and interact with agents such as caffeine, theophylline, and nonsteroidal anti-inflammatory drugs (Fig. 8.2.5.8). Knowledge of such predictors has led to the selection of agents with safer structural profiles. Despite this, adverse drug reactions have led to the withdrawal or modification of the licensed indications for several quinolones, notably temafloxacin, trovafloxacin, and sparfloxacin, emphasizing the importance of clinical recognition and reporting of adverse events. Few infectious conditions require lifelong therapy. The management of HIV infection has challenged this paradigm. To date, drugs directed at the causative viruses or complicating opportunistic infections are suppressive rather than achieving eradication.

Table 8.2.5.13 Dose-related adverse effects of selected antimicrobials

Drug	Adverse effect
Antibacterial drugs	General Superinfection by yeasts or <i>C. difficile</i> ; selection of drug-resistant bacteria from the normal flora
β -Lactams	Myelosuppression Neutropenia may occur after 1–2 weeks of high-dose IV therapy Drug fever Occurs during prolonged (>1 week), high-dose IV therapy (e.g. endocarditis) Central nervous stimulation/convulsions Can occur with overdose in renal failure
Aminoglycosides	Nephrotoxicity; ototoxicity Monitoring of serum concentrations minimizes but does not avoid toxicity; risk of toxicity is related to the duration of the dose and concomitant therapy
Vancomycin	Nephrotoxicity; ototoxicity May potentiate aminoglycoside nephrotoxicity
Macrolides (e.g. erythromycin)	Gastrointestinal stimulation This is a prokinetic effect of erythromycin which does not occur with all macrolides Ototoxicity; cardiac arrhythmias Only with high-dose IV therapy
Drug interactions	Increased serum concentrations of theophylline and cyclosporin Quinolones (e.g. ciprofloxacin) Central nervous stimulation Quinolones are weak GABA antagonists; this effect is potentiated by coadministration with NSAIDs, especially fenbufen
Drug interactions	May inhibit metabolism of theophylline
Oxazolidinone (e.g. linezolid)	Anaemia, neutropenia, thrombocytopenia; neuropathy; lactic acidosis Limit treatment to 28 days to reduce risk of haematological toxicity
Antifungal/antiprotozoal/antiviral drugs	Deoxycholate
Amphotericin B	Nephrotoxicity Decreased creatinine clearance and renal potassium wasting are universal at clinically effective doses Rigors/hyperthermia/hypotension Related to the rate of infusion
Ketoconazole	Inhibition of steroid synthesis Occurs with prolonged (>1 week) high-dose therapy
Aciclovir	Central nervous adverse effects; crystalluria Rare except with high-dose IV therapy
Quinine	Hypoglycaemia GABA, γ -aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug. Effect of F on side-effect profile has not been reported
Influence	phototoxicity and genetic toxicity
Metal binding and chelating site controls	interactions with antacids, milk, iron

supplements No side effects associated with this position Controls theophylline interaction and genetic toxicity Controls phototoxicity (major) and genetic toxicity. Minor effect in NSAID interactions Controls GABA binding (major), NSAID interaction (major), Theophylline interaction (major), genetic toxicity F R5 R1 R2 X8 R7 N O O C OH Fig. 8.2.5.8 Structure–activity side-effect relationships of the fluoroquinolone antibacterial drugs. GABA, γ -aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug. Redrawn from Domagala JM (1994). Structure–activity and structure–side-effect relationships for the quinolone antibacterials. *J Antimicrob Chemother*, 33, 685–706, by permission of Oxford University Press.

8.2.5 Antimicrobial chemotherapy 703 It is also important to note that the drugs used in the treatment of HIV are often licensed with limited information concerning their long-term safety. The potential for adverse reactions and especially interactions is considerable and requires careful attention to their detection and management. This has become an increasingly important challenge as life expectancy for those with HIV infection improves. It is important to balance drug safety while encouraging compliance and the maintenance of a reasonable state of health. Failure of antibiotic therapy Antimicrobial therapy may fail for several reasons. The agent selected may be inappropriate for the particular infection and fail to inhibit the target organism, or fail to reach the site of infection in sufficient concentration. For example, drugs such as nitrofurantoin and pivmecillinam, while achieving high urinary concentrations, fail to deal adequately with parenchymatous infection of the kidney or bacteraemia which may complicate acute pyelonephritis. The prostate also presents a chemotherapeutic challenge owing to the relatively low pH (c. 6.4) in chronic bacterial prostatitis. Drugs which are weak bases, such as trimethoprim either alone or in combination with sulfamethoxazole (co-trimoxazole), are preferred, especially since they are also lipid soluble. Ciprofloxacin has similar characteristics and has also produced favourable results. However, treatment of acute bacterial prostatitis sometimes needs to be prolonged (4 weeks and occasionally longer), especially if there is a history of chronic relapsing infection. The drug may be appropriate, but the dose selected may be inadequate. This may apply to such conditions as unsuspected bacterial endocarditis where high-dose parenteral antibiotic is required. Likewise, the concentration of penicillin required to deal with pneumococcal meningitis greatly exceeds that effective in the treatment of pneumococcal pneumonia; occasionally the two diseases coexist. Infections caused by *Legionella pneumophila* and *Chlamydia* spp. require drugs that achieve high intracellular concentrations such as the fluoroquinolones, macrolides, or tetracyclines. Resistance emerging during treatment is an uncommon cause of clinical failure but should be considered. Drug-resistant *Mycobacterium tuberculosis* can develop on therapy as a result of the emergence of minority populations of organisms resistant to such first-line drugs as rifampicin and isoniazid. The current multidrug regimens are, in part, designed to avoid this occurrence. Likewise, in those with HIV infection, drug-resistant virus is an increasingly important cause of treatment failure and requires good compliance with multidrug regimens to slow its rate of emergence. Failure of the patient to take the drug is an important consideration, particularly in these two infections; nonadherence can lead to the development of drug resistance. Mixed infections are commonly associated with intra-abdominal sepsis and occasionally with infections of the lung. They may fail to respond to treatment unless the regimen covers the full range of bacterial pathogens. In the case of intra-abdominal sepsis, the regimen should be active against anaerobic as well as aerobic bacterial pathogens. Another important cause of antibiotic failure is the continued presence of a focus of infection. This may be an abscess that requires surgical drainage or the removal of an implanted medical device such as an intravascular catheter. Much

more serious is infection of a prosthetic heart valve, hip joint, or central nervous system shunt where revision surgery carries significant risks. Many antibiotics fail to achieve therapeutic concentrations within abscess cavities, or are pH sensitive. Implant-associated infections present a similar challenge since bacteria often replicate slowly within a biofilm that is protective against normal host defences. Finally, it should be remembered that a persistently elevated temperature in the presence of what appears to be adequate antibiotic treatment can reflect drug fever or indeed fever complicating a non-infectious diagnosis. This emphasizes the importance of monitoring the response to treatment and repeated patient assessment. Practice guidelines and formularies The plethora of therapeutic agents currently available presents a considerable challenge to the prescriber. Guidance on the choice of agent and the management of disease is becoming increasingly important. This is not only to ensure that the selection of treatment is appropriate for the target infection and consistent with current patterns of antimicrobial susceptibility but also that it reflects an acceptable safety profile as well as being sensitive to the appropriate use of healthcare resources. Such guidance is increasingly provided designed for local use, within either a hospital or a community practice. It is often combined with a formulary which lists available drugs, and the institution's antibiotic policy which describes the objectives of its stewardship programme, how antibiotic use and resistance is monitored, ongoing audits and education, and how the whole process is managed. The guidelines frequently offer information on preferred and alternative regimens for particular infections. Within hospital practice, it is common for such formularies to identify drugs which may be prescribed freely according to specific indications and those for which expert advice an infection disease specialist should be sought. The latter applies particularly to drugs that require specific skill and experience in their use, need drug levels to be monitored, or are expensive. For example, the treatment of deep-seated fungal infections with amphotericin B requires careful clinical assessment and guidance on dosage and monitoring. Likewise, the treatment of HIV infection is increasingly a specialist area. Antibiotics which are expensive to prescribe such as parenteral or drugs, or last resort, carbapenems may be restricted. The guidelines will also have recommendations for the timing of transfer from parenteral to oral therapy in order to minimize the use of injectable agents. Formularies and guidelines have an educational role and allow the prescriber to become familiar with indications and safety of the most commonly used agents. Their use should be supported by educational activities both at undergraduate and postgraduate level. Ideally, the selection of agents for inclusion in the formulary should be based on sound evidence of efficacy, safety, and economic benefit. However, such evidence-based medicine is often lacking or incomplete for commonly treated infections, since clinical trials of antibiotics, although increasingly robust in their design, are largely conducted to support licensing requirements rather than to address clinical use. They generally demonstrate the noninferiority of a new agent in comparison with existing therapies. As a result, the

704 SECTION 8 Infectious diseases recommendations of formularies and practice guidelines are based on a matrix of information derived from knowledge of the in vitro profile of an agent, its pharmacokinetic-dynamic parameters, its clinical and microbiological efficacy, and its safety profile. This, in turn, is modified by custom and practice which explains why there is local and, sometimes, national and international variation in recommendations for some common indications such as community-acquired pneumonia. In low and middle-income countries, where medical resources are much more limited, greater reliance is placed on low-cost agents. The World Health Organization regularly updates its list of recommended essential drugs which includes anti-infective agents (Table 8.2.5.14). Despite the emphasis on low-cost agents, the drugs offered cover

most infections and prescribing needs of these countries. The agents available in individual countries often vary according to local interpretation of the needs for these 'essential' drugs. Recent developments in economically advanced countries have included an assessment of healthcare technologies for current management, national need, and the resources available. In the United Kingdom, the National Institute of Clinical Excellence (NICE, <https://www.nice.org.uk>) to assesses a variety of healthcare technologies including procedures as well as new therapies. Such assessments place greater emphasis on ensuring that new technologies are evaluated in a manner that more closely resembles clinical practice as well as demonstrating economic benefit, in contrast to drug licensing which addresses the quality, safety, and efficacy of new therapies. This emphasis is likely to require a greater partnership between healthcare systems and pharmaceutical companies to ensure that the place of new technologies is rapidly assessed and that their use is consistent with healthcare strategies.

FURTHER READING Albur MS, et al. (2012). Factors influencing the clinical outcome of methicillin-resistant *Staphylococcus aureus* bacteraemia. *Eur J Clin Microbiol Infect Dis*, 31, 295–301. Ambrose PG, et al. (2007). Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis*, 44, 79–86. Bennett WM, et al. (1994). Drug prescribing in renal failure: dosing guidelines for adults, 3rd edition. American College of Physicians, Philadelphia, PA. Chin TL, et al. (2015). *Escherichia coli* isolated from urine samples routinely referred by general practitioners in a large urban centre in South-West England. *J Antimicrob Chemother*, 70, 2167–9. Davies JM, et al. (2011). Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards Table 8.2.5.14 The World Health Organization (2015) model list of essential drugs (anti-infectives) Anthelmintics/antifilarials/antischistosomal and others Antibacterials Antituberculosis medicines Antifungals Antivirals Antiprotozoal Albendazole Amoxicillin±clavulanic acid Ethambutol Amphotericin B Aciclovir Diloxanide Levamisole Ampicillin Isoniazid Co-trimoxazole Abacavir Metronidazole Mebendazole Benzathine benzylpenicillin Pyrazinamide Fluconazole Lamivudine Miltefosine Niclosamide Benzylpenicillin Rifampicin Flucytosine Stavudine Stibogluconate Praziquantel Cephalexin Rifabutin Griseofulvin Tenofovir Amodiaquine Pyrantel Cefazolin Rifapentine Nystatin Zidovudine Artemether ± lumefantrine Diethylcarbamazine Cefixime Streptomycin Efavirenz Artesunate ± amodiaquine±mefloquine Ivermectin Ceftriaxone Nevirapine Chloroquine Triclabendazole Cloxacillin Atazanavir Primaquine Phenoxymethyl/penicillin Darunavir Quinine Procaine penicillin Ritonavir Proguanil Azithromycin Saquinavir Pyrimethamine Chloramphenicol Oseltamivir Sulfadiazine Ciprofloxacin Ribavirin Pentamidine Clarithromycin Valganciclovir Suramin Doxycycline Entecavir Eflornithine Erythromycin Sofosbuvir Melarsoprol Gentamicin Daclatasvir Nifurtimox Metronidazole Dasabuvir Benznidazole Nitrofurantoin Ribavirin Spectinomycin Co-trimoxazole Trimethoprim

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