

How pharmacists can promote the sensible use of antimicrobials

This second article in a series of three on antibiotics looks at the correct use of antimicrobials in secondary and primary care.

Hayley Wickens and **Paul Wade** examine the situations where inappropriate use can lead to resistance and treatment failure, and how pharmacists might contribute to minimising the development and spread of resistance

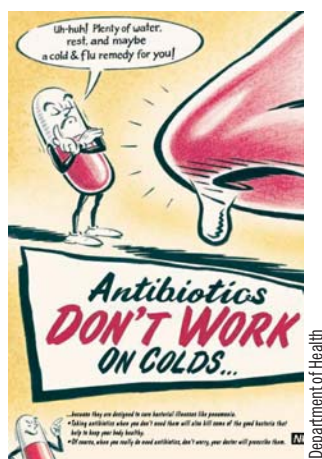
Ensuring appropriate and safe use of any drug in an individual patient is important. However, antimicrobials are the only class of drugs where irresponsible use in one patient may affect the potential use of these drugs in future patients — inappropriate use (see Panel 1 for examples) has been shown to drive the development of antimicrobial resistance. This makes infection more difficult to treat and has been shown to increase morbidity, mortality, duration of illness and cost.

Pharmacists are increasingly recognised as an integral part of the infection management team, especially in hospitals, and are ideally placed to advise on the selection of antimicrobials and the monitoring of patients on therapy.

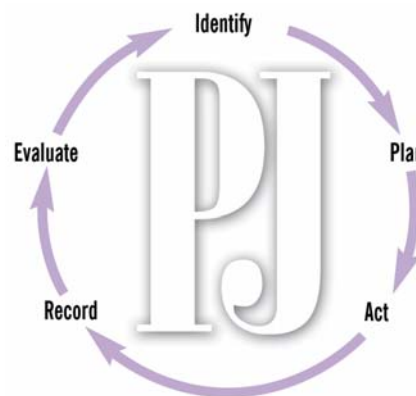
Clinical monitoring

As mentioned in the previous article in this series (*PJ*, 26 March, p365–8), infection can mimic a wide range of other conditions, so it is important to gather as much information from the various investigations available and use this appropriately when monitoring response to therapy.

Many infections will give rise to changes in haematological parameters and some of these can be used to follow the progress of the infection and its response to treatment. Bacterial sepsis will usually produce a rise in neutrophil count (although in cases of severe



Antibiotic resistance posters are available from the Department of Health



Identify knowledge gaps

1. Which clinical parameters are useful in monitoring the progress of an infection?
2. What can pharmacists do to prevent antibiotic resistance?
3. What does an antimicrobial pharmacist do?

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").

Panel 1: Examples of inappropriate use of antibiotics

- Use of antibiotics for a viral infection
- Use of an antibiotic for a longer period than necessary (many conditions have recommended treatment periods, eg, three days of trimethoprim or amoxicillin in uncomplicated urinary tract infection in women)
- Indiscriminate use of broad spectrum antibiotics (narrow spectrum agents should be used where possible)
- Concurrent use of antibiotics with the same spectrum of activity (but there are exceptions to this, eg, anti-tuberculosis therapy)
- Use of an antibiotic alone when it should be used with others to avoid the development of resistance (eg, rifampicin and fusidic acid)

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sepsis or atypical pneumonias there may be neutropenia) and this can be followed through the treatment course of antibiotics to, hopefully, a successful resolution. Examination of a peripheral blood film can identify some pathogens, such as *Plasmodium* spp in malaria, and the parasite count seen in a blood film can be used to monitor response to antimalarial therapy.

Inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) show how the body is responding to infection or inflammation, and levels can be raised in infection (although CRP can be lowered in viral infections). Both of these tests may be used to monitor response to therapy, with the CRP being useful in more acute situations. The ESR provides a marker of response in chronic conditions such as tuberculosis or bacterial endocarditis.

Several biochemical tests can be used to monitor infection. Liver function tests can be raised in many infections and can also be useful markers of antibacterial liver toxicity (eg,

with anti-tuberculous agents or antifungals, such as voriconazole).

Serum lactate is raised in patients with severe sepsis and is a useful marker of recovery of organ function during sepsis resolution. In patients with Legionnaire's disease serum sodium levels are often low. Renal function can often be deranged in patients with infections such as those involving the urinary tract or in more severe sepsis. Monitoring renal function is an essential part of pharmaceutical care in patients with sepsis because, not only can impaired renal function have a significant effect on drug dosing, but improvement in renal function can also be used as a marker of response to treatment.

Finally, the body's exposure to several infectious diseases can be determined by monitoring antibody responses to the particular antigen, measured in the blood and other body fluids. Such infections include Legionnaire's disease, meningococcal meningitis and septicaemia, pneumococcal or cryptococcal disease, and several viruses (including cytomegalovirus, hepatitis B, HIV and mumps).

Other investigations that can give useful information about progress of infections include radiology (such as chest X-ray resolution in pneumonia or shrinkage of abscess collection on ultrasound scan) and lung function tests (in pneumonia or more chronic diseases such as tuberculosis, or fungal infections such as invasive pulmonary aspergillosis).

Therapeutic drug monitoring

Some antimicrobials require therapeutic drug monitoring, but glycopeptides and aminoglycosides are of particular concern because they have a narrow therapeutic index.

Glycopeptides Vancomycin is highly effective against methicillin-resistant *Staphylococcus aureus* (MRSA), but is potentially both nephro- and ototoxic. Much of the available toxicity information is based on older, more impure preparations and the newer preparations are safer. Risk factors that can predict nephrotoxicity include:

- Concomitant use of other nephrotoxic agents (such as furosemide, aminoglycosides and co-trimoxazole)
- Prolonged therapy (in excess of three weeks)
- Continually elevated trough levels

Ototoxicity due to high vancomycin peaks is particularly unusual with the newer preparations and many centres no longer measure peak levels of vancomycin because evidence suggests that high trough levels rather than the transient high peaks are responsible for the majority of side effects. Trough levels are, however, essential for monitoring vancomycin therapy and should be measured two to three times a week, or more frequently depending on the clinical situation.

Currently, most centres use a range for the trough level of between 5–10mg/L to ensure

Table 1: Typical trough values for three aminoglycosides

Aminoglycoside	Trough level	
	Once-daily dosing*	Multiple-daily dosing*
Gentamicin (5mg/kg/day)	<1mg/L	1–2mg/L
Amikacin (15mg/kg/day)	<5mg/L	5–10mg/L
Tobramycin (5mg/kg/day)	<1mg/L	1–2mg/L

*Doses given are for adults with normal renal function. If renal function is impaired, dosage must be reduced or dosing interval increased

efficacy with minimal risk of toxicity, but there is increasing evidence that higher troughs might be needed in some types of infection (eg, MRSA pneumonia because vancomycin poorly penetrates lung tissues and fluids), and some centres administer vancomycin by continuous infusion, using steady state levels of 15–25mg/L as their normal range.

Monitoring may be considered for teicoplanin, to ensure therapeutic levels are reached; evidence for what constitutes a toxic level of teicoplanin is lacking.

Aminoglycosides Although aminoglycosides were originally licensed for multiple-daily dosing, once-daily administration (in particular for gentamicin, but also amikacin and tobramycin) is now routine in many centres. There are several reasons why once-daily dosing is an advantage. Pharmacodynamic studies with aminoglycosides have shown that they are rapidly bactericidal, with increased kill rate at higher drug concentrations. Thus, transient high concentrations of aminoglycosides are beneficial. This is in direct contrast to beta-lactam agents whose bactericidal activity depends on their concentrations being kept above a minimum inhibitory concentration. Aminoglycosides also exhibit a post-antibiotic effect, whereby persistent suppression of bacterial growth occurs after short exposures to a drug. This has been shown to occur with aminoglycosides and Gram negative organisms such as *Pseudomonas aeruginosa* or enterobacteriaceae and also for *S aureus*, but not for *Streptococcus pneumoniae*.

In addition, once-daily dosing has been shown to be as effective as multiple-daily dosing. It gives rise to either comparable or less drug-induced toxicity than multiple-daily dosing and is simpler to manage and less costly (in terms of acquisition costs and nursing time). Only trough levels are measured and typical reference values are given in Table 1.

However, once-daily administration of aminoglycosides is not suitable for all patients. In enterococcal endocarditis, equivocal data from animal models indicate that multiple-daily dosing should probably still be used, and care needs to be taken in patients with altered volume of distribution (eg, postpartum, or patients with ascites or burns).

Aminoglycosides are excreted by the kidneys so dosage intervals longer than 24 hours may be necessary in patients with

Pharmacists are ideally placed to offer advice on selection of antimicrobials and monitor the progress of patients on therapy

marked renal impairment if attempting once-daily dosing. However, there can be logistical difficulties in co-ordinating administration and monitoring at such extended dosing intervals. There is also concern about possible prolonged exposure to high trough concentrations.

More investigations into the use of once-daily dosing of aminoglycosides in other patient groups, such as pregnant women, are needed. Use in children and patients with cystic fibrosis is increasing.

Strategies to improve antimicrobial use

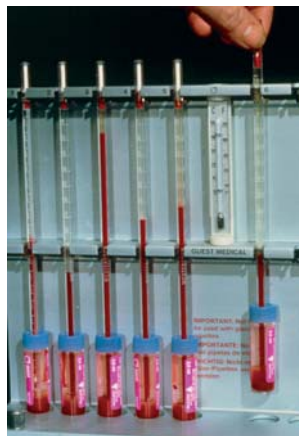
Every day in UK hospitals around 35 per cent of patients are prescribed antibiotics (either for treatment or prophylaxis) but the choice of antibiotic is often inappropriate and the duration of therapy prolonged. This can be explained by several factors. The extent of medical education on microbiology and infection is often inadequate. Many clinicians underuse the skills and facilities offered by their microbiology laboratory and fail to request appropriate investigations or seek advice on resistance patterns. In addition, the ever-increasing pressure on hospital beds can force early patient discharge and in some cases it can be tempting to treat an infection with a broad-spectrum antibiotic, before a culture result is obtained.

In an attempt to limit the emergence and spread of antimicrobial resistance, various studies have been carried out to examine how to best restrict antibiotic use. Agencies such as the World Health Organization, the Centres for Disease Control and Prevention in the US, the European Union and the UK Department of Health have issued their own guidance on how best to tackle the problem of increasing antimicrobial resistance. For example, use in animal feeds (as growth promoters) has been phased out.

In the UK, most anti-infectives are only available on prescription (although this is not the case in other countries), therefore, efforts to control use in the UK are centred mostly on primary care and hospital prescribing.

The main elements of the UK guidance are prudent use of antimicrobials, good infection control and surveillance of antimicrobial resistance and drug use. Any antimicrobial control strategy must, if it is to be successful, contain the following components:

- Good co-ordination and co-operation between the key players for antimicrobial use (eg, microbiologists, infectious diseases physicians, infection control staff, hospital clinicians and pharmacists)
- Good evidence-based guidelines for local antimicrobial use (including information on choice and dose of agent, route and duration of therapy, data on local resistance patterns and contacts for advice)
- Surveillance of antimicrobial use (including quantities, costs and appropriateness) [In primary care, prescription cost and analysis reports (PACT) are used, but



Science Photo Library

Erythrocyte sedimentation rate is a marker of response to treatment in chronic infections

Successful antimicrobial control strategies are multifactorial

there is no unified way to measure secondary care prescribing. Some hospitals use monthly reports generated by their electronic dispensary systems.]

- Good (and regularly updated) education on antimicrobial use for clinicians, nurses and pharmacists
- Good infection control practices (including early detection of problem patients — those carrying multi-resistant organisms — and regular promotion of practices, such as maintaining hand hygiene)

Hospital pharmacy In 2003, the Department of Health formally recognised the importance of clinical pharmacy in controlling antimicrobial use and £12m was made available to hospital pharmacists in England to facilitate activities in this field. There have since been several articles written discussing the role of “antimicrobial pharmacists” and some of their key activities are summarised in Panel 2. However, there is a comparative lack of evidence on the relative efficacy of interventions to improve antimicrobial prescribing practice and limit the spread of resistance.

Antibiotic cycling (where a hospital or unit uses a restricted rotational policy for empiric choice of antibiotic) has been examined in a few studies, mostly in intensive care. However, this may not be as effective in limiting the emergence of resistance as less restrictive policies that allow free selection of antimicrobials from a limited list (sometimes known as a heterogeneous use policy).

Facilitating the uptake of prescribing policies by clinical staff is of prime importance, but evidence is lacking as to the most effective way to do this. Restrictive interventions, in which “reserved use” antibacterials are physically removed from wards, may be more effective than educational interventions such as posters or teaching sessions alone. A combination of approaches might be most effective.

Panel 2: Activities of antimicrobial pharmacists

- Attending ward rounds and acting as a point of contact between pharmacy, microbiology and infectious diseases and infection control teams
- Providing advice on antimicrobial therapy (choice, dose and duration) for individual patients
- Preparing evidence-based prescribing guidelines for antimicrobials
- Promoting good prescribing practice (eg, intravenous to oral switches, “streamlining” broad-spectrum therapy, adherence to local guidelines)
- Monitoring antibiotic use (in terms of volume or “defined daily doses”) and expenditure
- Teaching and training in antimicrobial therapy for doctors, nurses, pharmacists, and undergraduate medical and pharmacy students

Panel 3: Counselling points

Patients should be advised:

- To complete the prescribed course, even if they feel better
- To take the antibiotics at regular intervals (eg, three times a day means every eight hours)
- About potential side effects and how they might be avoided
- How best to take antibiotics to improve absorption (ie, before, with or after food)
- Not to double the dose if the previous dose was missed
- Not to always expect antibiotics because some conditions are liable to be viral in origin and self-limiting

Community pharmacy More than 80 per cent of UK prescriptions for antibiotics are written in the community. Community pharmacists can contribute to the correct use of antibiotics through patient counselling to encourage successful therapy.

Before dispensing an antibiotic, the pharmacist should check with the patient whether he or she has any allergies, particularly to penicillin. Panel 3 lists some counselling points.

A Cochrane review of the evidence for hospital-based antibiotic interventions is to be published shortly (www.cochrane.org). Guidance for us of antibiotics in primary care is available from the Health Protection Agency.



Investing time in patient counselling encourages successful therapy

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. Visit www.cochrane.org and look at the evidence for interventions with respect to ensuring correct use of antibiotics. Think about how you could apply these to your practice.
2. Keep leaflets, such as "Antibiotics: don't wear me out" and an antibiotic resistance poster in your pharmacy. These can be obtained by writing to: The Department of Health, PO Box 777, London SE1 6XH.
3. Community pharmacists can visit the Health Protection Agency website (www.hpa.org.uk) and look at the guidance on antibiotic use in primary care. Hospital pharmacists can visit www.bsac.org.uk/pyxis and look at the guidance on treatment of hospital infections

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?

The pharmaceutical industry

New antimicrobials are essential for the continued successful treatment of infection but many major pharmaceutical companies are reducing or stopping altogether their research programmes in antimicrobial development. The last truly new class of agents to make it to the marketplace was the oxazolidinones (eg, linezolid) and these molecules were originally discovered in the 1970s.

There is a dearth of potential agents to assist in the fight against resistance. The various reasons for this are outside the scope of this article, but the economic and regulatory considerations that are forcing companies to make these decisions need to be addressed urgently, or our therapeutic arsenal may soon be exhausted.

There are several moves afoot in the US and Europe to provide incentives to antimicrobial development. However, at the same time regulations are being introduced which will discourage further development, generating mixed signals. For example, under new EU regulations, clinical trials must be bigger. This is not always possible in groups with infectious diseases. And, of course, larger trials mean higher costs.

It is imperative that everyone involved in the use of antimicrobials (including policy makers, pharmaceutical industry, prescribers, pharmacists and patients) recognises their role in this battle and works together towards the common aim of restricting antimicrobial usage, lessening the burden of antimicrobial resistance and reducing morbidity and mortality due to infection.

The next article in this series (to be published in the 23 April issue of *The Journal*) will concentrate on some of the more pressing clinical problems associated with antimicrobial resistance, such as vancomycin-resistant enterococci, multi-resistant Gram-negative organisms, and in particular, MRSA.

Resources

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Correction

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

This PDF has been corrected.