I doubt that there is any doctor alive in a western country who has had to manage a patient with a serious infection without antibiotics. The advent of antibiotic therapy, together with Lister’s discovery of antisepsis, has truly revolutionised medical and surgical treatment.

HISTORY OF ANTIBIOTIC TREATMENT
Vuillemin, in 1889, coined the word ‘antibiosis’, to describe antagonism between living organisms. In 1942, Selman Waksman, the discoverer of streptomycin, was the first person to use the word ‘antibiotic’.

Antibiotic is a ‘basterd’ word, derived from the Latin anti, meaning against, and the Greek word bios, meaning life. Its use should be confined to naturally occurring substances with antibacterial activity, whereas the word chemotherapy should be confined to synthetic compounds with antibacterial activity. It is difficult to adhere to this distinction, as many antibacterial agents are naturally occurring substances that have undergone chemical modification. I shall use the word antibiotic to refer to naturally occurring substances as well as synthetic antibacterial agents.

Extract of cinchona bark, which was shown in the 16th century to be effective in the treatment of malaria, was probably the first ‘antibiotic’ to be discovered. Paul Ehrlich invented the first effective chemotherapeutic agent when he showed that an arsenical compound, subsequently called ‘salvarsan’ (saved by arsenic), though very toxic, could be used to treat syphilis.

Though the bactericidal action of a substance produced by a species of the fungus Penicillium was described by Fleming in 1929, it was not until 1940 that Florey, in Oxford, demonstrated the therapeutic potential of this substance.

Meanwhile, in 1935, Domagk in Germany announced that a red dye, prontosil rubrum, was active against infections caused by streptococci in mice. The active component of this dye was sulphanilamide, the forerunner of the ‘sulpha’ drugs.

RATIONAL PRESCRIBING OF ANTIBIOTICS
The rational prescribing of antibiotics is much easier in hospital medicine than in...
general practice. The hospital doctor is able to examine his or her patient at regular intervals in order to decide whether or not the patient’s symptoms are caused by an infection. Furthermore, he or she can obtain the results of laboratory investigations more quickly than is the case in general practice.

Not only should GPs adopt a more pragmatic approach to the prescription of antibiotics, but they are also under pressure from patients to prescribe these drugs.

Most ‘common’ infections respond to antibiotics within two to three days. Absence of a significant response can be a result of various factors: the patient’s infection; the antibiotic is unable to reach the patient has an abscess; or the organism is resistant to the antibiotic that has been prescribed. In some situations, deciding whether a patient has an infection requires the sort of expertise that comes only from clinical experience.

If the patient has not responded to treatment within 48–72 hours, the diagnosis should be reassessed, rather than another antibiotic prescribed.

A differential white count can be helpful in distinguishing between an infective and non-infective condition mimicking an infection. However, patients who are immunosuppressed or taking steroids may not develop neutrophilia. The same phenomenon is seen in elderly patients. Furthermore, infections may not produce pyrexia in elderly patients.

As in all branches of therapeutics, it is best to have a sound knowledge of the uses of a few antibiotics, rather than a superficial knowledge of many.

Always measure the blood glucose concentration in a patient who presents with a severe or recurrent infection, especially if he has cellulitis.

INFECTIONS AFTER SPLENECTOMY
Remnants of the spleen may be present in patients who have had their spleen removed because of trauma. Such patients are not immunologically ‘asplenic’. Patients with conditions such as sickle cell disease may have a non-functioning spleen.

Patients without a spleen, or those with a non-functioning spleen, are more susceptible to bacterial infections, especially those due to capsulated organisms such as pneumococci and Haemophilus influenzae. Many such patients are prescribed a daily dose of phenoxymethylpenicillin (penicillin V), though there is no evidence that this prevents infections. Furthermore, H. influenzae is resistant to that antibiotic.

My advice is to tell these patients that they should always carry 3g of amoxicillin with them. Should they develop signs of an infection, they should take it at once, and then see a doctor as soon as possible. If the patient is allergic to penicillin (Figure 1), clarithromycin could be prescribed, although I think that a good case could be made for the use of rifampicin.

INTERPRETATION OF LABORATORY REPORTS
There is variation in the wording of reports. Some consultants use the term ‘normal flora’, which means that no organisms have been isolated that require the use of antibiotics. Others list the organisms that have been isolated. The latter method is becoming less common.

Most sites, particularly one that is moist such as the mouth or vagina, have a bacterial flora that is usually peculiar to that site – ‘normal flora’. Some specimens, such as the cerebrospinal fluid, should always be sterile. Organisms isolated from such sites should be assumed to be of clinical significance unless there is evidence to the contrary.

My practice was always to use the term ‘normal flora’ unless a recognised ‘pathogen’ was isolated. If I thought that the latter would definitely require treatment with antibiotics, for example group A haemolytic streptococci, I wrote the results of sensitivity tests on the report. If I thought that antibiotic treatment might be unnecessary, for example a growth of Staphylococcus aureus from an ulcer, I named the organism but did not give the results of sensitivity tests. The onus was then on the clinician looking after the patient to speak to me should he think that treatment with antibiotics was required.

ARE SAMPLES NECESSARY?
The value of a sample depends on the care with which it has been taken, a fact that is rarely emphasised when teaching nurses or medical students. Furthermore, some samples, for example swabs from skin ulcers in which there is no surrounding cellulitis, are useless as the result of culture will not affect the management of the patient.

USE OF ANTIBIOTICS IN GENERAL PRACTICE
Antibiotics are probably the most frequently prescribed drugs in the world, especially in general practice. Experts are continually exhorting doctors to restrict the prescribing of antibiotics. While that is sound in theory, it ignores the realities of practical medicine, particularly in the community.

Now that I work as a GP, rather than a consultant microbiologist, I take a more pragmatic approach to prescribing antibiotics, and usually give a patient the ‘benefit of the doubt’. Experts say that antibiotics should not be prescribed for chest infections as a matter of routine. However, if a patient tells me that he has a cough with purulent sputum, I prescribe an antibiotic, even if he is afebrile and there are no abnormalities on percussion or auscultation of the chest. Experience has taught me that such patients get better quicker than if I had not prescribed antibiotics.

In my opinion, the penicillins are one of the most effective groups of antibiotics.
The choice of antibiotics, particularly in general practice, becomes limited when a patient says that he is allergic to penicillin. Genuine allergy, in which the patient has an anaphylactic reaction to penicillin, is very rare, and is an absolute contraindication to giving any beta-lactam antibiotic. A clearly described skin rash is a contraindication to a penicillin but not to a cephalosporin (see Figure 1). Many patients who say that they are allergic to penicillin are unable to give a clear description of the allergic reaction.

In hospital practice, I used to prescribe a penicillin if the history of an allergic reaction was vague. The patient would be given intravenous hydrocortisone and chlorphenamine (Piriton) about half an hour before being given the penicillin. The risk was negligible as nursing and medical staff were available to observe the patient. I have never had a problem in that situation. Unfortunately, similar facilities are not available in general practice. In an increasingly litigious age, it is safer to prescribe an antibiotic other than a beta-lactam if the patient says that he is allergic to penicillin.

The taste of oral medicines is important when prescribing for children. ‘Amoxil’ tastes much better than generic brands of amoxicillin. Suspensions of flucloxacillin and penicillin V also have an unpleasant taste. It is important that GPs are aware of the taste of mixtures that they prescribe for children, as the latter will not take the medication if it has a foul taste.

Though combinations of antibiotics are often used in hospital, they are rarely required in general practice. The same applies to the use of antibiotics for prophylaxis against infections.

**FREQUENTLY PRESCRIBED ANTIBIOTICS**

Antibiotics that are frequently prescribed in general practice are listed in Box 1.

**Amoxicillin**

Amoxicillin is better absorbed than ampicillin, and its absorption is not affected by food.

**Co-amoxiclav**

Co-amoxiclav (Augmentin) is a combination of clavulanic acid, which inhibits some beta-lactamases, and amoxicillin. It can produce abnormal liver function tests. Strains of *E. coli*, *H. influenzae* and *Bacteroides fragilis* that are resistant to amoxicillin are sensitive to co-amoxiclav. It is also active against *S. aureus*, but has no activity against *P. aeruginosa*.

**Flucloxacillin**

Flucloxacillin has a similar range of activity to benzylpenicillin, but only 70% of the oral dose is absorbed, the rest passing out in the stools. Enteric bacteria, enterococci, *S. aureus* and *H. influenzae* are resistant to penicillin V. It remains a popular antibiotic for the treatment of sore throats caused by group A haemolytic streptococci.

**BOX 1. Frequently prescribed antibiotics**

- Amoxicillin
- Co-amoxiclav
- Penicillin V
- Benzylpenicillin
- Flucloxacillin
- Cephalosporins
- Macrolides
- Tetracyclines
- Quinolones
- Cotrimoxazole
- Trimethoprim
- Nitrofurantoin

They are both bactericidal, and have a similar range of antibacterial activity.

Amoxicillin is a good ‘general purpose’ antibiotic. It is active against haemolytic streptococci, most enterococci except *E. faecium*, meningococci, most strains of *H. influenzae*, anaerobes such as *Clostridium* species, and some species of *Bacteroides*. About 10% of pneumococci in this country are resistant to amoxicillin (the percentage varies between different parts of the country). About 60% of strains of *Escherichia coli*, the most common cause of urinary tract infections, are resistant. Most strains of *S. aureus* and all strains of *Pseudomonas aeruginosa* are resistant.

Amoxicillin is an appropriate antibiotic for the treatment of upper respiratory tract infections, including otitis media and sore throats caused by group A haemolytic streptococci, as it is much better absorbed than penicillin V. However, if the sore throat is caused by infection with the Epstein-Barr virus, the patient will inevitably develop a rash.

**Penicillin V**

Penicillin V has a similar range of activity to benzylpenicillin, but only 70% of the oral dose is absorbed, the rest passing out in the stools. Enteric bacteria, enterococci, *S. aureus* and *H. influenzae* are resistant to penicillin V. It remains a popular antibiotic for the treatment of sore throats caused by group A haemolytic streptococci.

**Benzylpenicillin**

Benzylpenicillin remains an effective antibiotic provided that the organism infecting the patient is sensitive to it. Group A haemolytic streptococci and meningococci are sensitive to it, as are the majority (about 90%) of strains of pneumococci in this country. Most strains of *S. aureus*, anaerobes other than *Clostridium* sp., are resistant. Enterobacteria are always resistant.

Benzylpenicillin is still a good antibiotic for the initial treatment of cases of meningococcal meningitis seen in general practice. Patients should be given one mega-unit stat before sending the patient to hospital. If the patient is known to be allergic to penicillin, but the allergy is not an anaphylactic reaction, give cefotaxime 2g iv stat.

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S. aureus (MRSA). It must be given on an empty stomach as absorption is reduced by food.

Patients with severe staphylococcal infections, such as osteomyelitis, should be treated in hospital; fluclosaxillin with the addition of rifampicin should be given by the intravenous route for two weeks. If there is a good response, oral therapy can be started, which means that the patient can be treated in the community. Liver function must be monitored in patients on a combination of flucloxaxillin and rifampicin. Flucloxaxillin alone can produce abnormal liver function tests.

A patient with a probable staphylococcal infection should receive a stat dose of 1g flucloxaxillin followed by 500mg every six hours. A dose of 250mg four times daily is, in my opinion, homeopathic.

Cephalosporins
All cephalosporins are derived from cephalexin, which was isolated from a mould called Cephalosporium acremonium in 1948. Cephalexin, the first cephalosporin to be used in clinical medicine, had to be given parenterally. It can cause renal damage, so is no longer used in clinical medicine.

A large number of cephalosporins have now been synthesised, some of which can be given by mouth, whereas others have to be given parenterally.

I often prescribed cefotaxime in hospital practice, but rarely use cephalosporins in general practice. The earlier cephalosporins to be synthesised have a similar range of activity to the penicillins; more recent ones have an extended range of activity and some, such as cefotadine, are active against P. aeruginosa. Cephalosporins have no activity against enterococci, and they are more likely to cause diarrhoea due to Clostridium difficile than other beta-lactam antibiotics. They have little activity against many anaerobes.

Cephalexin is active against most Gram-positive organisms, except enterococci, and it has reasonable activity against anaerobes, with the exception of B. fragilis. It is also active against S. aureus (but not MRSA). It would be a reasonable choice of antibiotic for a patient who had a mild (ie not anaphylactic) allergy to penicillin.

Macrolides
Macrolides are a group of closely related antibiotics produced by various species of streptomycete. They all possess a macrolactone ring, hence their name.

They have a range of activity against Gram-positive organisms similar to that of benzylpenicillin, although they are bacteriostatic rather than bactericidal. In addition, S. aureus is usually sensitive (some strains of MRSA are also sensitive). Some Gram-negative organisms such as Campylobacter sp., gonococci and meningococci are also sensitive. Macrolides are also active against Legionella sp., Corynebacterium diphtheriae and infections caused by rickettsia.

Macrolides are usually the antibiotic of choice for the treatment of infections in patients who, were they not allergic to a beta-lactam antibiotic, would have received penicillin.

Clarithromycin is probably the best macrolide to prescribe in general practice as it needs to be taken only twice a day. In combination with other drugs, erythromycin is used for the eradication of infection caused by Helicobacter pylori.

Most macrolides can cause abdominal discomfort. The estolate salt of erythromycin can cause severe hepatitis.

Tetracyclines
I do not believe that tetracyclines have a place in general practice, or hospital medicine, apart from from lymecycline, which is used to treat acne, and doxycycline, which is used as prophylaxis against malaria.

Quinolones
Nalidixic acid, the first quinolone to be used in clinical medicine, was synthesised in 1962. Ciprofloxacin is probably the most common quinolone to be used in clinical medicine. It is active against a wide range of Gram-negative organisms, including P. aeruginosa.

The use of ciprofloxacin in general practice should be restricted to the treatment of infections caused by P. aeruginosa, and urinary tract infections caused by organisms that are not sensitive to co-amoxiclav, nitrofurantoin or trimethoprim.

Although ciprofloxacin is also active against Legionella pneumophila, Bacillus anthracis and Chlamydia sp., this has little relevance to general practice. Its use can cause diarrhoea due to C. difficile, particularly in elderly patients.

Levofloxacin, the pure L-isomer of ciprofloxacin, is promoted for the treatment of pneumococcal pneumonia. It would not be my first choice of an antibacterial agent.

Cotrimoxazole
This synthetic agent is a combination of trimethoprim and sulphonamethoxazole. Toxicity is mainly caused by the sulphonamide component. It can cause blood dyscrasias, particularly in elderly patients. It has no advantage over less toxic antibacterial agents. Its use should be restricted to the prophylaxis and treatment of infections caused by Pneumocystis carinii in patients who are HIV positive.

Trimethoprim
This antibacterial agent inhibits the enzyme dihydrofolate reductase, interfering with the synthesis of folic acid. It is active against streptococci, S. aureus, some strains of MRSA, H. influenzae and many Gram-negative bacteria except P. aeruginosa.

Most anaerobes are resistant to it. It is well absorbed from the gut.
Trimethoprim is one of the drugs of first choice for the treatment of urinary tract infections and, if the organism is sensitive, for enteric fever. Haematological side-effects are rare, unlike the case with sulphonamides.

**Rifampicin**
This bactericidal drug is used in combination with isoniazid, ethambutol and pyrazinamide for the treatment of tuberculosis. The only use for it in general practice is for prophylaxis against meningococcal infection, for which a dose of 600mg twice daily for two days is sufficient. Though it is hepatotoxic, a patient is unlikely to have problems when it is used for only two days.

**Nitrofurantoin**
This synthetic agent can be given only by mouth. It is active against the common bacterial causes of urinary tract infection, with the exception of *Proteus mirabilis* and *P. aeruginosa*. It is absorbed from the proximal small intestine. Absorption depends on the brand used. Nausea is a common side-effect. Its use is restricted to the prophylaxis and treatment of urinary tract infections.

**DOMICILIARY ANTIBIOTIC THERAPY**
The use of intravenous antibiotics outside hospitals, domiciliary antibiotic therapy, is likely to be the most important change in antibiotic therapy during the next decade. Many patients who are otherwise well are kept in hospital just to be given intravenous antibiotics. Not only is that unnecessarily expensive, but also disagreeable for the patient. Careful organisation is required to ensure that a domiciliary intravenous antibiotic service works well. Such a service should be under the supervision of a consultant medical microbiologist or an infectious diseases physician. Patients should be seen at regular intervals to ensure that they are responding to treatment, and that the site of the intravenous cannula is not infected. Thus specially trained nurses will be needed in addition to medical staff.

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**FURTHER READING**
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