Antimicrobial therapy: principles of use

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Abstract

Prescribing antimicrobials is different from prescribing other medications, as there are wider repercussions that must be considered. Inappropriate or unnecessary use of antibiotics can lead to the generation of antimicrobial resistance in both the individual and the population as a whole. New antibiotic development has not kept up with the development of bacterial resistance, and the judicious use of antibiotics, known as antibiotic stewardship, is a vital tool in combatting the growth of multiresistant organisms. When choosing an antimicrobial agent, the prescriber must consider a myriad of factors, including the spectrum of action, the route of administration and the suspected site of infection. In addition, patient factors such as allergy status, age, renal and liver function and weight must be considered.

Keywords Adverse effects; antibiotic; antibiotic resistance; antimicrobial; *Clostridioides* (*Clostridium*) *difficile*; pharmacodynamics; pharmacokinetics

Key points

- Antibiotic stewardship is a vital tool in the fight against antibiotic resistance. Everyone has a role to play, from policy-makers to individual healthcare professionals
- In suspected sepsis, antibiotics should be given promptly. Local guidelines help guide empirical choices based on local resistance rates, but individual patient risk factors should also be considered
- The 'start smart then focus' approach facilitates early review and de-escalation of therapy to reduce resistance
- Increased resistance, particularly in Gram-negative infections, has led to the increased use of previously discarded, less effective and more toxic antibiotics, such as colistin
- Use of outpatient parenteral antimicrobial therapy is appropriate for certain infections and can help move care into the community

Antimicrobial mechanisms of action

The main mechanisms of action for antibiotics are inhibition of cell wall, protein or nucleic acid synthesis, and cell membrane disruption (Table 1, Figure 1).

Antibiotic resistance and available antibiotics

Bacteria are well adapted to developing antibiotic resistance, which can occur by mutation or by acquisition of resistance genes from other bacteria. Antibiotic use promotes the growth and transmission of the resistant strains.

The global spread of Gram-negative pathogens producing carbapenemases (enzymes that destroy carbapenems and other β-lactam antibiotics) is a major threat to the success of antibiotic treatments; these organisms also often carry resistance mechanisms to multiple antibiotic classes. As there are limited effective agents, treatment has often had to resort to older antibiotics, such as aztreonam, fosfomycin and colistin. These agents may be less effective, can have significant adverse effects and can be prone to the emergence of antibiotic resistance.

Although there has been a lack of new classes of antibiotic in recent decades, progress has been made in developing novel β-lactam–β-lactamase inhibitor combinations. These have varying degrees of activity against extended-spectrum β-lactamase (ESBL)-producing bacteria, multidrug-resistant *Pseudomonas* and some carbapenemase-producing organisms. Clinically available examples include ceftazidime–avibactam, aztreonam–avibactam, ceftolozane–tazobactam, imipenem–relebactam and meropenem–vaborbactam.

Metallo-β-lactamase (MBL)-producing organisms are resistant to most β-lactamase inhibitors and typically carry other resistance mechanisms, resulting in limited effective antibiotic choice. Aztreonam is active against MBL carbapenemases and can be combined with newer β-lactamase inhibitors, for example aztreonam–avibactam, to retain its activity in the presence of accompanying resistance mechanisms.

The first siderophore cephalosporin, cefiderocol, is highly stable against multidrug-resistant Gram-negative bacteria because of a unique mechanism of bacterial cell entry and stability against all four classes of β-lactamases, including MBLs.

Ceftaroline and ceftobiprole are newer fifth-generation cephalosporins with activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, the lipoglycopeptides dalbavancin and oritavancin have bactericidal activity against MRSA and have the added benefit of longer half-lives, facilitating out-patient management.

Delafloxacin is a fourth-generation fluoroquinolone with improved activity against Gram-positive pathogens including multidrug resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*. Unlike the β-lactam agents discussed above it is available in an oral formulation.

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Antibiotic classes and modes of action

Class	Examples	Mode of action
β-lactams	Penicillins, cephalosporins, carbapenems, monobactams	Inhibition of cell wall synthesis by binding to transpeptidases (penicillin-binding proteins), which prevents cross-linking of peptidoglycan
Glycopeptides	Vancomycin, teicoplanin, dalbavancin	Inhibition of cell wall synthesis by binding to molecules that are the cell wall building blocks
Aminoglycosides	Gentamicin, amikacin	Inhibition of protein synthesis by binding to bacterial ribosomes and disrupting mRNA translation
Tetracyclines	Doxycycline	Inhibition of protein synthesis by binding to bacterial ribosomes and preventing elongation of the peptide chain
Macrolides	Erythromycin, azithromycin	Inhibition of protein synthesis by disrupting ribosomal translocation
Chloramphenicol		Inhibition of protein synthesis by binding to ribosomes and inhibiting transfer RNA attachment
Oxazolidinones	Linezolid	Inhibition of protein synthesis by binding to bacterial ribosomes and preventing formation of the initiation complex
Rifamycins	Rifampicin	Binding and inhibition of bacterial RNA polymerase
Quinolones	Ciprofloxacin, levofloxacin	Inhibition of DNA synthesis via inhibition of DNA gyrase and topoisomerase intravenously
Diaminopyrimidines	Trimethoprim	Reduction of folic acid synthesis via inhibition of dihydrofolate reductase (inhibition of nucleic acid synthesis)
Sulfonamides	Sulfamethoxazole	Reduction of folic acid synthesis by competitive inhibition of *p*-aminobenzoic acid (inhibition of nucleic acid synthesis)
Nitroimidazoles	Metronidazole	Formation of radicals causing DNA strand breakage
Polymyxins	Colistin	Disruption of cell membrane by interaction with membrane phospholipids
Lipopeptides	Daptomycin	Disruption of cell membrane

Table 1

Tedizolid, an oxazolidone, is also available orally and has activity against multidrug-resistant Gram-positive pathogens.

Antibiotic stewardship

Antimicrobial stewardship (AMS) aims to enable the optimal selection, dosage and duration of antimicrobial treatment. The goal is to produce the best clinical outcome for the patient, in terms of both treating infection and avoiding drug toxicity. At the same time, good stewardship minimizes the impact on antimicrobial resistance (AMR), and uses drugs that are cost-effective wherever possible.[1]

Declining rates of *Clostridioides* (*Clostridium*) *difficile* infection (CDI) in the UK between 2007 and 2020 have been attributed to improvements in antibiotic stewardship, particularly restrictions on the use of broader spectrum cephalosporins and fluoroquinolones. However, since 2020 there has been a shift in trend with significant increases in both hospital- and community-onset CDI cases. The reason for the increase is unclear but may reflect changes in infection prevention during the coronavirus disease (COVID-19) pandemic, changes in use of antibiotics and increased detection. Data suggest there has been no significant change in the strain (ribotype) of *C. difficile* involved.

AMS comprises a core component of the UK government's AMR strategy 5-year national action plan (NAP). Several initiatives are active in the UK, including:

- the 'Start smart then focus' antimicrobial toolkit for inpatient care settings recommended by the Department of Health and Social Care Advisory Committee on Antimicrobial Prescribing Resistance and Healthcare Associated Infections (Figure 2)[2]
- the Treat Antibiotics Responsibly, Guidance, Education, Tools (TARGET) antibiotic toolkit for primary care, encompassing patient information resources, feedback on antibiotic prescribing data and training resources
- the Global Antimicrobial Stewardship Accreditation Scheme, developed by the British Society for Antimicrobial Chemotherapy (BSAC) and aiming to support and accredit effective AMS globally
- new digital tools that are emerging to support appropriate antimicrobial prescribing, such as the Scottish Antimicrobial Prescribing Group's Antimicrobial Companion app and the MicroGuide app. These applications, and similar tools, may offer the opportunity to improve patient outcomes and rationalize antibiotic prescribing
- enhanced surveillance of antibiotic prescribing including the English Surveillance Programme for Antimicrobial Utilisation and Resistance report and Antimicrobial Resistance and Healthcare Associated Infection Scotland monitors and interprets information on antibiotic use and AMR
- multiple initiatives from the BSAC, including the free ebook *Antimicrobial Stewardship* and multiple courses and webinars, such as the Massive Open Online Course on Antimicrobial Stewardship
- ReAct, an international, independent network dedicated to tackling the problem of antibiotic resistance

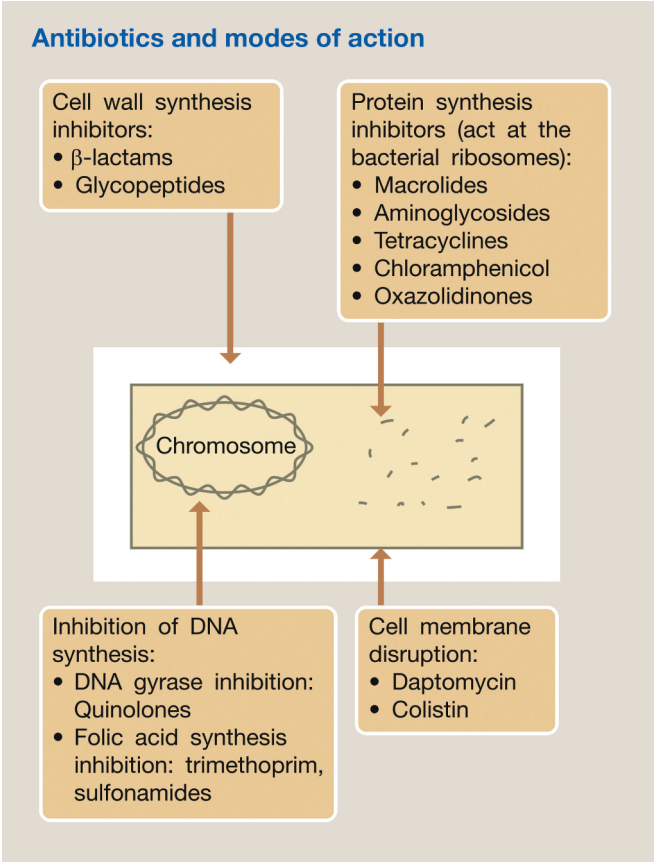

Figure 1

- the Global Action Plan on Antimicrobial Resistance, which brings together the World Health Organization with governing bodies from the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health.

Which antibiotic?

The choice of antimicrobial agent(s) involves multiple factors, including infection site, spectrum of activity and patient factors such as allergies and age.

Spectrum

Antibiotics are often started empirically, the choice being based on the most common causative organisms for a given source of infection. Examples of common sites of infection, pathogens and empirical therapy are outlined in Table 2. However, local guidelines should be preferentially used as they take into account local resistance data.

If the patient has additional risk factors for resistant organisms, the antibiotic choice may need to be adapted. Examples include previous colonization with a resistant pathogen (e.g. MRSA or ESBL-producing *Enterobacterales*), or travel to an area of the world where resistant organisms are common, such as carbapenemase-producing *Enterobacterales* in the Indian subcontinent and penicillin-resistant *Streptococcus pneumoniae* in parts of Europe.

Appropriate cultures should be taken wherever possible before antibiotics are started, although this must not delay antibiotic administration in patients with suspected sepsis. In this group, broad-spectrum antibiotics should be initiated within

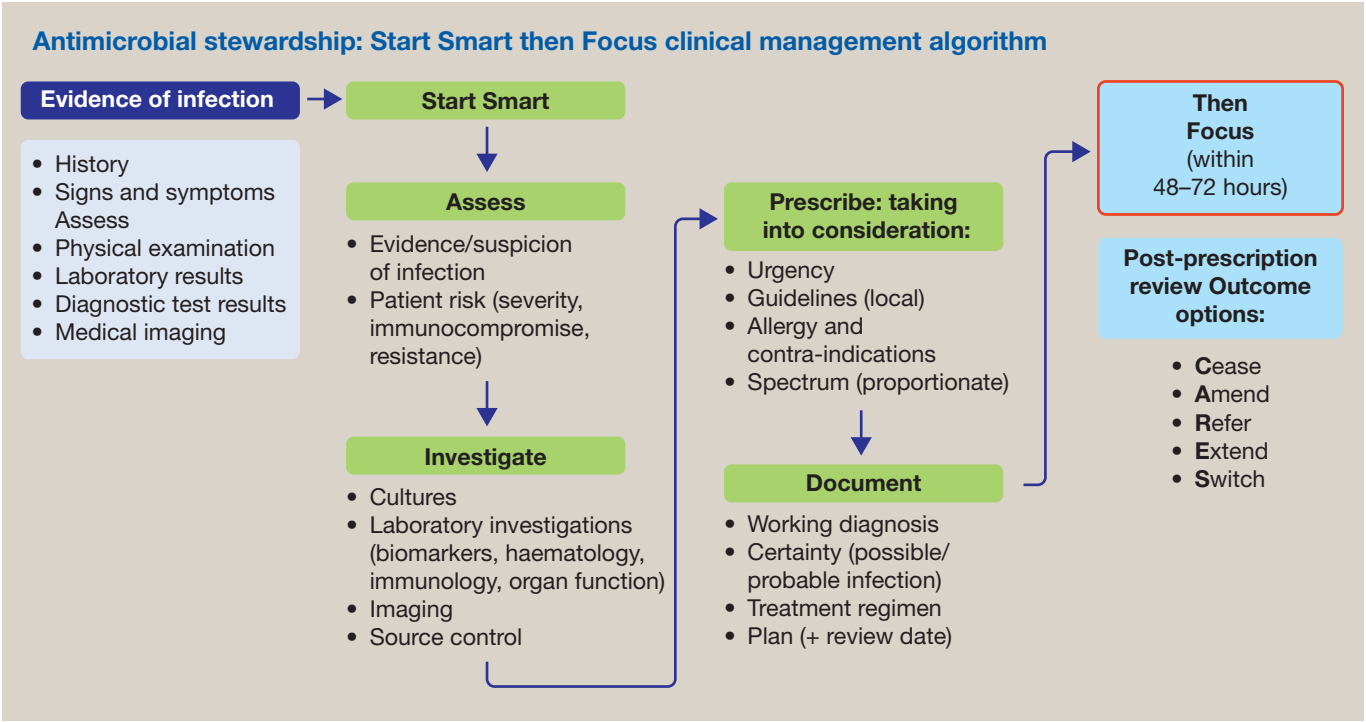

Figure 2 Reproduced with permission from the UK Health Security Agency (2023).[2]

Empirical antibiotics for a selection of important infections

Infection	Treatment	Likely pathogen(s)
Community-acquired pneumonia	Amoxicillin 500 mg orally three times daily ± clarithromycin 500 mg orally twice daily	*Streptococcus pneumoniae* *Haemophilus influenzae* *Mycoplasma pneumoniae*
Hospital-acquired pneumonia	Piperacillin—tazobactam 4.5 g i.v. four times daily	Gram-negative bacteria *Staphylococcus aureus*
Cystitis	Nitrofurantoin 50 mg orally four times daily	*Escherichia coli* *Klebsiella* spp. *Enterococcus* spp.
Pyelonephritis	Gentamicin 5—7 mg/kg i.v. daily with oral switch to a suitable alternative antibiotic based on culture results	*Escherichia coli* *Klebsiella* spp.
Cellulitis	Flucloxacillin 500 mg orally four times daily	*Staphylococcus aureus* β-haemolytic streptococci including *Streptococcus pyogenes*
Bacterial meningitis in adults	Ceftriaxone 2 g i.v. twice daily (+ amoxicillin 2 g i.v. 4-hourly if at increased risk of *Listeria* infection, including if >55 years old)	*Neisseria meningitidis* *Streptococcus pneumoniae* (*Listeria monocytogenes*)
Intra-abdominal infection (e.g. diverticular abscess)	Gentamicin 5—7 mg/kg i.v. daily + amoxicillin 1 g i.v. three times daily + metronidazole 500 mg i.v. three times daily	*Enterobacterales* (e.g. *Escherichia coli*) Faecal streptococci Anaerobes (e.g. *Bacteroides fragilis*)
Septic arthritis (native joint)	Flucloxacillin 2 g i.v. four times daily	*Staphylococcus aureus* *Streptococcus pyogenes*
Neutropenic sepsis	Piperacillin—tazobactam 4.5 g i.v. four times daily	Broad range of potential pathogens: *Pseudomonas aeruginosa*, *Enterobacterales*, anaerobes, streptococci, staphylococci

This is not based on any national guideline and is specific to the UK. In some cases a range of appropriate antibiotics may be available; the choices given are examples only. These suggestions may also not be appropriate for different populations with different resistance profiles.
i.v., intravenous.

Table 2

1 hour of recognizing the condition, in line with the Surviving Sepsis Campaign guidelines.[3] Empirical therapy should then always be reviewed with culture and sensitivity results and the clinical assessment of response to treatment.

Allergies

An allergy history must be taken before antibiotic prescription. This should include the severity of symptoms, timing of the reaction relative to drug administration, how long ago it was and any antibiotics tolerated since the reaction. Self-reported penicillin allergy is common (10% of the general population) but about 95% of penicillin allergy labels are incorrect when tested.

Concerning features in the history include an immediate hypersensitivity reaction (anaphylaxis or immediate-onset urticaria or angioedema) and severe cutaneous reactions (Stevens—Johnson syndrome, toxic epidermal necrolysis or DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)). In these cases, all β-lactams should be avoided.

A key theme in the UK NAP to confront AMR is optimizing the use of antimicrobials. Penicillin allergy is a common contraindication to the use of first-line antibiotics, requiring clinicians to use alternative treatments associated with AMR, reduced effectiveness and increased healthcare costs. The NAP states that access to penicillin allergy de-labelling services is vital to ensure patients are not unnecessarily denied penicillin treatments.

The provision of de-labelling at scale is only possible with the involvement of non-allergy specialists. Recent studies demonstrated that it is safe to offer a drug provocation test (DPT) to individuals at low risk of penicillin allergy without the need for prior skin testing.

Subsequently, the Standards of Care Committee of the British Society for Allergy and Clinical Immunology published a guideline for the evaluation and testing of patients with an unsubstantiated label of penicillin allergy. This guideline allows non-allergist clinicians outside allergy clinic settings to stratify the risk of allergy and suitability for DPT.

Amoxicillin is the drug of choice for DPT, unless the index penicillin is known to be different, in which case this penicillin should be used. Key to the success of de-labelling is communication of the result of DPT to the patient, general practitioner and other relevant healthcare professionals.

Children

Several antibiotics should be avoided in children:[4]

- Tetracyclines should not be used in children <12 years of age because of deposition in growing bones and teeth, causing tooth staining.
- Fluoroquinolones have been linked to arthropathy in immature animals, although similar effects in humans have not been demonstrated. They may be appropriate for

short courses in children, where the benefit is deemed to outweigh the risk.
- Nitrofurantoin should not be used in infants <3 months old because of the risk of haemolysis.
- Co-trimoxazole should not be used in neonates because of the risk of kernicterus.
- Chloramphenicol accumulation can lead to 'grey baby syndrome' in neonates.

Pregnancy

Certain antibiotics are not recommended in certain stages of pregnancy, because of their potential for adverse effects on the fetus. However, the risk of using these agents, which is often low, must be balanced against the risk from inadequate treatment of infection, especially with multiresistant pathogens. Caution is required for the following antibiotic classes:[4]

- Tetracyclines can deposit in bone and teeth.
- Fluoroquinolones have a possible link to arthropathy in animals.
- High-dose metronidazole has a possible, although not evidence-based, link to pre-term labour.
- Trimethoprim has a risk of teratogenicity during the first trimester because of folate antagonism.
- Nitrofurantoin carries a risk of neonatal haemolysis if used near to term.
- Aminoglycosides have a risk of vestibular/auditory nerve toxicity in the second and third trimesters, although the risk is probably very small.

Elderly patients

The higher risk of CDI in patients aged >65 years must be a major consideration when selecting an antibiotic. High-risk agents include cephalosporins, fluoroquinolones and clindamycin. Choice of antibiotic and dosage used should take into account the likelihood of decreased excretion, both renal and hepatic, in elderly individuals, with the resulting greater potential for adverse effects. This is especially the case in frail elderly people.

Renal disease

Dose adjustments based on creatinine clearance are commonly required (see Patient factors when selecting a dose, below). In addition, certain antibiotics should be completely avoided. Tetracycline should not be used as it can worsen renal failure. Nitrofurantoin is ineffective (as it is not secreted into the collecting system) and has a higher risk of peripheral neuropathy in patients with a reduced estimated glomerular filtration rate (eGFR). Aminoglycosides can quickly accumulate, resulting in an increased risk of nephro- and ototoxicity. Co-trimoxazole can raise creatinine concentrations by 10%, although the eGFR remains unchanged.

Liver disease

Some drugs, such as rifampicin and fusidic acid, are excreted in the bile. These can accumulate in liver failure and should be used with caution. Additionally, in patients with hepatic impairment, drugs that cause dose-related toxicity can do so at a lower dose and idiosyncratic reactions can occur more frequently. See below for more information on dose adjustment for certain drugs.

Obesity

Changes in fat and muscle mass ratios can affect the distribution of drugs. For lipophilic drugs, obesity results in a greater volume of distribution, so dosing should be based on total body weight. Conversely, hydrophilic drugs would be expected to stay in the circulation, so dosing should be based on ideal body weight. GFR can be increased in obesity, so excretion can be greater; however, concurrent co-morbidities such as hypertension and diabetes can counteract this. Dosing in obesity is complex and clinical judgement must be used.

Other considerations

Interactions between the antibiotic and other medications should always be considered. Specific antibiotics more prone to drug—drug interactions include rifampicin, linezolid and macrolides.

Antibiotics can have significant adverse effects in certain medical conditions, for example:

- myasthenia gravis — aminoglycosides, fluoroquinolones, tetracyclines and macrolides can cause a deterioration in symptoms
- porphyria — macrolides, tetracyclines and co-trimoxazole can precipitate an attack
- glucose 6-phosphate dehydrogenase deficiency — sulfonamides, fluoroquinolones and nitrofurantoin can cause haemolysis.

Which route?

The bioavailability of antibiotics varies; for example, several fluoroquinolones demonstrate >90% absorption of the administered oral dose into the bloodstream, whereas absorption of aminoglycosides and glycopeptides from the gastrointestinal tract is negligible.

Antibiotics should be given intravenously only in the following circumstances:

- to ensure high serum concentrations in the treatment of severe or deep infections (e.g. suspected sepsis, use of intravenous amoxicillin for endocarditis)
- where the person is unable to take medication enterally (e.g. because of vomiting)
- where there is concern regarding absorption from the gastrointestinal tract
- where there is no effective oral preparation
- where the dose required would be so high as to cause adverse effects, such as vomiting
- where the antibiotic is being given for an intravascular line infection.

In certain situations, the antibiotic has to be given enterally, for example in the treatment of *C. difficile* with vancomycin or fidaxomicin.

Topical antibiotics are appropriate for certain indications, for example:

- antibacterial eye ointment for the treatment of bacterial conjunctivitis (as systemic antibiotics do not achieve adequate concentrations at the eye surface)
- fusidic acid cream for small areas of impetigo
- antibiotic ear drops in conjunction with cleaning of the external ear for otitis externa
- nasal mupirocin for MRSA decolonization.

Other routes of administration include intraventricular (for treatment of shunt- or device-associated cerebral ventriculitis), intraperitoneal (for peritoneal dialysis-related peritonitis) and nebulization (e.g. tobramycin, used in cystic fibrosis and bronchiectasis).

Which dose?

The dosing of an antibiotic depends on its pharmacological properties and additional patient-specific factors.

Pharmacodynamics

Antimicrobials can demonstrate bactericidal (killing the pathogen) or bacteriostatic (inhibition of growth) activity. Some agents are bactericidal in some circumstances but bacteriostatic in others.

The efficacy of an antibiotic against a specific pathogen is measured by the minimum inhibitory concentration (MIC), which is the lowest concentration of drug that inhibits bacterial growth *in vitro*. The results are compared with known values for a specific antimicrobial agent and pathogen combination, to allow interpretation of the drug *in vivo* as sensitive, intermediate or resistant.

The optimal relationship between drug concentration and efficacy varies for different agents. Aminoglycosides, for example, demonstrate concentration-dependent killing, and efficacy depends on the ratio of the maximum drug concentration to the MIC. Aminoglycosides are often given once daily to allow the highest peak to be reached and then allow time for the drug to wash out to avoid toxicity.

β-lactams, however, demonstrate time-dependent killing, and efficacy is linked to the time that the drug concentration is above the MIC. This results in the need to administer most β-lactams as multiple daily doses, unless the drug has a particularly long half-life, as with ceftriaxone.

Using either continuous infusions or prolonged infusion times (>3 hours) when administering β-lactams has been shown in a meta-analysis to reduce all-cause mortality in critically ill patients. This is frequently used in critical care units but is yet to be widely adopted on general wards because of the increased workload.

Initial loading doses may be required to attain optimal concentrations as early as possible. Examples include teicoplanin, colistin and perhaps vancomycin.[4]

Patient factors when selecting a dose

Depending on their metabolism and route of excretion, dosage reduction is necessary for some antibiotics in hepatic and renal failure to avoid accumulation and toxicity. For patients in renal failure, dosage adjustments should be made for aminoglycosides (with consideration of use of an alternative agent), glycopeptides, daptomycin, many β-lactams (particularly in parenteral therapy), co-trimoxazole and colistin. For patients in hepatic failure, dosage adjustments should be made for tetracyclines, fusidic acid, metronidazole, chloramphenicol, rifampicin, isoniazid and pyrazinamide.[4]

For drugs dosed on a weight basis, obesity is a specific concern. Gentamicin, for example, is not well distributed into adipose tissue, and the dosage should be estimated using ideal body weight (derived from height/length) rather than total body weight.

Duration of antimicrobial courses

The evidence base for optimal antibiotic duration is lacking for many infections. For low-severity infections, very short courses are advised; for example, uncomplicated cystitis in a woman warrants only a 3-day oral course.

Longer antibiotic durations increase the risk of resistance and adverse effects, including CDI. Certain difficult-to-treat infections (e.g. osteomyelitis, infective endocarditis) require weeks or months of antibiotic treatment. Tuberculosis always requires extended treatment because of the slow metabolism of the organism.

The duration of treatment depends on the pathogen involved, the use of surgery in removing the focus of infection where appropriate, and the patient's response to treatment. Infections involving prosthetic devices that cannot be removed can require prolonged suppressive antibiotic courses.

Important adverse events related to antibiotic use

CDI, with the potential for pseudomembranous colitis, can occur after exposure to any antibiotic. The risk of infection is linked to the degree of disruption of the patient's normal gastrointestinal flora; higher risk agents include second- and third-generation cephalosporins (e.g. cefuroxime, ceftriaxone), fluoroquinolones (e.g. ciprofloxacin), clindamycin and co-amoxiclav.

Table 3 lists many of the other important adverse effects of antibiotics.[4]

Therapeutic drug monitoring for antimicrobials

The monitoring of trough serum concentration is essential to avoid toxicity in aminoglycoside use. If the trough concentration remains above the reference range, the dose being given is too high. In this instance the dose should be reduced, the dosing interval increased or the antibiotic changed to a different class. Occasionally, peak (post-dose) concentrations are taken to ensure adequate targets are reached — this is usually in infective endocarditis or drug-resistant tuberculosis.

Vancomycin trough concentration should be used as an index of therapeutic effect as well as to avoid potential toxicity. The trough vancomycin concentration should be in the target range, as if it is too low, the dose needs to be increased.

Assays can be used to optimize the dosing of a wide range of other antimicrobial agents.[5] The availability of these varies depending on local laboratory facilities, but drug monitoring can be undertaken for teicoplanin, daptomycin, linezolid, colistin, rifampicin, voriconazole and many others including β-lactams in critical care infections.

Combination antibiotic therapy

The use of combination antimicrobial therapy is indicated in several circumstances:

- synergistic activity, such as the use of gentamicin with β-lactams in streptococcal infective endocarditis, and β-lactam–β-lactamase inhibitor combinations (e.g. co-amoxiclav)
- to avoid resistance emerging during treatment, such as with the multidrug regimen used for tuberculosis, HIV and

Important adverse events associated with antibiotic use

Antibiotic	Important adverse events	Notes
Aminoglycosides (e.g. gentamicin)	Ototoxicity	Monitor renal function and trough drug concentration, and hearing if treatment prolonged
	Nephrotoxicity	
Chloramphenicol	Aplastic anaemia	Monitor FBC
	'Grey baby syndrome' (abdominal distension, pallid cyanosis, circulatory collapse in neonates with immature hepatic function)	Monitor drug concentration
Clindamycin	Diarrhoea, pseudomembranous colitis	Stop if diarrhoea develops
Colistin (i.v.)	Nephrotoxicity, neurotoxicity	Monitor drug concentration
Co-trimoxazole (trimethoprim and sulfamethoxazole)	Hyperkalaemia	Risks increased in patients who are elderly or have renal failure
	Blood dyscrasias including myelosuppression (rare)	Monitor FBC
	Stevens—Johnson syndrome (rare)	Stop immediately if rash or blood disorder develops
Daptomycin	Myositis, eosinophilic pneumonia, peripheral neuropathy	Monitor serum creatine kinase
Glycopeptides (e.g. vancomycin)	Red man syndrome (with rapid infusion)	Avoid rapid infusion
	Nephrotoxicity, ototoxicity, neutropenia	Monitor trough drug concentration — vancomycin
Linezolid	Myelosuppression	Monitor FBC
	Optic neuropathy (particularly if used for >28 days)	Warn patient to report visual disturbances
Macrolides (e.g. clarithromycin)	Prolongation of QT interval	Avoid use if increased risk of QT interval prolongation
Metronidazole	Disulfiram-type reaction with alcohol	Close monitoring for courses >10 days
	Peripheral neuropathy (prolonged courses)	
Nitrofurantoin	Peripheral neuropathy	Avoid if eGFR <45 ml/minute/1.73 m^2
Quinolones (e.g. ciprofloxacin)	Tendonitis, including tendon rupture	Stop if tendonitis suspected. Avoid concurrent corticosteroid use
	Lowered seizure threshold	Avoid if higher seizure risk
	Prolongation of QT interval (especially moxifloxacin)	Avoid use if increased risk of QT interval prolongation
	Small increased risk of aortic aneurysm, dissection and valve regurgitation	Use with caution in patients aged >60 years or with other risk factors
Rifampicin	Hepatotoxicity	Monitor liver function if treatment prolonged
Tetracyclines, especially minocycline	Hepatotoxicity, irreversible pigmentation, photosensitivity and dyspepsia	Monitor for reactions and liver function if treatment prolonged
	Lupus erythematosus-like syndrome	

FBC, full blood count; i.v., intravenous.

Table 3

the combined use of ceftriaxone and azithromycin to treat gonorrhoea
- polymicrobial infection such as intra-abdominal infection secondary to bowel perforation, using a combination of narrow-spectrum agents (e.g. amoxicillin, gentamicin, metronidazole) to target likely pathogens
- to expand the empirical antimicrobial spectrum if there are specific concerns about multiresistant pathogens.

Disadvantages of combination therapy are the increased risk of adverse effects, including CDI, and the potential for antagonism between agents; for example, the use of tetracycline with penicillin for meningitis has a worse outcome than if penicillin alone is used.

Outpatient parenteral antibiotic therapy (OPAT)

NHS England has recently published guidance on developing OPAT services.' The guidance was published 3 April 2025 and link is here: NHS England » Guidance to integrated care boards and providers on developing outpatient parenteral antimicrobial therapy (OPAT) services. BSAC's updated good practice recommendations for OPAT services should also be considered. The intended benefits of OPAT include:

- improving patient flow through hospitals and reducing discharge delays resulting from the need for intravenous treatment
- addressing the burden of AMR, which can necessitate intravenous antibiotics because of reduced drug susceptibility
- reducing heathcare-associated infections
- a more efficient use of resources
- improving patient choice.

Referrals to the OPAT service should be made by healthcare professionals, and patients should be selected by locally agreed criteria. Management plans and clinical responsibility must be well defined and documented, with regular review, including consideration of oral switching.

OPAT can help with admission avoidance of low-complexity infections such as cellulitis not responding to oral antibiotics, multiresistant lower urinary tract infections with no oral treatment options and exacerbations of bronchiectasis with no oral treatment options. More complex infections that may be suitable for OPAT include prosthetic joint infections, diabetic foot infection and infective endocarditis.

Historically, antibiotics that are administered once a day, such as ceftriaxone, teicoplanin, daptomycin and ertapenem, have been used. More recently, other options have become available, such as continuous infusion pumps that can deliver flucloxacillin or piperacillin–tazobactam at home.

Antibiotic prophylaxis

Prophylactic use of antibiotics should be limited to situations for which there is evidence that significant infection can be prevented. Where indicated, evidence supports a single dose for surgical prophylaxis except in special circumstances (e.g. major blood loss, prolonged surgery), and 24 hours of prophylaxis for patients undergoing arthroplasty.

Surgical prophylaxis should not be given in clean surgical procedures (i.e. operations in which no inflammation is encountered and the respiratory, alimentary or genitourinary tracts are not entered) that do not involve implantation of a prosthesis.

Penicillin V prophylaxis for asplenic patients is appropriate to prevent pneumococcal infection, and prophylaxis is indicated for public health reasons in the contacts of people with specific infections (e.g. pertussis, meningococcal disease, tuberculosis).

Prophylaxis against infective endocarditis in individuals with structural cardiac defects who are undergoing dental procedures is no longer advised in the UK. This is because of a lack of evidence for an association between the procedures and endocarditis, the lack of evidence for the effectiveness of the prophylaxis, the regular occurrence of bacteraemias from activities of daily living, and the potential adverse effects of the antibiotics.[4]

Potential future developments in antimicrobial use

Antibiotic resistance presents a continuing challenge both in the UK and globally. Although there has been recent promise from new agents (such as β-lactam–β-lactamase inhibitor combinations and new generations of existing antibiotic classes), the risk of pan-resistant organisms that are truly untreatable is growing. Further work to enable optimization of the drugs we have, as well as better diagnostics to identify bacterial pathogens and their susceptibilities earlier, will be vital in the future.

The role of AMS has never been more important, as it is the best tool to try to halt the spread of resistance. Infection specialist clinicians are vital to ensure that patients are given the right antibiotics and that other prescribers are supported in choosing the best drugs early. ◆

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FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 75-year-old woman presented with new confusion, headache and photophobia.

On clinical examination she had obvious neck stiffness. Examination of the cardiovascular, respiratory and gastrointestinal systems was normal. There was no rash. She had no known drug allergies.

What is the most appropriate empirical antibiotic treatment?

A. Ceftriaxone 2 g 12-hourly
B. Ceftriaxone 2 g 12-hourly and amoxicillin 2 g 4-hourly intravenously
C. Chloramphenicol 25 mg/kg 6-hourly
D. Meropenem 2 g 8-hourly
E. Piperacillin–tazobactam 4.5 g 8-hourly

Question 2

A 45-year-old woman presented with a 1-week history of worsening pain and swelling of her right lower leg. She reported occasional fever at home. She was otherwise well. She reported a family history, but no personal history, of penicillin allergy.

Investigation

- Doppler ultrasonography of the leg was normal

What is the most appropriate action?

A. Commence clindamycin
B. Commence doxycycline
C. Commence flucloxacillin
D. Perform a drug provocation test with amoxicillin
E. Refer to the immunology department for skin testing and commence clindamycin

Question 3

An 80-year-old man presented with symptoms of urinary urgency, dysuria and frequency with fever and loin pain. A midstream urine specimen sent by primary care 2 days before admission had grown $>10^5$ CFU/ml of *Escherichia coli* resistant to amoxicillin, trimethoprim and co-amoxiclav but sensitive to pivmecillinam and nitrofurantoin. The *E. coli* strain was an extended-spectrum β-lactamase (ESBL) producer.

What is the most appropriate action?

A. Request blood cultures, send a urine sample to the laboratory and await the results
B. Commence high-dose pivmecillinam
C. Commence nitrofurantoin
D. Commence a carbapenem (meropenem or ertapenem)
E. Follow local hospital guideline for urosepsis and commence intravenous co-amoxiclav plus gentamicin