Chapter 14

Chemotherapy of bacterial infections

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SYNOPSIS

We live in a world heavily populated by microorganisms of astonishing diversity. This chapter considers the bacteria that cause disease in individual body systems, the drugs that combat them, and how they are best used. The chapter discusses infection of:

- Blood.
- Paranasal sinuses and ears.
- Throat.
- Bronchi, lungs and pleura.
- Endocardium.
- Meninges.
- Intestines.
- Urinary tract.
- Genital tract.
- Bones and joints.
- Eye.

It also discusses mycobacteria, that infect many sites.

INFECTION OF THE BLOOD

Septicaemia is a medical emergency that moves clinically from sepsis (systemic inflammatory response syndrome, 'SIRS') via organ dysfunction ('severe sepsis') to septic shock as the associated mortality rates progress from 16% to 46%. In a shocked patient (i.e. with low blood pressure that does not promptly respond to circulatory volume enhancement) survival rates fall by over 7% for each hour of delay in commencing effective antibiotics. Urgent support of the circulation and other organs is necessary for survival, and rapid assessment by senior medical staff and early involvement of infection specialists have also been associated with an improved outcome and lowest antibiotic costs during treatment.

Usually, the infecting organism(s) is not known at the time of presentation and treatment must be instituted on the basis of a 'best guess' (i.e. 'empirical therapy'). The clinical circumstances and knowledge of local resistance patterns may provide clues. Examples of suitable choices are given in the list below: patients who have been in hospital for some time before presenting with septicaemia need antibiotic regimens that provide more reliable cover for multiply resistant pathogens, and examples of these are given in square brackets:

- Septicaemia accompanied by a spreading rash that does not blanch with pressure should be assumed to be meningococcal, and the patient must be referred to hospital urgently (after an immediate parenteral dose of benzylpenicillin): ceftriaxone.
- Community-acquired pneumonia: co-amoxiclav + clarithromycin.
- When septicaemia follows gastrointestinal or genital tract surgery, *Escherichia coli* (or other coliforms), anaerobic bacteria, e.g. *Bacteroides*, streptococci or enterococci are likely pathogens: piperacillin-tazobactam or gentamicin plus benzylpenicillin plus metronidazole [meropenem, plus vancomycin if MRSA is a risk].
- Septicaemia related to urinary tract infection usually involves *Escherichia coli* (or other Gram-negative bacteria), enterococci: gentamicin plus benzylpenicillin or piperacillin-tazobactam alone [meropenem plus vancomycin].
- Neonatal septicaemia is usually due to Lancefield Group B streptococcus or coliforms: benzylpenicillin plus gentamicin [vancomycin + ceftazidime].

- Staphylococcal septicaemia may be suspected where there is an abscess, e.g. of bone or lung, or with acute infective endocarditis or infection of intravenous catheters: high-dose flucloxacillin [vancomycin]. Uncomplicated *Staphylococcus aureus* bacteraemia should be treated for 14 days to reduce the risk of metastatic infection: patients with prolonged bacteraemia or who fail to settle promptly should be considered for treatment as for staphylococcal endocarditis.
- Severe cellulitis, bites and necrotising fasciitis accompanied by septicaemia should be treated with optimal cover for Lancefield Group A streptococcus, anaerobes and coliforms: piperacillin-tazobactam + clindamycin [meropenem + clindamycin].
- Septicaemia in patients rendered neutropenic by cytotoxic drugs frequently involves coliforms and *Pseudomonas* spp. translocating to the circulation directly from the bowel, while coagulase-negative staphylococci also commonly arise from central venous catheter infection: piperacillin-tazobactam, sometimes plus vancomycin.
- Staphylococcal toxic shock syndrome occurs in circumstances that include healthy women using vaginal tampons, in abortion or childbirth, and occasionally with skin and soft tissue infection and after packing of body cavities, such as the nose. Flucloxacillin is used, and elimination of the source by removal of the tampon and drainage of abscesses is also important.

Antimicrobials are given i.v. initially, and their combination with optimal circulatory and respiratory support and glycaemic control, and administration of hydrocortisone and recombinant human activated protein C for severe cases, provides the best outcome.

Patients who have had a splenectomy are at risk of fulminant septicaemia especially from capsulate bacteria, e.g. *Streptococcus pneumoniae, Neisseria meningitidis*. The risk is greatest in the first 2 years after splenectomy (but is lifelong), in children, and in those with splenectomy for haematological malignancy. Patients must be immunised against appropriate pathogens and receive continuous low-dose oral prophylaxis with phenoxymethylpenicillin (penicillin V), or erythromycin in those allergic to penicillin.

INFECTION OF PARANASAL SINUSES AND EARS

Sinusitis

As oedema of the mucous membrane hinders the drainage of pus, a logical first step is to open the obstructed passage with a sympathomimetic vasoconstrictor, e.g. ephedrine nasal drops. Antibiotic therapy produces limited additional clinical benefit, but the common infecting organism(s) – *Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes, Moraxella (Branhamella) catarrhalis* – usually respond to oral amoxicillin (with or without clavulanic acid) or doxycycline if serious. It is necessary to treat around 15 patients with antibiotic to cure one patient faster than the natural resolution rate.

In chronic sinusitis, correction of the anatomical abnormalities (polypi, nasal septum deviation) is often important, and diverse organisms, many of them normal inhabitants of the upper respiratory tract, may be cultured, e.g. anaerobic streptococci, *Bacteroides* spp. Judgement is required as to whether any particular organism is acting as a pathogen. Choice of antibiotic should be guided by culture and sensitivity testing; therapy may need to be prolonged.

Otitis media

Mild cases are normally viral and often resolve spontaneously, needing only analgesia and observation. A bulging, inflamed eardrum indicates bacterial otitis media usually due to *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella (Branhamella) catarrhalis, Streptococcus pyogenes* (Group A) or *Staphylococcus aureus*. Amoxicillin or co-amoxiclav is satisfactory, but the clinical benefit of antibiotic therapy is small in controlled trials and good outcomes with reduced use of antibiotics have been demonstrated if patients are given a prescription which they only fill if they worsen or fail to improve after 48 h (sometimes known as a 'WASP' – a 'wait and see' prescription). Children under the age of 2 years with bilateral otitis, and those with acute aural discharge (otorrhoea) benefit most from antibiotic treatment. Chemotherapy has not removed the need for myringotomy when pain is very severe, and also for later cases, as sterilised pus may not be completely absorbed and may leave adhesions that impair hearing. Chronic infection presents a similar problem to that of chronic sinus infection, above. Pneumococcal vaccination is modestly effective at reducing recurrences in children who are prone to them.

INFECTION OF THE THROAT

Pharyngitis is usually viral but the more serious cases may be due to *Streptococcus pyogenes* (Group A) (always sensitive to benzylpenicillin), which cannot be differentiated clinically from virus infection with any certainty. Prevention of complications is more important than relief of the symptoms, which seldom last long and corticosteroids are much more effective than antibiotics at shortening the period of pain.

There is no general agreement as to whether chemotherapy should be employed in mild sporadic sore throat, and

expert reviews reflect this diversity of opinion.[1,2,3] The disease usually subsides in a few days, septic complications are uncommon and rheumatic fever rarely follows. It is reasonable to withhold penicillin unless streptococci are cultured or the patient develops a high fever: some primary care physicians take a throat swab and give the patient a WASP prescription for penicillin which is only filled if streptococci are isolated. Severe sporadic or epidemic sore throat is likely to be streptococcal and the risk of these complications is limited by phenoxymethylpenicillin by mouth (clarithromycin or an oral cephalosporin in the penicillin-allergic), given, ideally, for 10 days, although compliance is bad once the symptoms have subsided and 5 days should be the minimum objective. Azithromycin (500 mg daily p.o.) for 3 days is effective as long as the streptococci are susceptible, with improved compliance, and 5-day courses of oral cephalosporins are as effective as 10 days of penicillin. Do not use amoxicillin if the circumstances suggest pharyngitis due to infectious mononucleosis, as the patient is very likely to develop a rash (see p. 176). In a closed community, chemoprophylaxis of unaffected people to stop an epidemic may be considered, for instance with oral phenoxymethylpenicillin 125 mg 12-hourly.

In scarlet fever and erysipelas, the infection is invariably streptococcal (Group A), and benzylpenicillin should be used even in mild cases, to prevent rheumatic fever and nephritis.

Chemoprophylaxis

Chemoprophylaxis of streptococcal (Group A) infection with phenoxymethylpenicillin is necessary for patients who have had one attack of rheumatic fever. Continue for at least 5 years or until aged 20 years, whichever is the longer period (although some hold that it should continue for life). Chemoprophylaxis should be continued for life after a second attack of rheumatic fever. A single attack of acute nephritis is not an indication for chemoprophylaxis. Ideally, chemoprophylaxis should continue throughout the year but, if the patient is unwilling to submit to this, cover at least the colder months (see also footnote p. 167).

Adverse effects are uncommon. Patients taking penicillin prophylaxis are liable to have penicillin-resistant viridans type streptococci in the mouth, so that during even minor dentistry, e.g. scaling, there is a risk of bacteraemia and thus of infective endocarditis with a penicillin-resistant organism in those with any residual rheumatic heart lesion. Patients taking penicillins are also liable to be carrying resistant staphylococci and pneumococci.

[1]Cooper R J, Hoffman J R, Bartlett J G et al 2001 Principles of appropriate antibiotic use for acute pharyngitis in adults: background. Annals of Internal Medicine 134:506.

[2]Del Mar C B, Glasziou P P, Spinks A B 2008 Antibiotics for sore throat (Cochrane review). Available online at: http://www2.cochrane.org/reviews/en/ab000023.html (accessed November 2011)

[3]Thomas M, Del Mar C, Glasziou P 2000 How effective are treatments other than antibiotics for acute sore throat? British Journal of General Practice 50:817.

Other causes of pharyngitis

Vincent's infection (microbiologically complex, including anaerobes, spirochaetes) responds readily to benzylpenicillin; a single i.m. dose of 600 mg is often enough except in a mouth needing dental treatment, when relapse may follow. Metronidazole 200 mg 8-hourly by mouth for 3 days is also effective.

Diphtheria (*Corynebacterium diphtheriae*). Antitoxin 10 000–100 000 units i.v. in two divided doses 0.5–2 h apart is given to neutralise toxin already formed according to the severity of the disease. Erythromycin or benzylpenicillin is also used, to prevent the production of more toxin.

Whooping cough (*Bordetella pertussis*). Chemotherapy is needed in unvaccinated children whose defences are compromised, have damaged lungs or are less than 3 years old. Erythromycin is usually recommended at the catarrhal stage and should be continued for 14 days (also as prophylaxis in cases of special need). It may curtail an attack if given early enough (before paroxysms have begun, and certainly within 21 days of exposure to a known case) but is not dramatically effective; it also reduces infectivity to others. A corticosteroid, salbutamol and physiotherapy may be helpful for relief of symptoms, but reliable evidence of efficacy is lacking.

INFECTION OF THE BRONCHI, LUNGS AND PLEURA

Bronchitis

Most cases of acute bronchitis are viral; where bacteria are responsible, the usual pathogens are *Streptococcus pneumoniae* and/or *Haemophilus influenzae*. It is questionable whether there is a role for antimicrobials in uncomplicated acute bronchitis, but amoxicillin, a tetracycline or trimethoprim is appropriate if treatment is considered necessary. Whether newer antimicrobials, e.g. moxifloxacin, confer significant outcome advantages to justify their expense is debatable.

In chronic bronchitis, suppressive chemotherapy with amoxicillin or trimethoprim may be considered during the colder months (in temperate, colder regions), for patients with symptoms of pulmonary insufficiency, recurrent acute exacerbations or permanently purulent sputum.

For intermittent therapy, the patient is given a supply of the drug and told to take it in full dose at the first sign of a 'chest' cold, e.g. purulent sputum, and to stop the drug after

3 days if there is rapid improvement. Otherwise, the patient should continue the drug until recovery takes place. If the exacerbation lasts for more than 10 days, there is a need for clinical reassessment.

Pneumonias

The clinical setting is a useful guide to the causal organism and hence to the 'best guess' early choice of antimicrobial. It is not possible reliably to differentiate between pneumonias caused by 'typical' and 'atypical' pathogens on clinical grounds alone and most experts advise initial cover for both types of pathogen in seriously ill patients. However, there is no strong evidence that adding 'atypical' cover to empirical parenteral treatment with a β-lactam antibiotic improves the outcome. Published guidelines often recommend hospital admission and parenteral and broader-spectrum therapy for the most severely affected patients as assessed by the 'CURB-65' score (one point is scored for each of Confusion, elevated serum *U*rea, *R*espiratory rate >30 breaths per minute, low *B*lood pressure, and age of 65 or above). Delay of 4 hours or more in commencing effective antibiotics in the most seriously ill patients is associated with increased mortality.

Pneumonia in previously healthy people (community acquired)

Disease that is segmental or lobar in its distribution is usually due to *Streptococcus pneumoniae* (pneumococcus). *Haemophilus influenzae* is a rare cause in this group, although it more often leads to exacerbations of chronic bronchitis and does cause pneumonia in patients infected with HIV. Benzylpenicillin i.v. or amoxicillin or clarithromycin p.o. are the treatments of choice if pneumococcal pneumonia is very likely; use clarithromycin, doxycycline or moxifloxacin in a penicillin-allergic patient. Seriously ill patients should receive benzylpenicillin (to cover the pneumococcus) plus ciprofloxacin (to cover *Haemophilus* and 'atypical' pathogens), and co-amoxiclav plus clarithromycin is an alternative that may have a lower propensity to promote *Clostridium difficile* diarrhoea. Where penicillin-resistant pneumococci are common, i.v. cefotaxime is a reasonable 'best guess' choice pending confirmation of susceptibilities from the laboratory, with vancomycin as an alternative. A wide variety of new antibiotics is under investigation for use in penicillin-resistant pneumococcal infections, including cephalosporins, e.g. ceftobiprole, penicillin relatives, e.g faropenem, quinolones, glycopeptides, e.g. oritavancin, and ketolides, e.g. cethromycin.

Pneumonia following influenza is often caused by *Staphylococcus aureus*, and 'best guess' therapy usually involves adding flucloxacillin to one of the regimens above. When staphylococcal pneumonia is proven, sodium fusidate or rifampicin p.o. plus flucloxacillin i.v. should be used in combination. Staphylococcal pneumonia that involves strains producing Panton-Valentine leucocidin toxin is frequently necrotising in nature, and linezolid or clindamycin have been shown to reduce toxin production at the ribosomal level so are recommended for inclusion when this condition is suspected.

'Atypical' cases of pneumonia may be caused by *Mycoplasma pneumoniae* or more rarely *Chlamydia pneumoniae* or *psittaci* (psittacosis/ornithosis), *Legionella pneumophila* or *Coxiella burnetii* (Q fever), and doxycycline or clarithromycin should be given by mouth. Treatment of ornithosis should continue for 10 days after the fever has settled, and that of mycoplasma pneumonia and Q fever for 3 weeks to prevent relapse.

At an early stage (i.e. at 24–48 h), once there is clinical improvement, i.v. administration should change to oral.

Pneumonia acquired in hospital

Pneumonia is usually defined as being nosocomial (Greek: *nosokomeian*, hospital) if it presents after at least 48 h in hospital. It occurs primarily among patients admitted with medical problems or recovering from abdominal or thoracic surgery and those who are on mechanical ventilators. The common pathogens are *Staphylococcus aureus*, Enterobacteriaceae, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*, and anaerobes after aspiration. Mild cases can be given co-amoxiclav unless they are known to be colonised with resistant bacteria, but for severe cases it is reasonable to initiate therapy with piperacillin-tazobactam (plus vancomycin if the local prevalence of MRSA is high) pending the results of sputum culture and susceptibility tests. Vancomycin or teicoplanin are equally effective for MRSA pneumonia as linezolid, and have an overall lower rate of adverse reactions.

Pneumonia in people with chronic lung disease

Normal commensals of the upper respiratory tract proliferate in damaged lungs especially following virus infections, pulmonary congestion or pulmonary infarction. Antibiotics should not be given to patients who do not demonstrate two or more of increased dyspnoea, sputum volume and sputum purulence. Mixed infection is common, and as *Haemophilus influenzae* and *Streptococcus pneumoniae* are often the pathogens, amoxicillin or trimethoprim is a reasonable choice in domiciliary practice; if response is inadequate, co-amoxiclav or a quinolone should be substituted, but there is no evidence that they are superior first line to the older choices.

Klebsiella pneumoniae is a rare cause of lung infection (Friedlander's pneumonia) in the alcoholic and debilitated elderly. Cefotaxime or piperacillin-tazobactam, possibly plus an aminoglycoside, is recommended.

Moraxella (previously *Branhamella*) *catarrhalis*, a commensal of the oropharynx, may be a pathogen in patients with chronic bronchitis; because many strains produce β-lactamase, co-amoxiclav or clarithromycin is used.

Pneumonia in immunocompromised patients

Pneumonia is common, e.g. in acquired immune deficiency syndrome (AIDS) or in those who are receiving immunosuppressive drugs.

Common pathogenic bacteria may be responsible (*Staphylococcus aureus*, *Streptococcus pneumoniae*), but often organisms of lower natural virulence (Enterobacteriaceae, viruses, fungi) are causal and necessitate strenuous efforts to identify the microbe including, if feasible, bronchial washings or lung biopsy.

- Until the pathogen is known the patient should receive broad-spectrum antimicrobial treatment, such as an aminoglycoside plus ceftazidime.
- Aerobic Gram-negative bacilli, e.g. Enterobacteriaceae, *Klebsiella* spp., are pathogens in half of the cases, especially in neutropenic patients, and respond to piperacillin-tazobactam or ceftazidime. These and *Pseudomonas aeruginosa* may respond better with addition of an aminoglycoside.
- The fungus *Pneumocystis carinii* is an important respiratory pathogen in patients with deficient cell-mediated immunity; treat with co-trimoxazole 120 mg/kg daily by mouth or i.v. in two to four divided doses for 14 days, as modified by serum assay, or with pentamidine (see p. 236).

Legionnaires' disease

Legionella pneumophila responds to erythromycin 4 g/day i.v. in divided doses, or clarithromycin, with the addition of rifampicin in more severe infections. Ciprofloxacin is probably a little more effective, although at the expense of a higher risk of adverse reactions.

Pneumonia due to anaerobic microorganisms

Pneumonia often follows aspiration of material from the oropharynx, or accompanies other lung pathology such as pulmonary infarction or bronchogenic carcinoma. In addition to conventional microbial causes, pathogens include anaerobic and aerobic streptococci, *Bacteroides* spp. and *Fusobacterium*. Co-amoxiclav or piperacillin-tazobactam may be needed for several weeks to prevent relapse.

Pulmonary abscess: treat the identified organism and employ aspiration or formal surgical drainage if necessary.

Empyema: aspiration or drainage is essential, followed by antibiotic treatment of the isolated organism.

ENDOCARDITIS

When there is suspicion, two or three blood cultures should be taken over a few hours and antimicrobial treatment commenced, to be adjusted later in the light of the results. Delay in treating only exposes the patient to the risk of grave cardiac damage or systemic embolism. Streptococci, enterococci and staphylococci are causal in 80% of cases, with viridans group streptococci having recently been overtaken by *Staphylococcus aureus* as the most common pathogens. In intravenous drug users, *Staphylococcus aureus* is particularly likely, although the potential list of pathogens is extensive in this group. Culture-negative endocarditis (in 8–10% of cases in contemporary practice) is usually due to previous antimicrobial therapy or to special culture requirements of the microbe; it is best regarded as being due to streptococci and treated accordingly.

Endocarditis on prosthetic valves presenting in the first few months after the operation usually involves *Staphylococcus aureus*, coagulase-negative staphylococci or Gram-negative rods. The infecting flora then becomes progressively more characteristic of native valve infections as time progresses.

Principles for treatment

- Use high doses of bactericidal drugs because the organisms are difficult to access in avascular vegetations on valves.
- Give drugs parenterally and preferably by i.v. bolus injection to achieve the necessary high peak concentration to penetrate the vegetations.
- Examine the infusion site daily and change it regularly to prevent opportunistic infection, which is usually with coagulase-negative staphylococci or fungi. Alternatively, use a central subclavian venous catheter.
- Continue therapy, usually for 2–4 weeks, and, in the case of infected prosthetic valves, 6 weeks. Prolonged courses may also be indicated for patients infected with enterococci or other strains with penicillin minimum inhibitory concentrations (MICs) above 0.5 mg/L, whose presenting symptoms have been present for over 6 weeks, for those with large vegetations, and those whose clinical symptoms and signs are slow to settle after treatment has started. Highly susceptible streptococcal endocarditis (penicillin MIC of 0.1 mg/L or below) can be treated successfully with 2 week courses.
- Valve replacement may be needed at any time during and after antibiotic therapy if cardiovascular function deteriorates or the infection proves impossible to control.
- Adjust the dose according to the sensitivity of the infecting organism – use the minimum inhibitory concentration test (MIC: see p. 163).

Dose regimens

The following regimens are commonly recommended (the reader is referred to the British Society for Antimicrobial Chemotherapy treatment guidelines 2006; currently under review, the European Society of Cardiology (2009) or to other published references for detailed advice):

1. Initial ('best guess') treatment should comprise benzylpenicillin (7.2 g i.v. daily in six divided doses), plus gentamicin (1 mg/kg body-weight 8-hourly – synergy allows this dose of gentamicin and minimises risk of adverse effects). Regular serum gentamicin assay is vital: trough concentrations should be below 1 mg/L and peak concentrations 3–5 mg/L; if *Staphylococcus aureus* is suspected, high-dose flucloxacillin plus rifampicin should be used. Patients allergic to penicillin and those with intracardiac prostheses or suspected MRSA infection should receive vancomycin plus rifampicin plus gentamicin. Patients presenting acutely (suggesting infection with *Staphylococcus aureus*) should receive flucloxacillin (8–12 g/day in four to six divided doses) plus gentamicin.
2. When an organism is identified and its sensitivity determined:
   - *Viridans group streptococci*: the susceptibility of the organism determines the antimicrobial(s) and its duration of use, ranging from benzylpenicillin plus gentamicin for 2 weeks, to vancomycin plus gentamicin for 6 weeks. Patients with uncomplicated endocarditis caused by very sensitive strains may be managed as outpatients; for these patients ceftriaxone 2 g/day for 4 weeks may be suitable.
   - *Enterococcus faecalis* (Group D): ampicillin 2 g 4-hourly or benzylpenicillin 2.4 g 4-hourly plus gentamicin 1 mg/kg 8–12-hourly i.v. for 4–6 weeks. The prolonged gentamicin administration carries a significant risk of adverse drug reactions, but is essential to assure eradication of the infection. Streptococci from endocarditis are checked for high-level gentamicin resistance (MIC above 128 mg/L) because cidal synergy is not seen with β-lactams in such strains. Alternative regimens for such infections include ampicillin plus streptomycin (if not similarly high-level resistant) or high-dose ampicillin alone.
   - *Staphylococcus aureus*: flucloxacillin 2 g 4–6-hourly i.v. for at least 4 weeks. In the presence of intracardiac prostheses, flucloxacillin is combined with rifampicin orally (or fusidic acid) for at least the first 2 weeks, and MRSA may be treated with vancomycin plus rifampicin plus fusidic acid (or gentamicin) for 4–6 weeks.
   - *Staphylococcus epidermidis* infecting native heart valves is managed as for *Staphylococcus aureus* if the organism is sensitive.
   - *Coxiella* or *Chlamydia*: give doxycycline 100 mg once daily orally, plus ciprofloxacin 500 mg 8-hourly for at least 3 years. Valve replacement is advised in many cases.
   - *Fungal endocarditis*: amphotericin plus flucytosine has been used, although experience is growing with the new azoles and echinocandins, and specialist advice should be sought. Valve replacement is usually essential.
   - *Culture-negative endocarditis*: benzylpenicillin plus gentamicin i.v. are given for 4–6 weeks.

Prophylaxis

Transient bacteraemia is provoked by dental procedures that induce gum bleeding, surgical incision of the skin, instrumentation of the urinary tract and parturition. However, even seemingly innocent activities such as brushing the teeth result in bacteraemia and are lifelong risks, whereas medical interventions are usually single. Adding this to the fact that even single antibiotic doses carry inevitable risks and the evidence base for their efficacy is lacking, expert working parties have re-evaluated the traditional wisdom of advocating prophylactic antibiotics for many procedures in patients with acquired or congenital heart defects.

If used, the drugs are given as a short course in high dose at the time of the procedure to coincide with the bacteraemia and avoid emergence of resistant organisms. The following recommendations on antimicrobial prophylaxis are based on those published in 2006 by the British Society for Antimicrobial Chemotherapy (see Guide to further reading); they are abbreviated and not every contingency is covered. The guidelines are based on a careful assessment of the risks of bacteraemia and reported cases of endocarditis after each procedure. Other national working parties may recommend different measures, and the physician should consult special sources and their local microbiologist, and exercise a clinical judgement that relates to individual circumstances. All oral drugs should be taken under supervision.

Adults who are not allergic to penicillins and who have not taken penicillin more than once in the previous month (including those with a prosthetic valve) require amoxicillin 3 g by mouth 1 h before the procedure.

Patients allergic to penicillins or who have taken penicillin more than once in the previous month should receive clindamycin 600 mg by mouth 1 h before the procedure. Azithromycin 500 mg is an alternative, available as a suspension for those unable to swallow capsules. If parenteral prophylaxis is required, use amoxicillin 1 g i.v. or clindamycin 300 mg i.v.

Patients having a series of separate procedures all requiring prophylaxis should receive amoxicillin or clindamycin alternately. Where practicable, a preoperative mouthwash of the antiseptic chlorhexidine gluconate (0.2%) should be used to reduce oral bacterial numbers.

Consult the guideline publication (above) for prophylactic regimens for children and other procedures, including instrumentation of the urogenital or gastrointestinal tracts, which are now recognised to carry a greater risk of endocarditis than dental procedures.

MENINGITIS

Speed of initiating treatment and accurate bacteriological diagnosis are the major factors determining the fate of the patient, especially with invasive meningococcal disease where fulminant meningococcal septicaemia still carries a 20–50% mortality rate (and supporting the circulation in the intensive care unit is as important a determinant of outcome as the rapid commencement of antibiotic therapy). With suspected meningococcal disease, unless the patient has a history of penicillin anaphylaxis, benzylpenicillin should be started by the general practitioner before transfer to hospital; the benefit of rapid treatment outweighs the reduced chance of identifying the causative organism. Molecular diagnostic methods such as the polymerase chain reaction (PCR) for bacterial DNA in CSF or blood enable rapid diagnosis even when the causative organisms have been destroyed by antibiotics.

Drugs must be given i.v. in high dose. The regimens below provide the recommended therapy, with alternatives for patients allergic to first choices, and septic shock requires appropriate management (see p. 191). Intrathecal therapy is now considered unnecessary (except for neurosurgical infections in association with indwelling CSF drains and shunts) and can be dangerous, e.g. encephalopathy with penicillin.

Initial therapy

Initial therapy should be sufficient to kill all pathogens, which are likely to be:

All ages over 5 years

For *Neisseria meningitidis* and *Streptococcus pneumoniae*, give benzylpenicillin 2.4 g 4-hourly followed, in the case of *Neisseria meningitidis*, by rifampicin for 2 days prior to discharge from hospital (to eradicate persisting organisms). Some prefer cefotaxime 2–3 g 6–8-hourly or ceftriaxone 2 g i.v. 12-hourly in all cases pending the results of susceptibility tests, and this may be generally preferred depending upon the local prevalence of penicillin resistance. In such cases, in elderly, pregnant or immunocompromised patients it is prudent to add amoxicillin initially to cover the possibility of listeria involvement. Optimal therapy for known or suspected penicillin-resistant pneumococcal meningitis comprises ceftriaxone 2 g i.v. 12-hourly plus vancomycin 15 mg/kg i.v. 12-hourly plus rifampicin 300 mg i.v. 12-hourly.

Children under 5 years

Neisseria meningitidis is now commonest and *Haemophilus influenzae*, formerly a frequent pathogen, is much less often isolated following immunisation programmes. *Streptococcus pneumoniae* is also less common than in older patients. Give a cephalosporin, e.g. ceftriaxone.

Neonates

For *Escherichia coli*, give cefotaxime or ceftazidime perhaps with gentamicin. For Group B streptococci, give benzylpenicillin plus gentamicin. Consult a specialist text for details of doses. Add ampicillin if *Listeria monocytogenes* is suspected.

Dexamethasone given i.v. (0.15 mg/kg 6-hourly for 4 days) and early appears to reduce long-term neurological sequelae, especially sensorineural deafness, in infants and children. In adults there is evidence to support dexamethasone therapy in pneumococcal meningitis, but outcome is not affected in meningitis caused by other pathogens.

Chloramphenicol remains a good alternative for 'blind' therapy in patients giving a history of β-lactam anaphylaxis.

Subsequent therapy

Necessarily, i.v. administration should continue until the patient can take drugs by mouth, but whether or when continuation therapy should be oral or i.v. is a matter of debate. Antimicrobials (except aminoglycosides) enter well into the CSF when the meninges are inflamed; relapse may be due to restoration of the blood–CSF barrier as inflammation reduces. The following are recommended (adult doses).

Neisseria meningitidis. Give benzylpenicillin 2.4 g 4-hourly or ceftriaxone 2 g i.v. 12-hourly for a minimum of 5 days.

Streptococcus pneumoniae. Give ceftriaxone 2 g i.v. 12-hourly or benzylpenicillin 2.4 g 4-hourly if the organism is penicillin-sensitive and continue for 10 days after the patient has become afebrile.

Haemophilus influenzae. Give ceftriaxone 2 g i.v. 12-hourly or chloramphenicol 100 mg/kg daily for 10 days after the temperature has settled. Subdural empyema, often presenting as persistent fever, is relatively common after haemophilus meningitis and may require surgical drainage.

Chemoprophylaxis

The three common pathogens (below) are spread by respiratory secretions. Asymptomatic nasopharyngeal carriers seldom develop meningitis but may transmit the pathogens to close personal contacts. Rifampicin by mouth is effective at reducing carriage rates.

Meningococcal meningitis often occurs in epidemics in closed communities, but also in isolated cases. Patients and close personal contacts should receive rifampicin 600 mg 12-hourly by mouth for 2 days. Single doses of ciprofloxacin (500 mg by mouth) or ceftriaxone (2 g i.m.) are alternatives, the latter of particular value for pregnant women.

Haemophilus influenzae type b has similar infectivity to that of the meningococcus; give rifampicin 600 mg by mouth daily for 4 days to unimmunised contacts.

Pneumococcal meningitis tends to occur in isolated cases and contacts do not need chemoprophylaxis.

INFECTION OF THE INTESTINES

(For *Helicobacter pylori*, see p. 533)

Both wit and truth are contained in the aphorism that 'travel broadens the mind but opens the bowels'. Antimicrobial therapy should be reserved for specific conditions with identified pathogens where benefit has been shown; acute diarrhoea can be caused by bacterial toxins in food, dietary indiscretions, anxiety and by drugs as well as by infection. Even if diarrhoea is infective, it may be due to viruses; or, if bacterial, antimicrobial agents may not reduce the duration of symptoms and may aggravate the condition by permitting opportunistic infection and encouraging *Clostridium difficile*-associated diarrhoea. Maintaining water and electrolyte balance either orally or by i.v. infusion with a glucose–electrolyte solution, and administration of an antimotility drug (except in small children, and those with with bloody, dysenteric stools, and in *Clostridium difficile* infection), are the mainstays of therapy in such cases (see Oral rehydration therapy, p. 537). Some specific intestinal infections do benefit from chemotherapy:

Campylobacter jejuni. Clarithromycin, azithromycin or ciprofloxacin by mouth eliminates the organism from the stools but is only clinically effective if commenced within the first 24–48 h of the illness and if is the patient is severely affected. Ciprofloxacin resistance has become common in parts of the world (e.g. Thailand).

Shigella. Mild disease requires no specific antimicrobial therapy but toxic shigellosis with high fever should be treated with ciprofloxacin or azithromycin by mouth for 5 days.

Salmonella. Give an antimicrobial for severe salmonella gastroenteritis, or for bacteraemia or salmonella enteritis in an immunocompromised patient. The choice lies between ciprofloxacin, azithromycin or a parenteral cephalosporin: ciprofloxacin resistance is rising in incidence in salmonella (including in *S. typhi*), especially in the Indian subcontinent.

Typhoid fever is a generalised infection and requires treatment with 14 days of i.v. ceftriaxone, oral or i.v. ciprofloxacin, or oral azithromycin. Chloramphenicol, amoxicillin or co-trimoxazole are less effective alternatives. Initial parenteral therapy can be switched to oral once the patient has improved and susceptibility of the causative pathogen determined. A longer period of treatment may be required for those who develop complications such as osteomyelitis or abscess.

A carrier state develops in a few individuals who have no symptoms of disease but who can infect others.[4] Organisms reside in the biliary or urinary tracts. Ciprofloxacin in high dose by mouth for 3–6 months may be successful for what can be a very difficult problem, requiring investigation for urinary tract abnormalities or even cholecystectomy.

Escherichia coli is a normal inhabitant of the bowel but some enterotoxigenic strains are pathogenic and are frequently a cause of travellers' diarrhoea. A quinolone, e.g. ciprofloxacin, azithromycin or the non-absorbable rifampicin-relative rifaximin are alternatives (see Travellers' diarrhoea, p. 537). Prophylactic use of an antimicrobial is not usual but, should it be deemed necessary, a quinolone or rifaximin is effective.

Verotoxic *Escherichia coli* (VTEC; O157) may cause severe bloody diarrhoea and systemic effects such as the haemolytic uraemic syndrome (HUS); antibiotic therapy has been shown in some trials to worsen the prognosis. In general, avoid using an antibiotic for bloody diarrhoea unless VTEC has been excluded bacteriologically.

Vibrio cholerae. Death in cholera is due to electrolyte and fluid loss in the stools, and this may exceed 1 L/h. Prompt replacement and maintenance of water and electrolyte balance with i.v. and oral electrolyte solutions is vital. A single dose of doxycycline, given early, significantly reduces the amount and duration of diarrhoea and eliminates the organism from the faeces (thus lessening the contamination of the environment). Ciprofloxacin or a macrolide (clarithromycin or azithromycin) are alternatives for resistant organisms. Oral zinc acetate supplements have been shown modestly to reduce the volume and duration of cholera diarrhoea in combination with antibiotics, probably by improving gut mucosal integrity and function in malnourished patients. Carriers may be treated by doxycycline by mouth in high dose for 3 days.

Suppression of bowel flora is thought by some to be useful in hepatic encephalopathy. Here, absorption of products of bacterial breakdown of protein (ammonium, amines) in the intestine leads to cerebral symptoms and even to coma. In acute coma, neomycin 6 g daily should

[4]The most famous carrier was Mary Mallon ('Typhoid Mary') who worked as a cook in New York City, USA, using various assumed names and moving through several different households. She caused at least 10 outbreaks with 51 cases of typhoid fever and three deaths. To protect the public, she was kept in detention for 23 years.

be given by gastric tube; as prophylaxis, 1–4 g/day may be given to patients with protein intolerance who fail to respond to dietary protein restriction (see also Lactulose, p. 551).

Selective decontamination of the gut may reduce the risk of nosocomial infection from gut organisms (including fungi) in patients who are immunocompromised or receiving intensive care (notably mechanical ventilation). The commonest regimen involves combinations of topical non-absorbable (framycetin, colistin, nystatin and amphotericin) and i.v. (cefotaxime) antimicrobials to reduce the number of Gram-negative bacilli and yeasts while maintaining a normal anaerobic flora. Alternatives include using the topical agents alone, or administering oral ciprofloxacin. Selective decontamination should be used with great care in hospitals with a high incidence of multiply resistant bacteria or *Clostridium difficile* diarrhoea.

Peritonitis is usually a mixed infection and antimicrobial choice must take account of coliforms and anaerobes, although the need to include cover for the other major component of the bowel flora, streptococci, is less certain. Piperacillin-tazobactam or a combination of gentamicin, benzylpenicillin plus metronidazole, or meropenem alone is usually appropriate, and can be stopped after the patient is clinically improved and their inflammatory markers (e.g. C-reactive protein) have normalised. Short courses of antibiotics (5–7 days) are associated with a good outcome for intestinal perforations that are surgically corrected within a day or two. Surgical drainage of peritoneal collections and abscesses may need to be repeated.

Chemoprophylaxis in surgery. See page 167.

Antibiotic-associated colitis and *Clostridium difficile* diarrhoea. See page 170.

Traveller's diarrhoea. See page 537.

INFECTION OF THE URINARY TRACT

(Excluding sexually transmitted infections)

Common pathogens include *Escherichia coli* (commonest in all patient groups), *Proteus* spp., *Klebsiella* spp., other Enterobacteriaceae, *Pseudomonas aeruginosa*, *Enterococcus* spp. and *Staphylococcus saprophyticus*.

Patients with abnormal urinary tracts, e.g. renal stones, prostatic hypertrophy, indwelling urinary catheters, are likely to be infected with a more varied and antimicrobial-resistant microbial flora. Identification of the causative organism and of its sensitivity to drugs is important because of the range of organisms and the prevalence of resistant strains.

For infection of the lower urinary tract a low dose may be effective, as many antimicrobials are concentrated in the urine. Infections of the substance of the kidney require the doses needed for any systemic infection. A large urine volume (over 1.5 L/day) and frequent micturition hasten elimination of infection.

Drug treatment of urinary tract infection falls into several categories:

Lower urinary tract infection

This is most commonly seen in young women with normal urinary tracts. Antibiotic treatment shortens the duration of symptoms but may cause adverse reactions, and 20–30% are free of symptoms at 5–7 days even without antibiotics. Initial treatment with co-amoxiclav, an oral cephalosporin (e.g. cefalexin) or trimethoprim, is usually satisfactory. Current resistance rates of 20–50% among common pathogens for trimethoprim and amoxicillin threaten their value for empirical therapy in many parts of the world. Therapy should normally last for 3 days and may need to be altered once the results of bacterial sensitivity are known.

Upper urinary tract infection

Acute pyelonephritis may be accompanied by septicaemia and is usually marked by fever and loin pain. In such patients it is advisable to start with co-amoxiclav i.v. or alternatively gentamicin (perhaps plus amoxicillin) i.v. If oral therapy is considered suitable, co-amoxiclav or ciprofloxacin is recommended for 2 weeks. This is an infection of the kidney substance and so needs adequate blood as well as urine concentrations, although a switch to an oral agent (guided by the results of susceptibility testing) to complete the course is recommended after the patient has clinically improved.

Upper or lower tract infection with extended-spectrum β-lactamase (ESBL) coliform strains has become more common in some locales, even in patients with no prior hospital contact (see page 185). Such bacteria are usually resistant also to ciprofloxacin, parenteral cephalosporins and gentamicin. Parenteral meropenem, ertapenem or amikacin, or oral pivmecillinam or fosfomycin may be effective.

Recurrent urinary tract infection

Attacks following rapidly with the same organism may be relapses and indicate a failure to eliminate the original infection. Attacks with a longer interval between them and produced by differing bacterial types may be regarded as due to reinfection, most often by ascending infection from the perineal skin. Repeated short courses of antimicrobials should overcome most recurrent infections but, if these fail, 7–14 days of high-dose treatment may be given, following which continuous low-dose prophylaxis may be needed with trimethoprim, nitrofurantoin or an oral cephalosporin. There is some evidence that daily ingestion of cranberry juice may reduce the frequency of relapse in women, perhaps by sugars within the juice interfering with adhesion of bacteria to the urinary epithelium. Vesicoureteric reflux

(passage of bladder urine back up the ureter to the kidney) accounts for about a third of urinary tract infections in children, and causes progressive renal damage. Long-term oral antibiotic prophylaxis in such patients is modestly effective at reducing symptomatic infections.

Asymptomatic infection ('asymptomatic bacteriuria')

This may be found by routine urine testing of pregnant women or patients with known structural abnormalities of the urinary tract. Such infection may explain micturition frequency or incontinence in the elderly. Appropriate antimicrobial therapy should be given, chosen on the basis of susceptibility tests, and normally for 7–10 days. Amoxicillin or a cephalosporin is preferred in pregnancy, although nitrofurantoin may be used if imminent delivery is not likely (see below).

Prostatitis

The commonest pathogens here are Gram-negative aerobic bacilli, although chlamydia may also be involved. A quinolone such as ciprofloxacin is commonly used, although trimethoprim, doxycycline or erythromycin are also effective. Being lipid soluble, these drugs penetrate the prostate in adequate concentration; they may usefully be combined. Response to a single, short course is often good, but recurrence is common and a patient can be regarded as cured only if he has been symptom-free without resort to antimicrobials for a year. Four weeks of oral therapy is often given for recurrent attacks.

Chemoprophylaxis

Chemoprophylaxis is sometimes undertaken in patients liable to recurrent attacks or acute exacerbations of ineradicable infection. It may prevent progressive renal damage in children who are found to have asymptomatic bacteriuria on routine screening. Nitrofurantoin (50–100 mg/day), nalidixic acid (0.5–1.0 g/day) or trimethoprim (100 mg/day) is satisfactory. The drugs are best given as a single oral dose at night.

Tuberculosis of the genitourinary tract is treated on the principles described for pulmonary infection (see p. 203).

Special drugs for urinary tract infections

General antimicrobials used for urinary tract infections are described elsewhere. A few agents find use solely for infection of the urinary tract:

Nitrofurantoin, a synthetic antimicrobial, is active against the majority of urinary pathogens except pseudomonads, and has increased in importance recently because it has retained activity against a useful proportion of urinary tract coliforms that have acquired resistance to trimethoprim, oral β-lactams and quinolones. It is well absorbed from the gastrointestinal tract and is concentrated in the urine ($t_{½}$ 1 h), but plasma concentrations are too low to treat infection of kidney tissue. Excretion is reduced when there is renal insufficiency, rendering the drug both more toxic and less effective. Adverse effects include nausea and vomiting (much reduced with the macrocrystalline preparation) and diarrhoea. Peripheral neuropathy occurs especially in patients with significant renal impairment, in whom the drug is contraindicated. Allergic reactions include rashes, generalised urticaria and pulmonary infiltration with lung consolidation or pleural effusion. Nitrofurantoin is safe in pregnancy, except near to term (because it may cause neonatal haemolysis), and it must be avoided in patients with glucose-6-phosphate dehydrogenase deficiency (see p. 101).

Nalidixic acid. See page 188.

Pivmecillinam 400 mg p.o. initially, then 200–400 mg p.o. three or four times daily.

Fosfomycin trometamol 3 g p.o. in a single dose.

GENITAL TRACT INFECTIONS

A general account of orthodox literature is given below, but treatment is increasingly the prerogative of specialists, who, as is so often the case, get the best results. Interested readers are referred to specialist texts. Sexually transmitted infections are commonly multiple. Tracing and screening of contacts plays a vital part in controlling spread and reducing re-infection. Recommended treatment regimens vary to some extent among countries, and this is in response to differences in antimicrobial susceptibility of the relevant pathogens and availability of antimicrobial agents.

Gonorrhoea

The problems of β-lactam and quinolone resistance in *Neisseria gonorrhoeae* infection are increasing (ciprofloxacin resistance rates rose from 2.1% in 2000 to 9.8% in 2002 in England and Wales, reaching over 60% in ethnic white patients in 2009), and selection of a particular drug will depend on sensitivity testing and a knowledge of resistance patterns in different locations. Cefixime and ceftriaxone resistance on testing in vitro are increasing, but not yet to levels that compromise therapeutic efficacy. Effective treatment requires exposure of the organism briefly to a high concentration of the drug. Single-dose regimens are practicable and improve compliance. The following schedules are effective:

Uncomplicated anogenital infections. High-dose cefixime 400 mg by mouth; spectinomycin i.v., or ceftriaxone 250 mg i.m. UK resistance rates for oral ciprofloxacin or

ofloxacin are now considered too high for recommendation unless the isolate is known to be susceptible.

Pharyngeal gonorrhoea responds less reliably, and i.m. ceftriaxone is recommended.

Coexistent infection. *Chlamydia trachomatis* is frequently present with *Neisseria gonorrhoeae*; tetracycline by mouth for 7 days or a single oral dose of azithromycin 1 g or ofloxacin 400 mg will treat the chlamydial urethritis.

Non-gonococcal urethritis

The vast majority of cases of urethritis with pus in which gonococci cannot be identified are due to sexually transmitted organisms, usually *Chlamydia trachomatis* (the most common bacterial sexually-transmitted infection worldwide) and sometimes *Ureaplasma urealyticum*. Tetracycline for 1 week, or single-dose azithromycin by mouth are effective.

Pelvic inflammatory disease

Several pathogens are usually involved, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma hominis*, and there may be superinfection with bowel and other urogenital tract bacteria. A combination of antimicrobials is usually required, e.g. ceftriaxone plus doxycycline plus metronidazole i.v. for severe, acute infection where chlamydia involvement is likely, or co-amoxiclav alone for post-partum chorioamnionitis.

Syphilis

Primary and secondary syphilis are effectively treated by a single dose of 2.4 million units (MU) benzathine penicillin i.m. Doxycycline or erythromycin orally for 2 weeks may be used for penicillin-allergic patients, and a single oral dose of 2 g azithromycin appears to have equivalent efficacy. *Treponema pallidum* is invariably sensitive to penicillin but macrolide resistance has been reported worldwide rarely except in infections in men who have sex with men.

Tertiary syphilis responds to doxycycline for 28 days or to 3 weekly doses of 2.4 MU benzathine penicillin i.m. *Neurosyphilis* requires higher serum concentrations for cure and should be treated with procaine penicillin 2.4 megaunits i.m. once daily for 17 days with oral probenecid 500 mg four times a day.

Congenital syphilis in the newborn should be treated with benzylpenicillin for 10 days at least. Some advocate that a pregnant woman with syphilis should be treated as for primary syphilis in each pregnancy, in order to avoid all danger to children. Therapy is best given between the third and sixth month, as there may be a risk of abortion if it is given earlier.

Results of treatment of syphilis with penicillin are excellent. Follow-up of all cases is essential, for 5 years if possible.

The *Herxheimer* (or Jarisch–Herxheimer) reaction is probably caused by cytokine (mainly tumour necrosis factor) release following massive slaughter of spirochaetes. Presenting as pyrexia, it is common during the few hours after the first penicillin injection; other features include tachycardia, headache, myalgia and malaise, which last for up to a day. It cannot be avoided by giving graduated doses of penicillin. Prednisolone may prevent it and should probably be given if a reaction is specially to be feared, e.g. in a patient with syphilitic aortitis.

Chancroid

The causal agent, *Haemophilus ducreyi*, normally responds to erythromycin for 7 days or a single dose of ceftriaxone or azithromycin.

Granuloma inguinale

Calymmatobacterium granulomatis infection responds to co-trimoxazole or doxycycline for 2 weeks or a single dose of azithromycin weekly for 4 weeks.

Bacterial vaginosis (bacterial vaginitis, anaerobic vaginosis)

Bacterial vaginosis is a common form of vaginal discharge in which neither *Trichomonas vaginalis* nor *Candida albicans* can be isolated and inflammatory cells are not present: it is diagnosed from the characteristic Gram's stain appearances of a vaginal swab. The condition is associated with overgrowth of several normal commensals of the vagina including *Gardnerella vaginalis*, Gram-negative curved bacilli and anaerobic organisms, the latter being responsible for the characteristic fishy odour of the vaginal discharge. The condition responds well to a single dose of metronidazole 2 g or 400 mg thrice daily for a week by mouth, with 7 days of topical clindamycin cream offering an alternative.

Candida vaginitis. See page 223.

Trichomonas vaginitis. See page 236.

INFECTION OF BONES AND JOINTS

Causative bacteria of ***osteomyelitis*** may arrive via the bloodstream or be implanted directly (through a compound fracture, chronic local infection of local tissue, or surgical operation). *Staphylococcus aureus* is the commonest isolate in all patient groups, and *Salmonella* species in the tropics. Chronic osteomyelitis of the lower limbs (especially when underlying chronic skin infection in the elderly) frequently involves obligate anaerobes (such as *Bacteroides* spp.) and coliforms.

Lymph node tuberculosis. In drug-susceptible lymph node tuberculosis a 6-month regimen is adequate. Affected lymph nodes may enlarge while the patient is on treatment or after the end of treatment without any evidence of mycobacterial relapse (immune reconstitution inflammatory syndrome (IRIS)). Cold abscesses of lymph nodes require needle drainage.

Adrenal steroid and tuberculosis. Corticosteroids are administered in adrenal gland involvement with Addison's disease, in meningeal and pericardial tuberculosis (see Fig. 14.1).

Tuberculosis in the immunocompromised. Such patients require special measures because they may be infected more readily when exposed; their infections usually involve large numbers of tubercle bacilli (multibacillary disease), and patients with AIDS are more likely to be infected with multiply antibiotic-resistant strains. While treating patients co-infected with HIV and tuberculosis, antituberculosis treatment (ATT) is started first and antiretroviral treatment (ART) is started subsequently. ART-naïve HIV/AIDS patients should be started on ART between 2 weeks and 2 months after anti-TB drugs, depending on CD4 cell counts. Patients already on ART require some modification in treatment; efavirenz should be used in place of nevirapine. Rifabutin should be preferred over rifampicin while using protease inhibitors. Patients while on ART and ATT may develop IRIS (within 3 months of treatment). In this paradoxical reaction, patients initially show some improvement and subsequently reveal either aggravation of existing lesions or appearance of fresh lesions. Development of IRIS does not require stopping of ART and usually non-steroidal anti-inflammatory drugs (NSAIDs) are sufficient. Drug-resistant TB should be ruled out. Usually at least four drugs are started, and patients are isolated until bacteriological results have been obtained and they have shown clinical improvement. If infections are proved to involve antibiotic-susceptible mycobacteria, therapy can continue with a conventional 6-month regimen with careful follow-up. Particular problems may occur with multiple drug interactions during antituberculous treatment of patients receiving antiretroviral therapy.

Antituberculosis drugs

Isoniazid

Isoniazid (INH, INAH, isonicotinic acid hydrazide) is selectively effective against *Mycobacterium tuberculosis* because it prevents the synthesis of components that are unique to mycobacterial cell walls. Hence it is bactericidal against actively multiplying bacilli (whether within macrophages or at extracellular sites) but is bacteriostatic against nondividing bacilli; it has little or no activity against other bacteria. Isoniazid is well absorbed from the alimentary tract and is distributed throughout the body water, including CSF. It should always be given in cases where there is special risk of meningitis (miliary tuberculosis and primary infection). Isoniazid is inactivated by conjugation with an acetyl group and the rate of the reaction is bimodally distributed. The $t_{½}$ is 1 h in fast and 4 h in slow acetylators; fast acetylators achieve less than half the steady-state plasma concentration of slow acetylators but standard oral doses (300 mg/day) on daily regimens give adequate tuberculocidal concentrations in both groups.

Adverse effects. Isoniazid is in general well tolerated. The most severe adverse effect is liver damage, ranging from a moderate rise in hepatic enzymes to severe hepatitis and death. Liver histology in isoniazid hepatitis is indistinguishable from acute viral hepatitis. It is probably caused by a chemically reactive metabolite(s), e.g. acetylhydrazine. Most cases are in patients aged over 35 years, and develop within the first 8 weeks of therapy; liver function should be monitored monthly during this period at least. High-dose isoniazid (16–20 mg/kg/day) may be useful in DR-TB.

Isoniazid is a structural analogue of pyridoxine and accelerates its excretion, the principal result of which is peripheral neuropathy with numbness and tingling of the feet, motor involvement being less common. Neuropathy is more frequent in slow acetylators, malnourished people, the elderly and those with HIV infection, liver disease, diabetes mellitus and alcoholism, chronic renal failure, malnutrition, pregnant and breast-feeding women. Such patients should receive pyridoxine 10 mg/day by mouth, which prevents neuropathy and does not interfere with the therapeutic effect; some prefer simply to give pyridoxine to all patients. Other adverse effects include mental disturbances, incoordination, optic neuritis and convulsions.

Isoniazid inhibits the metabolism of phenytoin, carbamazepine and ethosuximide, increasing their effect. Ideally, blood levels of these drugs should be monitored (therapeutic drug monitoring).

Rifampicin

Rifampicin has bactericidal activity against the tubercle bacillus, comparable to that of isoniazid. It is also used in leprosy.

It acts by inhibiting RNA synthesis, bacteria being sensitive to this effect at much lower concentrations than mammalian cells; it is particularly effective against mycobacteria that lie semi-dormant within cells. Rifampicin has a wide range of antimicrobial activity. Other uses include leprosy, severe legionnaires' disease (with erythromycin or ciprofloxacin), the chemoprophylaxis of meningococcal meningitis, and severe staphylococcal infection (with flucloxacillin or vancomycin).

Rifampicin is well absorbed from the gastrointestinal tract. It penetrates most tissues. Entry into the CSF when meninges are inflamed is sufficient to maintain therapeutic

concentrations at normal oral doses but transfer is reduced as inflammation subsides in 1–2 months.

Enterohepatic recycling takes place, and eventually about 60% of a single dose is eliminated in the faeces; urinary excretion of unchanged drug also occurs. The $t_{½}$ is 4 h after initial doses, but shortens on repeated dosing because rifampicin is a very effective enzyme inducer and increases its own metabolism (as well as that of several other drugs; see below).

Adverse reactions. Rifampicin rarely causes any serious toxicity. Adverse reactions include flushing and itching with or without a rash, and thrombocytopenia. Rises in plasma levels of bilirubin and hepatic enzymes may occur when treatment starts, but are often transient and are not necessarily an indication for stopping the drug; fatal hepatitis, however, has occurred. Hepatic function should be checked before starting treatment and at least for the first few months of therapy. Intermittent dosing, i.e. less than twice weekly, either as part of a regimen or through poor compliance, promotes an influenza-like syndrome (malaise, headache and fever, shortness of breath and wheezing), acute haemolytic anaemia and thrombocytopenia, and acute renal failure sometimes with haemolysis. These may have an immunological basis. Red discoloration of urine, tears and sputum is a useful indication that the patient is taking the drug. Rifampicin also causes an orange discoloration of soft contact lenses.

Interactions. Rifampicin is a powerful enzyme inducer and speeds the metabolism of numerous drugs, including warfarin, steroid contraceptives, narcotic analgesics, oral antidiabetic agents, phenytoin and dapsone. Appropriate increase in dosage, and alternative methods of contraception, are required to compensate for increased drug metabolism (see also paracetamol overdose, p. 246).

Rifabutin ($t_{½}$ 36 h) has similar activity and adverse reactions, and is used for prophylaxis of *Mycobacterium avium* infection in patients with AIDS, and for treatment of tuberculous and non-tuberculous mycobacterial infection in combination with other drugs. All rifamycins have high levels of cross-resistance. It is preferred over rifampicin when protease inhibitors are used for treating HIV-TB co-infection. Rifabutin and saquinavir should not be used together. Rifabutin and protease inhibitors are costlier drugs; dose reduction of rifabutin is required, as most protease inhibitors are inhibitors of CYP3A4 isoenzyme and significantly reduce clearance of rifabutin. The dose of rifabutin should be increased from 300 mg/day to 450–600 mg/day when it is co-administered with efavirenz. Adverse effects include gastrointestinal intolerance, bone marrow suppression, hepatotoxicity, uveitis and skin discoloration with normal serum bilirubin (pseudojaundice).

Rifaximin is a semi-synthetic rifamycin that is not absorbed from the gastrointestinal tract (less than 0.4%). Because of the very high faecal concentrations achieved after a 400-mg oral dose (about 8000 micrograms/g faeces), it has broad activity against the common bacterial causes of travellers' diarrhoea and has proved as effective as an oral quinolone or azithromycin (see p. 537), and adverse effects are rare. Efficacy of rifaximin treatment in acute hepatic encephalopathy is well documented. Its protective effect against breakthrough episodes of hepatic encephalopathy along with lactulose on a long-term basis is being evaluated, as rifaximin has a low risk of inducing bacterial resistance.

Pyrazinamide

Pyrazinamide is a derivative of nicotinamide and is included in first-choice combination regimens because of its particular ability to kill intracellular persisters, i.e. mycobacteria that are dividing or semi-dormant, often within cells. Its action is dependent on the activity of intrabacterial pyrazinamidase, which converts pyrazinamide to the active pyrazinoic acid; this enzyme is most effective in an acidic environment such as the interior of cells. In drug-sensitive tuberculosis it should not be administered beyond 2 months. It is inactive against *Mycobacterium bovis*. Pyrazinamide is well absorbed from the gastrointestinal tract and metabolised in the liver, very little unchanged drug appearing in the urine ($t_{½}$ 9 h). CSF concentrations are almost identical to those in the blood. Pyrazinamide is safe to use in pregnancy.

Adverse effects include hyperuricaemia and arthralgia, which is relatively frequent with daily but less so with intermittent dosing and, unlike gout, affects both large and small joints. Pyrazinoic acid, the principal metabolite of pyrazinamide, inhibits renal tubular secretion of urate. Symptomatic treatment with a non-steroidal anti-inflammatory drug is usually sufficient and it is rarely necessary to discontinue pyrazinamide because of arthralgia. Incidence of hepatitis which occurred with high doses has decreased with modern short-course schedules, but still requires close clinical and laboratory monitoring. Sideroblastic anaemia and urticaria also occur.

Ethambutol

Ethambutol, being bacteriostatic, is used in conjunction with other antituberculous drugs to delay or prevent the emergence of resistant bacilli. It is well absorbed from the gastrointestinal tract and effective concentrations occur in most body tissues including the lung; in tuberculous meningitis, sufficient may reach the CSF to inhibit mycobacterial growth but insignificant amounts enter CSF if the meninges are not inflamed. Excretion is mainly by the kidney, by tubular secretion as well as by glomerular filtration ($t_{½}$ 4 h); the dose should be reduced when renal function is impaired.

Adverse effects. In recommended oral doses (15 mg/kg/day), with dose adjustment for reduced renal function, ethambutol is relatively non-toxic. The main problem is rare

optic neuritis (unilateral or bilateral) causing loss of visual acuity, central scotomata, occasionally also peripheral vision loss and red–green colour blindness. The changes reverse if treatment is stopped promptly; if not, the patient may go blind. It is prudent to note any history of eye disease and to get baseline tests of vision before starting treatment with ethambutol. The drug should not be given to a patient with reduced vision who may not notice further deterioration. Patients should be told to read small print in newspapers regularly (with each eye separately) and, if there is any deterioration, to stop the drug immediately and seek advice. Patients who cannot understand and comply (especially children) should be given alternative therapy if possible. The need for repeated specialist ophthalmological monitoring is controversial. Peripheral neuritis occurs but is rare.

Antituberculosis drug-induced hepatitis

Among the first-line antituberculosis drugs, rifampicin, isoniazid and pyrazinamide are potentially hepatotoxic drugs. Additionally, rifampicin can cause asymptomatic jaundice without evidence of hepatitis. Rifampicin rarely causes hepatitis when administered alone and rifampicin and isoniazid are ~ 3 times less toxic in the absence of pyrazinamide. It is essential to rule out acute viral hepatitis by performing markers for viral hepatitis before diagnosing antituberculosis drug-induced hepatitis in developing nations. Drug-induced hepatitis can be life-threatening if drugs are continued despite its occurrence. All hepatotoxic drugs should be immediately stopped until complete biochemical recovery occurs. In the interim period, ethambutol, streptomycin and one of the fluoroquinolones should be administered. The best approach to reintroducing antituberculosis drugs is still debatable. The approach could be sequential or simultaneous. Some advocate reintroduction of all three drugs one by one as it allows identification of the culprit drug, while others prefer to use rifampicin first followed by isoniazid and if the patient tolerates both drugs avoid pyrazinamide.

Streptomycin

See page 180.

Thiacetazone

Thiacetazone is tuberculostatic and is used with isoniazid to inhibit the emergence of resistance to the latter drug. It is absorbed from the gastrointestinal tract, partly metabolised and partly excreted in the urine ($t_{½}$ 13 h). Usual adult dose is 150 mg/day. It is not used in HIV-TB co-infection because of severe cutaneous reactions; Asian patients may have higher incidence of Stevens–Johnson syndrome.

Adverse reactions include gastrointestinal symptoms, conjunctivitis and vertigo. More serious effects are erythema multiforme, haemolytic anaemia, agranulocytosis, cerebral oedema and hepatitis.

Second-line antituberculosis drugs

Kanamycin and amikacin

Both kanamycin ($t_{½}$ 2–4 h) and amikacin ($t_{½}$ 2–4 h) are bactericidal drugs of the aminoglycoside class, valuable in patients with resistance to streptomycin. Cross-resistance between kanamycin and amikacin is usual. The optimal dose is 15 mg/kg body-weight, usually 0.75–1.0 g/day i.m. Adverse effects are similar to streptomycin.

Capreomycin

Capreomycin ($t_{½}$ 4–6 h) is a bactericidal aminoglycoside derived from *Streptomyces capreolus*. There is no cross-resistance with other aminoglycosides. The usual dose is 20 mg/kg/day up to 1 g in a single dose daily i.m. for 40–120 days; the dose is then reduced to 2–3 times weekly as the risk of adverse effects increases sharply. Adverse effects are similar to streptomycin. Hypokalaemia, hypocalcaemia and hypomagnesaemia have been reported. Rarely, hepatitis and general cutaneous reactions may occur.

Thioamides

Ethionamide and prothionamide. Ethionamide ($t_{½}$ 2–3 h) and prothionamide ($t_{½}$ 2–3h) are bactericidal drugs. Their chemical structure resembles thioacetazone and there is frequent partial cross-resistance. The maximum optimum dose is 15–20 mg/kg/day up to 1 g/day and the usual dose is 750 mg/day in patients weighing 50 kg or more (or can be split in two doses: 500 mg in the morning and 250 in the evening) and 500 mg/day in patients weighing < 50 kg. These drugs are more acceptable when administered with orange juice or milk. Adverse reactions include gastrointestinal side-effects, depression, hallucinations, hepatitis, hypothyroidism and peripheral neuropathy. The drugs should be avoided during pregnancy.

Cycloserine and terizidone

Cycloserine ($t_{½}$ 10 h) is bacteriostatic at the usual dosage and terizidone is a combination of two molecules of cycloserine. The maximum daily dose is 15–20 mg/kg; the usual dose of cycloserine and terizidone is 500–750 mg/day (250 mg in the morning and 500 mg 12 hours later). Main adverse effects are related to the central nervous system (less with terizidone) and include headache, tremors, insomnia, depression, convulsions, altered behaviour and suicidal tendencies. Addition of pyridoxine (50 mg/250 mg of cycloserine and terizidone is recommended) decreases these adverse effects.

Chapter 15

Viral, fungal, protozoal and helminthic infections

Sani Aliyu

SYNOPSIS

- **Viruses** present a more difficult problem of chemotherapy than do higher organisms, e.g. bacteria, for they are intracellular parasites that use the metabolism of host cells.[1] Highly selective toxicity is, therefore, harder to achieve. In the past 15 years, identification of the molecular differences between viral and human metabolism has led to the development of many effective antiviral agents; four were available in 1990, now there are over 40.
- **Fungal infections** range from inconvenient skin conditions to life-threatening systemic diseases; the latter have become more frequent as opportunistic infections in patients immunocompromised by drugs or AIDS, or in those receiving intensive medical and surgical interventions in intensive care units.
- **Protozoal infections**. Malaria is the major transmissible parasitic disease in the world. Drug resistance is an increasing problem and differs with geographical location, and species of plasmodium.
- **Helminthic infestations** cause considerable morbidity. The drugs that are effective against these organisms are summarised.

[1] 'The large-scale screening for natural compounds able to kill bacteria in vitro, which was the basis for the boom of antibiotics in the 1950s, was not successful for antivirals ... The driving force for the boom of antivirals in this period has been the pressure to contain the HIV pandemic, combined with the increased understanding of the molecular mechanisms ... which has allowed the identification of new targets for therapeutic intervention.' (Rappuoli R 2004 From Pasteur to genomics: progress and challenges in infectious diseases. Nature Medicine 10:1177–1185.)

Viral infections

Antiviral agents are most active when viruses are replicating. The earlier that treatment is given, therefore, the better the result. Apart from primary infection, viral illness is often the consequence of reactivation of latent virus in the body. Patients whose immune systems are compromised may suffer particularly severe illness. Viruses are capable of developing resistance to antimicrobial drugs, with similar implications for the individual patient, for the community and for drug development. An overview of drugs that have proved effective against virus diseases appears in Table 15.1.

HERPES SIMPLEX AND VARICELLA ZOSTER

Aciclovir

Aciclovir ($t_{½}$ 3 h) is a nucleoside analogue that is selectively phosphorylated by virus-specific thymidine kinase. Phosphorylated aciclovir inhibits viral replication by acting as a substrate for viral DNA polymerase, thus accounting for its high therapeutic index. It is effective against susceptible herpes viruses if started early in the course of infection, but it does not eradicate persistent infection because viral DNA is integrated in the host genome. About 20% is absorbed from the gut, but this is sufficient for oral systemic treatment of some infections. It distributes widely in the body; the concentration in CSF is approximately half that of plasma, and the brain concentration may be even lower. These differences are taken into account in dosing for viral encephalitis (for which aciclovir must be given i.v.).

Table 15.1 Drugs of choice for virus infections

ORGANISM	DRUG OF CHOICE	ALTERNATIVE
Varicella zoster		
chickenpox	Aciclovir	Valaciclovir or famciclovir
zoster	Aciclovir or famciclovir	Valaciclovir
Herpes simplex		
keratitis	Aciclovir (topical)	
labial	Aciclovir (topical and/or oral)	Valaciclovir or famciclovir
genital	Aciclovir (topical and/or oral)	Valaciclovir
	Famciclovir (oral)	Penciclovir
encephalitis	Aciclovir	
disseminated	Aciclovir	Foscarnet
Human immunodeficiency virus (HIV)	Lamivudine/emtricitabine	Abacavir
	Tenofovir	Didanoside
	Zidovudine	Stavudine
	Lopinavir/ritonavir	Saquinavir
	Atazanavir	Darunavir
	Fosamprenavir	Tipranavir
	Efavirenz	Nevirapine
	Etravirine	
	Raltegravir	
	Enfuvirtide	
	Maraviroc	
Hepatitis B	Pegylated interferon α-2a and interferon 2b, lamivudine	Adefovir, tenofovir, entecavir, telbivudine
Hepatitis C	Pegylated interferon α-2a or interferon 2b plus ribavirin	
Hepatitis D	Interferon-α	Pegylated interferon α-2a and interferon 2b
Influenza A	Zanamivir, oseltamivir	Amantadine
Cytomegalovirus (CMV)	Valganciclovir, ganciclovir	Foscarnet, cidofovir
Respiratory syncytial virus	Ribavirin	Palivizumab
Papillomavirus (genital warts)	Imiquimod	
Molluscum contagiosum	Imiquimod	Cidofovir

Dose adjustment is required for patients with impaired renal function, as the drug is predominantly excreted in the urine. For oral and topical use the drug is given five times daily. It can be given twice daily orally for suppressive therapy.

Indications for aciclovir include:

Herpes simplex virus:

- Skin infections, including initial and recurrent labial and genital herpes, most effective when new lesions are forming; skin and mucous membrane infections (as tablets or oral suspension).
- Ocular keratitis (topical treatment with ophthalmic ointment is standard, oral treatment is also effective).
- Prophylaxis and treatment in the immunocompromised (oral, as tablets or suspension).
- Encephalitis and disseminated disease (i.v.).

Aciclovir-resistant herpes simplex virus has been reported in patients with AIDS but remains rare in immunocompetent

patients. Foscarnet (p. 221) and cidofovir (p. 221) have been used in these cases.

Varicella zoster virus:

- Chickenpox, particularly in the immunocompromised (i.v.) or in the immunocompetent with pneumonitis or hepatitis (i.v.).
- Shingles in immunocompetent persons (as tablets or suspension, and best started within 48 h of the appearance of the rash). Immunocompromised persons will often have more severe symptoms and require i.v. administration.

Adverse reactions are remarkably few. The ophthalmic ointment causes a mild transient stinging sensation and a diffuse superficial punctate keratopathy which clears when the drug is stopped. Oral or i.v. use may cause gastrointestinal symptoms, headache and neuropsychiatric reactions. Extravasation with i.v. use causes severe local inflammation. Crystal-induced acute renal failure is an important complication of i.v. therapy that can be avoided by ensuring good hydration during treatment.

Valaciclovir is a prodrug (ester) of aciclovir, i.e. after oral administration the parent aciclovir is released. It has an improved bio-availability (about 60%) due to the addition of an ester side chain, thus allowing for a less frequent, 8-hourly, dosing. It is used for treating herpes zoster infections and herpes simplex infections of the skin and mucous membranes.

Famciclovir ($t_{½}$ 2 h) is a prodrug of penciclovir, which is similar to aciclovir; it is used for herpes zoster and genital herpes simplex infections, and a single dose is effective at reducing the time to healing of labial herpes simplex. It need be given only 8-hourly. Penciclovir is also available as a cream for treatment of labial herpes simplex.

Idoxuridine was the first widely used antiviral drug; it is variably effective topically for ocular and cutaneous herpes simplex, with few adverse reactions. It has been superseded by aciclovir.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

According to World Health Organization data, 33 million people worldwide were living with human immunodeficiency virus (HIV) in 2008, with close to 3 million new infections yearly; almost 10 million were in need of antiretroviral therapy but more than half of these had no access to treatment.

General comments

- The aims of antiretroviral therapy are to delay disease progression and prolong survival by suppressing the replication of the virus. Optimal suppression also prevents the emergence of drug resistance and reduces the risks of onward transmission to sexual partners and the unborn children of HIV-infected mothers. Virological failure may be defined as primary where there is inability to reduce plasma HIV viral load to fewer than 50 copies per microlitre despite 6 months of antiretroviral therapy, or secondary if there is failure to maintain viral load suppression at less than 50 copies per microlitre.
- No current antiviral agents or combinations eliminate HIV infection, but the most effective combinations (so-called 'highly active antiretroviral therapy', HAART) produce profound suppression of viral replication in many patients and allow useful reconstitution of the immune system, measured by a fall in the plasma viral load and an increase in the numbers of cytotoxic T cells (CD4 count). Rates of opportunistic infections such as *Pneumocystis carinii* pneumonia and cytomegalovirus (CMV) retinitis are reduced when CD4 counts are restored, and life expectancy is markedly increased.
- Combination therapy reduces the risks of emergence of resistance to antiretroviral drugs, which is increasing in incidence even in patients newly diagnosed with HIV. Mutations in the viral genome either prevent binding of the drug to the active site of the protease or reverse transcriptase enzymes, or lead to removal of the drug from the reverse transcriptase active site. The potential for rapid development of resistance is immense because untreated HIV replicates rapidly (50% of circulating virus is replaced daily), the spontaneous mutation rate is high, the genome is small, the virus will develop single mutations at every codon every day, and for many antiretroviral agents a single mutation will render the virus fully resistant.
- The decision to begin antiretroviral therapy is based primarily on the CD4 cell count (most current recommendations are to start in patients with counts below 350 cells per microlitre). Early initiation of antiretroviral therapy should also be considered for patients with CD4 cell count above 350 cells per microlitre but a low CD4 percentage (e.g < 14%), those with an AIDS diagnosis (e.g. Kaposi sarcoma), hepatitis B and HIV co-infection where treatment is indicated, and in conditions where achieving a suppressed viral load is desired in order to prevent transmission (e.g. in pregnancy).
- There are currently more than 20 approved antiretroviral agents in four classes, plus various fixed drug combinations (Table 15.2).
- Current HAART regimens use a combination of drugs that act at different phases of the viral life cycle. The most frequently used combinations employ a backbone of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus either

Table 15.2 Classification and mechanism of antiretrovirals

CLASSIFICATION		MECHANISM OF ACTION	EXAMPLES
Reverse transcriptase inhibitors	Nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs)	Nucleoside analogues are incorporated into growing viral DNA chain, leading to chain termination	Zidovudine Lamivudine Emtricitabine Abacavir Tenofovir Disoproxil Stavudine Didanoside
	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Bind to a hydrophobic pocket near the active site of the reverse transcriptase enzyme, inhibiting DNA synthesis	Efavirenz Nevirapine Etravirine
Entry inhibitors	Entry blockers	Bind to CCR5 receptors on the surface of some CD4 cells, blocking entry of HIV virion	Maraviroc
	Fusion inhibitors	Bind to gp41, an HIV surface protein, interfering with fusion and T cell entry	Enfuvirtide
Protease inhibitors		Inhibit protease enzyme, required for cleavage of viral proteins and assembly	Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir
Integrase inhibitors		Block integrase, essential for insertion of viral DNA into host DNA	Raltegravir

a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (rPI). The choice for the individual patient is best made after reference to contemporary, expert advice (see the websites listed in the Guide to further reading).

- Alternative combinations are used if these variables deteriorate or unwanted drug effects occur. Antiretroviral resistance testing, both genetic (by searching viral RNA for sequences coding for resistance) and phenotypic (by testing antiretroviral agents against the patient's virus in cell culture), also guide the choice of drug regimen, especially after virological failure.
- Pregnancy and breast feeding pose special problems. The objectives of therapy are to minimise drug toxicity to the fetus while reducing the maternal viral load and the catastrophic results of HIV transmission to the neonate. Prevention of maternal–fetal and maternal–infant spread is the most cost-effective way of using antiretroviral drugs in less developed countries. Maternal–fetal transmission rates are related to maternal viral load, with rates of 0.1% reported when maternal viral load is less than 50 copies per microlitre while on HAART. Where resources permit, access to safe alternatives to breast feeding should be provided to infected mothers.
- Combination antiretroviral therapy, especially the thymidine nucleoside analogue reverse transcriptase inhibitors zidovudine and stavudine, causes redistribution of body fat in some patients – the 'lipodystrophy syndrome'. Protease inhibitors can disturb lipid and glucose metabolism to a degree that warrants a change to drugs with limited effects on lipid metabolism, e.g. ritonavir-boosted atazanavir, and the introduction of lipid-lowering agents.
- Impaired cell-mediated immunity leaves the host prey to opportunistic infections including: candidiasis, coccidioidomycosis, cryptosporidiosis, CMV disease, herpes simplex, histoplasmosis, *Pneumocystis carinii* pneumonia, toxoplasmosis and tuberculosis (often

with multiply resistant organisms). Treatment of these conditions is referred to elsewhere in this text.[2]

- Improvement in immune function as a result of antiretroviral treatment may provoke an inflammatory reaction against residual opportunistic organisms (immune reconstitution inflammatory syndrome, IRIS). Although infrequent, this may present with development of new infections or worsening opportunistic infections, e.g. tuberculosis and cryptococcal disease.
- Antiretroviral drugs may also be used in combination to reduce the risks of infection with HIV from injuries, e.g. from HIV-contaminated needles and following sexual exposure to a high-risk partner. The decision to offer such post-exposure prophylaxis (PEP), and the optimal combination of drugs used, is a matter for experts; administration must begin within a few hours of exposure and continue for 28 days.
- Some drugs described here have found additional indications, or are used only, for therapy of non-HIV infections, e.g. adefovir for chronic hepatitis B infection.

Nucleoside and nucleotide reverse transcriptase inhibitors

The HIV replicates by converting its single-stranded RNA into double-stranded DNA, which is incorporated into host DNA; this crucial conversion, the reverse of the normal cellular transcription of nucleic acids, is accomplished by the enzyme *reverse transcriptase*. Nucleoside reverse transcriptase inhibitors have a high affinity for the *reverse transcriptase* enzyme and are integrated by it into the viral DNA chain, causing premature chain termination. While all nucleoside reverse transcriptase inhibitors require activation by host enzymes to triphosphates prior to incorporation into the DNA chain, tenofovir (as the only nucleotide analogue) is unique in requiring only two phosphorylations for activation.

Zidovudine (AZT, Retrovir)

Zidovudine, a thymidine analogue, is the first antiretroviral licensed for the treatment of HIV-1. Resistance develops rapidly when used as monotherapy through the sequential accumulation of thymidine analogue mutations (TAMs) at codon 41, 67, 70, 215 and 219; conversely, point mutations at codon 184 selected by lamivudine and emtricitabine therapy enhance susceptibility to zidovudine (and stavudine) by delaying the emergence of TAMs.

Pharmacokinetics. Zidovudine is well absorbed from the gastrointestinal tract (it is available as capsules and syrup) and is rapidly cleared from the plasma ($t_{½}$ 1 h); concentrations in cerebrospinal fluid (CSF) are approximately half of those in plasma. Zidovudine is also available i.v. for patients temporarily unable to take oral medications, for neonates and for intrapartum use. The drug is inactivated mainly by glucuronidation in the liver, but 20% is excreted unchanged by the kidney. Zidovudine competitively inhibits the intracellular phosphorylation of stavudine, therefore use in combination with stavudine should be avoided.

Uses. Zidovudine is indicated for the treatment of HIV infection as part of a combination regimen. It is an established choice for the prevention of maternal–fetal transmission, both as part of a combination regimen antenatally in the mother and as monotherapy in the newborn. The enhanced CNS penetration of zidovudine makes it an important option for the treatment of HIV-associated neurocognitive disease (HAND). The drug is available as part of a fixed drug combination with lamivudine (as Combivir), and with abacavir and lamivudine (as Trizivir).

Adverse reactions early in treatment may include anorexia, nausea, vomiting, headache, dizziness, malaise and myalgia, but tolerance develops to these and usually the dose does not need to be altered. More serious are anaemia and neutropenia, which develop more commonly when the dose is high, with advanced disease, and in combination with ganciclovir, interferon-α and other marrow suppressive agents. A toxic myopathy (not easily distinguishable from HIV-associated myopathy) may develop with long-term use. Rarely, a syndrome of hepatic necrosis with lactic acidosis may occur with zidovudine (and with other reverse transcriptase inhibitors).

Didanosine

Didanosine (ddI) is a thymidine analogue with similar activity to zidovudine. It has a short plasma half-life ($t_{½}$ 1 h) but a much longer intracellular duration than zidovudine, and thus prolonged antiretroviral activity. Didanosine is rapidly but incompletely absorbed from the gastrointestinal tract (30–40%) and is widely distributed in body water; 30–65% is recovered unchanged in the urine. Drug absorption is affected by food and therefore it has to be taken on an empty stomach or at least 2 h after a meal. Didanosine may cause pancreatitis, lactic acidosis, hepatomegaly with steatosis and peripheral neuropathy. Other adverse effects include hyperuricaemia and diarrhoea, any of which may give reason to reduce the dose or discontinue the drug. Retinal changes and optic neuritis have also been reported. The combination of stavudine and didanosine is associated with a high risk of toxicity and should be avoided. Dose adjustment of didanosine is required when used in combination with tenofovir and in patients with renal insufficiency.

[2]For a comprehensive review, see Kaplan J E, Benson C, Holmes K H et al 2009 Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recommendations and Reports 58(RR-4):1–207.

Lamivudine and emtricitabine

Lamivudine (3TC) is a reverse transcriptase inhibitor with a relatively long intracellular half-life (14 h; plasma $t_{½}$ 6 h). Lamivudine is the most common nucleoside analogue used in HAART regimens due to its excellent tolerance profile. A nucleoside backbone of lamivudine with zidovudine (Combivir), abacavir (Kivexa) or emtricitabine and tenofovir (Truvada) as fixed drug combinations, appears to reduce viral load effectively and to be well tolerated. The drug is well absorbed from the gastrointestinal tract (86%) and excreted mainly by the kidney with minimal metabolism; dose modification is necessary in renal impairment.

Lamivudine was the first nucleoside analogue to be licensed for therapy of chronic hepatitis B infection, for which it should be used in combination with tenofovir (as part of a HAART regimen) in HIV co-infected patients. Emergence of resistant mutants of hepatitis B is troublesome (due to mutations of the viral reverse transcriptase/DNA polymerase), occurring in up to about 30% of patients after 1 year and 70% after 5 years of therapy.

The most common unwanted effects include headache and gastrointestinal upset. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. A higher dose of lamivudine is required for the treatment of HIV than for hepatitis B infection; patients with co-infection should receive doses appropriate for treatment of HIV.

Emtricitabine

Emtricitabine has a similar structure, tolerability, efficacy and resistance profile. It should not be used in combination with lamivudine, as it contains the same active constituent.

Abacavir

Abacavir ($t_{½}$ 2 h) has high therapeutic efficacy; it is usually well tolerated, but adverse effects include hypersensitivity reactions especially during the first 6 weeks of therapy, affecting about 8% of patients; the drug must be stopped immediately and avoided in future if hypersensitivity is suspected. The presence of the HLA-B*5701 allele predicts increased risk of hypersensitivity reaction in the Caucasian population; patients should be tested for the presence of this allele prior to starting therapy.

Tenofovir

Tenofovir ($t_{½}$ 17 h), administered orally as the prodrug tenofovir disoproxil fumarate, is also effective against hepatitis B virus. Some 80% is excreted renally and dose adjustment is recommended in patients with a creatinine clearance of less than 50 mL/min. Monitor closely for signs of new onset or acute renal impairment, electrolyte and renal tubular disturbance (Fanconi syndrome); avoid concomitant nephrotoxic drugs while on tenofovir.

Tenofovir competes with didanosine for renal tubular excretion, raising didanosine plasma concentrations with associated risk of pancreatitis, peripheral neuropathy and lactic acidosis. Severe acute exacerbation of hepatitis has been described following cessation of therapy for hepatitis B infection.

Stavudine

Stavudine (d4T) inhibits reverse transcriptase by competing with the natural substrate deoxythymidine triphosphate, and additionally is incorporated into viral DNA, causing termination of chain elongation ($t_{½}$ 1.5 h). Troublesome lipoatrophy has limited its use by most authorities outside the developing world. Hepatic toxicity and pancreatitis are reported, and a dose-related peripheral neuropathy may occur, all probably related to mitochondrial toxicity. Stavudine is more frequently associated with lactic acidosis than other nucleoside analogues.

Adefovir

Adefovir dipivoxil is a nucleoside analogue used for chronic hepatitis B infection, including against lamivudine-resistant strains. It is administered as the oral prodrug (plasma $t_{½}$ 8 h, intracellular $t_{½}$ of active metabolite 17 h). Adverse effects are uncommon, but include headache, abdominal pain and diarrhoea. Resistance emerges over time (30% after 5 years), but much less commonly than with lamivudine therapy, possibly due to the flexibility of the adefovir molecule, which allows it to conform to mutated binding sites. Dose adjustment is required for patients with renal impairment. Adefovir should not be co-prescribed with tenofovir. The recommended adefovir dose for hepatitis B therapy will not suppress HIV infection; HIV status should therefore be confirmed prior to commencing adefovir for hepatitis B infection, as unrecognised co-infection may lead to the emergence of HIV resistance.

Protease inhibitors

In its process of replication, HIV produces precursor proteins, which are subsequently cleaved by the protease enzyme into component parts and reassembled into virus particles; protease inhibitors disrupt this essential process.

Protease inhibitors reduce viral RNA concentration ('viral load'), increase the CD4 count and improve survival when used in combination with other agents. They are metabolised extensively by isoenzymes of the cytochrome

activity against HIV virions that preferentially bind to another surface chemokine co-receptor (CXCR4), found in about 60% of antiretroviral experienced patients. Hence a 'Trofile assay' is required to determine if a susceptible (CCR5 tropic) strain is present as the dominant quasispecies in a patient prior to commencing maraviroc therapy. It is recommended as part of a combination regimen in treatment-experienced patients with multidrug-resistant strains.

Integrase inhibitors

Raltegravir ($t_{½}$ 41 h) targets the HIV integrase enzyme, which is essential in integrating viral genetic material into the DNA of the host target cell. It is generally well tolerated and metabolised by glucuronidation. It has a low genetic barrier to resistance (arising from mutations in the integrase gene) and should be used with caution in patients at increased risk of myopathy or rhabdomyolysis.

Fixed-dose combinations of antiretroviral drugs are convenient, help to lessen pill burden and may improve compliance, but the components of the combination may differ in their dependence on metabolic inactivation or renal excretion; particular attention to these is necessary when use in patients with renal or hepatic impairment is proposed.

Fixed-dose combination antiretrovirals	
Combivir Kivexa (Europe), Epzicom (USA)	zidovudine and lamivudine abacavir and lamivudine
Truvada	tenofovir and emtricitabine
Trizivir	zidovudine and lamivudine and abacavir
Atripla	tenofovir and emtricitabine and efavirenz
Kaletra	lopinavir and ritonavir

INFLUENZA A

Neuraminidase inhibitors are highlighted by the emergence of avian influenza viruses with the potential for mutation to cause pandemic spread in the human population, although their clinical effectiveness is not high. The two antiviral drugs oseltamivir and zanamivir were widely used for the public health control of the 2009 influenza A (H1N1) pandemic.

Amantadine

Amantadine is effective only against influenza A; it acts by interfering with the uncoating and release of viral genome into the host cell. It is well absorbed from the gastrointestinal tract and is eliminated in the urine ($t_{½}$ 3 h). Following the emergence of the 2009 influenza A (H1N1) virus as the predominant circulating strain, resistance to amantadine is now almost universal; for this reason amantidine is no longer recommended for the treatment of influenza.

Adverse reactions include dizziness, nervousness, lightheadedness and insomnia. Drowsiness, hallucinations, delirium and coma may occur in patients with impaired renal function. Convulsions may be induced, and amantadine should be avoided in epileptic patients.

Amantadine for Parkinson's disease: see page 365.

Zanamivir (Relenza)

Zanamivir is a viral neuraminidase inhibitor that blocks both entry of influenza A and B viruses to target cells and the release of their progeny. It is administered as a dry powder twice daily in a 5-day course by a special inhaler. The limited bio-availability (2%) of zanamivir has made it the preferred antiviral in pregnancy. The duration of symptoms is reduced from about 6 to 5 days, with a smaller reduction in the mean time taken to return to normal activities. In high-risk groups the reduction in duration of symptoms is a little greater, and fewer patients need antibiotics. It is also effective for prophylaxis given as a once-daily inhalation.

The UK National Institute for Health and Clinical Excellence (NICE) recommends that zanamivir be reserved for:

- At-risk patients (those with chronic respiratory or cardiovascular disease, immunosuppression or diabetes mellitus, or over the age of 65 years).
- When virological surveillance in the community indicates that influenza virus is circulating.
- Only those presenting within 48 h of the onset of influenza-like symptoms.

Zanamivir retains activity against amantadine-resistant and some oseltamivir-resistant strains.

Unwanted effects are uncommon, but bronchospasm may be precipitated in asthmatics, and gastrointestinal disturbance and rash are occasionally seen.

Oseltamivir (Tamiflu)

Oseltamivir is an oral prodrug of a viral neuraminidase inhibitor. It reduces the severity and duration of symptoms caused by influenza A or B in adults and children if commenced within 36 h of the onset of symptoms. More specifically, the risk of respiratory complications such as secondary pneumonia, antibiotic use and hospital

admission are reduced. It is effective for post-exposure prophylaxis, where it should be started within 48 h of contact with the index case and continued daily for 10 days, a usage that might be appropriate for health-care workers and those especially likely to suffer serious complications from pre-existing illness. Prophylaxis may be given for 2 weeks after influenza immunisation while protective antibodies are being produced.

Oseltamivir is one option for treatment and prophylaxis of avian H5N1 and 2009 influenza A (H1N1) virus. In the event of a pandemic, treatment for 5 days and prophylactic use for up to 6 weeks (or until 48 h after last exposure) are suggested.

Unwanted effects are uncommon; some people experience gastrointestinal symptoms that are reduced by taking the drug with food.

Resistance to oseltamivir emerged in late 2007 among seasonal influenza A H1N1 viruses as a result of a spontaneous mutation at position 274 (His274Tyr) in the neuraminidase enzyme. So far, this mutation appears to be confined mostly to seasonal influenza A H1N1 strains, with the majority of 2009 influenza A (H1N1) viruses still susceptible to oseltamivir; the mutation also does not appear to confer resistance to zanamivir.

Peramivir is an experimental neuraminidase inhibitor formulated for intravenous use and currently undergoing phase III trials. The drug was granted temporary emergency use authorisation by the US Food and Drug Administration (FDA) during the 2009 influenza A (H1N1) pandemic for hospitalised patients with severe suspected or confirmed influenza A (H1N1) infection where oseltamivir or zanamivir therapy has failed or the inhalational or oral routes are considered unreliable.

CYTOMEGALOVIRUS

Ganciclovir

Ganciclovir resembles aciclovir in its mode of action, but is much more toxic. An acyclic analogue of guanosine, the drug is converted to a triphosphate form which competitively inhibits virion DNA polymerase, leading to chain termination. It is given i.v. and is eliminated in the urine, mainly unchanged ($t_{½}$ 4 h). Ganciclovir is active against several types of virus but toxicity limits its i.v. use to life- and sight-threatening CMV infection in immunocompromised patients, including CMV retinitis, pneumonitis, colitis and disseminated disease.

Valganciclovir is an oral prodrug of ganciclovir that provides systemic concentrations almost as high as those following i.v. therapy. It is used for treatment of CMV retinitis (acute treatment of peripheral retinal lesions and maintenance suppressive therapy) in patients with AIDS, and to prevent CMV disease in patients receiving immunosuppressive therapy following organ transplantation (especially liver transplants). A combined approach of ganciclovir-releasing intraocular implant plus oral valganciclovir is sometimes considered in patients with immediate sight-threatening CMV retinitis.

Ganciclovir-resistant CMV isolates have been reported, and require treatment with foscarnet or cidofovir.

Adverse reactions include neutropenia and thrombocytopenia, which are usually but not always reversible. Concomitant use of potential marrow-depressant drugs, e.g. co-trimoxazole, amphotericin B, azathioprine, zidovudine, should be avoided, and co-administration of granulocyte colony-stimulating factor may ameliorate the myelosuppressive effects. Other reactions are fever, rash, gastrointestinal symptoms, confusion and seizure (the last especially when imipenem is co-administered).

Foscarnet

Foscarnet finds use i.v. for CMV retinitis in patients with HIV infection when ganciclovir is contraindicated, and for aciclovir-resistant herpes simplex virus infection (see p. 213). It is generally less well tolerated than ganciclovir; adverse effects include renal toxicity (usually reversible), nausea and vomiting, neurological reactions and marrow suppression. Hypocalcaemia is seen especially when foscarnet is given with pentamidine, e.g. during treatment of multiple infections in patients with AIDS. Renal toxicity can be minimised with good hydration and dose modification. Foscarnet causes a contact dermatitis which can lead to unpleasant genital ulcerations due to high urine drug concentrations; this is potentially preventable with good urinary hygiene.

Cidofovir

Cidofovir is given by i.v. infusion (usually every 1–2 weeks) for CMV retinitis in patients with AIDS when other drugs are unsuitable or resistance is a problem. It has also been used i.v. and topically to produce resolution of molluscum contagiosum skin lesions in immunosuppressed patients, and it may be effective in other poxvirus infections. Nephrotoxicity is common with i.v. use, but is reduced by hydration with i.v. fluids before each dose and co-administration with probenecid. Other unwanted effects include bone marrow suppression, nausea and vomiting, and iritis and uveitis, and cause about 25% of patients to discontinue therapy.

Fomivirsen

Fomivirsen, an antisense oligonucleotide, is available in some countries as an intravitreal injection for CMV retinitis in HIV-infected patients who cannot tolerate or who have failed treatment with other drugs.