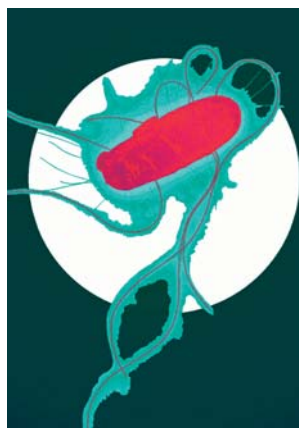


The right drug for the right bug

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 antibacterial-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.



E coli can cause cystitis

Dr Linda Stanward, UCT/SPL

Commensal or pathogen?

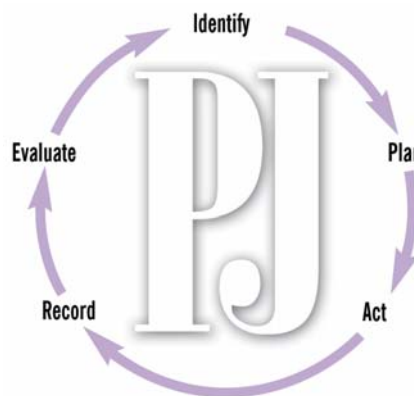
The human body carries a wide range of bacteria but few of these are able to cause infection in an immunocompetent host. Indeed, the majority are considered commensal or normal flora and can play an important role in host defence. For instance, eradication of the normal intestinal flora can permit overgrowth 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 investiga-



Identify knowledge gaps

1. Do you feel confident in advising clinicians on the choice of therapy for bacterial infection?
2. How can you distinguish between bacterial colonisation and bacterial infection?
3. What are the principal differences between antimicrobials in each class?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "drug therapy" (see appendix 4 of "Plan and record").

A nasal swab growing methicillin resistant *Staphylococcus aureus* (MRSA) is not grounds for treatment with intravenous vancomycin if the patient is otherwise well

tions (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 septicaemia 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

Table: Diseases, potential causative bacteria and typical treatment choices

Specific condition	Potential bacterial pathogen	Typical empiric treatment and special considerations
Meningitis	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , Group B streptococcus (seen in neonates). Less commonly, <i>Escherichia coli</i> and <i>Listeria monocytogenes</i> . Other Gram negative bacteria and <i>Staphylococcus</i> spp usually associated with neurosurgery	Cefotaxime or ceftriaxone provide broad cover and good cover. Causative agents can also be viral, mycobacterial or, rarely, fungi
Brain abscess	<i>S aureus</i> , anaerobic streptococci, <i>Bacteroides</i> spp, Gram negatives, such as <i>Escherichia</i> , <i>Proteus</i> , <i>Klebsiella</i> spp	Cefotaxime or ceftriaxone. The condition can, occasionally, be viral
Otitis media	<i>Str pneumoniae</i> , <i>H influenzae</i> , <i>Moraxella catarrhalis</i> , <i>S aureus</i> , mixed anaerobes	Amoxicillin or co-amoxiclav. Otitis media can also be viral (eg, adenovirus)
Otitis externa	<i>Pseudomonas aeruginosa</i> ("swimmer's ear"), <i>S aureus</i> (pustule)	Topical gentamicin. Less commonly fungal (<i>Candida albicans</i>)
Upper respiratory tract infections		
Pharyngitis/tonsillitis	<i>Str pyogenes</i> (group A)	Phenoxymethylpenicillin but note that 50 per cent of sore throats are viral
Epiglottitis	<i>H influenzae</i> , <i>Str pyogenes</i> (group A)	Ceftriaxone or cefotaxime
Sinusitis	<i>Str pneumoniae</i> , <i>H influenzae</i> , mixed anaerobes, <i>S aureus</i> , <i>M catharrhalis</i>	Co-amoxiclav. Sinusitis may be viral (eg, rhinovirus, influenza)
Lower respiratory tract infections		
Community-acquired	<i>Str pneumoniae</i> , <i>H influenzae</i> , <i>M catharrhalis</i> , "atypical organisms" (<i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> and, rarely, <i>Legionella pneumophila</i>)	Amoxicillin po or cefuroxime iv (depending on severity) +/- clarithromycin. "Guidelines for the treatment of community-acquired pneumonia"
Hospital-acquired	<i>E coli</i> , <i>Ps aeruginosa</i> and other Gram negative organisms, methicillin-resistant <i>S aureus</i>	Broad spectrum antibacterials are required until a definitive diagnosis is made on antibiotic sensitivity pattern. Infection can be viral. Fluoroquinolones are also used
Endocarditis	<i>Enterococcus</i> spp, Viridans group streptococci, <i>S aureus</i> , coagulase-negative staphylococci	Benzylpenicillin and gentamicin (synergistic action) or flucloxacillin
Gastrointestinal infections	<i>E coli</i> , <i>Shigella</i> spp, <i>Campylobacter jejuni</i> , <i>Salmonella</i> spp, <i>S aureus</i> , <i>Bacillus cereus</i> (toxin-mediated) <i>Clostridium difficile</i> (antibiotic-associated diarrhoea)	Gastrointestinal infections are generally self-limiting and of short duration. Antibiotics are considered necessary. In severe disease, ciprofloxacin is used. <i>Clostridium difficile</i> infections are treated with oral vancomycin or fidaxomicin. Stop broad spectrum antibacterials wherever possible. Give oral probiotics
Urinary tract infection (UTI)/Pyelonephritis	<i>E coli</i> , enterococci, <i>Klebsiella</i> spp, <i>Enterobacter</i> spp, <i>Pseudomonas</i> spp, <i>Proteus</i> spp.	For UTI, use amoxicillin, cefalexin or trimethoprim, depending on severity. For pyelonephritis, use cefuroxime or ceftriaxone. A longer course of treatment may be required and use of second-line drugs. Co-amoxiclav, cefuroxime or ceftriaxone are also used
Skin and soft tissue infection (cellulitis)	<i>S aureus</i> , <i>Str pyogenes</i> (group A)	Benzylpenicillin and flucloxacillin. Always check for co-existence of MRSA
Septic arthritis	<i>S aureus</i> , <i>Str pneumoniae</i> , occasionally Gram negatives	Cefuroxime empirically, but therapy should be guided by culture results
Osteomyelitis	<i>S aureus</i> , <i>Str pneumoniae</i> , coagulase-negative staphylococci (usually associated with implanted material). Many other organisms infrequently cause disease	Cefuroxime empirically, but therapy should be guided by culture results

questioning, thorough examination and thoughtful investigation can infection be reliably diagnosed or excluded (see "Resources").

Choice of antibacterial

The gold standard in treating infection is to tailor therapy to the organism grown from the site of infection. However, the infective organism is often unknown at the point of consultation. Currently, it takes about 24 hours to obtain provisional identification of an organism grown from a clinical specimen and at least a further 24 hours for results on antimicrobial sensitivities. A definitive microbiological diagnosis may not be possible even when appropriate specimens are taken; for instance, up to 40 per cent of sputum specimens from patients with clinically proven pneumonia will be culture-negative due to difficulties in cultivating the organisms *in vitro*. Empiric antibiotic treatment should, therefore, be started before results are available and knowledge of the typical pathogens and local antibiotic resistance patterns is essential (see Table). Once culture results have been obtained treatment may be streamlined.

The main antibacterials can be divided into three major classes according to their site of action

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 antibacterial 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.

central nervous system penetration. Ampicillin or amoxicillin is required for confirmed *Listeria* spp. Only bacterial, fungal and these will require appropriate therapy

may be fungal or parasitic

(eg, influenza, respiratory syncytial virus, enteroviruses)

(eg, *Candida* spp, *Aspergillus* spp)

causative agents are viral in origin

(eg, *Legionella* spp) or, occasionally, fungal

— clarithromycin if atypical organisms are suspected or rifampicin for *Legionella*. See British Thoracic Society "Community-acquired pneumonia"

Once diagnosis is made. Therapy may involve vancomycin plus ciprofloxacin, piperacillin-tazobactam or meropenem depending on the site of infection. Fungal infection is more likely in immunocompromised patients.

Flucloxacillin and gentamicin if staphylococci are suspected (often seen in intravenous drug users)

is often viral. Fluid replacement may be all that is required. Expert advice should be sought if antibacterials are used for *Salmonella* spp and erythromycin for *Campylobacter* spp

Oral metronidazole po for 10 days. Oral vancomycin is an alternative

Check for local resistance patterns. For an uncomplicated UTI in a young woman, three days' treatment should be sufficient. In men. Recurrent or complicated UTIs require further investigation, consideration of resistant organisms and possibly intravenous therapy. Ceftriaxone or cefepime are often used for pyelonephritis

Diagnosis of athlete's foot, which can be an entry point for organisms

Culture results

Culture results. Infections involving prostheses will require longer treatment

Penicillins Benzylpenicillin is active against staphylococci, streptococci and *Neisseria* spp but staphylococci can produce β -lactamases that render it ineffective. Modifications of the basic penicillin structure have led to the development of alternative agents, such as phenoxymethylpenicillin (which can be given orally), ampicillin and amoxicillin (which have activity against some Gram-negative organisms and also *Listeria* spp), flucloxacillin (which has increased activity against staphylococci due to stability against its β -lactamase enzyme) and piperacillin (which has important activity against *Pseudomonas* spp).

The spectrum of activity of the penicillins can be widened by concurrent use of a β -lactamase inhibitor, such as clavulanic acid or tazobactam.

Cephalosporins Cephalosporins are variants on the β -lactam ring structure with generally increased stability against β -lactamases. This group includes cefalexin (a useful oral agent for urinary tract infections), cefuroxime (the mainstay of many surgical prophylaxis regimens and useful in community-acquired

pneumonia and surgical sepsis), and cefotaxime and ceftriaxone, which have good broad-spectrum activity against both Gram-positive and Gram-negative organisms. These two cephalosporins are widely used as empiric therapy for meningitis and pneumonia and are thought to be clinically interchangeable except for differences in their pharmacokinetic profile — choice is influenced by preferred dosage regimen.

Ceftazidime, which has excellent activity against *Pseudomonas* spp, is often included in treatment regimens for neutropenic patients. These are usually patients who have undergone bone marrow ablation and whom pseudomonal infection can kill quickly.

Monobactams The only available monobactam is aztreonam. Its activity is restricted to Gram-negative aerobic organisms so it has limited clinical use.

Carbapenems Imipenem, meropenem and ertapenem are broad-spectrum agents and, as such, are important in empiric regimens for severe sepsis. However, these agents do not treat MRSA or *Stenotrophomonas maltophilia*. Significantly, ertapenem has no activity against *Pseudomonas* but due to its once-daily dosing regimen it can have important advantages for out-patient or long-term therapy.

Imipenem needs to be combined with cilastatin, an inhibitor of the renal dehydropeptidase enzyme which can break down the drug. Neither meropenem nor ertapenem is affected in this way.

Protein synthesis inhibitors Aminoglycosides Aminoglycosides are primarily active against enterobacteriaceae. They have little activity against intracellular bacteria, anaerobes or streptococci, although they do show synergy against the latter when used in combination with β -lactams or glycopeptides.

The most widely used aminoglycoside is gentamicin. This exhibits strong activity against *Pseudomonas* spp. One of the major drawbacks of aminoglycosides is their toxicity profile — renal impairment can occur in as many as 25 per cent of patients but this is usually reversible. Close monitoring of plasma levels and use of once-daily dosing should reduce the incidence of this side effect.

Macrolides 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.

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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:

- Clindamycin, 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 diaminopyridines Sulphonamides and diaminopyridines 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 sulfamethoxazole and trimethoprim (co-trimoxazole).

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.



Macrolide antibiotics mainly act against streptococci and staphylococci

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?

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.

Resources

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- British Thoracic Society Guidelines for the management of community acquired pneumonia in adults and an update can be found in Thorax 2001;56 (suppl 4):1–64 and at www.brit-thoracic.org.uk (accessed on 12 January 2005), respectively.

Correction

These pages had an incorrect publication date of 2004 instead of 2005.

This PDF has been corrected.