ANTIMICROBIALS INCLUDING antibiotics are a class of medication that combat infections and the diseases they cause (Campbell 2007). The term antibiotic is technically used for the natural products of the fermentation of special microorganisms. During fermentation the organisms produce the antibiotic material, which can then be isolated for use as a drug. The term antimicrobials includes not only antibiotics, but also synthetically formed compounds. In clinical practice, the terms antibiotic and antimicrobial are now used interchangeably (Scott 2009).

Antibiotics have revolutionised medical care and have had a significant role in reducing morbidity and mortality from diseases that were once widespread and untreatable. As a result of antibiotic development, surgery and other medical interventions once likely to result in significant sepsis are considerably safer (Campbell 2007, Frost 2007). However, despite the significance of antibiotics, the development of resistance mechanisms that have spread in several clinically important bacterial species now limits their effectiveness, which is a serious public health concern (Campbell 2007).

A working knowledge of antibiotics requires an insight into microbiology and general pharmacodynamic principles. This article introduces some key terms that are important in clinical microbiology and antibiotic therapy. It focuses mainly on how antibiotics work and briefly addresses mechanisms of antibiotic resistance. Strategies to reduce the inappropriate prescribing and use of antibiotics are also considered.

Antibiotics and selective toxicity

Antibiotics are effective against bacterial cells, also known as prokaryotic cells. Bacterial cells are structurally simpler and much smaller than the eukaryotic cells of humans (Cells Alive 2010, Tortora et al 2010). The use of antibiotics exploits the differences in cell structure between prokaryotic and eukaryotic cells (Frost 2007); this is known as selective toxicity (Hills 2010).

Selectivity is based on the principle that the drugs inhibit essential biochemical processes in the bacteria without severely affecting the cells of the host. For some antibiotic drugs, a considerable difference exists between the concentration that produces an effect on microorganisms and that which produces an effect on host cells. For other drugs, the difference is smaller. This implies that antibacterial drugs can have adverse effects on host cells if the concentration is high enough (Simonsen et al 2006).

Gram-positive and Gram-negative bacteria

Most bacteria possess a cell wall that surrounds and protects a fragile plasma membrane (Tortora et al 2010). A substance called peptidoglycan is a major constituent of many bacterial cells’ walls and provides structure and strength to the cell (Hills 2010). There are two main types of bacterial cell wall, which are differentiated under microscopy by Gram-staining. Staining simply...
Aerobic and anaerobic bacteria

Organisms that require oxygen to live are called obligate aerobes (Tortora et al 2010). Obligate aerobes (Tortora et al 2010) are disadvantaged because oxygen is unavailable. Many types of yeast are facultative anaerobes, as is the bacterium *Escherichia coli*, which is found in the human intestinal tract (Hills 2010, Tortora et al 2010).

Following staining, the bacterium is then grown on various selective media such as a nutrient broth or agar plate and/or is subjected to various tests. The aim is to differentiate further the bacterium into a species (for example, *Streptococcus* spp.) and then to make a formal identification of a species (for example, *Streptococcus pyogenes*).

Once a pure culture of a bacterium is obtained on the agar plate, the microbiologist incubates the culture with antibiotic discs (antibiotic-impregnated papers). This method is referred to as antibiotic sensitivity testing, and the aim is to determine which antibiotic would be effective against a particular bacterium in clinical practice. The sensitivities are then reported to the clinician, enabling targeted antibiotic therapy (Hills 2010).

**Bactericidal or bacteriostatic effect**

Antibiotics can be either bactericidal, which refers to killing the bacteria directly, or bacteriostatic, which refers to slowing down the reproduction of bacteria and allowing host defences to kill them (Frost 2007). These differences are not generally significant in terms of the response (Hills 2010). However, there are clinical situations when the selection of a bactericidal or bacteriostatic agent is important, for example when dealing with infections in immunocompromised patients, especially those with neutropenia. Bactericidal agents are essential in moderate or severe neutropenia. They are also indicated in the treatment of bacterial meningitis and infective endocarditis (Finch 2009).

**Antibacterial spectrum**

Reference is often made to the terms 'broad-spectrum' and 'narrow-spectrum' antibiotics. There is no clear definition of the significance of these terms. However, the broader the spectrum the more species of bacteria the antibiotic can kill. Generally, a broad-spectrum antibiotic would be able to attack a range of Gram-positive and Gram-negative organisms (Hills 2010).

**Mechanism of action**

There are four key mechanisms of action employed by antibacterial drugs, all of which are based on the concept of selective toxicity. These mechanisms include inhibition of (Hills 2010):
Bacterial cell wall synthesis.
Bacterial deoxyribonucleic acid (DNA) synthesis.
Bacterial protein synthesis.
Folate synthesis.

**Inhibition of bacterial cell wall synthesis**

Unlike prokaryotic cells, the eukaryotic cells of humans do not possess peptidoglycan or contain a cell wall. This makes the wall of the bacterial cell an ideal target for antibiotic therapy because the therapy will not target the human cell (Hills 2010).

Penicillins and cephalosporins (beta-lactam antibiotics) are examples of antibiotics that interrupt peptidoglycan synthesis. These antibiotics enter the bacterial cell and bind to enzymes known as penicillin-binding proteins. This results in the formation of a weak or deformed cell wall, which swells and then bursts (Karch 2008). Drugs that destroy the cell in this way have a bactericidal effect.

No other antibiotic has been more important than penicillin, which was discovered by Alexander Fleming in 1928. The original penicillins include benzylpenicillin (penicillin G) and penoxymethylpenicillin (penicillin V). Over time the structure of penicillin has been re-engineered to develop semi-synthetic penicillins such as amoxicillin and flucloxacillin. The cephalosporins such as cefalexin and cefradine are currently subdivided into four generations as a guide to their relative activity against different bacteria. Between them, the penicillins and cephalosporins are effective against a wide range of Gram-positive and Gram-negative bacteria, and some anaerobic bacteria (Palit 2009).

**Inhibition of bacterial DNA synthesis**

The substance inside the plasma membrane of the bacterial cell is called the cytoplasm and is about 80% water. The nucleoid is a major structure in the cytoplasm and usually contains a single loop of DNA known as the bacterial chromosome. This is the cell’s genetic information, which carries all the intelligence required for cell structure and function. Bacteria may also have DNA in separate loops within the cytoplasm known as plasmids. These molecules are not connected to the main bacterial chromosome and replicate independently. Plasmids can carry genes for activities such as antibiotic resistance (Frost 2007, Tortora et al 2010).

DNA replication and cell division are fundamental to the production of new bacterial cells, and some antibiotics work by inhibiting the manufacture of DNA. These antibiotics tend to be bactericidal in action and include the quinolones (such as ciprofloxacin) as well as drugs such as metronidazole, nitrofurantoin and rifampicin. Human cells also need to synthesise DNA, and so these drugs have to be designed carefully to achieve selective toxicity (Hills 2010). The quinolones inhibit the action of two enzymes, DNA gyrase and topoisomerase IV, that are essential for DNA replication. Damage to the DNA means the cell cannot be maintained, resulting in cell death (Karch 2008).

Rifampicin is a rifamycin antibiotic (derived from a bacterium called *Nocardia mediterranei*) which is mainly used to treat tuberculosis, but which has other indications such as adjunctive treatment in anti-staphylococcal therapy. It works by interfering with the manufacture of proteins that are essential to bacterial cell structure and function. Rifampicin achieves this by inhibiting the enzyme required for the formation of messenger ribonucleic acid (mRNA) (copies of the genetic code required to make new proteins within the bacteria cell). Resistance to rifampicin develops quickly and the drug should not be given as monotherapy, unless clinically indicated, for example in the prevention of a secondary case of bacterial meningitis (Simonsen et al 2006, Hills 2010).

The antibiotic metronidazole uses a chemical reaction to disrupt bacterial DNA. The reaction occurs in the absence of oxygen, which means the antibiotic is effective only against anaerobic bacteria. Metronidazole is effective where oxygen levels are low, for example in treating *Bacteroides* spp. in peritoneal infections (Frost 2007).

**Inhibition of bacterial protein synthesis**

Both human and bacterial cells contain structures known as ribosomes located in the cell cytoplasm. The ribosomes that are responsible for protein synthesis are smaller in bacteria than in humans (Frost 2007). Antibiotics that inhibit protein synthesis act selectively in that they have a greater affinity to bacterial ribosomes than to those of humans (Simonsen et al 2006).

Antibiotics that interfere with protein synthesis include the aminoglycosides, tetracyclines and macrolides (Hills 2010). The aminoglycosides (such as gentamicin) are bactericidal and cause misreading of the code on mRNA. This results in the bacteria creating proteins that are dysfunctional. Tetracyclines (such as oxytetracycline, doxycycline, minocycline and tetracycline) inhibit protein synthesis by blocking a molecule known as transfer RNA. This is the molecule that transports the amino acids essential for the manufacture of proteins. The macrolides (such as erythromycin and clarithromycin) bind to one of the ribosomal subunits and inhibit the ribosomes from functioning.
Inhibition of folate synthesis

Folate is essential for the manufacture of DNA (Hills 2010). In contrast to mammals that obtain folate from external sources (food), bacteria manufacture their own. Important antibiotics that inhibit folate synthesis include trimethoprim and the sulphonamides such as sulfadiazine.

The sulphonamides are now rarely used as monotherapy because of growing resistance (Frost 2007, Hills 2010). Acting separately, sulphonamides and trimethoprim are bacteriostatic. Combined as co-trimoxazole, they work synergistically and are usually bactericidal. The sulphonamides have a poor side-effect profile including serious blood dyscrasias, notably bone marrow depression and agranulocytosis especially in older patients, and frequent rashes (British National Formulary (BNF) 2011). Therefore co-trimoxazole is usually restricted to infections where other options are not suitable (Hills 2010). However, it is still used as prophylaxis or treatment for Pneumocystis jirovecii (previously P. carinii) pneumonia seen in immunocompromised patients.

Table 1 provides examples of infections, potential bacterial pathogens, antibiotic treatment and mode of action of antibiotics.

Antibiotic resistance

Bacteria have the ability to adapt and develop resistance to antibiotics. Some are inherently resistant, while others develop resistance through mutation or by receiving resistant-encoding genetic material from different strains (National Prescribing Centre (NPC) 2003). When first exposed to a new antibiotic, bacteria tend to be highly susceptible and only a few may survive from a population of billions. Those that survive usually have some genetic characteristic that accounts for their survival, and their offspring are similarly resistant. These genetic differences arise from random mutations and can be spread among bacteria.

Once acquired, the mutation is transmitted by normal reproduction, and the offspring carry the genetic characteristics of the parent microbe. Since bacteria reproduce rapidly it takes only a short time for an entire population of bacteria to become resistant to an antibiotic (Tortora et al 2010).

Drug resistance may also be carried by plasmids or small segments of DNA called transposons that can move from one piece of DNA to another. Some plasmids can be transferred between bacterial cells in a population and between different, but closely related bacterial populations. The potential for the development and spread of multi-drug resistance, where bacteria are resistant to several different classes of antibiotic agents, is a particular concern.

### Table 1

<table>
<thead>
<tr>
<th>Infection</th>
<th>Potential bacterial pathogens</th>
<th>Antibiotic treatment</th>
<th>Mode of action</th>
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</thead>
<tbody>
<tr>
<td>Skin and soft tissue infection</td>
<td>Staphylococcus aureus, Streptococcus pyogenes (group A).</td>
<td>Penicillin +/- flucloxacillin</td>
<td>Inhibition of bacterial cell wall synthesis.</td>
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<tr>
<td></td>
<td></td>
<td>(oral or intravenous depending on severity).</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis or tonsillitis</td>
<td>Strep. pyogenes (group A).</td>
<td>Phenoxymethylpenicillin, but note that 50% of sore throats are viral in origin.</td>
<td>Inhibition of bacterial cell wall synthesis.</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Escherichia coli.</td>
<td>Trimethoprim.</td>
<td>Inhibition of folate synthesis.</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>C. difficile.</td>
<td>Metronidazole.</td>
<td>Inhibition of bacterial deoxyribonucleic acid synthesis.</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Chlamydia trachomatis.</td>
<td>Erythromycin, doxycycline.</td>
<td>Inhibition of bacterial protein synthesis.</td>
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(Wiffen et al 2007, Hills 2010)
Meticillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Mycobacterium tuberculosis* are examples of this (NPC 2003).

On a positive note, the incidence of MRSA bacteraemia appears to be falling. Reporting of MRSA bacteraemia by NHS trusts has been mandatory in England since April 2001. A quarterly report produced by the Health Protection Agency (HPA) presents analyses for data collected from this surveillance scheme. For the surveillance period October to December 2008 to October to December 2010, the HPA (2011) reported a 51.3% decrease in the overall number of reports of MRSA in England, from 678 reports in the third quarter of 2008 to 330 reports in October to December 2010. In comparison with the previous quarter (July to September 2010), the HPA reported a 16.5% decrease in reports of MRSA (HPA 2011).

However, there are concerns about growing resistance in a number of Gram-negative bacteria. Livermore (2009) highlighted a pressing need for the development of new antibiotics against these bacteria. There is also concern about gonococcus, which is making a remarkable and worrying attempt to develop resistance to all the antibiotics that allow convenient oral therapy (Livermore 2009).

**Mechanisms of antibiotic resistance** Major mechanisms by which bacteria can develop resistance include:

- The antibiotic can be destroyed or inactivated by the production of an enzyme. This mechanism of resistance mainly affects the penicillins and cephalosporins (Tortora et al 2010).
- The antibiotic’s target molecule can adapt so the antibiotic no longer recognises and binds to the molecule. For example, changes in or absence of the penicillin-binding proteins that are the receptor sites for beta-lactam antibiotics can result in drug resistance (Frost 2007, Finch 2009).
- An antibiotic can also be inhibited from reaching its target site because the bacterial cell wall is modified, preventing the action of the drug. For example, some enterococci (Steptococcus spp. in the intestinal tract) have developed resistance to vancomycin in this way (Frost 2007).
- Efflux resistance is a mechanism whereby proteins in the cell wall adjust to pump out the antibiotic so it cannot reach an adequate intracellular concentration. Resistance to the tetracyclines, macrolides and quinolones may be linked to efflux mechanisms (Frost 2007).

The emergence of resistant bacteria is associated with the widespread use of antibiotics. This is a threat to public health and especially to older patients and those who are debilitated or immunocompromised (NPC 2006, 2008). Fears have been expressed that we will soon ‘run out’ of antibiotics and that classical infections will regain their status as major causes of mortality. However, the situation is complex, improving with some pathogens but deteriorating with others (Livermore 2009). Judicious prescribing of antibiotics may help to delay the development and spread of antibiotic resistance, and healthcare professionals have a responsibility to use antibiotics appropriately (NPC 2006).

The World Health Organization (2001) defines the appropriate use of antibiotics as ‘the cost-effective use of antimicrobials which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance’.

In England, the use of antibiotics decreased between 1995 and 2001. However, over the past few years it has been slowly, but consistently rising (NPC 2009). Penicillins make up the biggest proportion of antibiotic prescribing, with macrolides and tetracyclines also contributing significantly (NPC 2009). For further information, the NPC (2009) provides data-focused commentaries on antimicrobials.

Most antibiotic prescribing occurs in primary care (NPC 2008) and there are a number of strategies that GPs and primary care prescribers can use to reduce inappropriate prescribing, including (Department of Health (DH) 1998):
- No prescribing of antibiotics for simple coughs and colds.
- No prescribing of antibiotics for viral sore throats.
- Limit prescribing for uncomplicated cystitis to three days in otherwise fit women.
- Limit prescribing over the telephone to exceptional cases.

### Choosing an antibiotic

When antibiotic therapy is required it should be tailored to the patient, the infection and the causative organism. Consideration should be given to the dose, duration of use, dose interval and patient adherence to treatment, all of which influence the development of antibiotic resistance (NPC 2003). Local antibiotic formularies state the preferred local antibiotic choices for a range of common infections and often limit the drugs that may be used (Frost 2007, BNF 20011). Often these formularies will follow guidelines set by expert bodies and take into consideration local sensitivity patterns.
Advice can be sought from a consultant in infectious diseases or a medical microbiologist in situations where guidelines appear inappropriate or the patient does not respond to treatment (Frost 2007). Antibiotic pharmacists may also offer support in cases where the appropriateness of the antibiotic is unclear.

**Risks versus benefits** The benefits that result from antibiotic use have to be balanced carefully against the risks. Side effects can vary from gastrointestinal symptoms such as nausea, vomiting and diarrhoea, to those that are rare and sometimes life-threatening. The penicillins, which are the most widely used class of antibiotics, are associated with allergic reactions that can vary from rashes to occasional fatal anaphylaxis (Frost 2007, Palit 2009).

Hypersensitivity is linked to the basic structure of penicillin, and therefore individuals with an allergy to one will be allergic to all (Palit 2009). Between 0.5% and 6.5% of penicillin-sensitive patients will also be allergic to cephalosporins and patients with a history of immediate hypersensitivity to penicillins should not receive these antibiotics (BNF 2011).

Studies in patients with respiratory tract infections have suggested that, for every 16 people treated with antibiotics, one person has an adverse event, compared with placebo (Glasziou et al 2004).

Antibiotics when given for one infection can induce a secondary infection. A typical example would be the development of vaginal thrush in female patients being treated with a broad-spectrum antibiotic such as co-amoxiclav.

Clindamycin, the quinolones and the cephaplorins are commonly implicated in the development of *Clostridium difficile* infection (Hills 2010). This infection was previously referred to as ‘antibiotic colitis’. It presents with profuse watery diarrhoea that can be life-threatening in some patients. Stool specimens from symptomatic patients are usually sent to the microbiology laboratory for diagnosis. The mortality rate of patients with *C. difficile* infection rises with increasing age. It usually affects older people and patients who are debilitated (DH and HPA 2008).

When a patient presents with diarrhoea it is important to consider the possibility of an infectious cause. Detailed guidance has been developed for healthcare providers and commissioners on how to deal with *C. difficile* infection (DH and HPA 2008). The guidance highlights ten recommendations for dealing with this type of infection (DH and HPA 2008). Information about the side effects and risks associated with antibiotic use can be found in the prescribing notes in the BNF (2011). These notes should be consulted, in conjunction with information about the patient’s medical and drug history, before the decision to prescribe an antibiotic is made.

**Strategies to improve antibiotic prescribing**

According to the NPC (2009), improving antibiotic prescribing is not solely a matter of prescribing fewer antibiotics. It involves identifying people who are most likely to benefit from an antibiotic and prescribing for them, while offering support and symptomatic treatment to people who are unlikely to benefit, but who are at risk of side effects. Antibiotics may be prescribed inappropriately because the clinician is fearful of the clinical consequences of not prescribing or in an effort to prevent secondary infection (DH 1998). Other reasons cited for the overprescribing of antibiotics include patient pressure and demand (Frost 2007). Yet this demand may often be a mistaken perception by prescribers (Britten and Ukoumunne 1997).

When consulting patients it is important to establish their concerns and expectations about treatment to determine whether an antibiotic prescription is what is expected. If it is, but the clinician feels antibiotic therapy is inappropriate, then information and negotiation may be required to educate the patient on the limited effectiveness of antibiotics in some situations.

Delaying the prescription for antibiotics, rather than refusing to prescribe them, is another strategy that may reduce inappropriate prescribing of these drugs. Patient information leaflets can also help to reinforce a message and explain it in more detail.

The NPC website (www.npc.co.uk) provides excellent e-learning resources on the topic of common infections. Resources include workshops, a quiz and patient decision aids. The common infections category of the e-learning resources can be accessed at www.npc.nhs.uk/therapeutics/common_infections/index.php. Examples of patient information leaflets are available in the NHS Clinical Knowledge Summaries, which can be found at www.cks.nhs.uk.

**Conclusion**

Antibiotics are important therapeutic agents in the treatment of infections. The basis of treatment with antibiotics is that the drugs have
selective toxicity to bacterial cells, not host cells. Antibiotics work using a variety of mechanisms, which include attacking cell wall synthesis and inhibiting protein, folate and DNA synthesis.

Antibiotic resistance is a consequence of the use of antibiotics and as a result infectious diseases are now becoming more difficult to prevent and treat. Effective antibiotic stewardship strategies, dissemination of informative materials about the use of antibiotics, for example patient information leaflets, and delayed prescribing, are important. These are not complex interventions, but they may help to minimise inappropriate antibiotic use and in turn delay the development and spread of antibiotic resistance.

References


