Antibiotic prescribing: how can emergence of antibiotic resistance be delayed?

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Summary

The discovery of new antibiotic drugs has slowed significantly and widespread use of current antibiotics has resulted in the emergence of many multi-resistant bacterial pathogens. In order to preserve the activity of currently available antibiotics for as long as possible, care should be taken to only prescribe them when an infection is serious and is likely to respond significantly to treatment. Judicious prescribing will reduce the selective pressure on bacteria and thereby slow down the emergence of resistance. In the future, prevention through immunisation and reducing the spread of infection (infection control) will assume greater importance as a way of sidestepping the interplay of antibiotic use and bacterial resistance. It is particularly important to avoid empirical use of antibiotics for most patients with upper respiratory infections.

Key words: drug utilisation.

(Aust Prescr 2004;27:39–42)

Introduction

Antibiotic use remains the primary factor in the emergence and spread of antibiotic resistant organisms. The importance of minimising unnecessary exposure to antibiotics among humans and animals[1] has been rightly emphasised by many authors. There is increasing evidence that directly associates antibiotic use with the emergence of resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus, resistant Gram negative bacilli and *Clostridium difficile*. The recent widespread emergence of serious disease caused by strains of MRSA acquired in the community adds further urgency to the need to reduce antibiotic selective pressure.

Many studies have shown that more judicious use of antibiotics can reduce resistance, independent of traditional infection control measures.[2,3,4,5] However, the situation is complex as resistance, once selected, may not go away after withdrawal of the selective pressure. While there may be a higher metabolic cost for resistant bacteria to maintain the additional genetic material associated with resistance, many strains are able to compensate for this through further mutational change or deletion of non-essential DNA. Combinations of virulence factors and antibiotic resistance genes may make the pathogen better able to spread, colonise and invade a vulnerable patient.

Prevention of cross infection in all healthcare situations through adherence to infection control measures such as hand hygiene is a crucial part of infectious disease control. These measures provide a potent way of reducing the need to use antibiotics for treatment.

Principles of antibiotic prescribing

Antibiotics are prescribed for three reasons:

■ prophylaxis – where administration is designed to prevent serious infection in a defined at-risk situation

■ empiric therapy – where a clinical syndrome that may be due to infection is managed before evidence confirming the presence of infection or its cause is available

■ directed therapy – where antibiotics are aimed at micro-organisms which have been confirmed as the cause of an infection.

For each type of therapy, there are principles that aim to minimise the use of antibiotics and also ameliorate the selection of antibiotic resistance (see Box 1).[6]

> ### Box 1
> ### Principles of appropriate antibiotic use [6]
>
> Evidence-based indications
>
> Microbiology should guide therapy wherever possible
>
> Narrowest spectrum required
>
> Dosage and duration appropriate to the site, type and severity of infection
>
> Check up-to-date guidelines

Antibiotic prophylaxis

Prophylaxis is used for medical (for example, preventing relapses of rheumatic fever or the spread of meningococcal infection) and surgical purposes (prevention of wound infection). Recommendations to use antibiotic prophylaxis for a particular type of surgical operation are made after consideration of:

■ the incidence of surgical wound infection

■ the usual impact of this infection

- the demonstrated effectiveness of antibiotic prophylaxis in preventing these infections (randomised trial evidence).

Reducing bacterial resistance selection by antibiotic prophylaxis

Exposure to antibiotic surgical prophylaxis is often the initial selective pressure placed upon a patient's bacterial flora on entry to hospital. The flora is modified in such a way as to facilitate colonisation (and potential ensuing infection) with more resistant hospital bacteria. In order to minimise this adverse impact and to maximise effectiveness of antibiotic prophylaxis, narrow spectrum drugs should be used for the shortest time possible (Table 1).

Empiric therapy

Patients often present with symptoms that may be caused by infection. A decision then has to be made about the likely cause of infection and whether it needs drug treatment. On occasions empiric therapy is also used to prevent complications arising from a minor infection.

Are antibiotics indicated?

The decision to use antibiotics in a particular clinical situation is complex. It balances the natural history of the disease or syndrome, the potential seriousness of its outcomes, evidence that antibiotics affect these outcomes and the potential adverse effects of antibiotic therapy. We now recognise that antibiotics are a precious resource, crucial to the management of many potentially fatal infections (such as meningitis). In order to actively safeguard future antibiotic effectiveness in these diseases we must reduce our reliance on antibiotics for mild or self-limiting conditions in hospitals and the community.

Hospital

Difficulties often arise in intensive care units where clinical features are frequently non-specific. For instance, although antibiotics are usually given for lung consolidation in severely ill patients, it is estimated that fewer than 50% of these patients actually have an infective cause for the consolidation.[7]

Community

Most antibiotics are prescribed for patients with upper respiratory infection (acute otitis media, pharyngitis, sinusitis) and acute bronchitis. These conditions are most often caused by viruses and are of self-limited duration. Randomised trials show antibiotics have limited or no impact. The antibiotic guidelines published by Therapeutic Guidelines[6] place increasing emphasis on effective (non-antibiotic) symptom management, preventative measures such as immunisation and where possible, evidence-based selection of subsets of patients that are most likely to benefit from antibiotic therapy. For example, in acute otitis media, children presenting with systemic symptoms such as high fever or vomiting are more likely, than children without these symptoms, to benefit from antibiotic therapy.[8,9] The treatment of otitis media with antibiotics cannot be justified on the grounds of preventing mastoiditis as trial data show that this complication is rare in developed countries (1 per 1000 or less).[10]

Choice of antibiotic

If an antibiotic is indicated, a drug should be chosen that will limit the development of bacterial resistance (Table 2). The choice of drug is influenced by the likely pathogens and local resistance patterns.

Duration of empiric therapy

In hospital, the patient should be reassessed after 24–48 hours of empiric antibiotic therapy to decide whether infection is unlikely (cease therapy) or whether a firm diagnosis can be made (modify therapy as appropriate (see also Table 2)). In community practice, as a general rule, the minimum duration of treatment recommended in Therapeutic Guidelines: Antibiotic[6] should be prescribed.

Table 1

Reducing bacterial resistance selection in surgical prophylaxis with antibiotics

Principles	Common pitfalls
Use surgical prophylaxis only where there is a strong evidence-based indication	There is little current evidence to support use in inguinal hernia repair where prosthetic material is not inserted
Select the antibiotic with the narrowest antibacterial spectrum required	Using a 'third generation' cephalosporin for surgical prophylaxis: their broad spectrum makes them potent selectors for *C. difficile*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus. Additionally, some of these drugs may not have sufficient activity against *Staphylococcus aureus.*
Time the first dose to ensure sufficient drug concentrations at the operative site at the time of incision through to time of closure	Delay in initial dose significantly reduces the prophylactic effect Failure to repeat the dosing of a short-acting drug during a long operation
Minimise postoperative doses of prophylaxis	Dosing until surgical drains are removed (This results in no additive reduction in infection. It makes superinfection with antibiotic resistant bacteria more likely.)

Reducing bacterial resistance selection in empiric treatment with antibiotics

Principles	Common pitfalls
Assess patients carefully before therapy	Incorrect diagnosis made: e.g. acute otitis media: detection of middle ear fluid is often inaccurate and leads to diagnostic error
Treat infection, not contamination	Antibiotics directed at a blood culture skin contaminant
Treat infection, not colonisation	Antibiotics directed at: ■ urinary isolates in an asymptomatic patient, whatever the cell count or urinalysis findings ■ Gram negative wound isolates from chronic leg or foot ulcers
Aim empiric therapy at the likely pathogens with knowledge of local susceptibility patterns: ■ take appropriate cultures ■ use appropriate drug(s), dose and route ■ refer to Therapeutic Guidelines: Antibiotic and/or local clinical guidelines	Sepsis syndrome: inadequate number or no blood cultures taken Severe pneumonia: tests for viral infection not performed
Avoid overuse of vancomycin (glycopeptides) to reduce emergence of vancomycin resistance in staphylococci and enterococci[11]	Continued empiric use of vancomycin for presumed infections in patients whose cultures are negative for beta-lactam-resistant Gram positive micro-organisms
In hospital, assess patient after 24–48 hours of empiric therapy and decide: ■ bacterial infection unlikely – cease antibiotics ■ microbiological evidence available – change to directed therapy	Insufficient microbiology tests before therapy (e.g. viral studies in a patient with severe community-acquired pneumonia) Microbiological culture results not reviewed Patients left on antibiotics in the absence of a specific diagnosis

Directed therapy

When the cause of an infection is confirmed, antibiotic therapy is aimed at those micro-organisms. The confirmation may come from clinical or pathological information. Microbiological confirmation is preferred as it gives the greatest assurance that the correct antibiotic drug has been chosen. The involvement of a specific pathogen may be implied by evidence from microscopy, culture or direct detection through nucleic acid amplification (for example, polymerase chain reaction testing for meningococci in blood or cerebrospinal fluid).

Therapeutic Guidelines: Antibiotic[6] provides evidence-based recommendations for directed therapy for common infections. Correct selection of the antibiotic drug, its dosage and route are crucial to minimising the emergence of resistance during therapy. For instance, the common practice of prescribing prolonged (more than 10 days) monotherapy with oral ciprofloxacin for *Pseudomonas aeruginosa* respiratory infection usually leads to stable high level ciprofloxacin resistance in this organism. Another common pitfall is the use of oral monotherapy with rifampicin, fusidic acid or ciprofloxacin for infections due to MRSA, as resistance usually emerges during treatment. In both these circumstances, more resistant bacteria are created that frequently cause therapeutic difficulty in the patient or indeed another person who acquires the resistant strain from the treated patient.

Duration of treatment

Appropriate minimum durations of antibiotic therapy have only been investigated for a few infectious diseases. These include bacterial endocarditis, bone and joint disease and meningitis. Unfortunately, duration of therapy for some common sites of infection such as the lung is not well studied. In these situations, the decision to cease therapy is usually based on clinical criteria. Where possible, minimising the duration of therapy is a key way to reduce emergence of resistance.

Improving antibiotic prescribing

The human impact of antibiotic resistance is significant and increasing. Health professionals have a responsibility to use antibiotics in a manner that reduces the emergence of resistance (see Box 2).

The general practice programs operated by the National Prescribing Service (NPS) provide advice on appropriate antibiotic prescribing through:

■ one-to-one educational visits by NPS facilitators

■ practice case discussion meetings

■ actual case data collection and analysis

■ newsletters, patient information brochures and other resources.

In hospital practice, improving antibiotic prescribing is a complex challenge to infectious diseases, microbiology and pharmacy services.[13] Additional elements of successful hospital programs include:

■ regular monitoring of antibiotic usage and drug usage evaluation with feedback to prescribers[14]

■ active involvement of clinicians in the development and dissemination of consensus, evidence-based guidelines for antibiotic use

■ clinical decision support systems and other aids such as treatment cards or hand-held computerised guidelines

■ use of infectious disease consultancy services for advice in the management of complex cases

■ improvements in the use of diagnostic technology and microbiology to provide more specific diagnosis of infective syndromes

■ formulary control of certain broad spectrum drugs so as to reduce indiscriminate use.

Conclusion

Antibiotics are valuable therapeutic agents. Their widespread use has resulted in the emergence of many multi-resistant bacterial pathogens in hospitals and the community. In order to preserve the action of existing antibiotics, their use for prophylaxis, empiric or directed therapy should be reserved for situations where there is good evidence to support use and/or the consequences of infection are serious. It is increasingly important to avoid empiric antibiotic use for most patients with upper respiratory infections and pursue symptomatic treatment.

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Further reading

Campaign to prevent antimicrobial resistance in healthcare settings. Centers for Disease Control and Prevention. http://www.cdc.gov/drugresistance/healthcare/default.htm [cited 2004 Feb]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 51)

5. Using broad spectrum antibiotics reduces bacterial resistance.
6. A two-week course of ciprofloxacin often results in the development of resistance in *Pseudomonas aeruginosa*.