Chapter 13

Antibacterial drugs

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SYNOPSIS

The range of antibacterial drugs is wide and affords the clinician scope to select with knowledge of microbial susceptibilities and patient factors, e.g. allergy, site of infection, renal disease. Because members of each structural group are usually handled by the body in a similar way and have the same range of adverse effects, antibacterial drugs are here discussed in groups, primarily by their site of antibacterial action, and secondly by molecular structure.

CLASSIFICATION

Inhibition of cell wall synthesis

β-lactams, the structure of which contains a β-lactam ring. The major subdivisions are:

- *Penicillins,* whose official names usually include, or end in, 'cillin'.
- *Cephalosporins* and *cephamycins,* which are recognised by the inclusion of 'cef' or 'ceph' in their official names. In the UK recently all these names have been standardised to begin with 'cef'.

Other subcategories of β-lactams include:

- Carbapenems (e.g. meropenem).
- Monobactams (e.g. aztreonam).
- β-lactamase inhibitors (e.g. clavulanic acid).

Other inhibitors of cell wall synthesis include vancomycin and teicoplanin.

Inhibition of protein synthesis

Aminoglycosides. The names of those that are derived from streptomyces end in 'mycin', e.g. tobramycin. Others include gentamicin (from *Micromonospora purpurea* which is not a fungus, hence the spelling as 'micin') and semi-synthetic drugs, e.g. amikacin.

Tetracyclines, as the name suggests, are four-ringed structures and their names end in '-cycline'.

Macrolides: e.g. erythromycin. Clindamycin, structurally a lincosamide, has a similar action and overlapping antibacterial activity.

Other drugs that act by inhibiting protein synthesis include quinupristin-dalfopristin, linezolid, chloramphenicol and sodium fusidate.

Inhibition of nucleic acid synthesis

Sulfonamides. Usually their names contain 'sulpha' or 'sulfa'. These drugs and trimethoprim, with which they may be combined, inhibit synthesis of nucleic acid precursors.

Quinolones are structurally related to nalidixic acid; the names of the most recently introduced members of the group end in '-oxacin', e.g. ciprofloxacin. They act by preventing DNA replication.

Azoles all contain an azole ring and the names end in '-azole', e.g. metronidazole. They act by the production of short-lived intermediates toxic to DNA of sensitive organisms. Rifampicin inhibits bacterial DNA-dependent RNA polymerase.

Antimicrobials that are restricted to certain specific uses, i.e. tuberculosis, urinary tract infections, are described with the treatment of these conditions in Chapter 14.

Inhibition of cell wall synthesis

β-LACTAMS

Penicillins

Benzylpenicillin (1942) is produced by growing one of the penicillium moulds in deep tanks. In 1957 the penicillin nucleus (6-amino-penicillanic acid) was synthesised and it became possible to add various side-chains and so to make semi-synthetic penicillins with different properties. Penicillins differ widely in antibacterial spectrum. A general account of the penicillins follows and then of the individual drugs in so far as they differ.

Mode of action. Penicillins act by inhibiting the enzymes (penicillin binding proteins, PBPs) involved in the cross-linking of the peptidoglycan layer of the cell wall, which is weakened, and this leads to osmotic rupture. Penicillins are thus bactericidal and are ineffective against resting organisms which are not making new cell wall. The main defence of bacteria against penicillins is to produce enzymes, β-lactamases, which hydrolyse the β-lactam ring. Other mechanisms that have been described include modifications to PBPs to render them unable to bind β-lactams, reduced permeability of the outer cell membrane of Gram-negative bacteria, and pumps in the outer membrane which remove β-lactam molecules. Some particularly resistant bacteria may possess several mechanisms that act in concert. The remarkable safety and high therapeutic index of the penicillins is due to the fact that human cells, while bounded by a cell membrane, lack a cell wall. They exhibit time-dependent bacterial killing (see p.164).

Pharmacokinetics. Benzylpenicillin is destroyed by gastric acid and is unsuitable for oral use. Others, e.g. phenoxymethylpenicillin, resist acid and are absorbed in the upper small bowel. The plasma $t_{½}$ of penicillins is usually <2 h. They are distributed mainly in the body water and enter well into the CSF if the meninges are inflamed. Penicillins are organic acids and their rapid clearance from plasma is due to secretion into renal tubular fluid by the anion transport mechanism in the kidney. Renal clearance therefore greatly exceeds the glomerular filtration rate (127 mL/min). The excretion of penicillin can be usefully delayed by concurrently giving probenecid which competes successfully for the transport mechanism. Dosage of penicillins may need to be reduced for patients with severely impaired renal function.

Adverse effects. The main hazard with the penicillins is *allergic reactions*. These include itching, rashes (eczematous or urticarial), fever and angioedema. Rarely (about 1 in 10 000) there is anaphylactic shock, which can be fatal (about 1 in 50 000–100 000 treatment courses). Allergies are least likely when penicillins are given orally and most likely with topical application. Metabolic opening of the β-lactam ring creates a highly reactive penicilloyl group which polymerises and binds with tissue proteins to form the major antigenic determinant. The anaphylactic reaction involves specific IgE antibodies which can be detected in the plasma of susceptible persons.

There is *cross-allergy* between all the various forms of penicillin, probably due in part to their common structure, and in part to the degradation products common to them all. *Partial cross-allergy* exists between penicillins and cephalosporins (a maximum of 10%), which is of particular concern when the reaction to either group of antimicrobials has been angioedema or anaphylactic shock. Carbapenems (meropenem and imipenem-cilastatin) and, especially, the monobactam aztreonam apparently have a lower risk of cross-reactivity. One experimental study estimated the rate of reactivity to meropenem in patients with a previous history of immediate penicillin hypersensitivity reaction as a maximum of 5.2%.

When attempting to predict whether a patient will have an allergic reaction, a reliable history of a previous adverse response to penicillin is valuable. Immediate-type reactions such as urticaria, angioedema and anaphylactic shock can be taken to indicate allergy, but interpretation of maculopapular rashes is more difficult. Since an alternative drug can usually be found, a penicillin is best avoided if there is suspicion of allergy, although the condition is undoubtedly overdiagnosed and may be transient (see below).

When the history of allergy is not clear cut and it is necessary to prescribe a penicillin, the presence of IgE antibodies in serum is a useful indicator of reactions mediated by these antibodies, i.e. immediate (type I) reactions. Additionally, an intradermal test for allergy may be performed using standard amounts of a mixture of a major determinant (metabolite) (benzylpenicilloyl polylysine) and minor determinants (such as benzylpenicillin) of the allergic reaction; appearance of a flare and wheal reaction indicates a positive response. The fact that only about 10% of patients with a history of 'penicillin allergy' respond suggests that many who are so labelled are not, or are no longer, allergic to penicillin.

Other adverse effects include diarrhoea due to alteration in normal intestinal flora, which may progress to *Clostridium difficile*-associated diarrhoea. Neutropenia is a risk if penicillins (or other β-lactam antibiotics) are used in high dose and usually for a period of longer than 10 days. Rarely the penicillins cause anaemia, sometimes haemolytic, and thrombocytopenia or interstitial nephritis. Sometimes patients receiving parenteral β-lactams may develop fever with no other signs of an adverse reaction except occasionally for

a modestly raised CRP: this should always be considered in the investigation of such patients who seem otherwise well, and cautiously stopping antibiotic therapy usually produces a prompt resolution. Penicillins are presented as their sodium or potassium salts which are inevitably taken in significant amounts for patients with renal or cardiac disease if high dose of antimicrobial is used. Extremely high plasma penicillin concentrations cause convulsions. Co-amoxiclav and flucloxacillin given in high doses for prolonged periods in the elderly may cause hepatic toxicity.

Narrow-spectrum penicillins

Benzylpenicillin

Benzylpenicillin ($t_{½}$ 0.5 h) (penicillin G) has to be given with spaced doses that have to be large to maintain a therapeutic concentration, but the large therapeutic ratio of penicillin allows the resulting fluctuations to be tolerable.[1] Benzylpenicillin is eliminated by the kidney, with about 80% being actively secreted by the renal tubule and this can be blocked by probenecid.

Uses. Benzylpenicillin is highly active against *Streptococcus pneumoniae* and the Lancefield Group A, β-haemolytic streptococcus (*Streptococcus pyogenes*). Viridans streptococci are usually sensitive unless the patient has recently received penicillin. *Enterococcus faecalis* is less susceptible and, especially for endocarditis, penicillin should be combined with an aminoglycoside, usually gentamicin. This combination is synergistic unless the enterococcus is highly resistant to the aminoglycoside (minimal inhibitory concentration (MIC) of 128 mg/L or above); such strains are becoming more frequent in hospital patients and present major difficulties in therapy. Over 90% of *Staphylococcus aureus* are now resistant in hospital and domiciliary practice. Benzylpenicillin is a drug of choice for infections due to *Neisseria meningitidis* (meningococcal meningitis and septicaemia), *Bacillus anthracis* (anthrax), *Clostridium perfringens* (gas gangrene) and *tetani* (tetanus), *Corynebacterium diphtheriae* (diphtheria), *Treponema pallidum* (syphilis), *Leptospira* spp. (leptospirosis), *Actinomyces israelii* (actinomycosis) and for *Borrelia burgdorferi* (Lyme disease) in children. Penicillin resitance rates in *Neisseria gonorrhoeae* are high in many parts of the world.

Adverse effects are in general uncommon, apart from allergy (above). It is salutary to reflect that the first clinically useful antibiotic (1942) is still in use and remains among the least toxic.

Preparations and dosage for injection. Benzylpenicillin may be given i.m. or i.v. (by bolus injection or by continuous infusion). For a sensitive infection, benzylpenicillin[2] 600 mg 6-hourly is enough.

For relatively insensitive infections and where sensitive organisms are sequestered within avascular tissue (e.g. infective endocarditis) 7.2 g is given daily i.v. in divided doses. When an infection is controlled, a change may be made to the oral route with phenoxymethylpenicillin (amoxicillin is more reliably absorbed in adults).

Procaine penicillin, given i.m. only, liberates benzylpenicillin over 12–24 h, but it will not give therapeutic blood concentrations for some hours after injection, and peak concentrations are low.

Preparations and dosage for oral use. Phenoxymethylpenicillin (penicillin V), is resistant to gastric acid and so is moderately well absorbed, sometimes erratically in adults. It is less active than benzylpenicillin against *Neisseria gonorrhoeae* and *meningitidis*, and so is unsuitable for use in gonorrhoea and meningococcal meningitis, although satisfactory against *Streptococcus pneumoniae* and *Streptococcus pyogenes*, especially after the acute infection has been controlled by intravenous therapy. The dose is 500 mg 6-hourly.

All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food.

Antistaphylococcal penicillins

Certain bacteria produce β-lactamases which open the β-lactam ring that is common to all penicillins, thus terminating their antibacterial activity. β-lactamases vary in their activity against different β-lactams, with side-chains attached to the β-lactam ring stearically hindering access of the drug to the enzymes' active sites.

Examples of agents stable to staphylococcal β-lactamases include:

- *Flucloxacillin* ($t_{½}$ 1 h) is better absorbed and so gives higher blood concentrations than does cloxacillin. It may cause cholestatic jaundice, particularly when used for more than 2 weeks or given to patients > 55 years.
- *Cloxacillin* ($t_{½}$ 0.5 h) has been withdrawn from the market in some countries, including the UK.
- *Methicillin* and *oxacillin*: their use is now confined to laboratory sensitivity tests. Identification of methicillin-resistant *Staphylococcus aureus* (MRSA) in patients indicates the organisms are resistant to all β-lactam antibiotics and often to other antibacterial drugs.

Broad-spectrum penicillins

The activity of these semi-synthetic penicillins extends to include many Gram-negative bacilli. They do not resist β-lactamases, and their usefulness has reduced markedly in recent years because of the increased prevalence of organisms that produce these enzymes.

These agents are less active than benzylpenicillin against Gram-positive cocci, but more active than the β-lactamase-resistant penicillins (above). They have useful activity

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[1] I suppose at the answer that reduces most classes of students to tears when asked the trough:peak ratio for a drug given 6-hourly (half-life 0.5 h)? (answer: $2^{12} = 4096$).

[2] 1 000 000 units, 1 mega-unit.

against *Enterococcus faecalis* and many strains of *Haemophilus influenzae*. *Enterobacteriaceae* are unreliably susceptible. Members of this group differ more pharmacologically than antibacterially.

Amoxicillin ($t_{½}$ 1 h; previously known as amoxycillin) is a structural analogue of ampicillin (below) and is better absorbed from the gut (especially after food), and for the same dose achieves approximately double the plasma concentration. Diarrhoea is less frequent with amoxicillin than with ampicillin. The oral dose is 250 mg 8-hourly; a parenteral form is available but offers no advantage over ampicillin.

Co-amoxiclav (Augmentin). *Clavulanic acid* is a β-lactam molecule which has little intrinsic antibacterial activity but binds irreversibly to β-lactamases. Thereby it competitively protects the penicillin against bacterial β-lactamases, acting as a 'suicide' inhibitor. It is formulated in tablets as its potassium salt (equivalent to 125 mg of clavulanic acid) in combination with amoxicillin (250 or 500 mg), as co-amoxiclav, and is a satisfactory oral treatment for infections due to β-lactamase-producing organisms, notably in the respiratory or urogenital tracts. These include many strains of *Staphylococcus aureus*, *Escherichia coli* and an increasing proportion of *Haemophilus influenzae*. It also has useful activity against β-lactamase-producing *Bacteroides* spp. The $t_{½}$ is 1 h and the dose one tablet 8-hourly.

Ampicillin ($t_{½}$ 1 h) is acid-stable and is moderately well absorbed when swallowed. The oral dose is 250 mg–1 g 6–8-hourly; or i.m. or i.v. 500 mg 4–6-hourly. Approximately one-third of a dose appears unchanged in the urine. The drug is concentrated in the bile.

Adverse effects. Ampicillin may cause diarrhoea but the incidence (12%) is less with amoxicillin. Ampicillin and amoxicillin are commonly associated with *Clostridium difficile* diarrhoea, related to the frequency of their use rather than to high innate risk of causing the disease. Ampicillin and its analogues may cause a macular rash resembling measles or rubella, usually unaccompanied by other signs of allergy, and seen in patients with disease of the lymphoid system, notably *infectious mononucleosis* and lymphoid leukaemia. A macular rash should not be taken to imply allergy to other penicillins, which tend to cause a true urticarial reaction. Patients with renal failure and those taking allopurinol for hyperuricaemia also seem more prone to ampicillin rashes. Cholestatic jaundice has been associated with use of co-amoxiclav even up to 6 weeks after cessation of the drug; the clavulanic acid may be responsible.

Mecillinam

Pivmecillinam ($t_{½}$ 1 h) is an oral agent active against Gram-negative organisms including many extended-spectrum β-lactamase-producing (ESBL) Enterobacteriaceae, but inactive against *Pseudomonas aeruginosa* and its relatives and Gram-positive organisms. Pivmecillinam is hydrolysed in vivo to the active form mecillinam (which is poorly absorbed by mouth). It has been used to treat urinary tract infection.

Monobactam

Aztreonam ($t_{½}$ 2 h) is the first member of this class of β-lactam antibiotic. It is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Neisseria meningitidis* and *gonorrhoeae*. Aztreonam is used to treat septicaemia and complicated urinary tract infections, lower urinary tract infections and gonorrhoea.

Adverse effects include reactions at the site of infusion, rashes, gastrointestinal upset, hepatitis, thrombocytopenia and neutropenia. It may be used with caution in penicillin-allergic patients.

Antipseudomonal penicillins

Carboxypenicillins

These in general have the same antibacterial spectrum as ampicillin (and are susceptible to β-lactamases), but have the additional capacity to destroy *Pseudomonas aeruginosa* and indole-positive *Proteus* spp.

Ticarcillin ($t_{½}$ 1 h) is presented in combination with clavulanic acid (as Timentin), so to provide greater activity against β-lactamase-producing organisms. It is given by i.m. or slow i.v. injection or by rapid i.v. infusion.

Ureidopenicillins

These are adapted from the ampicillin molecule, with a side-chain derived from urea. They must be administered parenterally and are eliminated mainly in the urine. Accumulation in patients with poor renal function is less than with other penicillins as 25% is excreted in the bile. An unusual feature of their kinetics is that, as the dose is increased, the plasma concentration rises disproportionately, i.e. they exhibit *saturation (zero-order) kinetics*.

For pseudomonas septicaemia, a ureidopenicillin plus an aminoglycoside provides a synergistic effect but the co-administration in the same fluid results in inactivation of the aminoglycoside (as with carboxypenicillins, above).

Piperacillin ($t_{½}$ 1 h) is available as a combination with the β-lactamase inhibitor tazobactam (as Tazocin).

CEPHALOSPORINS

Cephalosporins were first obtained from a filamentous fungus *Cephalosporium* cultured from the sea near a Sardinian sewage outfall in 1945; their molecular structure is

closely related to that of penicillin, and many semi-synthetic forms have been introduced. They now comprise a group of antibiotics having a wide range of activity and low toxicity. The term cephalosporins will be used here in a general sense although some are strictly cephamycins, e.g. cefoxitin and cefotetan.

Mode of action is that of the β-lactams, i.e. cephalosporins impair bacterial cell wall synthesis and hence are bactericidal. They exhibit time-dependent bacterial killing (see p. 164).

Addition of various side-chains on the cephalosporin molecule confers variety in pharmacokinetic and antibacterial activities. The β-lactam ring can be protected by such structural manoeuvring, which results in compounds with improved activity against Gram-negative organisms, but less anti-Gram-positive activity. The cephalosporins resist attack by some β-lactamases, but resistance is mediated by other means.

Pharmacokinetics. Usually, cephalosporins are excreted unchanged in the urine, but some, including cefotaxime, form a desacetyl metabolite which possesses some antibacterial activity. Many are actively secreted by the renal tubule, a process which can be blocked with probenecid. As a rule, the dose of cephalosporins should be reduced in patients with poor renal function. Cephalosporins in general have a $t_{½}$ of 1–4 h although there are exceptions (e.g. ceftriaxone, $t_{½}$ 8 h). Wide distribution in the body allows treatment of infection at most sites, including bone, soft tissue, muscle and (in some cases) CSF. Data on individual cephalosporins appear in Table 13.1.

Classification and uses. The cephalosporins are conventionally categorised by 'generations' sharing broadly similar antibacterial and pharmacokinetic properties; newer agents have rendered this classification less precise but it retains sufficient usefulness to be presented in Table 13.1.

Adverse effects. Cephalosporins are well tolerated. The most usual unwanted effects are allergic reactions of the penicillin type, and gastrointestinal upset. Overall the rate of cephalosporin skin reactions such as urticarial rashes and pruritis lies between 1% and 3%. There is cross-allergy between penicillins and cephalosporins involving up to 10% of patients; if a patient has had a severe or immediate allergic reaction or if serum or skin testing for penicillin allergy is positive (see p. 176), then a cephalosporin should not be used. Pain may be experienced at the sites of i.v. or i.m. injection. If cephalosporins are continued for more than 2 weeks, reversible thrombocytopenia, haemolytic anaemia, neutropenia, interstitial nephritis or abnormal liver function tests may occur. The broad spectrum of activity of the third generation cephalosporins may predispose to opportunist infection with resistant bacteria or *Candida* albicans and to *Clostridium difficile* diarrhoea. In the UK, restriction of broad-spectrum cephalosporin use is one component of the bundle of measures aimed to reduce the incidence of *Clostridium difficile*-associated diarrhoea. Ceftriaxone achieves high concentrations in bile and, as the calcium salt, may precipitate to cause symptoms resembling cholelithiasis (biliary pseudolithiasis).

Ceftobiprole is an interesting new investigational parenteral cephalosporin which binds avidly to the mutated penicillin binding protein 2′ responsible for methicillin resistance in staphylococci. It has good activity in vitro and in animal models against MRSA and vancomycin-resistant strains and better activity than ceftriaxone against penicillin-resistant pneumococci. Clinical trials are underway in skin and soft tissue infection and pneumonia.

OTHER β-LACTAM ANTIBACTERIALS

Carbapenems

Members of this group have the widest spectrum of all currently available antimicrobials, being bactericidal against most Gram-positive and Gram-negative aerobic and anaerobic pathogenic bacteria. They are resistant to hydrolysis by most β-lactamases, including ESBLs. Only occasional pseudomonas relatives are naturally resistant, and acquired resistance is uncommon in all species.

Imipenem

Imipenem ($t_{½}$ 1 h) is inactivated by metabolism in the kidney to products that are potentially toxic to renal tubules; combining imipenem with cilastatin (as Primaxin), a specific inhibitor of dihydropeptidase – the enzyme responsible for its renal metabolism – prevents both inactivation and toxicity.

Imipenem is used to treat septicaemia, intra-abdominal infection and nosocomial pneumonia. In terms of imipenem, 1–2 g/day is given by i.v. infusion in 3–4 doses.

Adverse effects. It may cause gastrointestinal upset including nausea, blood disorders, allergic reactions, confusion and convulsions.

Meropenem ($t_{½}$ 1 h) is similar to imipenem, but is stable to renal dihydropeptidase and can therefore be given without cilastatin. It penetrates into the CSF and is not associated with nausea or convulsions.

Ertapenem ($t_{½}$ 4 h) is given as a single daily injection; because of this it has found a niche indication for parenteral therapy of multiply resistant Gram-negative bacteria out of hospital, such as ESBL-producing coliforms. It is, however, much less active against *Pseudomonas aeruginosa*, *Acinetobacter* and their relatives. Adverse events are uncommon, but include diarrhoea (4.8%), infusion vein phlebitis (4.5%) and nausea (2.8%).

Table 13.1 The cephalosporins

DRUG	$T_{½}$ (h)	EXCRETION IN URINE (%)	COMMENT
First generation			
Parenteral			
Cefazolin	2	90	Generally replaced by the newer cephalosporins
Cefradine (also oral)	1	86	
Oral			
Cefaclor	1	86	All very similar. Effective against common respiratory pathogens but (excepting cefaclor) poor activity against *Haemophilus influenzae*. More active against *Escherichia coli* than amoxicillin and trimethoprim. Uncomplicated upper and lower respiratory tract, urinary tract and soft tissue infections, and follow-on treatment once parenteral drugs have brought infection under control
Cefadroxil	2	88	
Cefalexin	1	88	
Second generation			
Parenteral			
Cefoxitin (a cephamycin) (Cefotetan is similar)	1	90	More resistant to β-lactamases than first-generation drugs; active against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria* spp., *Haemophilus influenzae* and many Enterobacteriaceae. Cefoxitin also kills *Bacteroides fragilis* in abdominal and pelvic infections. Cefuroxime may be given for community- acquired pneumonia (not when caused by *Mycoplasma pneumoniae*, *Legionella* or *Chlamydia*). The oral form, cefuroxime axetil, is also used for the range of infections listed for the first-generation oral cephalosporins (above)
Cefuroxime (also oral)	1	80	
Third generation			
Parenteral			
Cefpirome	2.3	75	More effective than second-generation against Gram-negative organisms while retaining activity against Gram-postive bacteria. Cefotaxime and ceftriaxone are used for serious infections such as septicaemia, pneumonia, and for meningitis. Ceftriaxone is also used for gonorrhoea and Lyme disease; also once-per day outpatient i.v. therapy
Cefotaxime	1	60	
Ceftazidime	2	88	
Ceftriaxone	8	56 (44 bile)	
Ceftobiprole	3.5	70	Additionally active against MRSA (in late clinical trials)
Oral			
Cefixime	4	23 (77 bile)	Active against a range of Gram-positive and Gram-negative organisms including *Staphylococcus aureus* (excepting cefixime), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria* spp., *Haemophilus influenzae* and (excepting cefpodoxime) many Enterobacteriaceae. Used to treat urinary, upper and lower respiratory tract infections
Cefprozil	2	40	
Cefpodoxime proxetil	2	80	

Penems

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Penems

Faropenem ($t_{½}$ approximately 1 h) is the first of this group to reach the clinical trial stage. Penems are hybrids of penicillins and cephalosporins, and faropenem is well absorbed by mouth, and is active against a wide range of Gram-positive and Gram-negative pathogens. It will probably be marketed first for upper and lower respiratory tract infection.

OTHER INHIBITORS OF CELL WALL SYNTHESIS AND MEMBRANE FUNCTION

Vancomycin

Vancomycin ($t_{½}$ 8 h), a 'glycopeptide' or 'peptolide', acts on multiplying organisms by inhibiting cell wall formation at a site different from the β-lactam antibacterials. It is bactericidal against most strains of clostridia (including *Clostridium difficile*), almost all strains of *Staphylococcus aureus* (including those that produce β-lactamase and methicillin-resistant strains), coagulase-negative staphylococci, viridans group streptococci and enterococci. Frankly resistant *Staphylococcus aureus* strains have been exceptionally rarely reported, although isolates with raised (but still formally susceptible) vancomycin MICs around 2–3 mg/L have been increasingly recognised and have a somewhat poorer outcome when the drug is used to treat serious, systemic infections such as endocarditis and bacteraemia. Detecting these borderline-susceptible strains reliably in the microbiology laboratory can be technically challenging. Combining vancomycin with linezolid, daptomycin or rifampicin may give better results in such cases, and therapeutic drug monitoring is important to keep trough concentrations at the upper end of the acceptable scale.

Vancomycin is poorly absorbed from the gut and is given i.v. for systemic infections as there is no satisfactory i.m. preparation. It distributes effectively into body tissues and is eliminated by the kidney.

Uses. Vancomycin is effective in cases of antibiotic-associated pseudomembranous colitis (caused by *Clostridium difficile* or, less commonly, staphylococci) in a dose of 125 mg 6-hourly by mouth. Combined with an aminoglycoside, it may be given i.v. for streptococcal endocarditis in patients who are allergic to benzylpenicillin and for serious infection with multiply resisant staphylococci. It is not as effective as flucloxacillin for serious infections caused by methicillin-susceptible *S. aureus*. Dosing is guided by plasma concentration monitoring with the aim of achieving trough concentrations between 10 and 20 mg/L (15–20 mg/L in patients being treated for infective endocarditis). Trough concentrations of up to 25 mg/L of recent vancomycin formulations have not been associated with significant toxicity, and may give better outcomes for the most severe infections and those with less-susceptible strains. There is actually no strong evidence that monitoring peak and/or trough serum vancomycin concentrations reduces the incidence of renal or ototoxicity. However, achieving adequate serum concentrations clearly correlates with both outcome and avoidance of rises in isolates' vancomycin MICs, so initial doses should be calculated on total body-weight even in obese subjects, and dose adjustments should be based on measured serum concentrations performed at least weekly in subjects with stable renal function (and more often in those with reduced or varying renal function).

Adverse effects. Tinnitus and deafness may occur, but may improve if the drug is stopped. Nephrotoxicity and allergic reactions also occur. Rapid i.v. infusion may cause a maculopapular rash, possibly due to histamine release (the 'red person' syndrome).

Teicoplanin is structurally related to vancomycin and is active against Gram-positive bacteria. The $t_{½}$ of 50 h allows once daily i.v. or i.m. administration. It is less likely than vancomycin to cause oto- or nephrotoxicity, but serum monitoring is required to assure adequate serum concentrations for severely ill patients and those with changing renal function.

Daptomycin ($t_{½}$ 9 h) is a recently released lipopeptide antibiotic, naturally produced by the bacterium *Streptomyces roseosporus* which was first isolated from a soil sample from Mount Ararat in Turkey.[3] It has activity against virtually all Gram-positive bacteria, including penicillin-resistant *Streptococcus pneumoniae* and MRSA, regardless of vancomycin resistance phenotype. It is unable to cross the Gram-negative outer membrane, rendering these bacteria resistant.

Daptomycin demonstrates concentration-dependent bactericidal activity, including moderately so against most enterococci (for which vancomycin is generally bacteriostatic). Initial binding to the Gram-positive cell membrane is followed by a variety of effects including membrane depolarisation (probably via the drug forming an ion channel across the membrane: this seems to be the main cidal mechanism) and reduced lipoteichoic acid and protein synthesis. A few *Clostridium* species appear innately resistant, but resistance has proved difficult to induce in vitro and reduction in susceptibility during clinical use has rarely been reported to date. The underlying mechanisms of resistance seem to involve a variety of physiological effects including an altered membrane potential. Staphylococci with increased vancomycin MICs are also less susceptible to daptomycin, and resistance to both agents is acquired progressively in a stepwise fashion.

[3]Eisenstein B I, Oleson F B Jr, Baltz R H 2010 Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. Clinical Infectious Diseases 50(Suppl. 1):S10–15.

It is administered by single daily intravenous injection, and is over 90% protein bound. Virtually no metabolism occurs and excretion is predominantly renal, with about 60% of a dose being recoverable unchanged from the urine. The standard dosage is 4 mg/kg per dose, with the frequency of dosing reduced to 48-hourly for patients with creatinine clearances below 30 mL/min. A higher dose of 6 mg/kg/day is being assessed for infective endocarditis. CSF penetration is only about 5%, but sufficient concentrations may be achieved to be useful, for example, for penicillin-resistant pneumococcal meningitis.

Adverse drug reactions have been reported at similar rates to vancomycin. Use of a longer dose interval has avoided the problems of skeletal muscle pain and rises in serum creatinine phosphokinase that were reported when daptomycin was first introduced in the 1980s in a twice-daily regimen – these adverse effects led to its development being interrupted. The effects were were fully reversible and probably related to the need to allow recovery time for drug action on the myocyte cell membrane, but patients receiving daptomycin should nevertheless be monitored for muscle pain or weakness. Weekly serum creatinine kinase assays should be performed during prolonged treatment courses; mild elevations are seen in about 7% of patients and are usually insignificant, but occasionally discontinuation of therapy is needed.

Daptomycin is approved in the UK for treatment of complicated skin and skin structure infections caused by Gram-positive bacteria and right-sided infective endocarditis caused by *Staphylococcus aureus* (mainly seen in i.v. drug users). Wider applications will doubtless appear and it may prove useful in, for example, endocarditis more generally, osteomyelitis and MRSA infections of orthopaedic hardware. It is usefully employed by outpatient antibiotic therapy clinics because of its single daily dosing and clinical safety. It is not approved for therapy of community-acquired pneumonia because of inferior outcomes which may be related to inhibition by pulmonary surfactant.

Oritavancin, dalbavancin and telavancin are semi-synthetic lipoglycopeptides with high, concentration-dependent bactericidal activity in vitro against most Gram-positive pathogens. Their modes of action probably resemble that of vancomycin, inhibiting the late stages of cell wall peptidoglycan synthesis. The large molecular size of these compounds impairs their diffusion in laboratory agars, creating technical difficulties in some antimicrobial susceptibility tests. The drugs are currently under assessment for clinical use in resistant and difficult Gram-positive infections, initially of skin and the soft tissues. Dalbavancin may be of particular use in outpatient antibiotic therapy clinics since it has a prolonged half-life ($t_{½}$ 5–7 days) and re-dosing may be required only weekly, and excretion occurs via both urine and faeces.

Cycloserine is used for drug-resistant tuberculosis (see p. 204).

Inhibition of protein synthesis

AMINOGLYCOSIDES

In the purposeful search that followed the demonstration of the clinical efficacy of penicillin, streptomycin was obtained from *Streptomyces griseus* in 1944, cultured from a heavily manured field, and also from a chicken's throat. Aminoglycosides resemble each other in their mode of action and pharmacokinetic, therapeutic and toxic properties.

Mode of action. The aminoglycosides act inside the cell by binding to the ribosomes in such a way that incorrect amino acid sequences are entered into peptide chains. Aminoglycosides are bactericidal and exhibit concentration-dependent bacterial killing (see p. 164).

Pharmacokinetics. Aminoglycosides are water-soluble and do not readily cross cell membranes. Poor absorption from the intestine necessitates their administration i.v. or i.m. for systemic use and they distribute mainly to the extracellular fluid; transfer to the cerebrospinal fluid is poor even when the meninges are inflamed. Their $t_{½}$ is 2–5 h.

Aminoglycosides are eliminated unchanged mainly by glomerular filtration, and attain high concentrations in the urine. Significant accumulation occurs in the renal cortex. Plasma concentration should be measured regularly (and frequently in renally impaired patients). With prolonged therapy, e.g. endocarditis (gentamicin), monitoring must be meticulous.

Current practice is to administer aminoglycosides as a single daily dose rather than as twice- or thrice-daily doses. Algorithms are available to guide such dosing according to patients' weight and renal function, and in this case only trough concentrations need to be assayed. Lean body-weight should be used because aminoglycosides distribute poorly in adipose tissue. Single daily dose therapy is probably less oto- and nephrotoxic than divided-dose regimens, and appears to be as effective. The immediate high plasma concentrations that result from single daily dosing are advantageous, e.g. for acutely ill septicaemic patients, as aminoglycosides exhibit concentration-dependent killing (see p. 164).

Antibacterial activity. Aminoglycosides are in general active against staphylococci and aerobic Gram-negative organisms including almost all the Enterobacteriaceae. Bacterial resistance to aminoglycosides is an increasing but patchily distributed problem, notably by acquisition of plasmids (see p. 169) which carry genes coding for the formation of drug-destroying enzymes. Gentamicin resistance is rare in community-acquired pathogens in many hospitals in the UK.

Uses include:

- *Gram-negative bacillary infection*, particularly septicaemia, renal, pelvic and abdominal sepsis. Gentamicin remains the drug of choice, but

tobramycin may be preferred for *Pseudomonas aeruginosa*. Amikacin has the widest antibacterial spectrum of the aminoglycosides but is best reserved for infection caused by gentamicin-resistant organisms. If local resistance rates are low, an aminoglycoside may be included in the initial best-guess regimen for treatment of serious septicaemia. A potentially less toxic antibiotic may be substituted when culture results are known (48–72 h), and toxicity is very rare after such a short course.

- *Bacterial endocarditis*. An aminoglycoside, usually gentamicin, usually comprises part of the antimicrobial combination for enterococcal, streptococcal or staphylococcal infection of the heart valves.
- *Other infections*: tuberculosis, tularaemia, plague, brucellosis.
- *Topical uses*. Neomycin and framycetin, too toxic for systemic use, are effective for topical treatment of infections of the conjunctiva or external ear. Tobramycin is given by inhalation for therapy of infective exacerbations of cystic fibrosis: sufficient systemic absorption may occur to recommend assay of serum concentrations in such patients.

Adverse effects. Aminoglycoside toxicity is a risk when the dose administered is high or of long duration, and the risk is higher if renal clearance is inefficient (because of disease or age), other potentially nephrotoxic drugs are co-administered (e.g. loop diuretics, amphotericin B) or the patient is dehydrated. It may take the following forms:

- *Ototoxicity*. Both vestibular (especially with gentamicin and streptomycin) and auditory (amikacin, neomycin) damage may occur, causing hearing loss, vertigo, nystagmus and tinnitus which may be permanent (see above). Tinnitus may give warning of auditory nerve damage. Early signs of vestibular toxicity include motion-related headache, dizziness or nausea. Serious ototoxicity can occur with topical application, including ear drops. At least five mutations in the mitochondrial gene encoding 12 S rRNA have been found that predispose patients to irreversible aminoglycoside hearing loss, and the possibility of screening individuals before commencing therapy is being investigated. Anti-free radical agents such as salicylate may reduce aminoglycoside toxicity.
- *Nephrotoxicity*. Dose-related changes, which are usually reversible, occur in renal tubular cells, where aminoglycosides accumulate. Low blood pressure, loop diuretics and advanced age are recognised as added risk factors.
- *Neuromuscular blockade*. Aminoglycosides may impair neuromuscular transmission and aggravate (or reveal) myasthenia gravis, or cause a transient myasthenic syndrome in patients whose neuromuscular transmission is normal.
- *Other reactions* include rashes and haematological abnormalities, including marrow depression, haemolytic anaemia and bleeding due to antagonism of factor V.

For gentamicin and tobramycin, oto- and nephrotoxicity are increased if peak concentrations exceed 12–14 mg/L consistently, or troughs exceed 2 mg/L. For amikacin the corresponding concentrations are 32–34 mg/L and 10 mg/L.

Individual aminoglycosides

Gentamicin is active against aerobic Gram-negative bacilli including *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus* and *Pseudomonas*. In streptococcal and enterococcal endocarditis gentamicin is combined with benzylpenicillin, in staphylococcal endocarditis with an antistaphylococcal penicillin, and in enterococcal endocarditis with ampicillin (true synergy is seen provided the enterococcus is not highly resistant to gentamicin).

Dose is 3–5 mg/kg body-weight per day (the highest dose for more serious infections) either as a single dose or in three equally divided doses. The rationale behind single-dose administration is to achieve high peak plasma concentrations (10–14 mg/L, which correlate with therapeutic efficacy) and more time at lower trough concentrations (16 h at <1 mg/L, which are associated with reduced risk of toxicity). Therapy should rarely exceed 7 days. Patients with cystic fibrosis eliminate gentamicin rapidly and require higher doses. Gentamicin applied to the eye gives effective corneal and aqueous humour concentrations.

Tobramycin is similar to gentamicin; it is more active against most strains of *Pseudomonas aeruginosa* and may be less nephrotoxic.

Amikacin is mainly of value because it is more resistant to aminoglycoside-inactivating bacterial enzymes than gentamicin. It is finding new application in the initial management of multiply resistant Gram-negative sepsis, especially in areas with high rates of ESBL-producing coliforms. Peak plasma concentrations should be kept between 20–30 mg/L and trough concentrations below 10 mg/L.

Netilmicin is active against some strains of bacteria that resist gentamicin and tobramycin; it may be less oto- and nephrotoxic.

Neomycin and *framycetin* are principally used topically for skin, eye and ear infections. Enough absorption can occur from both oral and topical use to cause eighth cranial nerve damage, especially if there is renal impairment.

Streptomycin, superseded as a first-line choice for tuberculosis, may be used to kill resistant strains of the organism.

Spectinomycin is active against Gram-negative organisms but its clinical use is confined to gonorrhoea in patients allergic to penicillin, or to infection with gonococci that are β-lactam drug resistant, although resistance to it is reported.

TETRACYCLINES

Tetracyclines have a broad range of antimicrobial activity and differences between the individual members have traditionally been small, but new tetracyclines and tetracycline relatives are now being developed with even wider spectra of activity that include some bacteria with acquired resistance to other classes of antibiotic.

Mode of action. Tetracyclines interfere with protein synthesis by binding to bacterial ribosomes and their selective action is due to higher uptake by bacterial than by human cells. They are bacteriostatic.

Pharmacokinetics. Most tetracyclines are only partially absorbed from the alimentary tract, enough remaining in the intestine to alter the flora and cause diarrhoea. They are distributed throughout the body and cross the placenta. Tetracyclines in general are excreted mainly unchanged in the urine and should be avoided when renal function is severely impaired, although doxycycline and minocycline are eliminated by non-renal routes and are preferred for patients with impaired renal function.

Uses. Tetracyclines are active against nearly all Gram-positive and Gram-negative pathogenic bacteria, but increasing bacterial resistance and low innate activity limit the clinical use of most members of the class. Although 4-quinolone usage has replaced them especially in the developed world, they remain drugs of first choice for infection with chlamydiae (psittacosis, trachoma, pelvic inflammatory disease, lymphogranuloma venereum), mycoplasma (pneumonia), rickettsiae (Q fever, typhus), *Bartonella* spp., and borreliae (Lyme disease, relapsing fever) (for use in acne, see p.273). Doxycycline is used in therapeutic and prophylactic regimens for malaria (see p. 230) and is active against amoebae and a variety of other protozoa. Their most common other uses are as second-line therapy of minor skin and soft tissue infections especially in β-lactam allergic patients; surprisingly, many MRSA strains currently remain susceptible to tetracyclines in the UK.

An unexpected use for a tetracycline is in the treatment of chronic hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) when water restriction has failed. Demeclocycline produces a state of unresponsiveness to ADH, probably by inhibiting the formation and action of cyclic AMP in the renal tubule. It is effective and convenient to use in SIADH because this action is both dose-dependent and reversible.

Adverse reactions. Heartburn, nausea and vomiting due to gastric irritation are common, and attempts to reduce this with milk or antacids impair absorption of tetracyclines (see below). Diarrhoea and opportunistic infection may supervene. Disorders of epithelial surfaces, perhaps due partly to vitamin B complex deficiency and partly to mild opportunistic infection with yeasts and moulds, lead to sore mouth and throat, black hairy tongue, dysphagia and perianal soreness. Vitamin B preparations may prevent or arrest alimentary tract symptoms.

Due to their chelating properties with calcium phosphate, tetracyclines are selectively taken up in the teeth and growing bones of the fetus and of children. This causes hypoplasia of dental enamel with pitting, cusp malformation, yellow or brown pigmentation and increased susceptibility to caries. After the 14th week of pregnancy and in the first few months of life even short courses can be damaging. Prolonged tetracycline therapy can also stain the fingernails at all ages.

The effects on the bones after they are formed in the fetus are of less clinical importance because pigmentation has no cosmetic disadvantage and a short exposure to tetracycline is unlikely significantly to delay growth.

Inhibition of protein synthesis in man causes blood urea to rise (the anti-anabolic effect); the increased nitrogen load can be clinically important in renal failure and in the elderly.

Tetracyclines induce photosensitisation and other rashes. Liver and pancreatic damage can occur, especially in pregnancy and with renal disease, when the drugs have been given i.v. Rarely tetracyclines cause benign intracranial hypertension (not always benign, because permanent visual damage may occur: signs and symptoms of raised intracranial pressure present, also known as 'pseudotumour cerebri'), dizziness and other neurological reactions. These may develop after tetracyclines have been taken for 2 weeks or a year, and the visual function of any patient taking tetracyclines who develops headaches or visual disturbance should be assessed carefully and their fundi examined.

Interactions. Dairy products reduce absorption to a degree but antacids and iron preparations do so much more by chelation to calcium, aluminium and iron.

Individual tetracyclines

Tetracycline is eliminated by the kidney and in the bile ($t_{½}$ 6 h). Because of incomplete absorption from the gut i.v. doses need be less than half of the oral dose to be similarly effective. The dose is 250–500 mg 6-hourly by mouth.

Doxycycline is well absorbed from the gut, even after food. It is excreted in the bile, in the faeces which it reenters by diffusing across the small intestinal wall and, to some extent, in the urine ($t_{½}$ 16 h). These non-renal mechanisms compensate effectively when renal function is impaired and no reduction of dose is necessary; 200 mg is given on the first day, then 100 mg/day.

Minocycline differs from other tetracyclines in that its antibacterial spectrum includes *Neisseria meningitidis* and it has been used for meningococcal prophylaxis. It is well absorbed from the gut, even after a meal, partly metabolised in the liver and partly excreted in the bile and urine ($t_{½}$ 15 h). Dose reduction is not necessary when renal function is impaired; 200 mg initially is followed by 100 mg

12-hourly. Minocycline, but not other tetracyclines, may cause a reversible vestibular disturbance with dizziness, tinnitus and impaired balance, especially in women.

Other tetracyclines include demeclocycline (see above), lymecycline and oxytetracycline.

Tigecycline ($t_{½}$ 42 h) is the first of the glycylcyclines to be licensed. These are close relatives of the tetracyclines – tigecycline shares the same molecular structure as minocycline with the addition of a 9-glycylamide group as a side chain on the tetracycline ring. The molecule binds to the 30 S bacterial ribosomal subunit, blocking entry of amino-acyl tRNA molecules to the A site and preventing amino acid chain elongation. Probably because of stearic hindrance from the 9-glycylamide structure and avid ribosomal binding, tigecycline is unaffected by the two commonest tetracycline resistance mechanisms – ribosomal alteration and efflux pumps. Consequently the compound displays useful bacteriostatic activity against a wide range of pathogens including streptococci and staphylococci (including vancomycin-resistant enterococci (VRE) and MRSA), Gram-negative bacilli (including *Legionella* spp., although not *Proteus* spp. or *Pseudomonas* spp. and their relatives) and anaerobes.

It is licensed for skin and soft tissue infection, complicated intra-abdominal infections and community-acquired pneumonia, in which trial outcomes have shown equivalent efficacy to carbapenems and other similar agents. Resistance has emerged during treatment of a variety of serious infections. A somewhat higher mortality rate than comparator agents (4% vs. 3%) has been reported by post-marketing surveillance during treatment of a range of serious infections: this observation requires scientific investigation before tigecycline's use is re-evaluated, but caution is warranted.

It is only available for parenteral use and is administered as a 100 mg first dose followed by 50 mg twice daily. Distribution is widespread throughout the body, although little crosses the blood–brain barrier and concentrations achieved in the urine are below the tigecycline MIC of many pathogens. Limited metabolism occurs, with about 60% of a dose eliminated via the gut and bile and 33% in the urine (only 22% as unchanged tigecycline). No dosage adjustment is required in renal failure or dialysis, and a dose reduction is required only in severe hepatic failure. A similar range and rate of side-effects to the tetracyclines has been reported.

MACROLIDES

Erythromycin

Erythromycin ($t_{½}$ 2–4 h) binds to bacterial ribosomes and interferes with protein synthesis; it is bacteriostatic and exhibits time-dependent killing (see p. 164). It is effective against Gram-positive organisms because these accumulate the drug more efficiently, and its antibacterial spectrum is similar to that of penicillin.

Absorption after oral administration is best with erythromycin estolate, even if there is food in the stomach. Hydrolysis of the estolate in the body releases the active erythromycin which diffuses readily into most tissues; the $t_{½}$ is dose-dependent and elimination is almost exclusively in the bile and faeces.

Uses. Erythromycin is the drug of choice for:

- *Mycoplasma pneumoniae* in children, although in adults a tetracycline may be preferred.
- *Legionella* spp., with or without rifampicin, although some authorities prefer a quinolone.
- Diphtheria (including carriers), pertussis and for some chlamydial infections.

In gastroenteritis caused by *Campylobacter jejuni*, erythromycin is effective in eliminating the organism from the faeces, although it does not reduce the duration of the symptoms unless given very early in the illness.

Erythromycin is an effective alternative choice for penicillin-allergic patients infected with *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* or *Treponema pallidum*.

Acne; see page 273.

Dose is 250 mg 6-hourly or twice this in serious infection and four times for legionnaires' disease.

Adverse reactions. Erythromycin is remarkably non-toxic, but the estolate can cause cholestatic hepatitis. This is probably an allergy, and recovery is usual, but the estolate should not be given to a patient with liver disease. Other allergies are rare. Gastrointestinal disturbances occur frequently (up to 28%), particularly diarrhoea and nausea, but opportunistic infection is uncommon.

Interactions. Erythromycin and the other macrolides are enzyme inhibitors and interfere with the cytochrome P450 metabolic inactivation of some drugs, e.g. warfarin, ciclosporin, tacrolimus, digoxin, carbamazepine, theophylline, disopyramide, increasing their effects. Reduced inactivation of terfenadine may lead to serious cardiac arrhythmias, and of ergot alkaloids may cause ergotism. Increased serum erythromycin concentrations are seen with co-administration of azole antifungal agents, some calcium channel blockers and anti-HIV protease inhibitors (ritonavir, saquinavir). Combination of erythromycin with strong inhibitors of P450 enzymes has been associated with an increased risk of sudden cardiac death (azole antifungal agents, diltiazem, verapamil and troleandomycin).

Clarithromycin acts like erythromycin and has a similar spectrum of antibacterial activity, i.e. mainly against Gram-positive organisms, although it is usefully more active against *Haemophilus influenzae*. The usual dose is 250 mg 12-hourly or twice that for serious infections. It is rapidly and completely absorbed from the gastrointestinal tract, 60% of a dose is inactivated by metabolism which is saturable (note that the $t_{½}$ increases with dose: 3 h after 250 mg, 9 h after 1200 mg) and the remainder is eliminated in the

urine. Clarithromycin is used for respiratory tract infections including atypical pneumonias and soft tissue infections. It is concentrated intracellularly, achieving concentrations which allow effective therapy in combination for mycobacterial infections such as *Mycobacterium avium-intracellulare* in patients with AIDS. Gastrointestinal tract adverse effects are uncommon (7%). Interactions: see erythromycin (above).

Azithromycin has additional activity against a number of important Gram-negative organisms including *Haemophilus influenzae* and *Neisseria gonorrhoeae*, and also *Chlamydiae*, but is a little less effective than erythromycin against Gram-positive organisms.

Azithromycin achieves high concentrations in tissues relative to those in plasma. It remains largely unmetabolised and is excreted in the bile and faeces ($t_{½}$ 50 h). Azithromycin is used to treat respiratory tract and soft tissue infections and sexually transmitted diseases, especially genital *Chlamydia* infections, and is effective for travellers' diarrhoea, especially when combined with loperamide. It has been used in patients with cystic fibrosis who are colonised with *Pseudomonas aeruginosa*: azithromycin may have synergistic activity with other anti-pseudomonal agents, and its modest anti-inflammatory effects may also reduce the intensity of symptoms. Gastrointestinal effects (9%) are less than with erythromycin but diarrhoea, nausea, dyspepsia and abdominal pain occur. In view of its high hepatic excretion, use in patients with liver disease should be avoided. Interactions: see erythromycin (above).

Telithromycin ($t_{½}$ 10 h) is the first of the ketolides, semisynthetic relatives of the macrolides which bind to the 50 S bacterial ribosomal subunit, preventing translation and ribosome assembly. Its molecular differences from erythromycin make it more acid stable and less susceptible to bacterial export pumps, while increasing its ribosomal binding. Its spectrum of activity includes most erythromycin-resistant strains of *Streptococcus pneumoniae*, but it is not active against erythromycin-resistant staphylococci, including most MRSA.

It is licensed for once-daily oral therapy of upper and lower respiratory tract infections and good efficacy has been demonstrated with relatively short courses (e.g. 5 days). Bioavailability is approximately 57% and is unaffected by food intake. It is generally well tolerated, although it causes diarrhoea more commonly than the newer macrolides and some patients experience transient visual disturbance (blurred or double vision). Rare cases of serious hepatotoxicity have been reported although dose adjustment is not required in hepatic failure. Some authorities recommend halving the daily dose with severe renal failure, and it is a potent inhibitor of cytochrome P450 liver enzymes, resulting in interactions with, for example, itraconazole, rifampicin, midazolam and atorvastatin.

Clindamycin, structurally a lincosamide rather than a macrolide, binds to bacterial ribosomes to inhibit protein synthesis. Its antibacterial spectrum is similar to that of erythromycin (with which there is partial cross-resistance – so-called 'inducible MLS resistance') and benzylpenicillin; inducible resistance is variable in prevalence in common pathogens in different parts of the world, with the result that clindamycin can be a useful second-line agent for oral treatment of some difficult infections (e.g. MRSA osteomyelitis) as long as susceptibility testing is correctly performed. Clindamycin is well absorbed from the gut and distributes to most body tissues including bone. The drug is metabolised by the liver and enterohepatic cycling occurs with bile concentrations 2–5 times those of plasma ($t_{½}$ 3 h). Significant excretion of metabolites occurs via the gut.

Clindamycin is used for staphylococcal bone and joint infections, dental infections and serious intra-abdominal sepsis (in the last, it is usually combined with an agent active against Gram-negative pathogens such as gentamicin). Because of its ability to inhibit production of bacterial protein toxins, it is the antibiotic of choice for serious invasive *Streptococcus pyogenes* infections (although surgical resection of affected tissue plays a prime role) and it is also an alternative to linezolid for treatment of Panton-Valentine leukocidin-producing strains of *Staphylococcus aureus* (see p. 210). It is a second choice in combination for some *Toxoplasma* infections (see p. 236). Topical preparations are used for therapy of severe acne and non-sexually transmitted infection of the genital tract in women.

The most serious **adverse effect** is antibiotic-associated (pseudomembranous) colitis (see p. 170); clindamycin should be stopped if any diarrhoea occurs.

OTHER INHIBITORS OF PROTEIN SYNTHESIS

Chloramphenicol

Chloramphenicol has a broad spectrum of activity and is primarily bacteriostatic, but may be bactericidal against *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae*.

Pharmacokinetics. Chloramphenicol succinate is hydrolysed to active chloramphenicol and there is much individual variation in the capacity to perform this reaction. Chloramphenicol is inactivated by conjugation with glucuronic acid in the liver ($t_{½}$ 5 h in adults). In the neonate, the process of glucuronidation is slow, and plasma concentrations are extremely variable, especially in premature neonates in whom monitoring of plasma concentration is essential. Chloramphenicol penetrates well into all tissues, including the CSF and brain even in the absence of meningeal inflammation.

Uses. Chloramphenicol's role in meningitis and brain abscess has largely been superseded, but it is a second-line agent for these indications. Chloramphenicol may be used for salmonella infections (typhoid fever, salmonella

septicaemia) but ciprofloxacin is now preferred. Topical administration is effective for bacterial conjunctivitis.

Adverse effects. Systemic use of chloramphenicol is dominated by the fact that it can cause rare (between 1:18 000 and 1:100 000 courses) though serious bone marrow damage which may be a dose-dependent, reversible depression of erythrocyte, platelet and leucocyte formation that occurs early in treatment (type A adverse drug reaction), or an idiosyncratic (probably genetically determined), non-dose-related, and usually fatal aplastic anaemia which may develop during, or even weeks after, prolonged treatment, and sometimes on re-exposure to the drug (type B adverse reaction). This has also occurred, very rarely, with eye drops. Marrow depression may be detected at an early and recoverable stage by frequent checking of the full blood count.

The 'grey baby' syndrome occurs in neonates as circulatory collapse in which the skin develops a cyanotic grey colour. It is caused by failure of the liver to conjugate, and of the kidney to excrete the drug.

Sodium fusidate

Sodium fusidate is a steroid antimicrobial which is used almost exclusively against β-lactamase-producing staphylococci. Because staphylococci may rapidly become resistant via a one-step genetic mutation, the drug should be combined with another antistaphylococcal drug, e.g. flucloxacillin. Sodium fusidate is readily absorbed from the gut and distributes widely in body tissues including bone. It is metabolised and very little is excreted unchanged in the urine; the $t_{½}$ is 5 h.

Uses. Sodium fusidate is a valuable drug for treating severe staphylococcal infections, including osteomyelitis, and is available as i.v. and oral preparations. In an ointment or gel, sodium fusidate is used topically for staphylococcal skin infection. Another gel preparation is used for topical application to the eye: this contains such a high fusidic acid concentration that it possesses useful activity against most bacteria that cause conjunctivitis.

Adverse effects. It is well tolerated, but mild gastrointestinal upset is frequent. Jaundice may develop, particularly with high doses given intravenously, and liver function should be monitored.

RESISTANCE TO ANTIMICROBIALS: LINEZOLID, QUINUPRISTIN-DALFOPRISTIN AND FOSFOMYCIN

Linezolid and quinupristin-dalfopristin (Synercid) were developed in response to the emergence of multiply resistant Gram-positive pathogens during the 1990s. Both have clinically useful activity against MRSA (including vancomycin intermediate and resistant strains), vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*. They are currently reserved for treatment of infections caused by such bacteria and for use in patients who are allergic to more established antibiotics. Difficult decisions are being faced about how such novel but expensive antimicrobial agents should be used:

> ***No antibiotic should be used recklessly, however difficult it appears to be to select for resistance in vitro. On the other hand, the attitude that 'All new antibiotics should be locked away' risks stifling innovation whilst denying life-saving treatments . . . Debates on the use of new anti-Gram-positive agents are sure to intensify . . . and it is vital that they take place on a basis of science not knee-jerk restrictions or over-zealous marketing.***[4]

These agents are inactive against most Gram-negative bacteria.

Linezolid, a synthetic oxazolidinone, is the first member of the first totally new class of antibacterial agents to be released to the market for 20 years, the first new agent approved for therapy of MRSA for over 40 years, and the first oral antibiotic active against VRE. It has a unique mode of action, binding to domain V of the 23 S component of the 50 S ribosomal subunit and inhibiting formation of the initiation complex between transfer-RNA, messenger RNA and the ribosomal subunits. It is bacteriostatic against most Gram-positive bacteria, but is bactericidal against pneumococci.

Resistance has been reported so far in occasional enterococcus and *Staphylococcus aureus* isolates from immunocompromised patients and others with chronic infections who had been treated with linezolid for long periods; a handful of examples from other species have also been found. Linezolid-resistant isolates possess modified 23 S ribosomal RNA genes, and the level of resistance correlates with the number of gene copies the organisms carry. Most Gram-negative bacteria are resistant by virtue of possessing membrane efflux pumps, although many obligate anaerobes are susceptible.

It is eliminated via both renal and hepatic routes ($t_{½}$ 6 h) with 30–55% excreted in the urine as the active drug. Oral and parenteral formulations are available, and the usual dose is 600 mg 12-hourly by both routes; absorption after oral administration is rapid, little affected by food, and approaches 100%. Dose modification in hepatic or renal impairment is not necessary. Distribution includes to the CSF, eye and respiratory tract, although variability in concentrations achieved is seen with systemic sepsis, cystic fibrosis

[4]Livermore D M 2000 Quinupristin/dalfopristin and linezolid: where, when, which and whether to use? Journal of Antimicrobial Chemotherapy 46:347–350.

and burn injuries and also in neonates, and it is noteworthy that linezolid resistance has developed during treatment of patients with low serum concentrations.

Linezolid is licensed in the UK for skin, soft tissue and respiratory tract infections, and it is usually restricted on grounds of cost to those caused by multiply resistant pathogens. The oral formulation has proven useful for follow-on therapy of severe and chronic infections caused by bacteria resistant to other agents, e.g. MRSA osteomyelitis, although its drug cost is high for both oral and parenteral preparations.

Adverse effects include nausea, vomiting and headache, with much the same frequency as with penicillin and macrolide therapy. Reversible optic and irreversible peripheral neuropathy have been reported and, importantly, marrow suppression may occur, especially where there is pre-existing renal disease or patients are also receiving other drugs that may have adverse effects on marrow or platelet function, so full blood counts and neurological assessments should be performed weekly. Patients should not generally receive linezolid for longer than 2 weeks unless available alternatives carry disadvantages; this is frequently the case, for example, during treatment of multiply resistant pathogens such as MRSA, where comparative studies have generally shown equivalent efficacy and similar rates of adverse events. Linezolid is active against multi-drug and extensively drug-resistant *Mycobacterium tuberculosis*, non-tuberculous mycobacteria and *Nocardia* spp. and seems effective therapeutically, although course lengths have been limited by high rates of myelosuppression and neuropathy. Potentiation of the pressor activity of monoamine oxidase inhibitors and other interactions with adrenergic, serotonergic and dopaminergic drugs may occur and it may also interact with foods of high tyramine content such as aged meats, cheese, beer and wine.

Quinupristin-dalfopristin is a 30%:70% combination of two streptogramin molecules: the dalfopristin component binds first to the 50 S bacterial ribosome, inducing a conformational change which allows the additional binding of quinupristin. The combination results in inhibition of both aminoacyl-tRNA attachment and the peptidyl transferase elongation step of protein synthesis, resulting in premature release of polypeptide chains from the ribosome. The summative effect is bactericidal. Acquired resistance is currently rare, but a variety of possible mechanisms of resistance have been reported including methylation of the 23 S RNA molecule (also involved in erythromycin resistance), enzymatic hydrolysis and phosphorylation and efflux pumps. Most strains of *Enterococcus faecalis* are naturally resistant, but *E. faecium* is susceptible, as are the respiratory pathogens *Legionella pneumophila, Moraxella catarrhalis* and *Mycoplasma pneumoniae*. Other Gram-negative bacteria have impermeable membranes and hence are resistant. The $t_{½}$ is 1.5 h. Quinupristin-dalfopristin is available for administration only by i.v. injection; the usual dose is 7.5 mg/kg every 8 h.

It is licensed in the UK for *Enterococcus faecium* infections, skin and soft tissue infection, and hospital-acquired pneumonia, but recently supplies have become difficult to obtain.

Injection to peripheral veins frequently causes phlebitis, so a central line is required. Arthralgia and myalgia are seen in about 10% of patients. No dosage reduction is recommended in renal impairment, but the dose should be reduced in moderate hepatic impairment and it should generally be avoided if the impairment is severe.

Fosfomycin, a phosphonic acid derivative, was originally extracted from a *Streptomyces* sp. bacterium in 1969, but is now fully synthetic. Oral preparations have been used in a number of countries for over 20 years mainly for urinary tract infection, and a disodium derivative is available for intravenous and intramuscular use.

Fosfomycin is bactericidal against many Gram-positive and Gram-negative bacteria via inhibition of uridine diphosphate-GlcNAc enol-pyruvyltransferase (MurA). It enters bacterial and mammalian cells via an active transport system. Susceptible bacteria include most coliforms, *Staphylococcus aureus* and *epidermidis, Streptococcus pneumoniae* and *Enterococcus faecalis*. In some cases synergy has been demonstrated with β-lactam antibiotics. Predictably resistant species include *Acinetobacter* spp., *Listeria monocytogenes* and anaerobes, while few *Pseudomonas aeruginosa* or *Enterococcus faecium* are inhibited. Fosfomycin has a small molecular size and relatively long half life ($t_{½}$ 5.7 h) and so penetrates most tissues, including the CSF and eye. Few data are available on drug interactions, although reported adverse events are uncommon, mainly including mild gastrointestinal disturbance (in 5–6%) and rashes (4%), and pain and inflammation at the infusion and injection site of the parenteral preparation (3%).

Most published experience is with single 3 g oral doses for lower urinary tract infection, where fosfomycin activity persists in the urine for 48 h and is as effective as 3–5-day courses of conventional agents: it is one convenient choice for ESBL-producing coliforms. A 3 g once-daily regimen for 3 days may be used for complicated urinary tract infection. Prolonged and successful use is reported for a wide variety of serious infections where treatment had been complicated by bacterial resistance and host allergy to other agents, including infections with penicillin-resistant pneumococci, MRSA, ESBL coliforms and vancomycin-resistant *E. faecalis*. Resistance can emerge during therapy of the individual, mediated by conjugation of glutathione to the antibiotic molecule by bacterial metalloglutathione transferase, but surveys in countries where the drug has been used for two decades have shown a consistently low (3%) primary resistance rate in urinary tract pathogens and there is no cross-resistance to other antimicrobial classes. Fosfomycin is currently not licensed in the UK but is available via the European license on a named patient basis.

Inhibition of nucleic acid synthesis

SULFONAMIDES AND SULFONAMIDE COMBINATIONS

Sulfonamides now have their place in medicine mainly in combination with trimethoprim. Because of the risks of adverse drug reactions associated with their use, this is generally restricted to specific indications where other therapeutic agents have clearly inferior efficacy. Many sulfonamide compounds have recently been withdrawn from the market. Their individual names are standardised in the UK to begin with 'sulfa-'.

The enzyme dihydrofolic acid (DHF) synthase (see below) converts *p*-aminobenzoic acid (PABA) to DHF which is subsequently converted to tetrahydric folic acid (THF), purines and DNA. The sulfonamides are structurally similar to PABA, successfully compete with it for DHF synthase, and thus ultimately impair DNA formation. Most bacteria do not use preformed folate, but humans derive DHF from dietary folate which protects their cells from the metabolic effect of sulfonamides. Trimethoprim acts at the subsequent step by inhibiting DHF reductase, which converts DHF to THF. The drug is relatively safe because bacterial DHF reductase is much more sensitive to trimethoprim than is the human form of the enzyme. Both sulfonamides and trimethoprim are bacteriostatic.

Pharmacokinetics. Sulfonamides for systemic use are absorbed rapidly from the gut. The principal metabolic path is acetylation and the capacity to acetylate is genetically determined in a bimodal form, i.e. there are slow and fast acetylators (see Pharmacogenetics), but the differences are of limited practical importance in therapy. The kidney is the principal route of excretion of drug and acetylate.

Systemic use

Sulfonamide-trimethoprim combination. *Co-trimoxazole* (sulfamethoxazole plus trimethoprim); the optimum synergistic in vitro effect against most susceptible bacteria is achieved with 5:1 ratio of sulfamethoxazole to trimethoprim, although concentrations achieved in the tissues vary considerably. Each drug is well absorbed from the gut, has a $t_{1/2}$ of 10 h and is 80% excreted by the kidney; consequently, the dose of co-trimoxazole should be reduced when renal function is impaired.

Trimethoprim on its own is now used in many conditions for which the combination was originally recommended, and it may cause fewer adverse reactions (see below). The combination is, however, retained for the following:

- Prevention and treatment of pneumonia due to *Pneumocystis carinii* infection in immunosuppressed patients (for therapy, high doses of 120 mg/kg/day in 2–4 divided doses are used and therapeutic drug monitoring is essential).
- Prevention and treatment of toxoplasmosis, and treatment of nocardiasis and *Stenotrophomonas maltophilia* infection (90–120 mg/kg/day dosing).

Sulfadiazine ($t_{1/2}$ 10 h), sulfametopyrazine ($t_{1/2}$ 38 h) and sulfadimidine (sulfamethazine) ($t_{1/2}$ approximately 6 h, dose dependent) are available in some countries for urinary tract infections, meningococcal meningitis and other indications,but resistance rates are high.

Silver sulfadiazine is used topically for prophylaxis and treatment of infected burns, leg ulcers and pressure sores because of its wide antibacterial spectrum (which includes pseudomonads).

Miscellaneous

Sulfasalazine (salicylazosulfapyridine) is used in inflammatory bowel disease (see p. 541); in effect the sulfapyridine component acts as a carrier to release the active 5-aminosalicylic acid in the colon (see also rheumatoid arthritis, p. 252).

Adverse effects of sulfonamides include malaise, diarrhoea and rarely cyanosis (due to methaemoglobinaemia). These may all be transient and are not necessarily indications for stopping the drug. Crystalluria may rarely occur.

Allergic reactions. include: rash, fever, hepatitis, agranulocytosis, purpura, aplastic anaemia, peripheral neuritis and polyarteritis nodosa. Rarely, severe skin reactions including erythema multiforme bullosa (Stevens–Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) occur.

Haemolysis may occur in glucose-6-phosphate dehydrogenase-deficient subjects. Patients with AIDS have a high rate of allergic systemic reactions (fever, rash) to co-trimoxazole used for treatment of *Pneumocystis carinii* pneumonia.

Trimethoprim

Trimethoprim ($t_{1/2}$ 10 h) has emerged as a useful broad-spectrum antimicrobial on its own, active against many Gram-positive and Gram-negative aerobic organisms excepting the enterococci and *Pseudomonas aeruginosa;* the emergence of resistant organisms is becoming a problem especially for treatment of urinary tract infection. The drug is rapidly and completely absorbed from the gastrointestinal tract and is largely excreted unchanged in the urine. Trimethoprim is effective as sole therapy in treating urinary and respiratory tract infections and for low-dose prophylaxis of urinary tract infections.

Adverse effects are fewer than with co-trimoxazole and include: skin rash, anorexia, nausea, vomiting, abdominal pain and diarrhoea.

QUINOLONES

(4-quinolones, fluoroquinolones)

The first widely used quinolone, nalidixic acid, was discovered serendipitously as a by-product of chloroquine synthesis. It is effective for urinary tract infections because it is concentrated in the urine, but it has little systemic activity. Fluorination of the quinolone structure was subsequently found to produce compounds that were up to 60 times more active than nalidixic acid and killed a wider range of organisms. These newer '4-quinolones' act principally by inhibiting bacterial (but not human) DNA gyrase (topoisomerase II and IV), thus preventing the supercoiling of DNA, a process that is necessary for compacting chromosomes in the bacterial cell; they are bactericidal and exhibit concentration-dependent bacterial killing (see p. 164). In general quinolones are extremely active against Gram-negative organisms and most have useful activity against *Pseudomonas aeruginosa*, mycobacteria and *Legionella pneumophila*. Most are less active against Gram-positive organisms (resistance commonly emerges) and anaerobes. Resistance typically arises via mutation of the target enzymes and these are coded on mobile plasmids; efflux pumps may also contribute. Quinolone resistance rates of a wide range of Gram-negative bacteria have risen alarmingly worldwide during the past 10 years, and clinical cross-resistance across all members of the group is common.

Pharmacokinetics. Quinolones are well absorbed from the gut, and widely distributed in tissue. Mechanisms of inactivation (hepatic metabolism, renal and biliary excretion) are detailed below for individual members. There is substantial excretion and re-absorption via the colonic mucosa, and patients with renal failure or intestinal malfunction, e.g. ileus, are prone to accumulate quinolones.

Uses vary between individual drugs (see below).

Adverse effects include gastrointestinal upset and allergic reactions (rash, pruritus, arthralgia, photosensitivity and anaphylaxis). High rates of quinolone usage in hospitals have been associated with outbreaks of diarrhoea caused by *Clostridium difficile*, so reduced use is one component of the bundles of recommended control measures (see p. 170). CNS effects may develop with dizziness, headache and confusion. Convulsions have occurred during treatment (avoid or use with caution where there is a history of epilepsy or concurrent use of NSAIDs, which potentiate this effect). Reversible arthropathy has developed in weight-bearing joints in immature animals exposed to quinolones. Quinolones should be used only for serious infections and then with caution in children and adolescents; however, ciprofloxacin is licensed for treatment of *Pseudomonas aeruginosa* lung infection in children over 5 years of age with cystic fibrosis. Rupture of tendons, notably the Achilles, has occurred, more commonly in the elderly and those taking corticosteroids concurrently. Levofloxacin and ofloxacin are less likely than ciprofloxacin to cause corneal precipitates during topical therapy to the eye and are preferred for this as much as for their enhanced anti-Gram-positive activity.

Some are potent liver enzyme inhibitors and impair the metabolic inactivation of other drugs including warfarin, theophylline and sulphonylureas, increasing their effect. Magnesium- and aluminium-containing antacids impair absorption of quinolones from the gastrointestinal tract, probably through forming a chelate complex; ferrous sulphate and sucralfate also reduce absorption.

Individual members of the group include the following:

Ciprofloxacin ($t_{½}$ 3 h) is effective against a range of bacteria but particularly the Gram-negative organisms (see above). Chlamydia and mycoplasma are susceptible. Ciprofloxacin is indicated for use in infections of the urinary, gastrointestinal and respiratory tracts, tissue infections, gonorrhoea and septicaemia. It has proven especially useful for oral therapy of chronic Gram-negative infections such as osteomyelitis, and for acute exacerbations of *Pseudomonas* infection in cystic fibrosis. It has been used for the prophylaxis and therapy of anthrax, including cases resulting from bioterrorism. The dose is 250–750 mg 12-hourly by mouth, 200–400 mg 12-hourly i.v. but halved when the glomerular filtration rate is < 20 mL/min. Ciprofloxacin impairs metabolism of theophylline and of warfarin, both of which should be monitored carefully when co-administered.

Norfloxacin ($t_{½}$ 3 h) is used for acute or chronic recurrent urinary tract infections.

Ofloxacin ($t_{½}$ 4 h) has modestly greater Gram-positive, but less Gram-negative activity than ciprofloxacin. It is used for urinary and respiratory tract infections, gonorrhoea, and topically for eye infection.

Nalidixic acid ($t_{½}$ 6 h) is now used principally for the prevention of urinary tract infection. It may cause haemolysis in glucose-6-phosphate dehydrogenase-deficient subjects.

Others *Levofloxacin* ($t_{½}$ 7 h) has greater activity against *Streptococcus pneumoniae* than ciprofloxacin and is used for respiratory and urinary tract infection. *Moxifloxacin* ($t_{½}$ 9–12 h) has strong anti-Gram-positive activity and is also effective against many anaerobes, but it is only weakly active against *Pseudomonas*. It is recommended as a second-line agent for upper and lower respiratory tract infections including those caused by 'atypical' pathogens and penicillin-resistant *Streptococcus pneumoniae*. QT prolongation occurs, and moxifloxacin is contraindicated in patients with cardiac failure or rhythm disorders. It has balanced renal and hepatic excretion so dose modification in renal failure is not necessary.

AZOLES

This group includes:

- Metronidazole and tinidazole (antibacterial and antiprotozoal) which are described here.
- Fluconazole, itraconaz… ketoconazole, isocona… described under Antifi…
- Albendazole, mebend… which are described u… drugs (p. 236).

Metronidazole

…n obligate anaerobic micr… metronidazole is converte… …ion of its nitro group: th… …nucleic acid formation; it i…

Pharmacokinetics. Metro… …oral or rectal administratio… …eliminated in the urine, p… …metabolites. The $t_{½}$ is 8 h.

Uses. Metronidazole's clin…

- Treatment of sepsis to w… *Bacteroides* spp. and ana… including post-surgical … infection and septicaem… of brain or lung.
- Antibiotic-associated ps… (caused by *Clostridium d…*
- Trichomoniasis of the u…
- Amoebiasis (*Entamoeba* … intestinal and extra-inte…
- Giardiasis (*Giardia lamb…*
- Acute ulcerative gingivit… (*Fusobacterium* spp. and …
- Anaerobic vaginosis (Ga… anaerobes).

Dose. Established anaerobic… …nidazole by mouth 400 m… …hourly for 3 days followed by… …ion 500 mg 8-hourly. A topi… …reducing the odour associate… …fungating tumours.

Adverse effects include n… …furred tongue and an unpl… …mouth; also headache, dizzi… …caria and angioedema occu… …curs if treatment is prolong… …if the dose is high. Large do… …cinogenic in rodents and the … …long-term studies have failed … …in humans.

A disulfiram-like effect (see … because metronidazole inhi… …dehydrogenase; patients shou…

Tinidazole is similar to metr… …effects, but has a longer $t_{½}$ … …unchanged in the urine. The…

- Fluconazole, itraconazole, clotrimazole, econazole, ketoconazole, isoconazole and miconazole which are described under Antifungal drugs (p. 223).
- Albendazole, mebendazole and thiabendazole which are described under Anthelminthic drugs (p. 236).

Metronidazole

In obligate anaerobic microorganisms (but not in aerobes) metronidazole is converted into an active form by reduction of its nitro group: this binds to DNA and prevents nucleic acid formation; it is bacteriostatic.

Pharmacokinetics. Metronidazole is well absorbed after oral or rectal administration and distributed widely. It is eliminated in the urine, partly unchanged and partly as metabolites. The $t_{½}$ is 8 h.

Uses. Metronidazole's clinical indications are:

- Treatment of sepsis to which anaerobic organisms, e.g. *Bacteroides* spp. and anaerobic cocci, are contributing, including post-surgical infection, intra-abdominal infection and septicaemia, osteomyelitis and abscesses of brain or lung.
- Antibiotic-associated pseudomembraneous colitis (caused by *Clostridium difficile*).
- Trichomoniasis of the urogenital tract in both sexes.
- Amoebiasis (*Entamoeba histolytica*), including both intestinal and extra-intestinal infection.
- Giardiasis (*Giardia lamblia*).
- Acute ulcerative gingivitis and dental infections (*Fusobacterium* spp. and other oral anaerobic flora).
- Anaerobic vaginosis (*Gardnerella vaginalis* and vaginal anaerobes).

Dose. Established anaerobic infection is treated with metronidazole by mouth 400 mg 8-hourly; by rectum 1 g 8-hourly for 3 days followed by 1 g 12-hourly; or by i.v. infusion 500 mg 8-hourly. A topical gel preparation is useful for reducing the odour associated with anaerobic infection of fungating tumours.

Adverse effects include nausea, vomiting, diarrhoea, furred tongue and an unpleasant metallic taste in the mouth; also headache, dizziness and ataxia. Rashes, urticaria and angioedema occur. Peripheral neuropathy occurs if treatment is prolonged and epileptiform seizures if the dose is high. Large doses of metronidazole are carcinogenic in rodents and the drug is mutagenic in bacteria; long-term studies have failed to discover oncogenic effects in humans.

A disulfiram-like effect (see p. 147) occurs with alcohol because metronidazole inhibits alcohol and aldehyde dehydrogenase; patients should be warned appropriately.

Tinidazole is similar to metronidazole in use and adverse effects, but has a longer $t_{½}$ (13 h). It is excreted mainly unchanged in the urine. The longer duration of action of tinidazole may be an advantage, e.g. in giardiasis, trichomoniasis and acute ulcerative gingivitis, in which tinidazole 2 g by mouth in a single dose is as effective as a course of metronidazole.

MINOR ANTIMICROBIALS

These are included because they are effective topically without serious risk of allergy, while toxicity or chemical instability limits or precludes their systemic use.

Mupirocin. is primarily active by inhibition of tRNA synthetase in Gram-positive organisms, including those commonly associated with skin infections. It is available as an ointment for use, e.g. in folliculitis and impetigo, and to eradicate *Staphylococcus aureus* site, e.g. in carriers of resistant staphylococci and to clear nasal carriage before surgery (see p. 168). It is also effective at reducing rates of staphylococcal peritonitis in patients receiving chronic ambulatory peritoneal dialysis, and for this indication it needs only to be applied to the nares for a few days per month. Re-colonisation after eradication of carriage occurs quite swiftly, with 5–30% being positive around 4 days after treatment, and 85–100% after a month.

Moderate resistance (by mutation of the of tRNA synthetase enzyme) is quite common in staphylococci in hospitals that have extensive mupirocin usage. Such strains may fail to be eradicated from the nares, but their numbers are usually significantly reduced so that therapeutic aims may still be achieved (i.e. reduction of the numbers of staphylococci entering the patient's wound perioperatively, hence a reduction in postoperative wound infection rates). However, high-level resistance (MIC of 512 mg/L or above) is transferable by a plasmid and leads to failure rates of around 75%. Mupirocin is rapidly hydrolysed in the tissues.

Retapamulin, a tricyclic pleuromutilin derived from the edible mushroom *Clitopilus scyphoides*, binds to a site on the 50 S bacterial ribosomal subunit and is active against streptococci and staphylococci, including MRSA, anaerobes, but almost no Gram-negative bacteria. For treatment of infected eczema and similar conditions it is applied in a thin layer to the skin twice daily and covered with a sterile bandage or gauze dressing if desired. Systemic absorption is very low and the most commonly reported adverse reaction is allergy at the application site.

POLYPEPTIDE ANTIBIOTICS

Colistin ($t_{½}$ 6 h) is a polypeptide effective against Gram-negative organisms. It is sometimes used orally for bowel decontamination, by inhalation via a saline nebuliser in patients with cystic fibrosis who are infected with *Pseudomonas aeruginosa*, and is applied to skin, including external