The right drug for the right bug

Since the introduction of penicillin into clinical use in the 1940s, antibacterials have saved millions of lives. However, the lengthening shadow of antimicrobial resistance threatens a return to the pre-antibiotic era. In the first of three articles, Hayley Wickens and Paul Wade review the decision-making process for antibacterial therapy and give an overview of the drugs available.

Infection is a leading cause of morbidity and mortality in hospitals and empiric use of antibacterials is common. However, prescribers face a dilemma: initial antibacterial therapy must cover all the likely infective organisms for the presentation (inadequate initial therapy is associated with a poor outcome) but excessive use of broad-spectrum agents contributes to the selection of antibiotic-resistant organisms that are associated with increased morbidity, mortality and length of hospital stay. The 1998 House of Lords Select Committee on Science and Technology report into antimicrobial resistance estimated that up to 50 per cent of antimicrobials prescribed in hospitals may be inappropriate. This article aims to assist pharmacists in advising clinicians on choosing appropriate antibacterials.

Commensal or pathogen?

The human body carries a wide range of bacteria but few of these are able to cause infection in an immunocompetent host. Indeed, the majority are considered commensal or normal flora and can play an important role in host defence. For instance, eradication of the normal intestinal flora can permit overgrowth of pathogens such as Clostridium difficile, causing antibiotic-associated colitis. On the other hand, a commensal in the wrong place can be just as harmful as a true pathogen. For example, if Escherichia coli, an essential component of the intestinal flora, enters the bladder, a urinary tract infection can ensue.

Pathogens can produce a wide range of virulence factors, distinguishing them from commensals. Examples include the ability to interact with cell proteins, to adhere to host cells, to invade host cells to avoid phagocytosis or produce a polysaccharide capsule that gives protection from phagocytes. Examples of such encapsulated organisms include Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae.

Finally, some pathogens have the ability to produce either exotoxins (secreted during growth) or endotoxins (components of the Gram negative cell wall), which may be responsible for some, or all, of the clinical effects seen during infection.

Colonisation or infection?

The diagnosis of infection is often based on systemic signs, such as fever and tachycardia, and local symptoms, including production of coloured sputum, pain on urinating and white blood cells in the urine, and local erythema or presence of pus. Other investigations (eg, imaging and biopsies) can aid diagnosis. If a patient is colonised, as opposed to infected, such symptoms and signs are likely to be absent. Therefore, a nasal swab growing methicillin resistant Staphylococcus aureus (MRSA) is not grounds for treatment with intravenous vancomycin if the patient is otherwise well.

Raised white blood cell and platelet counts and elevations in inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, can also suggest infection in an acutely ill patient, but the ability of an infection to mimic other conditions, such as connective tissue disorders (eg, systemic lupus erythematosus) or malignancy, introduces diagnostic uncertainty. In addition, some infective organisms can present in many ways. For example, S aureus can cause infections ranging from simple skin infections to septicemia and toxic shock syndrome. It is also important to recognise that immunocompromised or severely ill patients may not be able to mount the immune response that causes such symptoms and signs.

It is for the above reasons that interpretation of the culture results in conjunction with the clinical findings is crucial. Only by careful
may be streamlined. Culture results have been obtained treatment resistance patterns is essential (see Table). Once the typical pathogens and local antibiotic relating the organisms before results are available and knowledge of antibiotic sensitivities. A definitive microbiological diagnosis may not be possible even when a clinical specimen and at least a further 24 hours for results on antimicrobial agents grown from the organism. At least 40 per cent of sputum specimens from patients with clinically proven pneumonia will up to 40 per cent of sore throats, especially in “swimmer’s ear”, Staphylococcus spp usually associated with neurosurgery.

### Table: Diseases, potential causative bacteria and typical treatment choices

<table>
<thead>
<tr>
<th>Specific condition</th>
<th>Potential bacterial pathogens</th>
<th>Typical empiric treatment and special considerations</th>
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<tbody>
<tr>
<td>Meningitis</td>
<td>*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Group B streptococci (seen in neonates). Less commonly, <em>Escherichia coli</em> and <em>Listeria monocytogenes</em>. Other Gram negative bacteria and <em>Staphylococcus</em> spp usually associated with neurosurgery.</td>
<td>Cefotaxime or ceftriaxone provide broad cover and good cerebrospinal fluid penetration. Causative agents can also be viral, mycobacterial or, rarely, fungal.</td>
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<td>Brain abscess</td>
<td><em>S aureus</em>, anaerobic streptococci, <em>Bacteroides</em> spp, Gram negatives, such as <em>Escherichia</em>, <em>Proteus</em>, <em>Klebsiella</em> spp.</td>
<td>Cefotaxime or ceftriaxone. The condition can, occasionally, be viral (Amoxicillin or co-amoxiclav). Otitis media can also be viral (Topical gentamicin, less common fungal (Candida albicans).</td>
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<tr>
<td>Otitis media</td>
<td><em>S pneumoniae, H influenzae, Moraxella catharrhalis, S aureus, mixed anaerobes</em>.</td>
<td>Amoxicillin or co-amoxiclav. Otitis media can also be viral (Topical gentamicin, less common fungal (Candida albicans).</td>
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<tr>
<td>Otitis externa</td>
<td><em>Pseudomonas aeruginosa (“swimmer’s ear”), S aureus (pustule)</em>.</td>
<td>Amoxicillin or co-amoxiclav. Otitis media can also be viral (Topical gentamicin, less common fungal (Candida albicans).</td>
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<tr>
<td>Upper respiratory tract infections</td>
<td><em>Pharyngitis/tonsillitis</em> Str pyogenes (group A)</td>
<td>Phenoxymethylpenicillin but note that 50 per cent of sore throats are viral. Give amoxicillin.</td>
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<td></td>
<td><em>Epiglottitis</em> H influenzae, Str pyogenes (group A)</td>
<td>Ceftriaxone or cefotaxime</td>
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<td></td>
<td><em>Sinusitis</em> Str pneumoniae, H influenzae, mixed anaerobes, S aureus, M catarrhalis</td>
<td>Co-amoxiclav. Sinusitis may be viral (eg, rhinovirus, influenza).</td>
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<td></td>
<td><em>Hospital-acquired</em> E coli, Ps aeruginosa and other Gram negative organisms, methicillin-resistant <em>S aureus</em></td>
<td>Broad spectrum antibacterials are required until a definitive antibiotic sensitivity pattern. Infection can be viral: For <em>H influenzae</em>, <em>S pneumoniae</em> and <em>M catarrhalis</em> Amoxicillin or co-amoxiclav. Otitis media can also be viral (Topical gentamicin, less common fungal (Candida albicans).</td>
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<td></td>
<td><em>Endocarditis</em> Enterococcus spp, Viridans group streptococci, <em>S aureus</em>, coagulase-negative <em>Staphylococcus</em> spp</td>
<td>Benzylpenicillin and gentamicin (synergistic action) or fluoroquinolones.</td>
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<td></td>
<td>Clostridium difficile (antibiotic-associated diarrhoea)</td>
<td>Stop broad spectrum antibacterials wherever possible. Give Metronidazole or vancomycin.</td>
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<td><em>Urinary tract infection (UTI)/Pyelonephritis</em> E coli, enterococci, <em>Klebsiella</em> spp, <em>Enterobacter</em> spp, <em>Pseudomonas</em> spp, <em>Proteus</em> spp</td>
<td>For UTI, use amoxicillin, cefalexin or trimethoprim, depending on severity. Longer course of treatment may be required and use of second-line drugs. Co-amoxiclav, cefuroxime</td>
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<td></td>
<td><em>Skin and soft tissue infection (cellulitis)</em> S aureus, Str pyogenes (group A)</td>
<td>Benzylpenicillin and flucloxacillin. Always check for co-existent MRSA.</td>
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<td><em>Septic arthritis</em> S aureus, <em>S pneumoniae</em>, occasionally Gram negatives</td>
<td>Ceftazidime empirically, but therapy should be guided by culture and sensitivity.</td>
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<td></td>
<td><em>Osteomyelitis</em> S aureus, <em>S pneumoniae</em>, coagulase-negative <em>Staphylococcus</em> (usually associated with implanted material). Many other organisms infrequently cause disease</td>
<td>Ceftazidime empirically, but therapy should be guided by culture and sensitivity.</td>
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</table>

The main antibacterials can be divided into three major classes according to their site of action: the cell wall, protein synthesis or nucleic acid synthesis pathways. An ideal antibiotic will act on a cell structure or function that is unique to the bacterial cell, thus sparing the host cell from adverse effects.

#### Cell wall active agents

Cell wall active agents include β-lactams and glycopeptides. β-Lactams have high selective toxicity against bacterial cell walls. They include penicillins, cephalosporins, monobactams and carbapenems. These bind to penicillin-binding proteins in the bacterial cell wall which will inhibit cell wall production. The glycopeptides (eg, vancomycin and teicoplanin) inhibit cell wall elongation. However, their molecular size prevents them from penetrating Gram-negative outer membranes and so they are active only against Gram-positive organisms. They are active against β-lactam-resistant staphylococci and streptococci, including MRSA, although emerging resistance is of major concern.
A fungal or parasitic infection (e.g., influenza, respiratory syncytial virus, enteroviruses) is more likely in patients with cancer, neutropenia or who have undergone bone marrow ablation. Fever and signs of inflammation, such as a white blood cell count increased to as many as 25 per cent of patients but this can be reversible. Close monitoring of plasma drug levels and use of once-daily dosing should be sought if antibacterials are used to treat infections caused by these organisms. Macrolides act mainly against streptococci and staphylococci and are often used to treat infections caused by these organisms in patients intolerant of penicillin. They have little or no activity against enteric Gram-negative organisms. Erythromycin, clarithromycin and azithromycin have a similar spectrum of activity but important differences in their toxicity profiles and their pharmacokinetics. Erythromycin or clarithromycin is routinely used in the management of severe community-acquired pneumonia because they are active against so-called “atypical” organisms, such as Chlamydia and Mycoplasma spp.
**Tetracyclines** Tetracyclines act against Gram-positive, Gram-negative and atypical organisms but their use has been limited by the development of resistance. The main differences between the members of the class are in pharmacokinetics or toxicity rather than in antibacterial activity and the most commonly used agents are doxycycline and minocycline.

**Other agents** Other protein synthesis inhibitors include:

- Chlormycine, which has activity against staphylococci and streptococci and also anaerobes
- Fusidic acid, which is mainly used for its anti-staphylococcal activity and its ability to penetrate bone, thus making it ideal for use in staphylococcal osteomyelitis (however, it must be used in conjunction with another anti-staphylococcal agent because use of fusidic acid alone rapidly leads to the development of resistance)
- Quinupristin-dalfopristin and linezolid — newer antibacterials that were developed to combat resistance seen in Gram-positive organisms

**Agents affecting nucleic acid synthesis**

**Sulphonamides and dianmopyridines** Sulphonamides and dianmopyridines block steps in the synthetic pathways for folic acid, which is essential for the production of the nucleoside thymidine. Sulphonamides and trimethoprim block sequential steps in the pathway and this synergistic action is exploited by combining sulfanmethoxazole and trimethoprim (cotrimoxazole).

Trimethoprim is often used alone, particularly for the treatment of uncomplicated urinary tract infections. It may also be useful in the oral treatment of infections caused by MRSA. It is less toxic than the sulphonamides and co-trimoxazole.

**Nitroimidazoles** Metronidazole and tinidazole have excellent activity against anaerobes. Metronidazole is most commonly used and is an excellent addition to a regimen if there is concern about the involvement of anaerobic organisms such as in intra-abdominal sepsis, brain abscess or following trauma.

**Quinolones** Quinolones act by inhibiting DNA topoisomerases. The most commonly used quinolone is ciprofloxacin, which has excellent activity against Gram-negative organisms, including *Pseudomonas* spp, but reduced activity against Gram-positive ones. It is currently a mainstay of many regimens for the management of serious infection, particularly intra-abdominal or urinary sepsis.

More recently, derivatives with increased activity against streptococci and a more favourable pharmacokinetic profile allowing once-daily administration, have been developed but the true place of these new agents in therapy remains to be seen.

**Pharmacokinetics**

In order to choose the most appropriate drug, knowledge of the pharmacokinetics and pharmacodynamics of the available agents is needed. Significant determinants of clinical outcome include interpatient variability in oral absorption, presence of infection at difficult-to-reach sites (eg, endocarditis) or within a collection (eg, in abscesses), infection by encapsulated organisms or infection in tissues, such as bone and prostate, or cerebrospinal fluid.

Intestinal elimination is an important factor. If an antibacterial drug is poorly absorbed or partly eliminated through the faeces then it could exert its effects on organisms found in the gut. This could give rise to the emergence of resistant strains or the overgrowth of more harmful organisms.

Pharmacodynamic considerations, such as the impact of post-antibiotic effects, biofilm (an organised structure containing many layers of bacteria) formation and the relationship between pharmacodynamic parameters and clinical outcome are gaining more currency in the day-to-day management of infections (see “Resources”).

**Combination therapy**

There are several reasons for using combinations of antibacterials. These include the presence of a mixed infection where a single drug may not give sufficiently broad coverage. Combinations of antibacterials with enzyme inhibitors (eg, co-amoxiclav, piperacillin/tazobactam) can restore or extend the activity of the antibacterial component of the combination.

One aim of using antibacterial combinations is to try to reduce the toxicity associated with high doses of the individual agents: a low dose of aminoglycoside is given with β-lactams to treat streptococcal endocarditis, giving rise to a better outcome with the combination than the individual agents alone. Conversely, some combinations can give rise to antagonism, although this may be more of a theoretical concern. An example would be the combined use of penicillins, which require bacterial growth for their action, with a bacteriostatic agent, which inhibits bacterial growth.

Combination therapy may also be used to help prevent the selection of drug-resistant mutants.

**Action: practice points**

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Obtain a copy of your hospital trust or primary care organisation antibiotic policy or guidelines. Work through the recommendations to identify the rationale behind each choice.
2. Develop a good working knowledge of the uses and toxicity associated with the antibacterials you commonly see in practice.
3. Review the advice you would give when dispensing antibiotics.

**Evaluate**

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

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**Resources**