Antimicrobial therapy: principles of use

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Abstract

Antibiotics are unique among therapeutic agents. While their use is directed at treating or preventing microbial disease, their efficacy is continuously threatened by drug resistance. Such resistance is readily transmitted between micro-organisms that in turn may disseminate in the healthcare or wider environment. Infectious disease varies in severity by age and underlying risk factors. Choice of therapy requires a risk assessment to ensure safe and effective prescribing practice. A set of principles that supports good prescribing practice has evolved specific to infectious disease management. Drug selection is based on knowledge of its antimicrobial spectrum and the known or likely pathogens responsible for a target infection. The dose, route and duration of treatment are all affected by the nature of the drug and the infecting organism. The pharmacodynamic relationship between the susceptibility of the pathogen and the pharmacokinetic profile of the drug increasingly informs optimal dosage regimens. Inappropriate or unnecessary prescribing is associated with higher rates of resistance, adds to the cost of disease management and increases the risk of drug toxicity. Drug resistance requires a continuous updating of prescribing recommendations and often limits choice. Good prescribing practice is key to maintaining effective management of infectious disease for current and future generations.

Keywords antibiotic resistance; antibiotics; adverse reactions; drug safety; pharmacokinetics; pharmacodynamics

What's new?

- Antimicrobial resistance continues to be the drive change in antibiotic prescribing recommendations
- New resistance threats from multi-resistant Gram-negative pathogens including multi-drug-resistant *E. coli*, *Klebsiella*, *Acinetobacter* and *Psedomonas* spp.
- Prescribing guidance is increasingly supported by local and national evidence based recommendations
- There is increasing pressure to reduce inappropriate prescribing particularly for community viral upper respiratory tract infection
- Greater public engagement in prescribing practice to ensure appropriate use and reduce the risks from drug-resistant organisms

Antimicrobial drugs have unique characteristics that distinguish them from other therapeutic agents. They are targeted primarily at invading micro-organisms, against which they exhibit selective toxicity. Infection may occur at any site; therefore, therapeutic drugs must be distributed widely at appropriate concentrations. The risk:benefit ratio varies depending on the severity of the infection. Antibiotics that are used prophylactically must have a low side-effect profile. In addition to their action on infecting micro-organisms, antibiotics often affect the normal flora of the skin and mucous membranes. This can result in superinfection and occasionally drug resistance, which may affect the patient and can have a wider ecological impact. Excessive or inappropriate use is linked to high rates of drug resistance.

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The following general principles of choice and use of antimicrobial agents apply to the treatment and chemoprophylaxis of bacterial, fungal, viral and parasitic infections.

Clinical assessment

Ideally, the initial clinical assessment of the patient should be supported by laboratory investigations to establish a definitive microbiological diagnosis and to determine the susceptibility of the infection to various drugs. Clinical assessment can confidently predict a specific microbial aetiology in only a few infectious diseases.

- Erysipelas is caused primarily by *Streptococcus pyogenes;* impetigo may be caused by *S. pyogenes* or *Staphylococcus aureus.*
- The clinical manifestations of herpes simplex virus (HSV) infections are usually diagnostic.
- *Streptococcus pneumoniae* is the usual cause of community-acquired pneumonia, but other micro-organisms must be considered (e.g. meticillin-resistant *S. aureus* (MRSA) in nursing-home residents).
- Most of the common viral exanthems that are not preventable by immunization occur in childhood.
- Meningitis in infancy is usually caused by *Neisseria meningitidis* or *S. pneumoniae* in countries where immunization has eliminated *Haemophilus influenzae* infection. In neonates, *Escherichia coli* and group B streptococci predominate.
- Dysuria and frequency accompanied by loin pain indicates acute pyelonephritis, which is usually caused by Gram-negative enteric pathogens and for which an injectable cephalosporin, co-amoxiclav or ampicillin plus gentamicin in the presence of severe sepsis, is appropriate.

A history of recent travel can suggest a possible microbial aetiology for acute gastroenteritis and alerts laboratory staff to undertake the appropriate investigations. Immunosuppression and profound immunodeficiency are important determinants of infection. The underlying deficiency (e.g. HIV infection, neutropenia) also affects the clinical expression of the disease.

Fever complicating neutropenia that fails to respond to broad-spectrum antibacterial drugs should prompt consideration of viral or fungal disease. When there is evidence of lung

involvement clinically or radiographically, invasive pulmonary aspergillosis is highly likely, for which treatment with voriconazole or amphotericin is indicated.

Laboratory investigations

Initially, most prescribing of antibiotics is empirical. It is important to establish the microbial cause of an infection in hospitalized and severely ill patients or when initial treatment is unsuccessful. Appropriate samples should be taken before beginning antimicrobial therapy, but this should not delay treatment. In certain life-threatening conditions (e.g. meningococcal meningitis, septicaemia), prompt administration of penicillin in the community at the first medical assessment can be life-saving. This does not prevent subsequent precise microbial diagnosis; the CSF culture is often sterilized rapidly, yet the pathogen may still be visible in CSF or may be cultured from a throat swab, and bacterial DNA may be detectable by polymerase chain reaction analysis.

Susceptibility provides valuable epidemiological information on antibiotic resistance trends in the community and in specific hospital environments (e.g. ICU, transplant units, burns units). Drug resistance is also increasing in non-bacterial pathogens. Thymidine kinase-deficient mutants of HSV that are resistant to aciclovir are emerging. *Candida albicans* is exhibiting increasing resistance to fluconazole, and intrinsically resistant species (e.g. *Candida krusei*) have become more common.

The *in vitro* susceptibility of micro-organisms does not necessarily equate with or reflect the clinical efficacy of drugs. Some pathogens (e.g. *Legionella pneumophila*, *Salmonella enterica serovar typhi*) are intracellular and, despite *in vitro* evidence that they are susceptible to a wide range of antibiotics, only drugs that concentrate intracellularly (e.g. erythromycin, clarithromycin, ciprofloxacin and levofloxacin) are clinically effective. This emphasizes the need for good clinical trial data to guide treatment strategies.

Impact of antibiotic resistance

One of the main pressures for change in prescribing practice is antibiotic resistance. Since antibiotics became widely available, there have been major changes in the susceptibility of many common target pathogens (Table 1). Resistance in Gram-negative bacteria such as coliforms, *Pseudomonas aeruginosa* and non-fermenters (e.g. *Acinetobacter* spp.) occurs mainly in hospitals. Antibiotic resistance in hospitals commonly arises in high-dependency areas where the staff:patient ratio is high, patients are very ill and their normal defences are breached by, for example, mechanical ventilation.

Resistance is also increasing in community pathogens such as *E. coli* while rates have stabilized or declined for *H. influenzae* and *S. pneumoniae*.[1] *S. pneumoniae* with reduced susceptibility to penicillin is a global problem which has resulted in major changes in the management of serious pneumococcal infection.[2] However, where conjugate pneumococcal vaccine has been introduced, resistance rates have also declined.[3]

Ampicillin and trimethoprim and, more worryingly, ciprofloxacin are becoming increasingly ineffective against urinary tract infection (UTI). There is no clear guidance on the incidence of antibiotic resistance at which alternative therapy is required.

Changes in prescribing practice resulting from antibiotic resistance

Pathogen	Antimicrobial agents previously predictably effective for which susceptibility testing is now necessary
• *Staphylococcus aureus*	Penicillin, meticillin, mupirocin
• *Streptococcus pneumoniae*	Penicillin, tetracycline, erythromycin
• *Streptococcus pyogenes*	Erythromycin, tetracycline
Enterococci	Ampicillin, teicoplanin, vancomycin
• *Neisseria gonorrhoeae*	Penicillin, tetracycline, ciprofloxacin
• *Neisseria meningitidis*	Sulphonamides
• *Haemophilus influenzae*	Ampicillin, chloramphenicol
• Enterobacteriaceae	Ampicillin, cephalosporins, trimethoprim, ciprofloxacin
• *Salmonella* spp.	Ampicillin, sulphonamides, chloramphenicol, ciprofloxacin
• *Shigella* spp.	Ampicillin, tetracycline, sulphonamides
• *Pseudomonas aeruginosa*	Gentamicin, ceftazidime

Table 1

In the author's opinion, in UTI, a clinical failure rate of 10% or more that is shown to result from *in vitro* resistance indicates that alternative empirical therapy should be given. This is certainly the case in more serious and potentially life-threatening infections.

Mechanisms of resistance: antibacterial drugs act at various sites (Figure 1) in the bacterium to inhibit growth; resistance may therefore occur by several mechanisms.

- In resistant strains, the target site may be absent, lost or bypassed. Resistance may therefore be intrinsic, as in the case of the lack of activity of erythromycin or chloramphenicol against *P. aeruginosa*.

Site of action of some common antibacterial drugs

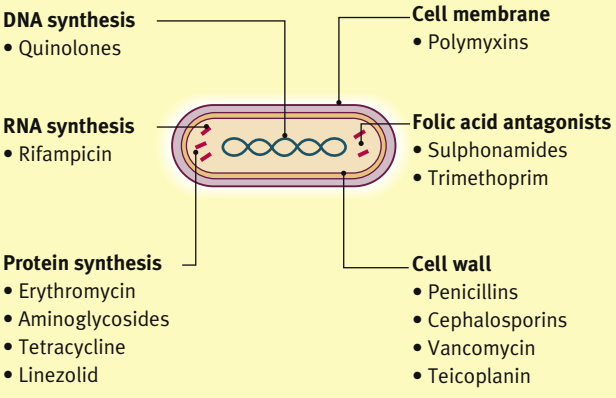

Figure 1