Antimicrobials

6

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Learning Outcomes
At the end of this chapter, you will be able to:

- Discuss pharmacologically important differences of different types of microorganism.
- Provide an understanding of different drug targets in microorganisms.
- Provide an understanding of factors that govern the choice of antimicrobial agents.

6.1 Introduction

This chapter will consider the role that antimicrobial medications have in the treatment of infection and healthcare more generally. This will be realised by considering infection from an ecological perspective; that is, the world is a changing and dynamic community of organisms, of which humans are only a very small part. It is this aspect that makes treating infectious diseases so challenging, because infections are the result of an interaction between two organisms, both of which are evolving to exploit or reject the other. Consequently, the relationship is ever changing and dynamic; in the case of humans, this is most notably being seen in the development of immunity throughout the lifespan.

Although some microorganisms can cause disease, most do not, and seeing all microorganisms as dangerous is to misunderstand our relationship with them and reliance upon them. As will be explained, most microorganisms on the planet live in the soil and in the sea and will never encounter a human, let alone cause infection. For those that do, and in terms of understanding how infections are treated, the

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focus throughout is on a concept known as selective toxicity: how can we damage or inhibit the infecting microorganism without damaging the host?

Because there are general principles that apply across the different groups of microorganism, each group will be considered in turn, starting with bacteria and viruses which cause most infections. These are followed by fungi, and finally protozoa and helminths, which are only briefly referred to because severe diseases caused by these are rare in most developed countries, although globally protozoa such as those that cause malaria are a major problem. Throughout the chapter, the reader is asked to consider the vital question above; how can we damage or inhibit the infecting microorganism without damaging the host?

6.2 Microbial Ecology

The world in which we live is a complex and diverse one containing many different species and communities of different organisms. It is estimated that there are around $4–6 \times 10^{30}$ prokaryotes in the world (these are non-nucleated organsisms and comprise bacteria and archea), in contrast to the approximately 7.7×10^{9} (7.7 billion) humans (Whitman et al. 1998). Fortunately, very few microorganisms cause disease; it has been estimated that there are in the region 1407 pathogenic species of organism, of which bacteria comprise 538, fungi 307, helminths 287, viruses 208, and protozoa 57 (Woolhouse and Gowtage-Sequeria 2005). Although this estimate is somewhat elderly and probably underestimates this number, even doubling this would still represent a small proportion of the total number of organisms. Some of these, around 816, are shared with animals, known as zoonoses; and around 13% are new or re-emerging pathogens. Recently, emerged diseases include human immunodeficiency virus (HIV) and severe acute respiratory syndrome (SARS), while other infections such as tuberculosis (TB) and influenza continue to circulate and in the case of influenza to evolve and change at a rapid rate.

The human body is similarly diverse, providing a home for many different types and species of microorganism. In most cases, these organisms receive benefit from the relationship without causing any harm to the host, the technical term for this being that they are commensal. This is in contrast with mutual relationships where both benefit, or parasitic ones where one benefits but damages the other. Some parts of the body have a large number of organisms, while others are normally sterile, examples of the latter being most internal organs, bones and the blood and central nervous system. If microorganisms do infect these normally sterile sites, the resulting infection is known as an invasive infection. Because this means that microorganisms have gained access to a normally sterile site, such infections are often associated with injury or serious disease. Many of the most serious infections such as meningitis, septicaemia and osteomyelitis are invasive infections.

The normal range of microorganisms found in a particular part of the body is known as the flora or microbiome, and sometimes these play an important part in host defence, for example, the normal microbiome of the gastrointestinal tract is important in preventing pathogens from colonising and growing in the gastrointestinal tract, and one of the main risk factors for *Clostridium difficile* infection is the

use of broad spectrum antimicrobials that damage this flora. Maintenance of a healthy and balanced flora is important for this and other reasons, for example, it is thought that it helps to regulate the immune system and reduce the risk of allergy (Belkaid and Hand 2014). In addition to not using antibiotics unnecessarily, other factors such as diet may be important, this being the rationale for the use of pre- and probiotics; prebiotics being non-digestible substances that encourage a healthy flora, while probiotics are the organisms themselves (sometimes referred to in advertising as 'friendly' or 'good' bacteria).

6.3 Treating Infections: Selective Toxicity

The aim of antimicrobial therapy is to kill or inhibit the infecting organism without damaging the host; this is known as selective toxicity. This is commonly accomplished through the use of antimicrobial drugs. The terminology surrounding the drugs used to treat infections is complex; a strict definition of the term antibiotic, for example, is that it is a substance produced by one living organism that kills or inhibits the growth of another. This definition excludes completely synthetic products which are antimicrobials, a broader term referring to any substance that has this effect.

Many of the antimicrobials in common use are true antibiotics, being isolated from bacteria and fungi, but some are not. For example, penicillin is made by a number of fungi in the genus *Penicillium* and vancomycin by a bacterium known as *Amycolatopsis orientalis*, and both are therefore true antibiotics, while ciprofloxacin and linezolid are synthetic products and so are technically antimicrobials. Some drugs, such as the newer penicillins, are semi-synthetic, which means that they have a natural base that has been altered synthetically. In practice this makes very little difference, but it does have implications for the development of resistance, as it means that some resistance genes are found in the producing organism or the environment; for example, a bacterium producing an antibacterial substance must itself be resistant to the substance it is producing if it is not to kill itself. From a resistance perspective, this becomes problematic if these resistance genes spread into medically significant bacteria (Davies and Davies 2010).

The aim of selective toxicity means that pharmaceutical companies developing antimicrobials have to identify structures or metabolic processes in the microorganism that is different to or absent from the host. In the case of bacteria, our evolutionary relationship is distant meaning we have had a lot of time to evolve to be different and there are many selective targets; however, this is not the case with fungi to which we are relatively similar on a cellular basis. Viruses present a more difficult problem again, as they do not have their own metabolic or growth capabilities; instead, they use those of the host cell; technically, they are known as obligate intracellular organisms. Therefore, damaging viruses or preventing their growth usually means damaging the infected host cells, and while the immune system is able to differentiate infected from non-infected cells, it is more difficult to find drugs that are able to do this. This explains why drug formularies contain many antibacterial drugs and far fewer antifungal and antiviral drugs and why some of the latter are

associated with the toxicities and adverse effects resulting from poor selective toxicity; that is they damage the microorganism but also the host. Protozoa are even more problematic because they often have a complex life cycle, are relatively similar to human cells in many respects, and are often found in developing countries with limited healthcare budgets.

6.4 Bacteria

Many serious infections are caused by bacteria, and the first task in their treatment is their identification. There are many ways of identifying bacteria, for example, by shape; by their ability to take up and retain certain stains (e.g. Gram's stain); by their susceptibility to antimicrobials (antibiogram); or, increasingly, by molecular methods. The first three of these are known as phenotypic traits, that is, they are observable characteristics; the latter are genotypic, being based on bacterial genetics. Although most tests used in everyday practice identify phenotypic characteristics, molecular and genetic methods such as the polymerase chain reaction (PCR) are becoming increasingly important.

Bacteria are prokaryotes, that is, they do not have a nucleus and, consequently, are relatively simple organisms. Because they are only distantly related to humans, there are a lot of selective targets, some of the more important of which are shown in Table 6.1. The bacterial cell wall is an important target because it is a structure that is lacking from human cells and is made of a substance known as peptidoglycan, which again human cells do not have; thus, it is a very good selective target. Bacterial

Table 6.1 Common targets in bacteria (Tenover 2006)

Target and mode of action	Examples of drug groups	Examples of drugs
Damage cell wall	β-lactams	Penicillins, cephalosporins
	Glycopeptides	Vancomycin
	β-lactam with β-lactamase inhibitor	Amoxicillin/clavulanic acid (co-amoxiclav)
Prevent protein synthesis by binding to ribosome	Macrolides	Erythromycin
	Chloramphenicol	Chloramphenicol
	Lincosamides	Clindamycin
	Streptogramins	Quinupristin-dalfopristin
	Oxazolidanones	Linezolid
	Aminoglycosides	Gentamycin
	Tetracyclines	Tetracycline
Prevent nucleic acid synthesis	Flouroquinolones	Ciprofloxacin
	Rifampicin	Rifampicin
Inhibit metabolic pathway	Sulfonamides	Sulfamethoxazole
	Folic acid analogues	Trimethoprim
Disrupt membrane structure	Polymixins	Colistin
	Lipopeptides	Daptomycin

ribosomes are a target not because these are lacking in humans, but because they are of different sizes, so most drugs that bind to bacterial ribosomes do not bind to the human equivalents. Similarly, some of the enzymes involved in the reproduction of bacterial nucleic acid are different to their equivalents in humans. Folic acid synthesis is an example of a metabolic process that differs between bacteria and humans; while bacteria synthesise their own folic acid, humans gain theirs from the diet. Hence, blocking the synthesis of folic acid production is selective against bacteria.

The evolutionarily distant relationship of bacteria to humans means that there are lots of differences between human and bacterial cells and so lots of selective targets. However, the clinician still needs to identify the infecting organism, establish the best treatment and deliver that treatment in a way that can resolve the infection. Although the details differ, many of these principles are common to most infections and are considered later in the chapter.

6.5 Fungi

Because fungi are relatively closely related to humans, compared to bacteria, they have had less time to evolve differences, and so fewer selective targets exist (Table 6.2). This means that there are far fewer drugs to treat fungal infections than there are to treat bacterial infections, and many of those which do exist, particularly older antifungal drugs, have toxicities associated with them. A further complication is that many people who have severe systemic fungal diseases also have comorbidities, in particular, immunodeficiencies, further compromising the ability to treat the infection. Fungi can take two main forms: a yeast-like form that usually grows on surfaces and a hyphal form where it grows as finger-like projections that can force their way between cells and so become invasive; this is sometimes referred to as being a 'mould' (one may see these growing on bread). *Candida* species are examples of the former, and *Aspergillus* the latter; in addition, some fungi can take both forms known as dimorphic fungi.

Most antifungal agents work by inhibiting the cell wall or membrane which is the main difference between fungal and human cells. Human cells do not have a cell wall, and the fungal cell wall, which contains glucan and chitin, is the target for a range of drugs. The other main target is ergosterol which is a component of the fungal cell membrane, a structure that humans do have, but in fungi the membrane sterol is ergosterol, in humans the equivalent is cholesterol. Although there is a

Table 6.2 Main antifungal targets

Target	Drugs
Cell wall—Glucan inhibitors	Echinocandins (caspofungin, micafungin)
Cell membrane—Ergosterol binders	Polyenes (amphotericin B, nystatin)
Cell membrane—Ergosterol inhibitors	Azoles (ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole, ravuconazole)

difference between these two sterols, the difference is not great, reducing the selective toxicity and explaining some of the toxicities associated with the main drugs that bind to this, the polyene drugs amphotericin B and nystatin. Amphotericin, which has historically been the most important drug for treatment of severe fungal disease, has a range of toxicities including nausea, vomiting, rigours, fever and hypotension or hypertension. However, of most concern is its effect upon the renal system, where it can cause nephrotoxicity, particularly in those individuals with existing renal problems, on high doses, who are dehydrated or on other nephrotoxic drugs (Laniado-Laborín and Cabrales-Vargas 2009).

These adverse effects are reduced in those drugs that inhibit its production rather than bind to it and in liposomal preparations where the amphotericin molecules are enclosed in a lipid membrane. Additionally, polyenes are not absorbed through the gastrointestinal tract, making nystatin a safe drug for the topical treatment of superficial fungal infections. Less commonly used drugs include flucytosine which inhibits fungal nucleic acid synthesis, griseofulvin which has the same effect upon microtubules and the polyoxins and nikkomycin which inhibit chitin in the fungal cell wall (Kathiravan et al. 2012).

6.6 Viruses

Viruses are simple organisms that have no metabolism of their own. Consequently, they have to use the metabolism of host cells to replicate, making them obligate intracellular pathogens. This is problematic for treating viral infections because it means there are few selective targets, and while the immune system is able to differentiate infected from non-infected cells, it is hard to produce drugs that can damage or inhibit infected cells while leaving uninfected cells alone; and targeting all cells would lead to severe toxicity or even death. Consequently, most therapies in this area have tended to maximise immunity through immunisation rather than treat established infections.

Viruses that can most successfully be treated are usually those which have something in their structure or replication cycle which is different to or not found in human cells. The first viruses to be successfully treated were the herpes viruses, in particular, cytomegalovirus (CMV), varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV1) and type 2 (HSV2). These can be treated using drugs such as acyclovir that inhibit viral DNA polymerase, which is the enzyme that copies viral DNA during replication. Its selective toxicity stems from its specificity for the viral polymerase rather than the human equivalent, and because the drugs are inactive in the form given needing to be activated by phosphorylation which is preferentially done by a viral enzyme known as thymidine kinase. Although humans also have this enzyme, the drug is specific for the viral version, hence its selective toxicity.

The treatment of influenza has undergone major changes in recent years. Earlier treatments, such as amantadine and rimantadine which are Matrix-2 (M2) inhibitors, are acted by binding to a viral protein; however, these are not recommended for general use today. Newer drugs in use today inhibit the activity of neuraminidase, which is needed by the virus to leave the infected cell and so complete its replication cycle, the two main drugs being oseltamivir and zanamivir.

Most research in the treatment of viral infections has been undertaken on HIV. HIV is a retrovirus, meaning that it uses a viral-specific enzyme known as reverse transcriptase to turn the viruses RNA genome into DNA which can be integrated into the genome of the infected cell. Although human cells make DNA copies of DNA when cells replicate and RNA copies of DNA for protein production, they never convert RNA to DNA in the way that retroviruses such as HIV do, and because of this reverse transcriptase is a highly selective and important target for anti-HIV drugs. There are two groups of drugs that target this enzyme, the nucleoside reverse transcriptase inhibitors (NRTI) and the non-nucleoside reverse transcriptase inhibitors (NNRTI). Another viral enzyme, protease, is the third major target as it is required for viral assembly and maturation and is again different to human enzymes. Drugs that target this enzyme are known as protease inhibitors (PIs).

Newer drugs target the process of viral binding and entry into the cell and the viral integrase enzyme that inserts viral DNA into the cellular genome. The former group is particularly important, as these drugs have the potential to prevent cells becoming infected in the first place, not merely preventing or reducing viral replication after infection. In order to maximise the effectiveness of these drugs and to reduce the risk of resistance developing, they are given in combinations of at least three drugs from two of the groups; these combinations are known as (highly active antiretroviral therapy or ART/HAART).

Different approaches to treating viruses are shown in the treatment of hepatitis B and C viruses. Because hepatitis B has both RNA and DNA polymerases, some of the reverse transcriptase inhibitors used for the treatment of HIV also have activity against it. Other approaches to the treatment of this virus and hepatitis C virus include therapies aimed at improving the immune response, known as immunomodulators; these include drugs such as interferons, which are antiviral substances produced by the body in response to viral infections (Antonelli and Turriziani 2012; Littler and Oberg 2005).

6.7 Protozoa and Helminths

Protozoa, like fungi are relatively closely related to humans, and because of this and probably also the fact that most severe protozoal disease is suffered by those in developing countries, there are relatively few treatments for many protozoal diseases. Although it is rare to see severe protozoal disease in most developed countries, on a global scale they are responsible for significant morbidity and mortality (Chabé et al. 2017). Helminths are worms, which rarely reproduce in humans but are transmitted through the environment and are often asymptomatic in the human host (Grencis 2015).

The most common protozoal disease is malaria, which in humans is caused by either *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* or *Plasmodium knowlesi*. Because plasmodia are carried and transmitted by a mosquito which is not endemic to most of Europe, primary transmission does not occur here, malaria almost always being an imported disease. Most severe infection is associated with *Plasmodium falciparum.* Because

the treatments are complex, and resistance patterns vary widely, it is necessary to consult the current guidelines whenever a case of malaria is encountered (Phillips et al. 2017).

The most important intervention for the control of malaria is not treatment with drugs but efforts to reduce the incidence of the mosquito that carries the *Plasmodium* protozoa, such as the removal of still water pools, or to separate them from humans, particularly at times when they are most likely to bite, for example, by using bed nets. Visitors to malaria-endemic countries are advised to take antimalarial prophylaxis, but this is not always an option for the indigenous residents.

6.7.1 Choosing an Antimicrobial

It is important when treating infections that the most appropriate antimicrobial is used. Choosing an antimicrobial regimen is complex and involves clinical experience and interpreting test results, but at the same time being careful not to overuse drugs that might ultimately result in resistance and reduced effectiveness in the future. There are four questions that a clinician needs to ask in this respect (Leibovici et al. 1999):

1. Based on the prescriber's knowledge and the results of tests, is this the right drug for the known or likely infection?
2. Is the balance of likely benefit against harm appropriate in this case?
3. Given the cost of the drug, is its use appropriate?
4. Is there an equally good option which would be less likely to promote resistant organisms?

Recent guidance from NICE in the United Kingdom (National Institute for Health and Care Excellence 2015) states that when prescribing antimicrobials the prescriber should follow any local or national guidance on:

- Prescribing the shortest effective course.
- At the most appropriate dose.
- Using the best route of administration.

Unlike any other treatments though, the antimicrobial prescriber has an additional consideration, which is the likelihood of antimicrobial resistance developing at either the individual or population levels.

In some cases treatment can be delayed until test results are known (remembering that false-negative results, or contamination resulting in a false-positive may occur); but in others such as febrile neutropenia, this is not possible and empirical therapy may be needed while awaiting test results.

There are a variety of tests that are used in informing antimicrobial use, but they all aim to help the clinician find the best drug for the infecting organism. Depending upon the results, each drug-microorganism combination can be put into one of three categories (Rodloff et al. 2008):

1. Susceptible—The bacterium is inhibited in vitro by a concentration of the drug that is associated with a high likelihood of therapeutic success.
2. Intermediately resistant —The bacterium is inhibited in vitro by a concentration of the drug that is associated with an uncertain therapeutic effect.
3. Resistant—The bacterium is inhibited in vitro by a concentration of the drug that is associated with a high likelihood of therapeutic failure.

These are usually calculated using breakpoints and the drug-bacterium minimum inhibitory concentration. A breakpoint is a specified concentration of an antimicrobial which is used to define susceptibility or resistance of a bacteria to it. The susceptibility of a particular organism is based on this and the minimum inhibitory concentration or MIC of the specific organism, which is the lowest (or minimum) concentration of the antimicrobial which inhibits the growth of the organism. If the MIC is equal to or less than the breakpoint that defines susceptibility, the bacteria is categorised as being susceptible to that antibiotic; if it is more, it is either resistant or intermediately resistant (British Society for Antimicrobial Chemotherapy 2018).

For example, the current breakpoint between susceptibility and resistance for vancomycin for the treatment of *Staphylococcus aureus* is defined by the minimum concentration of the drug that will stop the bacterium from growing, currently set at a level of 2 mg/L. If it is less than or equal to this, it is sensitive; if above this, it is resistant. This is based on the minimum concentration that inhibits growth; it is not necessarily the same as the concentration that kills the bacterium (the minimum bactericidal concentration). For practical reasons, most tests are based on inhibition rather than killing the bacteria. There is no intermediate category between these two outcomes as vancomycin is a toxic drug and higher doses cannot usually be given to account for this. This is in contrast to drugs such as penicillin, where higher doses can usually be safely given.

The most common tests used are those using phenotypic traits (these are things that are measureable or observable); for example, microscopy, culture and sensitivity (MC&S), but genotypic tests looking for specific microbial genes and molecular tests are increasingly being used. These have the benefit of not requiring the laboratory to be able to grow the organism, as it does for tests such as MC&S. Such techniques include polymerase chain reaction (PCR), high-throughput genome sequencing and matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF MS).

When interpreting any test result, one must be aware of the possibilities of false-positive, or in this case the more likely scenario of false-negative results, where the test fails to identify an infecting organism. While there are many reasons why this may occur, an important consideration is that laboratory conditions do not replicate those found in the human body, and in particular the attempt to culture individual species does not reflect the polymicrobial nature of the body where multiple species and subspecies interact.

6.8 Delivering the Drug

Choosing the best drug to treat a particular infection is only part of the answer. The next part is to deliver the drug to the site of the infection in sufficient quantities or

concentrations to achieve the desired outcome. The science of how drugs move from the site of administration to site of activity and their subsequent elimination is known as pharmacokinetics, while the concentration of the drug as it relates to its clinical effect is known as pharmacodynamics.

As most drugs are taken orally or given intravenously, getting a drug into the bloodstream is relatively straightforward. However, most infections occur in the tissues, and so the drug needs to be able to leave the bloodstream and get to the site of the infection. In some cases, where the blood supply is poor or absent, this can be particularly problematic. For example, the cornea has a limited blood supply, which is why many eye medications are given as eye drops. More problematic can be infections of implantable devices, such as orthopaedic implants, necrotic tissue or abscesses, all of which have limited or no blood supply. Therefore, the serum concentration of a drug is unlikely to be representative of the actual concentration at the site of infection, unless this is the bloodstream. One way of remembering this is that whatever the blood results are saying about serum concentrations of antimicrobials, 'it is the tissue that is the issue'.

Another problematic type of infection is that which occurs on hard surfaces, such as orthopaedic implants. Layers of bacteria and other microorganisms can form, known as biofilms. While those on the top of the film can be treated, those in the deeper layers of the biofilm are more difficult to treat, partly because of the physical protection of those above, but also because they are often metabolically less active. Biofilms that form on implantable devices, such as orthopaedic implants, also benefit from the lack of blood supply making it difficult to deliver sufficient concentrations of the drug to the site of the infection, making them even more difficult to treat successfully. Biofilms can be extremely complicated, and in some cases a number of different organisms can form a stable and difficult to treat community of organisms.

6.9 Antimicrobial Dosing

Most antimicrobial drugs express their effect either through being static (e.g. bacteriostatic) or cidal (bactericidal). Static drugs stop the organism from growing but do not necessarily kill it; cidal drugs generally kill the microorganism at concentrations that can be achieved clinically.

Antimicrobials may also be concentration or time-dependent. Concentration dependent drugs usually have a longer action, and many are taken up by the target organism. In these cases, the important issue with regard to dosing is not how many doses a patient has, but what concentration of the drug can be achieved, so these are generally given in fewer but larger doses. With time-dependent drugs on the other hand, the important parameter is not the maximum dose, but the length of time that the drug persists above the MIC at the site of infection. These drugs tend to be given in smaller but more frequent doses. Gentamicin is an example of a concentration-dependent drug; hence, it is usually given in one large dose, while penicillin which is time-dependent is normally given a multiple daily doses to maximise its time over the MIC.

In general, the best approach to treatment is to give a single highly targeted antimicrobial. However, there are many exceptions to this rule, for example, in those who are immunosuppressed and for whom waiting for test results is not an option or who might be at an increased risk of polymicrobial infection with more than one organism. In these cases, the treatment approach might be to give combination empirical therapy (empirical meaning treatment based not on test results, but on knowledge and experience of what they are most likely to have). As there is limited information available, such therapies are often less targeted and broad spectrum antimicrobial medications are prescribed (the spectrum referring to the range of organisms targeted by the drug). In addition to broadening the spectrum of the therapy, combinations might also show synergy, that is, the drugs work better together than on their own. However, by increasing the spectrum of the therapy the risk of drug interactions and adverse reactions is increased, as is the cost of the treatment, and more damage is likely to be done to the normal flora of the body, increasing the risk of opportunistic infections such as *C. difficile*.

6.10 Resistance

Antimicrobial resistance has become a matter of increasing concern in recent years. It is important to be clear about the difference between intrinsic and acquired resistance. Intrinsic resistance occurs where some feature of an organism means that it is inherently undamaged by an antimicrobial. For example, Gram-negative bacteria have an outer membrane that prevents glycopeptides such as vancomycin from accessing the cell wall where the drug is active, making the bacteria intrinsically resistant to these drugs (Cox and Wright 2013). This being a feature of this group of bacteria, there is nothing that can be done to prevent this. A more serious problem is that of acquired resistance, where a previously susceptible organism develops a new resistance to one or more groups of antibiotics. The latter is known as multiple resistance and is often seen in MRSA. One particularly concerning development is the acquisition of vancomycin resistance by MRSA, which may already be resistant to a range of antimicrobials including all β-lactams apart from perhaps the new 5th generation cephalosprins which are active against MRSA, macrolides, aminoglycosides, fluoroquinolones and tetracyclines; and for which vancomycin would normally be the treatment of choice (Appelbaum 2007; Foster 2017).

Bacteria can become resistant in two main ways: the first is that they undergo a genetic mutation that changes an antimicrobial target in some way (Hughes and Andersson 2017) and the second is that they acquire resistance genes from another bacterium or the environment. While the first of these are chance events, the sheer number of bacteria means that such mutations probably occur quite frequently. Most of these will not cause resistance, and may actually be damaging to the bacterium, but a small number may confer resistance allowing that bacterium to survive or grow in the presence of the antimicrobial.

Probably more problematic than this is the acquisition of resistance genes, either from other bacteria or the environment (Sultan et al. 2018). This most commonly occurs in one of three ways (Gillings and Stokes 2012):

1. Acquisition of resistance genes from the environment, a process known as transformation (remember that many antimicrobials are produced by organisms which therefore need resistance genes to survive their own antiboitic).
2. Transfer of resistance genes from one bacterium to another by viruses, a process known as transduction.
3. The direct physical transfer of resistance genes from one bacterium to another, through a process known as conjugation.

Conjugation usually involves larger genetic elements that may contain a number of different resistance genes, or possible genes for toxins or other traits that aid bacterial survival. There are a number of different types of such genetic elements, the most complex being plasmids which may contain many different genes, and acquisition of such a plasmid by a bacterium might confer multiple resistances upon that bacterium. Plasmids may also contain genes encoding for toxins, in which case the bacterium may be capable of causing severe disease.

The development of resistance is almost inevitable when antimicrobials are used. This is because populations of microorganisms are heterogenous, that is to say all are a little different; for example, some will be very susceptible to an antimicrobial, while others may be a less susceptible. This is sometimes referred to as heteroresistance. Often a resistance mechanism reduces growth rates of organisms that have it, meaning that they are less likely to predominate than their susceptible equivalents. For example, a thickened cell-wall might reduce susceptibility but it might also take longer to grow. However, the use of that antimicrobial, particularly if the dose is not sufficient or it is not given for sufficient time may result in it killing the susceptible organisms but not the less susceptible ones, turning the disadvantage of resistance into an advantage and allowing them to 'take over'. Over time this leads to selection of resistant organism, the use of the antimicrobial resulting in 'selection pressure' for resistance. Although this may seem complicated, it is a simple Darwinian

Table 6.3 Mechanisms of resistance in bacteria (Giedraitienė et al. 2011; Kapoor et al. 2017)

Category of resistance	Example of resistance	Examples of organisms
Altered target prevents the drug from binding	Altered penicillin binding proteins in cell wall	Methicillin resistant *S. aureus*
	Change in cell wall structure	Glycopeptide resistant *S. aureus*
Decreased permeability or uptake prevents the drug from entering the cell	Change in outer membrane permeability	Multiple resistances in *Pseudomonas aeruginosa*
Efflux mechanisms pump the drug out of the cell	Acquired and chromosomally encoded efflux pumps	*Acinetobacter baumannii* multiple resistance
Enzymatic degradation breaks the drug down or changes its structure	β-lactamase enzymes that degrade β-lactam drugs	*Klebsiella peumoniae* that produce extended spectrum β-lactamases
Target overproduction overwhelms the drug	Overproduction of cell wall components targeted by glycopeptides	Vancomycin intermediately resistant *S. aureus*

selection occurring as a result of antimicrobial use. This is the reason why antimicrobials are fundamentally different to all other medicines; they have both an individual effect (curing the infection) and a population effect (selection for resistance), and sometimes these conflict (Sandoval-Motta and Aldana 2016). The main mechanisms of resistance are shown in Table 6.3.

The World Health Organization adopted a global action plan on antimicrobial resistance in 2015 (World Health Organization 2015), which contained five objectives:

1. To improve awareness and understanding of antimicrobial resistance
2. To strengthen the knowledge and evidence base through surveillance and research
3. To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
4. To optimize the use of antimicrobial medicines in human and animal health
5. To increase investment in new medicines, diagnostic tools, vaccines and other interventions

The last point, although perhaps the most obvious, is not without its difficulties, in particular the long development period required for human medicines and the relatively poor financial return that drug companies receive from antimicrobials compared to other drug groups.

6.10.1 Antimicrobial Policies

All healthcare organisations should have an antimicrobial policy, which aims to guide clinicians as to the best and most rational use of these drugs. Such policies have a number of aims, specifically to:

1. Ensure that a sufficient range of antimicrobials remain available
2. Guide prescribing
3. Avoid their unnecessary use
4. Reduce the emergence and spread of resistance
5. Promote good practice
6. Contain costs
   (Mayon-White and Wiffen 2005)

Although the exact content will differ between institutions as the type of patient treated and local resistance patterns might vary, they should include guidance as to the treatment of common infections, including dosages and special considerations or cautions, details of who to contact for advice in the treatment of infection and details of restricted drugs, for example, new or expensive drugs, or those which for other reasons such as resistance are restricted. Some of this information is available on a national basis from the British National Formulary or other national formularies, although this needs to be read and interpreted in light of local conditions.

6.11 Opportunistic Infections

Some groups are at particularly high risk of infection, for example, newborn infants because of their immature immune system and reliance upon others for their hygiene and daily care, and those who are immune suppressed either due to an immunosuppressive disease or because they are having immunosuppressive therapy. The range of microorganisms that can cause infections in these groups is often very wide and may include microorganisms that would not normally cause disease; these are referred to as opportunistic infections (they literally take the opportunity of immune suppression to cause disease). One example of this is the first cases of acquired immune deficiency syndrome (AIDS) that were reported in the United States; they were noted because apparently otherwise healthy young men were becoming infected with *Pneumocystis carinii* (now known as *Pneumocystis jirovecii*), a fungus that does not normally cause disease in healthy people (Centres for Disease Control and Prevention 1981). Of course, it is now known that they were not healthy, as the opportunistic infection occurred because of immunosuppression due to AIDS.

Because the range of microorganisms that can cause infections is wider than that normally encountered, and because they often have other risk factors such as recurrent hospitalisations, the treatment of infection in these groups poses a particular challenge. Furthermore, because of the rarity of some of the infections that they have, treatment options and experience may be limited. A genearal approach may be to give broad spectrum antimicrobials, the exact regimen being adjusted according to specific risk factors, with frequent reassessment and the switching of antimicrobials and consideration of the introduction of antifungals if there is no improvement after 48 hours.

6.12 New Therapies

Although the development of new antimicrobial drugs would seem one answer to the development of resistance, there are problems with relying on this. Firstly, the new therapeutics need to be available. However, secondly there are specific issues related to antimicrobials, in particular: the limited time which people will take, typically no more than 7–10 days for most people; many infections occur in people or places with limited financial resources making pricing important; and in order to reduce the risk of resistance, developing new drugs is likely to be restricted whatever the cost may be. Some new drugs have been developed, and a selection is shown in Table 6.4. Other possible treatments include those aimed at boosting the immune response such as vaccines and pre-formed antibody products, and bacteriophage therapies, these being viruses that infect bacteria.

6.13 Preventing Infections

Although most attention is placed upon treating infections, prevention is a better strategy, and relatively simple public health interventions can have significant results. With regard to medicines, the most common way of preventing infections is

Table 6.4 New drugs approved in Europe and United States, or at an advanced stage of development (Leone et al. 2019; Rai et al. 2013)

Drug	Notes
Ceftaroline-fosamil	Cephalosporin, active against Gram-positive including MRSA and VISA
Ceftobiprole-medocaril	Cephalosporin active against Gram-positive including MRSA
Ceftazidime-avibactam	Cephalosporin/β-lactamase inhibitor active against Gram-negative
Ceftolozane-tazobactam	Cephalosporin/β-lactamase inhibitor active against Gram-negative including *Pseudomonas aeruginosa*
Meropenem-vaborbactam	Carbapenem/β-lactamase inhibitor active against broad spectrum
Imipenem-relebactam-cilastatin	Carbapenem/β-lactamase inhibitor active against broad spectrum
Aztreonam-avibactam	Monobactam/β-lactamase inhibitor against Gram-negative including *Pseudomonas aeruginosa*
Cefiderocol	Carbapenem active against Gram-negative including *Pseudomonas aeruginosa*
Tedizolid	Oxazolidinone active against Gram-positive including MRSA and VRE
Eravacycline	Tetracycline active against broad spectrum
Omadacycline	Tetracycline active against broad spectrum
Plazomicin	Aminoglycoside active against broad spectrum
Dalbavancin	Lipoglycopeptide active against Gram-positive
Oritavancin	Lipoglycopeptide active against Gram-positive
Delafloxacin	Fluoroquinolone active against broad spectrum
Daptomycin	Lipopeptide active against Gram-positive bacteria
Telithromycin	Ketolide active against broad spectrum
Tigecycline	Glycylcycline active against broad spectrum

through prophylaxis; this is a treatment not to cure an existing infection but to prevent infection.

There are a number of different groups who might benefit from antimicrobial prophylaxis, for example:

- Patients undergoing some types of surgery where there is a high risk of contamination, such as surgery involving the placement of a prosthesis or implant, clean surgery or clean-contaminated surgery or contaminated surgery (National Institute for Health and Care Excellence 2019).
- Those who are severely immunosuppressed: the exact details of what prophylaxis they require will depend upon the nature, extent and length of their immunosuppression, but may include antibacterials, antifungals and antivirals.
- People who are functionally or anatomically asplenic should be considered for lifelong pneumococcal prophylaxis with penicillins or macrolides (Davies et al. 2011).

The use of prophylaxis for long periods of time is not without its risks however, as it might hasten the development of resistance, increase the risk of secondary infections if the prophylaxis damages the normal flora and may be expensive.

Another approach to prophylaxis is passive immunisation, where pre-formed antibodies are given. This may be specific for an organism, for example, V-ZIg (varicella-zoster immunoglobulin antibodies), or be pooled antibodies from a large number of people, in which case it will provide antibodies against a large number of organisms, but at a lower level. It is important to note that as with antimicrobial prophylaxis and unlike active immunisation this does not provide long-term protection (Berger 2018).

6.14 Summary

- Microorganisms are ubiquitous and outnumber other forms of life many times, but most are not harmful to humans.
- The key to treating infections is selective toxicity, that is, the ability to damage the infecting organism without damaging the host.
- Bacteria have many selective targets because of their distant evolutionary relationship with humans Fungi and protozoa have fewer selective targets, and viruses fewer still because they use host metabolism to reproduce.
- Antimicrobial resistance is an increasing problem and is driven by the selective effect of antimicrobial use.

Multiple Choice Questions

1. The real meaning of the term antibiotic is:
   (a) Any substance used to treat an infection
   (b) A substance produced by one living organism that kills or inhibits the growth of another
   (c) An antibacterial drug only
   (d) An antiviral drug only

2. Viruses are difficult to treat because:
   (a) They replicate rapidly.
   (b) They are very small.
   (c) They use host cell metabolism to replicate.
   (d) They are often resistant to commonly used antimicrobials.

3. Antimicrobial resistance usually occurs because:
   (a) Of the common use of older, cheaper drugs.
   (b) The use of the wrong drugs.
   (c) The use of the wrong doses.
   (d) Their use selects for resistant organisms through natural selection.

4. In terms of the number and range of drugs available:
   (a) Bacterial infections are easier to treat than fungal infections.
   (b) Fungal infections are easier to treat than bacterial infections.

(c) Both are equally easy to treat.
(d) Most infections cannot be treated.

5. Selective toxicity refers to:
   (a) Antimicrobials that are toxic to both human and microbial cells
   (b) Antimicrobials that are toxic to neither human or microbial cells
   (c) Antimicrobials that are more toxic to human than microbial cells
   (d) Antimicrobials that are more toxic to microbial than human cells

6. When treating a patient with an infection:
   (a) You should always wait for the culture results before starting treatment.
   (b) Never wait for the culture results—always treat straight away.
   (c) Asses if the severity of infection permits receipt of culture results before starting treatment.
   (d) Always treat with broad spectrum antimicrobials, so it does not matter.

7. A negative blood culture result in a patient with a fever:
   (a) Proves that the patient does not have an infection, the fever is due to something else.
   (b) Suggests it but does not prove it, it may be a false-negative result.
   (c) Needs more time to become positive as the patient has a fever.
   (d) Is of no clinical significance and should be ignored.

8. The main measure of susceptibility of a microorganism to a drug is:
   (a) The maximum dose that can be given
   (b) The minimum inhibitory concentration
   (c) The minimum toxic concentration
   (d) The minimum cidal concentration

Answers

1. b
2. c
3. d
4. a
5. d
6. c
7. b
8. b

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