06-6 Principles of infectious disease

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100 • PRINCIPLES OF INFECTIOUS DISEASE tackling infection in resource-poor countries. Microorganisms are continually mutating and evolving; the emergence of new infectious agents and antimicrobial-resistant microorganisms is therefore inevitable. This chapter describes the biological and epidemiological principles of infectious diseases and the general approach to their prevention, diagnosis and treatment. Specific infectious diseases are described in Chapters 11–13 and many of the organ-based chapters. Infectious agents The concept of an infectious agent was established by Robert Koch in the 19th century (Box 6.1). Although fulfilment of ‘Koch’s postulates’ became the standard for the definition of an infectious agent, they do not apply to uncultivable organisms (e.g. Mycobacterium leprae, Tropheryma whipplei) or members of the normal human flora (e.g. Escherichia coli, Candida spp.). The following groups of infectious agents are now recognised. Viruses Viruses are incapable of independent replication. Instead, they subvert host cellular processes to ensure synthesis of their nucleic acids and proteins. Viruses’ genetic material (the genome) consists of single- or double-stranded DNA or RNA. Retroviruses transcribe their RNA into DNA in the host cell by reverse transcription. An antigenically unique protein coat (capsid) encloses the genome, and together these form the nucleocapsid. In many viruses, the nucleocapsid is packaged within a lipid envelope. Enveloped viruses are less able to survive in the environment and are spread by respiratory, sexual or blood-borne routes, including arthropod-based transmission. Non-enveloped viruses survive better in the environment and are predominantly transmitted by faecal–oral or, less often, respiratory routes. A generic virus life cycle is shown in

Figure 6.2. A virus that infects a bacterium is a bacteriophage (phage). Prokaryotes: bacteria (including mycobacteria and actinomycetes) Prokaryotic cells are capable of synthesising their own proteins and nucleic acids, and are able to reproduce autonomously, although they lack a nucleus. The bacterial cell membrane is bounded by a peptidoglycan cell wall, which is thick (20–80 nm) in Gram-positive organisms and thin (5–10 nm) in Gram-negative ones. The Gram-negative cell wall is surrounded by an outer membrane containing lipopolysaccharide. Genetic information is contained within a chromosome but bacteria may also contain rings of extra-chromosomal DNA, known as plasmids, which can be transferred between organisms, without cells having to divide. Bacteria may be embedded in a polysaccharide capsule, 'Infection' in its strict sense describes the situation where microorganisms or other infectious agents become established in the host organism's cells or tissues, replicate, cause harm and induce a host response. If a microorganism survives and replicates on a mucosal surface without causing harm or illness, the host is said to be 'colonised' by that organism. If a microorganism survives and lies dormant after invading host cells or tissues, infection is said to be 'latent'. When the infectious agent, or the host response to it, is sufficient to cause illness or harm, then the process is termed an 'infectious disease'. Most pathogens (infectious agents that can cause disease) are microorganisms but some are multicellular organisms. The manifestations of disease may aid pathogen dissemination (e.g. diarrhoea). The term 'infection' is often used interchangeably with 'infectious disease' but not all infections are 'infectious', i.e. transmissible from person to person. Infectious diseases transmitted between hosts are called communicable diseases, whereas those caused by organisms that are already colonising the host are described as endogenous. The distinction is blurred in some situations, including health care-associated infections such as meticillinresistant Staphylococcus aureus (MRSA) or Clostridium difficile infection (CDI), in which colonisation precedes infection but the colonising bacteria may have been recently transmitted between patients. The chain of infection (Fig. 6.1) describes six essential elements for communicable disease transmission. Despite dramatic advances in hygiene, immunisation and antimicrobial therapy, infectious agents still cause a massive burden of disease worldwide. Key challenges remain in Fig. 6.1 Chain of infection. The infectious agent is the organism that causes the disease. The reservoir is the place where the population of an infectious agent is maintained. The portal of exit is the point from which the infectious agent leaves the reservoir. Transmission is the process by which the infectious agent is transferred from the reservoir to the human host, either directly or via a vector or fomite. The portal of entry is the body site that is first accessed by the infectious agent. Finally, in order for disease to ensue, the person to whom the infectious agent is transmitted must be a susceptible host. Susceptible host Exit Entry Transmission Infectious agent Reservoir 6.1 Definition of an infectious agent – Koch's postulates

1. The same organism must be present in every case of the disease
2. The organism must be isolated from the diseased host and grown in pure culture
3. The isolate must cause the disease, when inoculated into a healthy, susceptible animal
4. The organism must be re-isolated from the inoculated, diseased animal

Eukaryotes: fungi, protozoa and helminths Eukaryotic cells contain membrane-bound organelles, including nuclei, mitochondria and Golgi apparatus. Pathogenic eukaryotes are unicellular (e.g. fungi, protozoa) or complex multicellular organisms (e.g. nematodes, trematodes and cestodes, p.

288). and motile bacteria are equipped with flagella. Although many prokaryotes are capable of independent existence, some (e.g. Chlamydia trachomatis, Coxiella burnetii) are obligate intracellular organisms. Bacteria that can grow in artificial culture media are classified and identified using a range of characteristics (Box 6.2); examples are shown in Figures 6.3 and 6.4. Fig. 6.2 A generic virus life cycle. Life cycle components common to most viruses are host cell attachment and penetration, virus uncoating, nucleic acid and protein synthesis, virus assembly and release. Virus release is achieved either by budding, as illustrated, or by lysis of the cell membrane. Life cycles vary between viruses. Host cell 2 Penetration Receptor-mediated endocytosis or, in some enveloped viruses, membrane fusion (shown here)

Uncoating Nucleic acid is liberated from the phagosome (if endocytosed) and/or capsid by complex enzymatic and/or receptor-mediated processes Interaction between host receptor molecule and virus ligand (determines host-specificity of the virus) Adsorption

Lipid envelope Capsid Nucleic acid Virus Assembly 5 Assembly of virus components is mediated by host and/or viral enzymes Release 6 Complete virus particles are released by budding of host cell membrane (shown here) or disintegration of host cell

Synthesis Nucleic acid and protein synthesis is mediated by host and/or viral enzymes. This takes place in nucleus or cytoplasm, depending on the specific virus Gram stain reaction (see Fig. 6.3) • Gram-positive (thick peptidoglycan layer), Gram-negative (thin peptidoglycan) or unstainable Microscopic morphology • Cocci (round cells) or bacilli (elongated cells) • Presence or absence of capsule Cell association • Association in clusters, chains or pairs Colonial characteristics • Colony size, shape or colour • Effect on culture media (e.g. β-haemolysis of blood agar in haemolytic streptococci; see Fig. 6.4) Atmospheric requirements • Strictly aerobic (requires O2), strictly anaerobic (requires absence of O2), facultatively aerobic (grows with or without O2) or microaerophilic (requires reduced O2) Biochemical reactions • Expression of enzymes (oxidase, catalase, coagulase) • Ability to ferment or hydrolyse various biochemical substrates Motility • Motile or non-motile Antibiotic susceptibility • Identifies organisms with invariable susceptibility (e.g. to optochin in Streptococcus pneumoniae or metronidazole in obligate anaerobes) Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF-MS) • A rapid technique that identifies bacteria and some fungi from their specific molecular composition Sequencing bacterial 16s ribosomal RNA gene • A highly specific test for identification of organisms in pure culture and in samples from normally sterile sites Whole-genome sequencing • Although not yet in routine use, whole-genome sequencing (WGS) offers the potential to provide rapid and simultaneous identification, sensitivity testing and typing of organisms from pure culture and/or directly from clinical samples. As such, WGS is likely to replace many of the technologies described above over the next few years (p. 58) 6.2 How bacteria are identified

102 • PRINCIPLES OF INFECTIOUS DISEASE Fig. 6.3 Flow chart for bacterial identification, including Gram film appearances on light microscopy (×100). (MALDI-TOF-MS = matrix-assisted laser desorption/ionisation time-of-flight mass spectroscopy) Gram-positive bacilli Colony morphology, growth characteristics (e.g. growth in anaerobic atmosphere), Gram stain appearance, MALDI-TOF-MS identification Colony morphology, growth characteristics, oxidase reaction, sugar fermentation/MALDI-TOF-MS identification Colony morphology, growth characteristics, lactose fermentation, oxidase reaction, MALDI-TOF-MS identification Colony morphology (e.g. haemolysis),

Gram stain appearance, agglutination reactions, coagulase test, catalase Examples Actinomycetes Arcanobacterium haemolyticum Bacillus spp. Corynebacterium diphtheriae Lactobacillus spp. Listeria monocytogenes Nocardia spp. Clostridium spp. or Examples Neisseria meningitidis Neisseria gonorrhoeae Moraxella catarrhalis Examples Escherichia coli Klebsiella pneumoniae Proteus spp. Enterobacter spp. Serratia spp. Salmonella spp. Shigella spp. Yersinia spp. Vibrio spp. Pseudomonas aeruginosa Gram-positive cocci–clusters Examples Staphylococcus aureus Coagulase-negative staphylococci Gram-negative cocci Gram stain Gram-negative bacilli Gram-positive cocci Gram-positive cocci–chains Examples Oral streptococci Streptococcus pneumoniae (often pairs) Beta-haemolytic streptococci Enterococci (short chains) Fig. 6.4 Beta-haemolytic streptococci (A) and alpha-haemolytic streptococci (B) spread on each half of a blood agar plate (backlit). This image is half life size. ×0.5. Beta-haemolysis renders the agar transparent around the colonies (A) and alpha-haemolysis imparts a green tinge to the agar (B). B A Fungi exist as either moulds (filamentous fungi) or yeasts. Dimorphic fungi exist in either form, depending on environmental conditions (see Fig. 11.59, p. 300). The fungal plasma membrane differs from the human cell membrane in that it contains the sterol, ergosterol. Fungi have a cell wall made up of polysaccharides, chitin and mannoproteins. In most fungi, the main structural component of the cell wall is β-1,3-D-glucan, a glucose polymer. These differences from mammalian cells are important because they offer useful therapeutic targets. Protozoa and helminths are often referred to as parasites. Many parasites have complex multi-stage life cycles, which involve animal and/or plant hosts in addition to humans. Prions Although prions are transmissible and have some of the characteristics of infectious agents, they are not microorganisms and are not diagnosed in microbiology laboratories. Prions are covered on page 250. Normal microbial flora The human body is colonised by large numbers of microorganisms (collectively termed the human microbiota). These colonising

Fig. 6.5 Human non-sterile sites and normal flora in health. Pharynx Haemophilus spp. Moraxella catarrhalis Neisseria spp. (including N. meningitidis) Staph. aureus Strep. pneumoniae Strep. pyogenes (group A) Oral streptococci (α-haemolytic) Oral cavity Oral streptococci (α-haemolytic) Anaerobic Gram-positive bacilli (including Actinomyces spp.) Anaerobic Gram-negative bacilli Prevotella spp. Fusobacterium spp. Candida spp. Small bowel Distally, progressively increasing numbers of large bowel bacteria Candida spp. Large bowel Enterobacteriaceae Escherichia coli Klebsiella spp. Enterobacter spp. Proteus spp. Enterococci E. faecalis E. faecium Streptococcus anginosus group Strep. anginosus Strep. intermedius Strep. constellatus Anaerobic Gram-positive bacilli Clostridium spp. Anaerobic Gram-negative bacilli Bacteroides spp. Prevotella spp. Candida spp. Scalp As for skin Nares Staph. aureus Coagulase-negative staphylococci Skin Coagulase-negative staphylococci Staph. aureus Corynebacterium spp. Propionibacterium spp. Malassezia spp. Hands Resident: as for skin Transient: skin flora (including meticillin-resistant and other Staph. aureus), bowel flora (including Clostridium difficile, Candida spp. and Enterobacteriaceae) Vagina Lactobacillus spp. Staph. aureus Candida spp. Enterobacteriaceae Strep. agalactiae (group B) Perineum As for skin As for large bowel bacteria, also referred to as the ‘normal flora’, are able to survive and replicate on skin and mucosal surfaces. The gastrointestinal tract and the mouth are the two most heavily colonised sites in the body and their microbiota are distinct, in both composition and function. Knowledge of non-sterile body sites and their normal flora is required to inform microbiological sampling strategies and interpret culture results (Fig. 6.5). The microbiome

is the total burden of microorganisms, their genes and their environmental interactions, and is now recognised to have a profound influence over human health and disease. Maintenance of the normal flora is beneficial to health. For example, lower gastrointestinal tract bacteria synthesise and excrete vitamins (e.g. vitamins K and B12); colonisation with normal flora confers ‘colonisation resistance’ to infection with pathogenic organisms by altering the local environment (e.g. lowering pH), producing antibacterial agents (e.g. bacteriocins (small antimicrobial peptides/proteins), fatty acids and metabolic waste products), and inducing host antibodies that cross-react with pathogenic organisms. Conversely, normally sterile body sites must be kept sterile. The mucociliary escalator transports environmental material deposited in the respiratory tract to the nasopharynx. The urethral sphincter prevents flow from the non-sterile urethra to the sterile bladder. Physical barriers, including the skin, lining of the gastrointestinal tract and other mucous membranes, maintain sterility of the submucosal tissues, blood stream and peritoneal and pleural cavities, for example. The normal flora contribute to endogenous disease mainly by translocation to a sterile site but excessive growth at the ‘normal’ site (overgrowth) can also cause disease. Overgrowth is exemplified by dental caries, vaginal thrush and ‘blind loop’ syndrome (p. 808). Translocation results from spread along a surface or penetration though a colonised surface, e.g. urinary tract infection caused by perineal/enteric flora, and surgical site infections, particularly of prosthetic materials, caused by skin flora such as staphylococci. Normal flora also contribute to disease by cross-infection, in which organisms that are colonising one individual cause disease when transferred to another, more susceptible, individual. The importance of limiting perturbations of the microbiota by antimicrobial therapy is increasingly recognised. Probiotics are microbes or mixtures of microbes that are given to a patient to prevent or treat infection and are intended to restore a beneficial profile of microbiota. Although probiotics have been used in a number of settings, whether they have demonstrable clinical benefits remains a subject of debate.

104 • PRINCIPLES OF INFECTIOUS DISEASE Histoplasma capsulatum), are able to survive in intracellular environments, including after phagocytosis by macrophages. Pathogenic bacteria express different genes, depending on environmental stress (pH, iron starvation, O2 starvation etc.) and anatomical location. Genetic diversity enhances the pathogenic capacity of bacteria. Some virulence factor genes are found on plasmids or in phages and are exchanged between different strains or species. The ability to acquire genes from the gene pool of all strains of the species (the ‘bacterial supragenome’) increases diversity and the potential for pathogenicity. Viruses exploit their rapid reproduction and potential to exchange nucleic acid with host cells to enhance diversity. Once a strain acquires a particularly effective combination of virulence genes, it may become an epidemic strain, accounting for a large subset of infections in a particular region. This phenomenon accounts for influenza pandemics (see Box 6.10). The host response Innate and adaptive immune and inflammatory responses, which humans use to control the normal flora and respond to pathogens, are reviewed in Chapter 4. Pathogenesis of infectious disease The harmful manifestations of infection are determined by a combination of the virulence of the organism and the host response to infection. Despite the obvious benefits of an intact host response, an excessive response is undesirable. Cytokines and antimicrobial factors contribute to tissue injury at the site of infection, and an excessive inflammatory response may lead to hypotension and organ dysfunction (p. 196). The contribution of the immune response to disease manifestations is exemplified by the immune reconstitution inflammatory syndrome (IRIS). This is seen, for example, in human immunodeficiency virus (HIV) infection, post-transplantation neutropenia or tuberculosis (which causes suppression of T-cell function): there is a paradoxical worsening of the clinical

condition as the immune dysfunction is corrected, caused by an exuberant but dysregulated inflammatory response. The febrile response Thermoregulation is altered in infectious disease, which may cause both hyperthermia (fever) and hypothermia. Fever is mediated mainly by 'pyrogenic cytokines' (e.g. interleukins IL-1 and IL-6, and tumour necrosis factor alpha (TNF-α)), which are released in response to various immunological stimuli including activation of pattern recognition receptors (PRRs) by microbial pyrogens (e.g. lipopolysaccharide) and factors released by injured cells. Their ultimate effect is to induce the synthesis of prostaglandin E2, which binds to specific receptors in the preoptic nucleus of the hypothalamus (thermoregulatory centre), causing the core temperature to rise. Rigors are a clinical symptom (or sign if they are witnessed) characterised by feeling very cold ('chills') and uncontrollable shivering, usually followed by fever and sweating. Rigors occur when the thermoregulatory centre attempts to correct a core temperature to a higher level by stimulating skeletal muscle activity and shaking. There are data to support the hypothesis that raised body temperature interferes with the replication and/or virulence of pathogens. The mechanisms and possible protective role of infection-driven hypothermia, however, are poorly understood, and require further study. Host–pathogen interactions 'Pathogenicity' is the capability of an organism to cause disease and 'virulence' is the extent to which a pathogen is able to cause disease. Pathogens produce proteins and other factors, termed virulence factors, which contribute to disease. • Primary pathogens cause disease in a proportion of individuals to whom they are exposed, regardless of the host's immunological status. • Opportunistic pathogens cause disease only in individuals whose host defences are compromised, e.g. by an intravascular catheter, or when the immune system is compromised, by genetic susceptibility or immunosuppressive therapy. Characteristics of successful pathogens Successful pathogens have a number of attributes. They compete with host cells and colonising flora by various methods, including sequestration of nutrients and production of bacteriocins. Motility enables pathogens to reach their site of infection, often sterile sites that colonising bacteria do not reach, such as the distal airway. Many microorganisms, including viruses, use 'adhesins' to attach to host cells initially. Some pathogens can invade through tissues. Many bacterial and fungal infections form 'biofilms'. After initial adhesion to a host surface, bacteria multiply in biofilms to form complex three-dimensional structures surrounded by a matrix of host and bacterial products that afford protection to the colony and limit the effectiveness of antimicrobials. Biofilms forming on man-made medical devices such as vascular catheters or grafts can be particularly difficult to treat. Pathogens may produce toxins, microbial molecules that cause adverse effects on host cells, either at the site of infection, or remotely following carriage through the blood stream. Endotoxin is the lipid component of Gram-negative bacterial outer membrane lipopolysaccharide. It is released when bacterial cells are damaged and has generalised inflammatory effects. Exotoxins are proteins released by living bacteria, which often have specific effects on target organs (Box 6.3). Intracellular pathogens, including viruses, bacteria (e.g. Salmonella spp., Listeria monocytogenes and Mycobacterium tuberculosis), parasites (e.g. Leishmania spp.) and fungi (e.g. 6.3 Exotoxin-mediated bacterial diseases Disease Organism Antibiotic-associated diarrhoea/ pseudomembranous colitis Clostridium difficile (p. 230) Botulism Clostridium botulinum (p. 1126) Cholera Vibrio cholerae (p. 264) Diphtheria Corynebacterium diphtheriae (p. 265) Haemolytic uraemic syndrome Enterohaemorrhagic Escherichia coli (E. coli O157 and other strains) (p. 263) Necrotising pneumonia Staphylococcus aureus (p. 250) Tetanus Clostridium tetani (p. 1125) Toxic shock syndrome Staphylococcus aureus (p. 252) Streptococcus pyogenes (p. 253)

organism and its background. Examples include Gram staining of bacteria and Ziehl–Neelsen or auramine staining of acid- and alcohol-fast bacilli (AAFB) in tuberculosis (the latter requires an ultraviolet light source). In histopathological examination of tissue samples, multiple stains are used to demonstrate not only the presence of microorganisms but also features of disease pathology. • Dark field microscopy (in which light is scattered to make organisms appear bright on a dark background) is used, for example, to examine genital chancre fluid in suspected syphilis. • Electron microscopy may be used to examine stool and vesicle fluid to detect enteric and herpesviruses, respectively, but its use has largely been supplanted by nucleic acid detection (see below). • Flow cytometry can be used to analyse liquid samples (e.g. urine) for the presence of particles based on properties such as size, impedance and light scatter. This technique can detect bacteria but may misidentify other particles as bacteria too. Investigation of infection The aims of investigating a patient with suspected infection are to confirm the presence of infection, identify the specific pathogen(s) and identify its susceptibility to specific antimicrobial agents in order to optimise therapy. The presence of infection may be suggested by identifying proteins that are produced in response to pathogens as part of the innate immune and acute phase responses (p. 70). Pathogens may be detected directly (e.g. by culturing a normally sterile body site) or their presence may be inferred by identifying the host response to the organism, (‘indirect detection’, Box 6.4). Careful sampling increases the likelihood of diagnosis (Box 6.5). Culture results must be interpreted in the context of the normal flora at the sampled site (see Fig. 6.5). The extent to which a microbiological test result supports or excludes a particular diagnosis depends on its statistical performance (e.g. sensitivity, specificity, positive and negative predictive value, p. 4). Sensitivity and specificity vary according to the time between infection and testing, and positive and negative predictive values depend on the prevalence of the condition in the test population. The complexity of test interpretation is illustrated in Figure 6.8 below, which shows the ‘windows of opportunity’ afforded by various testing methods. Given this complexity, effective communication between the clinician and the microbiologist is vital to ensure accurate test interpretation. Direct detection of pathogens Some direct detection methods provide rapid results and enable detection of organisms that cannot be grown easily on artificial culture media, such as Chlamydia spp.; they can also provide information on antimicrobial sensitivity, e.g. Mycobacterium tuberculosis. Detection of whole organisms Whole organisms are detected by examination of biological fluids or tissue using a microscope. • Bright field microscopy (in which the test sample is interposed between the light source and the objective lens) uses stains to enhance visual contrast between the 6.5 How to provide samples for microbiological sampling Communicate with the laboratory • Discuss samples that require processing urgently or that may contain hazardous or unusual pathogens with laboratory staff before collection • Communication is key to optimising microbiological diagnosis. If there is doubt about any aspect of sampling, it is far better to discuss it with laboratory staff beforehand than to risk diagnostic delay by inappropriate sampling or sample handling Take samples based on a clinical diagnosis • Sampling in the absence of clinical evidence of infection is rarely appropriate (e.g. collecting urine, or sputum for culture) Use the correct container • Certain tests (e.g. nucleic acid and antigen detection tests) require proprietary sample collection equipment Follow sample collection procedures • Failure to follow sample collection instructions precisely can result in false-positive (e.g. contamination of blood culture samples) or false-negative (e.g. collection of insufficient blood for culture) results Label sample and request form correctly • Label sample containers and request forms according to local policies, with demographic identifiers, specimen type and time/date collected • Include clinical details on request forms • Identify samples carrying a high risk of infection (e.g. blood liable to contain a blood-borne virus)

with a hazard label Use appropriate packaging • Close sample containers tightly and package securely (usually in sealed plastic bags) • Attach request forms to samples but not in the same compartment (to avoid contamination, should leakage occur) Manage storage and transport • Transport samples to the microbiology laboratory quickly • If pre-transport storage is required, conditions (e.g. refrigeration, incubation, storage at room temperature) vary with sample type • Notify the receiving laboratory prior to arrival of unusual or urgent samples, to ensure timely processing 6.4 Tests used to diagnose infection Non-specific markers of inflammation/infection • e.g. White cell count in blood sample (WCC), plasma C-reactive protein (CRP), procalcitonin, serum lactate, cell counts in urine or cerebrospinal fluid (CSF), CSF protein and glucose Direct detection of organisms or organism components • Microscopy • Detection of organism components (e.g. antigen, toxin) • Nucleic acid amplification (e.g. polymerase chain reaction) Culture of organisms • ± Antimicrobial susceptibility testing Tests of the host's specific immune response • Antibody detection • Interferon-gamma release assays (IGRA)

106 • PRINCIPLES OF INFECTIOUS DISEASE even in rapid-culture systems. Certain organisms, such as Mycobacterium leprae and Tropheryma whipplei, cannot be cultivated on artificial media, and others (e.g. Chlamydia spp. and viruses) grow only in culture systems, which are slow and labour-intensive. Blood culture The terms 'bacteraemia' and 'fungaemia' describe the presence of bacteria and fungi in the blood. 'Blood-stream infection' (p. 225) is the association of bacteraemia/fungaemia with clinical evidence of infection. The presence of bacteraemia/fungaemia can be determined by inoculating a liquid culture medium with freshly drawn blood, which is then incubated in a system that monitors it constantly for growth of microorganisms (e.g. by detecting products of microbial respiration using fluorescence; Fig. 6.6). If growth is detected, organisms are identified and sensitivity testing is performed. Traditionally, identification has been achieved by Gram stain appearance and biochemical reactions. However, matrix-assisted laser desorption/ionisation time-of-flight mass spectroscopy (MALDI-TOF-MS; see Box 6.2) is being used increasingly to identify organisms. MALDI-TOF-MS produces a profile of proteins of different sizes from the target microorganism and uses databases of such profiles to identify the organism (Fig. 6.7). It is rapid and accurate. Taking multiple blood samples for culture at different times allows differentiation of transient (one or two positive samples) and persistent (majority are positive) bacteraemia. This can be clinically important in the identification of the source of infection (p. 530). Indirect detection of pathogens Tests may be used to detect the host's immune (antibody) response to a specific microorganism, and can enable the diagnosis of infection with organisms that are difficult to detect by other methods or are no longer present in the host. The term 'serology' describes tests carried out on serum and includes both antigen (direct) and antibody (indirect) detection. Antibody detection Organism-specific antibody detection is applied mainly to blood (Fig. 6.8). Results are typically expressed as titres: that is, the reciprocal of the highest dilution of the serum at which antibody is detectable (for example, detection at serum dilution of 1 : 64 gives a titre of 64). 'Seroconversion' is defined as either a change from negative to positive detection or a fourfold rise in titre between acute and convalescent serum samples. An acute sample is usually taken during the first week of disease and the convalescent sample 2–4 weeks later. Earlier diagnosis can be achieved by detection of immunoglobulin M (IgM) antibodies, which are produced early in infection (p. 68). A limitation of these tests is that antibody production requires a fully functional host immune system, so there may be false-negative results in immunocompromised patients. Also, other than in chronic infections and with IgM detection, antibody tests usually provide a retrospective diagnosis. Antibody detection methods are described

below (antigen detection methods are also described here as they share similar methodology). Enzyme-linked immunosorbent assay The principles of the enzyme-linked immunosorbent assay (ELISA, EIA) are illustrated in Figure 6.9. These assays rely on linking Detection of components of organisms Components of microorganisms detected for diagnostic purposes include nucleic acids, cell wall molecules, toxins and other antigens. Commonly used examples include Legionella pneumophila serogroup 1 antigen in urine and cryptococcal polysaccharide antigen in cerebrospinal fluid (CSF). Most antigen detection methods are based on in vitro binding of specific antigen/antibody and are described below. Other methods may be used, such as tissue culture cytotoxicity assay for C. difficile toxin. In toxin-mediated disease, detection of toxin may be of greater relevance than identification of the organism itself (e.g. stool C. difficile toxin). Nucleic acid amplification tests In a nucleic acid amplification test (NAAT), specific sequences of microbial DNA and RNA are identified using a nucleic acid primer that is amplified exponentially by enzymes to generate multiple copies of a target nucleotide sequence. The most commonly used amplification method is the polymerase chain reaction (PCR; see Fig. 3.11, p. 53). Reverse transcription (RT) PCR is used to detect RNA from RNA viruses (e.g. hepatitis C virus and HIV-1). The use of fluorescent labels in the reaction enables ‘real-time’ detection of amplified DNA; quantification is based on the principle that the time taken to reach the detection threshold is proportional to the initial number of copies of the target nucleic acid sequence. In multiplex PCR, multiple primer pairs are used to enable detection of several different organisms at once. Determination of nucleotide sequences in a target gene(s) can be used to assign microorganisms to specific strains, which may be relevant to treatment and/or prognosis (e.g. in hepatitis C infection, p. 877). Genes that are relevant to pathogenicity (such as toxin genes) or antimicrobial resistance can also be detected; for example, the mecA gene is used to screen for MRSA. NAATs are the most sensitive direct detection methods and are also relatively rapid. They are used widely in virology, where the possibility of false-positive results from colonising or contaminating organisms is remote, and are applied to blood, respiratory samples, stool and urine. In bacteriology, PCR is used to examine CSF, blood, tissue and genital samples, and multiplex PCR is being developed for use in faeces. PCR is particularly helpful for microorganisms that cannot be readily cultured, e.g. Tropheryma whipplei, and is being used increasingly in mycology and parasitology. Culture Microorganisms may be both detected and further characterised by culture from clinical samples (e.g. tissue, swabs and body fluids). • Ex vivo culture (tissue or cell culture) was widely used in the isolation of viruses but has been largely supplanted by NAAT. • In vitro culture (in artificial culture media) of bacteria and fungi is used to confirm the presence of pathogens, allow identification, test antimicrobial susceptibility and subtype the organism for epidemiological purposes. Culture has its limitations: results are not immediate, even for organisms that are easy to grow, and negative cultures rarely exclude infection. Organisms such as Mycobacterium tuberculosis are slow-growing, typically taking at least 2 weeks,

Immunofluorescence assays Indirect immunofluorescence assays (IFAs) detect antibodies by incubating a serum sample with immobilised antigen (e.g. cells known to be infected with virus on a glass slide); any virus-specific antibody present in the serum binds to antigen and is then detected using a fluorescent-labelled anti-human immunoglobulin (‘secondary’ antibody). Fluorescence is visualised using a microscope. This method can also detect organisms in clinical samples (usually tissue or centrifuged cells) using a specific antibody in place of immobilised

antigen to achieve capture. Complement fixation test In a complement fixation test (CFT), patient serum is heat-treated to inactivate complement and mixed with the test antigen. Any specific antibody in the serum will complex with the antigen. Complement is then added to the reaction. If antigen–antibody an antibody with an enzyme that generates a colour change on exposure to a chromogenic substrate. Various configurations allow detection of antigens or specific subclasses of immunoglobulin (e.g. IgG, IgM, IgA). ELISA may also be adapted to detect PCR products, using immobilised oligonucleotide hybridisation probes and various detection systems. Immunoblot (Western blot) Microbial proteins are separated according to molecular weight by polyacrylamide gel electrophoresis (PAGE) and transferred (blotted) on to a nitrocellulose membrane, which is incubated with patient serum. Binding of specific antibody is detected with an enzyme–anti-immunoglobulin conjugate similar to that used in ELISA, and specificity is confirmed by its location on the membrane. Immunoblotting is a highly specific test, which may be used to confirm the results of less specific tests such as ELISA (e.g. in Lyme disease, p. 255). Fig. 6.6 An overview of the processing of blood cultures. *In laboratories equipped with MALDI-TOF-MS (p. 106), rapid definitive organism identification may be achieved at stage 6 and/or stage 8. Department of Microbiology 1 Patient sampling Contamination minimised by aseptic technique. Maximise sensitivity by sampling correct volume 2 Sample handling Follow local instructions for safety, labelling, and numbers of samples and bottles required 3 Specimen transport Transport samples to laboratory as quickly as possible. Follow manufacturer's instructions for the blood culture system used if temporary storage is required 4 Incubation Incubate at 35–37°C for 5–7 days. Microbial growth is usually detected by constant automatic monitoring of CO2. If no growth, specimen is negative and discarded 5 Growth detection Time to positivity (TTP) is usually 12–24 hrs in significant bacteraemia, but may be shorter in overwhelming sepsis or longer with fastidious organisms (e.g. Brucella spp.) 6 Preliminary results* A Gram film of the blood culture medium is examined and results are communicated immediately to the clinician to guide antibiotic therapy 7 Incubation A small amount of the medium is incubated on a range of culture media. Preliminary susceptibility testing may be carried out 8 Culture results* Preliminary susceptibility results are communicated to the clinician 9 Definitive results Further overnight incubation is often required for definitive identification of organisms (by biochemical testing) and additional susceptibility testing; identification by MALDI-TOF MS (Fig. 6.7) is more rapid Overnight incubation required Urgent communication required 10 Reporting A final summary is released when all testing is complete. For clinical care, communication of interim results (Gram film, preliminary identification and susceptibility) is usually more important than the final report. Effective clinical–laboratory communication is vital

 For example, in the Weil–Felix test, if a patient's serum contains antibodies to rickettsial species they cause agglutination when Proteus spp. surface (O) antigens are added because the antibodies cross-react with the Proteus antigens. The test lacks sensitivity and specificity but is still used to diagnose rickettsial infection in resource-limited settings. The Widal test reaction uses a suspension of Salmonella typhi and S. paratyphi 'A' and 'B', treated to retain only 'O' and 'H' antigens. These antigens are kept to detect corresponding antibodies in serum from a patient suspected of having typhoid fever. The test is not specific but is still used in some parts of the world. • In indirect (passive) agglutination, specific antigen is attached to the surface of carrier particles, which agglutinate when incubated with patient samples that contain specific antibodies. • In reverse passive agglutination (an antigen detection test), the carrier particle is coated with antibody rather than antigen. Other tests Immunodiffusion involves

antibodies and antigen migrating through gels, with or without the assistance of electrophoresis, and forming insoluble complexes where they meet. The complexes are seen on staining as ‘precipitin bands’. Immunodiffusion is used in the diagnosis of dimorphic fungi (p. 300) and some forms of aspergillosis (p. 596). Immunochromatography is used to detect antigen. The system consists of a porous test strip (e.g. a nitrocellulose membrane), at one end of which there is target-specific antibody, complexed with coloured microparticles. Further specific antibody is immobilised in a transverse narrow line some distance along the strip. Test material (e.g. blood or urine) is added to the antibody–particle complexes, which then migrate along the strip by capillary action. If these are complexed with antigen, they will be immobilised by the specific antibody and visualised as a transverse line across the strip. If the test is negative, the antibody–particle complexes will bind to a line of immobilised anti-immunoglobulin antibody placed further along the strip, which acts as a negative control. Immunochromatographic tests are rapid and relatively cheap to perform, and are appropriate for point-of-care testing, e.g. in HIV 1 and malaria (p. 276). complexes are present, the complement will be ‘fixed’ (consumed). Sheep erythrocytes, coated with an anti-erythrocyte antibody, are added. The degree of erythrocyte lysis reflects the remaining complement and is inversely proportional to the quantity of the specific antigen–antibody complex present. Agglutination tests When antigens are present on the surface of particles (e.g. cells, latex particles or microorganisms) and cross-linked with antibodies, visible clumping (or ‘agglutination’) occurs. • In direct agglutination, patient serum is added to a suspension of organisms that express the test antigen. Fig. 6.7 The workings of matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS). Adapted from Sobin K, Hameer D, Ruparel T. Digital genotyping using molecular affinity and mass spectrometry. Nature Rev Genet 2003; 4:1001–1008. Lighter m/z Mass spectrum Detector Flight tube Laser Sample plate Voltage grid Intensity Heavier Separation region (electric field-free) Fig. 6.8 Detection of antigen, nucleic acid and antibody in infectious disease. The acute sample is usually taken during the first week of illness, and the convalescent sample 2–4 weeks later. Detection limits and duration of detectability vary between tests and diseases, although in most diseases immunoglobulin M (IgM) is detectable within the first 1–2 weeks. Acute sample Nucleic acid (NA) detection Antigen (Ag) detection IgM NA Ag IgG Limit of detection Antibody detection: IgM Antibody detection: IgG (seroconversion) Antibody detection: IgG (fourfold rise in titre) Convalescent sample Windows of diagnostic opportunity Serum levels

Antibody-independent specific immunological tests The interferon-gamma release assay (IGRA) is being used increasingly to diagnose latent tuberculosis infection (LTBI). The principle behind IGRA is discussed on page 594. IGRA cannot distinguish between latent and active tuberculosis infection and is therefore appropriate for use only in countries where the background incidence of tuberculosis is low. Antimicrobial susceptibility testing If growth of microorganisms in culture is inhibited by the addition of an antimicrobial agent, the organism is considered to be susceptible to that antimicrobial. Bacteriostatic agents cause reversible inhibition of growth and bactericidal agents cause cell death; the terms fungistatic/fungicidal are equivalent for antifungal agents, and virustatic/virucidal for antiviral agents. The lowest concentration of antimicrobial agent at which growth is inhibited is the minimum inhibitory concentration (MIC), and the lowest concentration that causes cell death is the minimum bactericidal concentration (MBC). If the MIC is less than or equal to a predetermined breakpoint threshold, the organism is considered susceptible, and if the MIC is greater than the breakpoint, it is resistant. Breakpoints are determined for each

antimicrobial agent from a combination of pharmacokinetic (p. 17) and clinical data. The relationship between in vitro antimicrobial susceptibility and clinical response is complex, as response also depends on immune status, pharmacokinetic variability (p. 17), comorbidities that may influence pharmacokinetics or pharmacodynamics, and antibiotic dosing, as well as MIC/MBC. Thus, although treating a patient according to the results of susceptibility testing increases the likelihood of recovery, it does not guarantee therapeutic success. Susceptibility testing is often carried out by disc diffusion (Fig. 6.10). Antibiotic-impregnated filter paper discs are placed on agar plates containing bacteria; antibiotic diffuses into the agar, resulting in a concentration gradient centred on the disc. Bacteria are unable to grow where the antibiotic concentration exceeds the MIC, which may therefore be inferred from the size of the zone of inhibition. The MIC is commonly measured in diagnostic laboratories using ‘diffusion strips’. Fig. 6.9 Antibody (Ab) and antigen (Ag) detection by enzyme-linked immunosorbent assay (ELISA). This can be configured in various ways. A Patient Ab binds to immobilised specific Ag and is detected by addition of anti-immunoglobulin–enzyme conjugate and chromogenic substrate. B Patient Ab binds to immobilised Ig subclass-specific Ab and is detected by addition of specific Ag, followed by antibody–enzyme conjugate and chromogenic substrate. C Patient Ab and antibody–enzyme conjugate bind to immobilised specific Ag. Magnitude of colour change reaction is inversely proportional to concentration of patient Ab. D Patient Ag binds to immobilised Ab and is detected by addition of antibody–enzyme conjugate and chromogenic substrate. In A, the conjugate Ab is specific for human immunoglobulin. In B–D, it is specific for Ag from the disease-causing organism. Antibody capture ELISA Patient Ab Ig subclass-specific Ab Ab specific to Ag from the disease-causing organism Specific Ag Chromogenic substrate Antibody–enzyme conjugate Competitive antibody detection ELISA Double antibody sandwich ELISA (for antigen detection) Antibody detection ELISA A B C D Fig. 6.10 Antimicrobial susceptibility testing by disc diffusion (panels 1-4) and minimum inhibitory concentration (MIC, panel 5).

1. The test organism is spread over the surface of an agar plate.
2. Antimicrobial-impregnated discs (A–F) are placed on the surface and the plate is incubated (e.g. overnight). 3–4. After incubation, zones of growth inhibition may be seen. The organism is considered susceptible if the diameter of the zone of inhibition exceeds a pre-determined threshold.
3. In a ‘diffusion strip’ test, the strip is impregnated with antimicrobial at a concentration gradient that decreases steadily from top to bottom. The system is designed so that the MIC value is the point at which the ellipse cuts a scale on the strip (arrow). 4, Kindly supplied by Charlotte Symes. Zone of inhibition Zone of inhibition

A B C D E F A B C D E F

 known and thought to have been controlled or eradicated, it is considered to be re-emerging. Many emerging diseases are caused by organisms that infect animals and have undergone adaptations that enable them to infect humans. This is exemplified by HIV-1, which is believed to have originated in higher primates in Africa. The geographical pattern of some recent emerging and re-emerging infections is shown in Figure 6.11. Reservoirs of infection The US Centers for Disease Control (CDC) define a reservoir of infection as any person, other living organism, environment or combination of these in which the infectious agent lives and replicates and on which the infectious agent is dependent for its survival. The

infectious agent is transmitted from this reservoir to a susceptible host. Human reservoirs Both colonised individuals and those with infection can act as reservoirs, e.g. with Staph. aureus (including MRSA), Strep. pyogenes and C. difficile. For infected humans to act as reservoirs, the infections caused must be long-lasting in at least a proportion of those affected, to enable onward transmission (e.g. tuberculosis, sexually transmitted infections). Humans are the only reservoir for some infections (e.g. measles). Animal reservoirs The World Health Organization (WHO) defines a zoonosis as ‘a disease or infection that is naturally transmissible from vertebrate animals to humans’. Infected animals may be asymptomatic. Zoonotic agents may be transmitted via any of the routes described below. Primary infection with zoonoses may be transmitted onward between humans, causing secondary disease (e.g. Q fever, brucellosis, Ebola). Environmental reservoirs Many infective pathogens are acquired from an environmental source. However, some of these are maintained in human or animal reservoirs, with the environment acting only as a conduit for infection. Epidemiology of infection The communicability of infectious disease means that, once a clinician has diagnosed an infectious disease, potential exposure of other patients must also be considered. The patient may require separation from other patients (‘isolation’), or an outbreak of disease may need to be investigated in the community (Ch. 5). The approach will be specific to the microorganism involved (Chs 11–13) but the principles are outlined below. Geographical and temporal patterns of infection Endemic disease Endemic disease has a constant presence within a given geographical area or population. The infectious agent may have a reservoir, vector or intermediate host that is geographically restricted, or may itself have restrictive environmental requirements (e.g. temperature range, humidity). The population affected may be geographically isolated or the disease may be limited to unvaccinated populations. Factors that alter geographical restriction include: • expansion of an animal reservoir (e.g. Lyme disease from reforestation) • vector escape (e.g. airport malaria) • extension of host range (e.g. schistosomiasis from dam construction) • human migration (e.g. carbapenemase-producing Klebsiella pneumoniae) • public health service breakdown (e.g. diphtheria in unvaccinated areas) • climate change (e.g. dengue virus and Rift Valley fever). Emerging and re-emerging disease An emerging infectious disease is one that has newly appeared in a population, or has been known for some time but is increasing in incidence or geographical range. If the disease was previously Fig. 6.11 Geographical locations of some infectious disease outbreaks, with examples of emerging and re-emerging diseases. (CPE = carbapenemase-producing Enterobacteriaceae; MDR-TB = multidrug-resistant tuberculosis; MERS-Co-V = Middle East respiratory syndrome coronavirus; XDR-TB = extensively drug-resistant tuberculosis) CPE Ebola virus disease Cholera Cholera Cholera Cryptococcus gattii Cryptococcus gattii Zika virus Zika virus Cyclospora Chikungunya virus Chikungunya virus XDR-TB MERS-Co-V Anthrax MDR-TB

and humans in MRSA. Fomites are inanimate objects such as door handles, water taps and ultrasound probes, which are particularly associated with health care-associated infection (HCAI). The likelihood of infection following transmission of a pathogen depends on organism factors (virulence, p. 104) and host susceptibility. The incubation period is the time between exposure and development of symptoms, and the period of infectivity is the period after exposure during which the patient is infectious to others. Knowledge of incubation periods and of periods of infectivity is important in controlling the spread of disease, although for many diseases these estimates are imprecise (Boxes 6.6 and 6.7). Deliberate release Deliberate release of pathogens with the

intention of causing disease is known as biological warfare or bioterrorism, depending on the scale and context. Deliberate release incidents have included a 750-person outbreak of Salmonella typhimurium caused by contamination of salads in 1984 (Oregon, USA) and 22 cases of anthrax (five fatal) from the mailing of finely powdered (weaponised) anthrax spores in 2001 (New Jersey, USA). Diseases with high potential for deliberate release include anthrax, plague, tularaemia, smallpox and botulism (through toxin release). Infection prevention and control Infection prevention and control (IPC) describes the measures applied to populations with the aim of breaking the chain of infection (see Fig. 6.1, p. 100). Health care-associated infection The risk of developing infection following admission to a health-care facility (health care-associated infection, HCAI) in Transmission of infection Communicable diseases may be transmitted by one or more of the following routes: • Respiratory route: inhalation. • Faecal–oral route: ingestion of material originating from faeces. • Sexually transmitted infections: direct contact between mucous membranes. • Blood-borne infections: direct inoculation of blood or body fluids. • Direct contact: very few organisms are capable of causing infection by direct contact with intact skin. Most infection by this route requires contact with damaged skin (e.g. surgical wound). • Via a vector or fomite: the vector/fomite bridges the gap between the infected host or reservoir and the uninfected host. Vectors are animate, and include mosquitoes in malaria, dengue and Zika virus infection, fleas in plague 6.7 Periods of infectivity in common childhood infectious diseases Disease Infectious period Chickenpox1 From 4 days before until 5 days after appearance of the rash (transmission before 48 hrs prior to the onset of rash is rare)4 Measles2 From 4 days before onset to 4 days after onset of the rash Mumps3 From 2–3 days before to 5 days after disease onset5 Rubella3 From 10 days before until 15 days after the onset of the rash, but most infectious during prodromal illness4 Scarlet fever1 Unknown6 Whooping cough1 Unknown6,7 1From Richardson M, Elliman D, Maguire H, et al. Pediatr Infect Dis J 2001; 20:380–388. 2Centers for Disease Control, USA; cdc.gov/measles/hcp/. 3Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas and Bennett's Principles and practice of infectious diseases, 8th edn. Philadelphia: Elsevier; 2015. 4–6Exclude from contact with non-immune and immunocompromised people for 5 days from 4onset of rash, 5onset of parotitis, or 6start of antibiotic treatment. 7Exclude for 3 weeks if untreated. Durations are approximate and vary between information sources, and these recommendations may differ from local or national guidance. 6.6 Incubation periods of important infections1 Infection Incubation period Short incubation periods Anthrax, cutaneous3 9 hrs to 2 weeks Anthrax, inhalational3 2 days2 Bacillary dysentery5 1–6 days Cholera3 2 hrs to 5 days Dengue haemorrhagic fever6 3–14 days Diphtheria6 1–10 days Gonorrhoea4 2–10 days Influenza5 1–3 days Meningococcaemia3 2–10 days Norovirus1 1–3 days SARS coronavirus3 2–7 days2 Scarlet fever5 2–4 days Intermediate incubation periods Amoebiasis6 1–4 weeks Brucellosis4 5–30 days Chickenpox5 11–20 days Lassa fever3 3–21 days Malaria3 10–15 days Measles5 6–19 days Mumps5 15–24 days Poliomyelitis6 3–35 days Psittacosis4 1–4 weeks Rubella5 15–20 days Typhoid5 5–31 days Whooping cough5 5–21 days Long incubation periods Hepatitis A5 3–7 weeks Hepatitis B4 6 weeks to 6 months Leishmaniasis, cutaneous6 Weeks to months Leishmaniasis, visceral6 Months to years Leprosy (Hansen's disease)3 5–20 years Rabies4 2–8 weeks2 Trypanosoma brucei gambiense infection6 Months to years Tuberculosis5 1–12 months 1Incubation periods are approximate and may differ from local or national guidance. 2Longer incubation periods have been reported. 3WHO. 4Health Protection Agency (now Health Protection England). 5Richardson M, Elliman D, Maguire H, et al. Pediatr Infect Dis J 2001; 20:380–388. 6Centers for Disease Control, USA. (SARS = severe acute respiratory syndrome)

112 • PRINCIPLES OF INFECTIOUS DISEASE Fig. 6.12 Commonly encountered health care-associated infections (HCAIs) and the factors that predispose to them. Temporary central venous catheter infection Staphylococcus aureus (incl. MRSA) Coagulase-negative staphylococci Coliforms Candida Prosthetic joint infection Coagulase-negative staphylococci Staphylococcus aureus Streptococci Coliforms Propionibacterium acnes Surgical site infection Staphylococcus aureus Beta-haemolytic streptococci Coliforms Anaerobes Cuffed/tunnelled central venous catheter infection Coagulase-negative staphylococci Staphylococcus aureus (incl. MRSA) Coliforms Candida Pseudomonas spp. Enterococcus spp. External ventricular drain and ventriculoperitoneal shunt infection Coagulase-negative staphylococci Staphylococcus aureus Diphtheroids Pseudomonas aeruginosa Peritoneal dialysis-related peritonitis Staphylococcus aureus Coagulase-negative staphylococci Coliforms Pseudomonas spp. Breast implant infection Staphylococcus aureus Coagulase-negative staphylococci the developed world is about 10%. Many nosocomial bacterial infections are caused by organisms that are resistant to numerous antibiotics (multi-resistant bacteria), including MRSA, extendedspectrum β-lactamases (ESBLs) and carbapenemase-producing Enterobacteriaceae (CPE), and glycopeptide-resistant enterococci (GRE). Other infections of particular concern in hospitals include C. difficile (p. 264) and norovirus (p. 249). Some examples are shown in Figure 6.12. IPC measures are described in Box 6.8. The most important is maintenance of good hand hygiene (Fig. 6.13). Hand (CPE = carbapenemase-producing Enterobacteriaceae; GRE = glycopeptide-resistant enterococci; MRSA = meticillin-resistant Staphylococcus aureus) Institutions • Handling, storage and disposal of clinical waste • Containment and safe removal of spilled blood and body fluids • Cleanliness of environment and medical equipment • Specialised ventilation (e.g. laminar flow, air filtration, controlled pressure gradients) • Sterilisation and disinfection of instruments and equipment • Food hygiene • Laundry management Health-care staff • Education • Hand hygiene, including hand-washing (see Fig. 6.13) • Sharps management and disposal • Use of personal protective equipment (masks, sterile and non-sterile gloves, gowns and aprons) • Screening health workers for disease (e.g. tuberculosis, hepatitis B virus, MRSA) • Immunisation and post-exposure prophylaxis Clinical practice • Antibiotic stewardship (p. 115) • Aseptic technique • Perioperative antimicrobial prophylaxis • Screening patients for colonisation or infection (e.g. MRSA, GRE, CPE) Response to infections • Surveillance to detect alert organism (see text) outbreaks and antimicrobial resistance • Antibiotic chemoprophylaxis in infectious disease contacts, if indicated (see Box 6.18) • Isolation (see Box 6.9) • Reservoir control • Vector control 6.8 Measures used in infection prevention and control (IPC)

Fig. 6.13 Hand-washing. Good hand hygiene, whether with soap/water or alcohol handrub, includes areas that are often missed, such as fingertips, web spaces, palmar creases and the backs of hands. Adapted from the ‘How to Handwash’ URL: who.int/gpsc/5may/How_To_Handwash_Poster.pdf Wash hands only when visibly soiled! Otherwise use handrub! Duration of the entire procedure: 40–60 sec.

Wet hands with water using elbow-operated or nontouch taps (if available) Apply enough soap to cover all hand surfaces Rub hands palm to palm

Right palm over left dorsum with interlaced fingers and vice versa Palm to palm with fingers interlaced Backs of fingers to opposing palms with fingers interlaced

Rotational rubbing of left thumb clasped in right palm and vice versa Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa Rinse hands with water

Dry thoroughly with a single-use towel If hand-operated taps have been used, use towel to turn off tap ...and your hands are clean decontamination (e.g. using alcohol gel or washing) is mandatory before and after every patient contact. Decontamination with alcohol gel is usually adequate but hand-washing (with hot water, liquid soap and complete drying) is required after any procedure that involves more than casual physical contact, or if hands are visibly soiled. In situations where the prevalence of C. difficile is high (e.g. a local outbreak), alcohol gel decontamination between patient contacts is inadequate as it does not kill C. difficile spores, and hands must be washed. Some infections necessitate additional measures to prevent cross-infection (Box 6.9). To minimise risk of infection, invasive procedures must be performed using strict aseptic technique. Airborne transmission Contact transmission Droplet transmission Precautions Negative pressure room with air exhausted externally or filtered N95 masks or personal respiratiors for staff; avoid using non-immune staff Private room preferred (otherwise, inter-patient spacing ≥ 1 m) Gloves and gown for staff in contact with patient or contaminated areas Private room preferred (otherwise, inter-patient spacing ≥ 1 m) Surgical masks for staff in close contact with patient Infections managed with these precautions Measles Tuberculosis, pulmonary or laryngeal, confirmed or suspected Enteroviral infections in young children (diapered or incontinent) Norovirus2 C. difficile infection Multidrug-resistant organisms (e.g. MRSA, ESBL, GRE, VRSA, penicillin-resistant Strep. pneumoniae)3 Parainfluenza in infants and young children Rotavirus RSV in infants, children and immunocompromised Viral conjunctivitis, acute Diphtheria, pharyngeal Haemophilus influenzae type B infection Herpes simplex virus, disseminated or severe Influenza Meningococcal infection Mumps Mycoplasma pneumoniae Parvovirus (erythrovirus) B19 (erythema infectiosum, fifth disease) Pertussis Plague, pneumonic/bubonic Rubella Strep. pyogenes (group A), pharyngeal Infections managed with multiple precautions Smallpox, monkeypox, VZV (chickenpox or disseminated disease)4 Adenovirus pneumonia SARS, viral haemorrhagic fever2 6.9 Types of isolation precaution1 1Recommendations based on 2007 CDC guideline for isolation precautions. May differ from local or national recommendations. 2Not a CDC recommendation. 3Subject to local risk assessment. 4Or in any immunocompromised patient until possibility of disseminated infection excluded. (ESBL = extended-spectrum β-lactamase; GRE = glycopeptide-resistant enterococci; MRSA = meticillin-resistant Staph. aureus; RSV = respiratory syncytial virus; SARS = severe acute respiratory syndrome; VRSA = vancomycin-resistant Staph. aureus; VZV = varicella zoster virus)

 6.10 Terminology in outbreaks of infection Term Definition Classification of related cases of infectious disease* Cluster An aggregation of cases of a disease that are closely grouped in time and place, and may or may not exceed the expected number Epidemic The occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time Outbreak Synonymous with epidemic. Alternatively, a localised, as opposed to generalised, epidemic Pandemic An epidemic occurring over a very wide area (several countries or continents) and usually affecting a large proportion of the population Classification of affected patients (cases) Index case The first case identified in an

outbreak Primary cases Cases acquired from a specific source of infection Secondary cases Cases acquired from primary cases Types of outbreak Common source outbreak Exposure to a common source of infection (e.g. water-cooling tower, medical staff member shedding MRSA). New primary cases will arise until the source is no longer present Point source outbreak Exposure to a single source of infection at a specific point in time (e.g. contaminated food at a party). Primary cases will develop disease synchronously Person-toperson spread Outbreak with both primary and secondary cases. May complicate point source or common source outbreak *Adapted from cdc.gov. (MRSA = meticillin-resistant Staphylococcus aureus) 6.11 Reasons for including an infectious disease on a regional/national list of reportable diseases* Reason for inclusion Examples Endemic/local disease with the potential to spread and/or cause outbreaks Influenza, Salmonella, tuberculosis Imported disease with the propensity to spread and/or cause outbreaks Typhoid, cholera (depending on local epidemiology) Evidence of a possible breakdown in health protection/public health functions Legionella, Cryptosporidium Evidence of a possible breakdown in food safety practices Botulism, verotoxigenic E. coli Evidence of a possible failure of a vaccination programme Measles, poliomyelitis, pertussis Disease with the potential to be a novel or increasing threat to human health SARS, MERS-CoV, multi-resistant bacteria Evidence of expansion of the range of a reservoir/vector Lyme disease, rabies, West Nile encephalitis Evidence of possible deliberate release Anthrax, tularaemia, plague, smallpox, botulism *Given the different geographical ranges of individual diseases and wide national variations in public health services, vaccination programmes and availability of resources, reporting regulations vary between regions, states and countries. Many diseases are reportable for more than one reason. (MERS-CoV = Middle East respiratory syndrome coronavirus; SARS = severe acute respiratory syndrome) Outbreaks of infection Descriptive terms are defined in Box 6.10. Confirmation of an infectious disease outbreak usually requires evidence from ‘typing’ that the causal organisms have identical phenotypic and/or genotypic characteristics. If this is found not to be the case, the term pseudo-outbreak is used. When an outbreak of infection is suspected, a case definition is agreed. The number of cases that meet the case definition is then assessed by case-finding, using methods ranging from administration of questionnaires to national reporting systems. Case-finding usually includes microbiological testing, at least in the early stages of an outbreak. Temporal changes in cases are noted in order to plot an outbreak curve, and demographic details are collected to identify possible sources of infection. A case–control study, in which recent activities (potential exposures) of affected ‘cases’ are compared to those of unaffected ‘controls’, may be undertaken to establish the outbreak source, and measures are taken to manage the outbreak and control its spread. Good communication between relevant personnel during and after the outbreak is important to inform practice in future outbreaks. Surveillance ensures that disease outbreaks are either prevented or identified early. In hospitals, staff are made aware of the isolation of alert organisms, which have the propensity to cause outbreaks, and alert conditions, which are likely to be caused by such organisms. Analogous systems are used nationally; many countries publish lists of organisms and diseases, which, if detected (or suspected), must be reported to public health authorities (reportable or notifiable diseases). Reasons for a disease to be classified as reportable are shown in Box 6.11. Immunisation Immunisation may be passive or active. Passive immunisation is achieved by administering antibodies targeting a specific pathogen. Antibodies are obtained from blood, so confer some of the risks associated with blood products (p. 933). The protection afforded by passive immunisation is immediate but of short duration (a few weeks or months); it is used to prevent or attenuate infection before or after exposure (Box 6.12). Vaccination Active immunisation is achieved by vaccination with whole organisms or organism components (Box

6.13). Types of vaccine Whole-cell vaccines consist of live or inactivated (killed) microorganisms. Component vaccines contain only extracted or synthesised components of microorganisms (e.g. polysaccharides or proteins). Live vaccines contain organisms with attenuated (reduced) virulence, which cause only mild symptoms but induce T-lymphocyte and humoral responses (p. 68) and are therefore more immunogenic than inactivated whole-cell vaccines. The use of live vaccines in immunocompromised individuals is not generally recommended, but they may be used by specialists following a risk/benefit assessment. Component vaccines consisting only of polysaccharides, such as the pneumococcal polysaccharide vaccine (PPV), are poor activators of T lymphocytes and produce a short-lived antibody response without long-lasting memory. Conjugation of polysaccharide to a protein, as in the Haemophilus influenzae type B (Hib) vaccine and the protein conjugate pneumococcal

vaccinated to curtail further spread. Vaccination is aimed mainly at preventing infectious disease. However, vaccination against human papillomavirus (HPV) was introduced to prevent cervical and other cancers that complicate HPV infection. Vaccination guidelines for individuals are shown in Box 6.14. Vaccination becomes successful once the number of susceptible hosts in a population falls below the level required to sustain continued transmission of the target organism (herd immunity). Naturally acquired smallpox was declared to have been eradicated worldwide in 1980 through mass vaccination. In 1988, the WHO resolved to eradicate poliomyelitis by vaccination; the number of cases worldwide has since fallen from approximately 350 000 per annum to 74 in 2015. Recommended vaccination schedules vary between countries. In addition to standard vaccination schedules, catch-up schedules are specified for individuals who join vaccination programmes later than the recommended age. Antimicrobial stewardship Antimicrobial stewardship (AMS) refers to the systems and processes applied to a population to optimise the use of antimicrobial agents. The populations referred to here may be a nation, region, hospital, or a unit within a health-care organisation (e.g. ward or clinic). AMS aims to improve patient outcomes and reduce antimicrobial resistance (AMR). IPC and AMS complement each other (Fig. 6.14). Elements of AMS include treatment guidelines, antimicrobial formularies and ward rounds by infection specialists. vaccine (PCV), activates T lymphocytes, which results in a sustained response and immunological memory. Toxoids are bacterial toxins that have been modified to reduce toxicity but maintain antigenicity. Vaccine response can be improved by co-administration with mildly pro-inflammatory adjuvants, such as aluminium hydroxide. Use of vaccines Vaccination may be applied to entire populations or to subpopulations at specific risk through travel, occupation or other activities. In ring vaccination, the population immediately surrounding a case or outbreak of infectious disease is *Active immunisation is preferred if contact is with a patient who is within 1 week of onset of jaundice. 6.12 Indications for post-exposure prophylaxis with immunoglobulins Human normal immunoglobulin (pooled immunoglobulin)* • *Hepatitis A (unvaccinated contacts*) • Measles (exposed child with heart or lung disease) Human specific immunoglobulin • Hepatitis B (sexual partners, inoculation injuries, infants born to infected mothers) • Tetanus (high-risk wounds or incomplete or unknown immunisation status) • Rabies • Chickenpox (immunosuppressed children and adults, pregnant women) 6.13 Vaccines in current clinical use Live attenuated vaccines • Measles, mumps, rubella (MMR) • Oral poliomyelitis (OPV, not used in UK) • Rotavirus • Tuberculosis (bacille Calmette–Guérin, BCG) • Typhoid (oral typhoid vaccine) • Varicella zoster virus Inactivated (killed) whole-cell vaccines • Cholera • Hepatitis A • Influenza • Poliomyelitis (inactivated polio virus, IPV) •

Rabies Component vaccines • Anthrax (adsorbed extracted antigens) • Diphtheria (adsorbed toxoid) • Hepatitis B (adsorbed recombinant hepatitis B surface antigen, HBsAg) • Haemophilus influenzae type B (conjugated capsular polysaccharide) • Human papillomavirus (recombinant capsid proteins) • Meningococcal, quadrivalent A, C, Y, W135 (conjugated capsular polysaccharide) • Meningococcal, serogroup C (conjugated capsular polysaccharide) • Pertussis (adsorbed extracted antigens) • Pneumococcal conjugate (PCV; conjugated capsular polysaccharide, 13 serotypes) • Pneumococcal polysaccharide (PPV; purified capsular polysaccharide, 23 serotypes) • Tetanus (adsorbed toxoid) • Typhoid (purified Vi capsular polysaccharide) 6.14 Guidelines for vaccination against infectious disease • The principal contraindication to inactivated vaccines is an anaphylactic reaction to a previous dose or a vaccine component • Live vaccines should not be given during an acute infection, to pregnant women or to the immunosuppressed, unless the immunosuppression is mild and the benefits outweigh the risks • If two live vaccines are required, they should be given either simultaneously in opposite arms or 4 weeks apart • Live vaccines should not be given for 3 months after an injection of human normal immunoglobulin (HNI) • HNI should not be given for 2 weeks after a live vaccine • Hay fever, asthma, eczema, sickle-cell disease, topical glucocorticoid therapy, antibiotic therapy, prematurity and chronic heart and lung diseases, including tuberculosis, are not contraindications to vaccination Fig. 6.14 The relationship between infection prevention and control (IPC) and antimicrobial stewardship (AMS). Antimicrobial stewardship Infection prevention and control Effective antimicrobial stewardship reduces health care-associated infections Effective infection control reduces the need for antimicrobials

116 • PRINCIPLES OF INFECTIOUS DISEASE • when no single agent’s spectrum covers all potential pathogens (e.g. polymicrobial infection) • when there is a need to reduce development of antimicrobial resistance in the target pathogen, as the organism would need to develop resistance to multiple agents simultaneously (e.g. antituberculous chemotherapy, p. 592; antiretroviral therapy (ART), p. 324). Antimicrobial resistance Microorganisms have evolved in the presence of naturally occurring antibiotics and have therefore developed resistance mechanisms (categorised in Fig. 6.16) to all classes of antimicrobial agent (antibiotics and their derivatives). Intrinsic resistance is an innate property of a microorganism, whereas acquired resistance arises by spontaneous mutation or horizontal transfer of genetic material from another organism (e.g. via a plasmid, p. 100). Plasmids often encode resistance to multiple antibiotics. The mecA gene encodes a penicillin-binding protein, which has a low affinity for penicillins and therefore confers resistance to β-lactam antibiotics in staphylococci. Extended-spectrum β-lactamases (ESBLs) are frequently encoded on plasmids, which are transferred relatively easily between bacteria, including Enterobacteriaceae. Plasmid-encoded carbapenemases have been detected in strains of Klebsiella pneumoniae (e.g. New Delhi metallo-β-lactamase 1, NDM-1). Strains of MRSA have been described that also have reduced susceptibility to glycopeptides through the development of a relatively impermeable cell wall. Treatment of infectious diseases Key components of treating infection are: • optimising antimicrobial therapy while minimising selection for antimicrobial resistance and the impact on commensal flora • addressing predisposing factors, e.g. glycaemic control in diabetes mellitus; viral load control in HIV-1-associated opportunistic infection • considering adjuvant therapy, e.g. removal of an infected medical device or necrotic tissue • managing complications, e.g. severe sepsis (systemic inflammatory response syndrome, or SIRS, p. 196) and acute kidney injury (p. 411). For communicable disease, treatment must also take into account contacts of the infected patient, and may include IPC interventions such as isolation, antimicrobial prophylaxis, vaccination and contact tracing. Principles of antimicrobial therapy In some situations (e.g.

pneumonia) it is important to start appropriate antimicrobial therapy promptly, whereas in others prior confirmation of the diagnosis and pathogen is preferred. The principles underlying the choice of antimicrobial agent(s) are discussed below. The WHO ‘World Antibiotic Awareness Week’ campaign is a yearly event aimed at highlighting the importance of prudent antimicrobial prescribing (see ‘Further information’). Antimicrobial action and spectrum Antimicrobial agents may kill or inhibit microorganisms by targeting essential and non-essential cellular processes, respectively. The range, or spectrum, of microorganisms that is killed or inhibited by a particular antimicrobial agent needs consideration when selecting therapy. Mechanisms of action of the major classes of antibacterial agent are listed in Box 6.15 and appropriate agents for some common infecting organisms are shown in Box 6.16. In severe infections and/ or immunocompromised patients, it is customary to use bactericidal agents in preference to bacteriostatic agents. Empiric versus targeted therapy Empiric antimicrobial therapy is selected to treat a suspected infection (e.g. meningitis) before the microbiological cause is known. Targeted or ‘directed’ therapy can be prescribed when the pathogen(s) is known. Empirical antimicrobial regimens need to have activity against the range of pathogens that could be causing the infection in question; because broad-spectrum agents affect many more bacteria than needed, they select for antimicrobial resistance. ‘Start Smart – Then Focus’ (Fig. 6.15) describes the principle of converting from empiric therapy to narrow-spectrum targeted therapy. Optimum empiric therapy depends on the site of infection, patient characteristics and local antimicrobial resistance patterns. National or local guidelines are often used to inform antimicrobial prescribing decisions. Combination therapy It is sometimes appropriate to combine antimicrobial agents: • when there is a need to increase clinical effectiveness (e.g. biofilm infections) 6.15 Target and mechanism of action of common antibacterial agents Aminoglycosides, chloramphenicol, macrolides, lincosamides, oxazolidinones • Inhibition of bacterial protein synthesis by binding to subunits of bacterial ribosomes Tetracyclines • Inhibition of protein synthesis by preventing transfer RNA binding to ribosomes Beta-lactams • Inhibition of cell wall peptidoglycan synthesis by competitive inhibition of transpeptidases (‘penicillin-binding proteins’) Cyclic lipopeptide (daptomycin) • Insertion of lipophilic tail into plasma membrane causing depolarisation and cell death Glycopeptides • Inhibition of cell wall peptidoglycan synthesis by forming complexes with D-alanine residues on peptidoglycan precursors Nitroimidazoles • The reduced form of the drug causes strand breaks in DNA Quinolones • Inhibition of DNA replication by binding to DNA topoisomerases (DNA gyrase and topoisomerase IV), preventing supercoiling and uncoiling of DNA Rifamycins • Inhibition of DNA synthesis by inhibiting DNA-dependent RNA polymerase Sulphonamides and trimethoprim • Inhibition of folate synthesis by dihydropteroate synthase (sulphonamides) and dihydrofolate reductase (trimethoprim) inhibition

6.16 Antimicrobial options for common infecting bacteria Organism Antimicrobial options* Gram-positive organisms Enterococcus faecalis Ampicillin, vancomycin/teicoplanin Enterococcus faecium Vancomycin/teicoplanin, linezolid Glycopeptide-resistant enterococci Linezolid, tigecycline, daptomycin MRSA Clindamycin, vancomycin, rifampicin (never used as monotherapy), linezolid, daptomycin, tetracyclines, tigecycline, co-trimoxazole Staphylococcus aureus Flucloxacillin, clindamycin Streptococcus pyogenes Penicillin, clindamycin, vancomycin Streptococcus pneumoniae Penicillin, cephalosporins, levofloxacin, vancomycin Gram-negative organisms Escherichia coli, ‘coliforms’ (enteric Gram-negative bacilli) Amoxicillin, trimethoprim, cefuroxime,

ciprofloxacin, co-amoxiclav Enterobacter spp., Citrobacter spp. Ciprofloxacin, meropenem, ertapenem, aminoglycosides ESBL-producing Enterobacteriaceae Ciprofloxacin, meropenem, ertapenem (if sensitive), temocillin, aminoglycosides Carbapenemase-producing Enterobacteriaceae Ciprofloxacin, aminoglycosides, tigecycline, colistin Haemophilus influenzae Amoxicillin, co-amoxiclav, macrolides, cefuroxime, cefotaxime, ciprofloxacin Legionella pneumophila Azithromycin, levofloxacin, doxycycline Neisseria gonorrhoeae Ceftriaxone/cefixime, spectinomycin Neisseria meningitidis Penicillin, cefotaxime/ceftriaxone, chloramphenicol Pseudomonas aeruginosa Ciprofloxacin, piperacillin–tazobactam, aztreonam, meropenem, aminoglycosides, ceftazidime/cefepime Salmonella typhi Ceftriaxone, azithromycin (uncomplicated typhoid), chloramphenicol (resistance common) Strict anaerobes Bacteroides spp. Metronidazole, clindamycin, co-amoxiclav, piperacillin–tazobactam, meropenem Clostridium difficile Metronidazole, vancomycin (oral), fidaxomicin Clostridium spp. Penicillin, metronidazole, clindamycin Fusobacterium spp. Penicillin, metronidazole, clindamycin Other organisms Chlamydia trachomatis Azithromycin, doxycycline Treponema pallidum Penicillin, doxycycline *Antibiotic selection depends on multiple factors, including local susceptibility patterns, which vary enormously between geographical areas. There are many appropriate alternatives to those listed. (ESBL = extended-spectrum β-lactamase; MRSA = meticillin-resistant Staphylococcus aureus) Fig. 6.15 Stages in the selection and refinement of antimicrobial therapy: ‘Start Smart – Then Focus’. 1 Empiric therapy Based on: • Predicted susceptibility of likely pathogens • Local antimicrobial policies 2 Targeted therapy Based on: • Predicted susceptibility of infecting organism(s) • Local antimicrobial policies 3 Susceptibility-guided therapy Based on: • Susceptibility testing results Antimicrobial susceptibility results Clinical diagnosis Information available: • Organ system involved • Endogenous or exogenous infection • Likely pathogens • Infecting organism(s) • Likely antimicrobial susceptibility Level of knowledge of infecting organism(s) Antimicrobial spectrum of agent(s) used • Antimicrobial susceptibility of infecting organism(s) Laboratory investigations: microbiological diagnosis

 be stopped when there is no longer any clinical evidence of infection. Pharmacokinetics and pharmacodynamics Pharmacokinetics of antimicrobial agents determine whether adequate concentrations are obtained at the sites of infection. Septic patients often have poor gastrointestinal absorption, so the preferred initial route of therapy is intravenous. Knowledge of anticipated antimicrobial drug concentrations at sites of infection is critical. For example, achieving a ‘therapeutic’ blood level of gentamicin is of little practical use in treating meningitis, as CSF penetration of the drug is poor. Knowledge of routes of antimicrobial elimination is also critical; for instance, urinary tract infection is ideally treated with a drug that is excreted unchanged in the urine. Pharmacodynamics describes the relationship between antimicrobial concentration and microbial killing. For many agents, antimicrobial effect can be categorised as ‘concentrationdependent’ or ‘time-dependent’. The concentration of antimicrobial achieved after a single dose is illustrated in Figure 6.17. The maximum concentration achieved is Cmax and the measure of overall exposure is the area under the curve (AUC). The efficacy of antimicrobial agents whose killing is concentration-dependent (e.g. aminoglycosides) increases with the amount by which Cmax exceeds the minimum inhibitory concentration (Cmax : MIC ratio). For this reason, it has become customary to administer aminoglycosides (e.g. gentamicin) infrequently at high doses (e.g. 7 mg/kg) rather than frequently at low doses. This has the added advantage of minimising toxicity by reducing the likelihood Factors promoting antimicrobial resistance include the inappropriate use of antibiotics (e.g. to treat viral infections), inadequate

dosage or unnecessarily prolonged treatment, and use of antimicrobials as growth promoters in agriculture. However, any antimicrobial use exerts a selection pressure that favours the development of resistance. Combination antimicrobial therapy may reduce the emergence of resistance in the target pathogen but not in the normal flora that it also affects. Despite use of combination therapy for M. tuberculosis, multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and rifampicin) and extremely drug-resistant tuberculosis (XDR-TB, resistant to isoniazid and rifampicin, any fluoroquinolone and at least one injectable antimicrobial antituberculous agent) have been reported worldwide and are increasing in incidence. The term ‘post-antibiotic era’ has been coined to describe a future in which the acquisition of resistance by bacteria will have been so extensive that antibiotic therapy is rendered useless. A more realistic scenario, which is currently being experienced, is a gradual but inexorable progression of resistance, necessitating the use of ever more toxic and expensive antimicrobials. Duration of therapy Treatment duration reflects the severity of infection and accessibility of the infected site to antimicrobial agents. For most infections, there is limited evidence available to support a specific duration of treatment (Box 6.17). Depending on the indication, initial intravenous therapy can often be switched to oral as soon as the patient is apyrexial and improving. In the absence of specific guidance, antimicrobial therapy should Fig. 6.16 Examples of mechanisms of antimicrobial resistance. (CAT = chloramphenicol acetyltransferase; ESBLs = extended-spectrum β-lactamases; MRSA = meticillin-resistant Staph. aureus; NDM-1 = New Delhi metallo-β-lactamase 1). Impermeability/reduced permeability Carbapenem resistance in Pseudomonas spp. Aminoglycoside resistance in anaerobes (uptake requires O2-dependent transport mechanism) Antimicrobial target Antimicrobial agent Active efflux of antimicrobial agent Tetracycline resistance in Gram-positive and Gram-negative bacteria Fluconazole resistance in Candida spp. Target modification β-lactam resistance in MRSA – altered penicillin-binding protein Glycopeptide resistance in enterococci – altered peptidoglycan amino acid sequence Rifampicin resistance in M. tuberculosis – RNA polymerase mutation Ciprofloxacin resistance in Enterobacteriaceae – DNA gyrase mutation Linezolid resistance in staphylococci and enterococci – 23S rRNA methylation Enzymatic degradation of agent β-lactam resistance in many organisms (penicillinase in Staph. aureus; ESBLs, ampC and NDM-1 in Enterobacteriaceae) Chloramphenicol resistance in staphylococci (CAT)

6.17 Duration of antimicrobial therapy for some common infections* Infection Duration of therapy Viral infections Herpes simplex encephalitis 2–3 weeks Bacterial infections Gonorrhoea Single dose Infective endocarditis (streptococcal, native valve) 4 weeks ± gentamicin for first 2 weeks Infective endocarditis (prosthetic valve) 6 weeks Osteomyelitis 6 weeks Pneumonia (community-acquired, severe) 7–10 days (no organism identified), 14–21 days (Staph. aureus or Legionella spp.) Septic arthritis 2–4 weeks Urinary tract infection (male) 2 weeks Urinary tract infection, upper tract, uncomplicated (female) 7 days Urinary tract infection, lower (female) 3 days Mycobacterial infections Tuberculosis (meningeal) 12 months Tuberculosis (pulmonary) 6 months Fungal infections Invasive pulmonary aspergillosis Until clinical/radiological resolution and reversal of predisposition Candidaemia (acute disseminated) 2 weeks after last positive blood culture and resolution of signs and symptoms *All recommendations are indicative. Actual duration takes into account predisposing factors, specific organisms and antimicrobial susceptibility, adjuvant therapies, current guidelines and clinical response. Fig. 6.17 Antimicrobial pharmacodynamics. The curve represents drug concentrations after a single dose of an antimicrobial agent. Factors that*

determine microbial killing are Cmax : MIC ratio (concentration-dependent killing), time above MIC (time-dependent killing) and AUC : MIC ratio. Time after dose Time above MIC Peak concentration (Cmax) Minimum inhibitory concentration (MIC) Area under the curve (AUC) Concentration of drug accumulation. Conversely, the β-lactam antibiotics and vancomycin exhibit time-dependent killing, and their efficacy depends on Cmax exceeding the MIC for a certain time (which is different for each class of agent). This is reflected in the dosing interval of benzylpenicillin, which is usually given every 4 hours in severe infection (e.g. meningococcal meningitis), and may be administered by continuous infusion. For other antimicrobial agents, the pharmacodynamic relationships are more complex and often less well understood. With some agents, bacterial inhibition persists after antimicrobial exposure (post-antibiotic and post-antibiotic sub-MIC effects). Therapeutic drug monitoring Therapeutic drug monitoring is used to confirm that levels of antimicrobial agents with a low therapeutic index (e.g. aminoglycosides) are not excessive, and that levels of agents with marked pharmacokinetic variability (e.g. vancomycin) are adequate. Specific recommendations for monitoring depend on individual clinical circumstances; for instance, different pre- and post-dose levels of gentamicin are recommended, depending on whether it is being used in traditional divided doses, once daily or for synergy in endocarditis (p. 530). Antimicrobial prophylaxis Antimicrobial prophylaxis is the use of antimicrobial agents to prevent infection. Primary prophylaxis is used to reduce the risk of infection following certain medical procedures (e.g. colonic resection or prosthetic hip insertion), following exposure to a specific pathogen (e.g. Bordetella pertussis) or in specific situations such as post-splenectomy (Box 6.18). It should be 6.18 Recommendations for antimicrobial prophylaxis in adults Infection risk Recommended antimicrobial Bacterial Diphtheria (prevention of secondary cases) Erythromycin Gas gangrene (after high amputation or major trauma) Penicillin or metronidazole Lower gastrointestinal tract surgery Cefuroxime + metronidazole, gentamicin + metronidazole, or co-amoxiclav (single dose only) Meningococcal disease (prevention of secondary cases) Rifampicin or ciprofloxacin Rheumatic fever (prevention of recurrence) Phenoxymethylpenicillin or sulfadiazine Tuberculosis (prevention of secondary cases) Isoniazid ± rifampicin Whooping cough (prevention of secondary cases) Erythromycin Viral HIV, occupational exposure (sharps injury) Combination tenofovir/ emtricitabine and raltegravir. Modified if index case's virus known to be resistant Influenza A (prevention of secondary cases in adults with chronic respiratory, cardiovascular or renal disease, immunosuppression or diabetes mellitus) Oseltamivir Fungal Aspergillosis (in high-risk haematology patients) Posaconazole (voriconazole or itraconazole alternatives if intolerant) Pneumocystis pneumonia (prevention in HIV and other immunosuppressed states) Co-trimoxazole, pentamidine or dapsone Protozoal Malaria (prevention of travelassociated disease) Specific antimalarials depend on travel itinerary (p. 278) *These are based on current UK practice. Recommendations may vary locally or nationally. Antimicrobial prophylaxis for infective endocarditis during dental procedures is not currently recommended in the UK.

 Beta-lactam antibiotics These antibiotics have a β-lactam ring structure and exert a bactericidal action by inhibiting enzymes involved in cell wall synthesis (penicillin-binding proteins, PBPs). They are classified in Box 6.21. Pharmacokinetics • Good drug levels are achieved in lung, kidney, bone, muscle and liver, and in pleural, synovial, pericardial and peritoneal fluids. • CSF levels are low, except when meninges are inflamed. • Activity is not inhibited in abscess (e.g. by low pH and PO2, high protein or neutrophils). • Beta-lactams are subject to an 'inoculum effect' – activity is reduced in the presence of a high organism burden (PBP expression is down-regulated by high organism density). • Generally safe in

pregnancy (except imipenem/cilastatin). Adverse effects Immediate (IgE-mediated) allergic reactions are rare but lifethreatening. Approximately 90% of patients who report a penicillin allergy do not have a true IgE-mediated allergy. Other reactions, such as rashes, fever and haematological effects (e.g. low white cell count), usually follow more prolonged therapy (more than 2 weeks). A large proportion of patients with infectious mononucleosis develop a rash if given aminopenicillins; this does not imply lasting allergy. The relationship between allergy to penicillin and allergy to cephalosporins depends on the specific cephalosporin used; there is significant cross-reactivity with first-generation cephalosporins but cross-reactivity to second-/ third-generation cephalosporins is less common. Avoidance of cephalosporins, however, is recommended in patients who have IgE-mediated penicillin allergy (p. 84). Cross-reactivity between penicillin and carbapenems is rare (approximately 1% by skin testing) and carbapenems may be administered if there are no suitable alternatives and appropriate resuscitation facilities are available. The monobactam aztreonam (p. 121) is the β-lactam least likely to cross-react in patients with penicillin allergy. Gastrointestinal upset and diarrhoea are common, and a mild reversible hepatitis is recognised with many β-lactams. More severe forms of hepatitis can be observed with flucloxacillin and co-amoxiclav. Leucopenia, thrombocytopenia, coagulation associated with minimal adverse effects. In the case of exposure, it may be combined with passive immunisation (see Box 6.12). Secondary prophylaxis is used in patients who have been treated successfully for an infection but remain predisposed to it. It is used in haemato-oncology patients in the context of fungal infection and in HIV-positive individuals with an opportunistic infection until a defined level of immune reconstitution is achieved. Antibacterial agents For details of antibacterial usage in pregnancy and old age, see Boxes 6.19 and 6.20. 6.20 Problems with antimicrobial therapy in old age • Clostridium difficile infection: all antibiotics predispose to some extent, but second- and third-generation cephalosporins, co-amoxiclav and fluoroquinolones (e.g. ciprofloxacin) especially so. • Hypersensitivity reactions: rise in incidence due to increased previous exposure. • Renal impairment: may be significant in old age, despite ‘normal’ creatinine levels (p. 386). • Nephrotoxicity: more likely, e.g. first-generation cephalosporins, aminoglycosides. • Accumulation of β-lactam antibiotics: may result in myoclonus, seizures or coma. • Reduced gastric acid production: gastric pH is higher, which causes increased penicillin absorption. • Reduced hepatic metabolism: results in a higher risk of isoniazid-related hepatotoxicity. • Quinolones: associated with delirium and may increase the risk of seizures. 6.21 Beta-lactam antibiotics Penicillins • Natural penicillins: benzylpenicillin, phenoxymethylpenicillin • Penicillinase-resistant penicillins: meticillin, flucloxacillin, nafcillin, oxacillin • Aminopenicillins: ampicillin, amoxicillin • Carboxy- and ureido-penicillins: ticarcillin, piperacillin, temocillin Cephalosporins • See Box 6.22 Monobactams • Aztreonam Carbapenems • Imipenem, meropenem, ertapenem, doripenem 1Data extracted from Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press; (medicinescomplete. com) [accessed on 16 March 2013]. • Glycopeptides • Linezolid • Meropenem • Penicillins 2Theoretical risk of teratogenicity, not supported by available clinical evidence. 6.19 Antimicrobial agents in pregnancy1 Contraindicated • Chloramphenicol: neonatal ‘grey baby’ syndrome – collapse, hypotension and cyanosis • Fluconazole: teratogenic in high doses • Quinolones: arthropathy in animal studies • Sulphonamides: neonatal haemolysis and methaemoglobinaemia • Tetracyclines, glycylcyclines: skeletal abnormalities in animals in first trimester; fetal dental discoloration and maternal hepatotoxicity with large parenteral doses in second or third trimesters • Trimethoprim: teratogenic in first trimester Relatively contraindicated • Aminoglycosides: potential damage to fetal auditory and vestibular nerves in second and third trimesters • Metronidazole: avoidance of high dosages is recommended2 Not known to be harmful;

use only when necessary • Aciclovir • Cephalosporins • Clarithromycin • Clindamycin • Erythromycin

retain good activity against Strep. pneumoniae and β-haemolytic streptococci. Ceftriaxone is administered once daily and is therefore a suitable agent for outpatient intravenous (parenteral) antimicrobial therapy (OPAT). • Fourth-generation agents, e.g. cefipime, have a broad spectrum of activity, including streptococci and some Gram-negatives, including P. aeruginosa. • Fifth-generation agents, such as ceftobiprole and ceftaroline, have an enhanced spectrum of Gram-positive activity that includes MRSA, and also have activity against Gram-negative bacteria; some, such as ceftobiprole, are active against P. aeruginosa. The spectrum of cephalosporins has also been enhanced by adding β-lactamase inhibitors. Monobactams Aztreonam is the only available monobactam. It is active against Gram-negative bacteria, except ESBL-producing organisms, but inactive against Gram-positive organisms or anaerobes. It is a parenteral-only agent and may be used safely in most penicillin-allergic patients other than those with an allergy to ceftazidime, which shares a common side chain with aztreonam. Carbapenems These intravenous agents have the broadest antibiotic activity of the β-lactam antibiotics, covering most clinically significant bacteria, including anaerobes (e.g. imipenem, meropenem, ertapenem). Macrolide and lincosamide antibiotics Macrolides (e.g. erythromycin, clarithromycin and azithromycin) and lincosamides (e.g. clindamycin) are bacteriostatic agents. Both classes bind to the same component of the ribosome, so they are not administered together. Macrolides are used for Legionella, Mycoplasma, Chlamydia and Bordetella infections. Azithromycin is employed for single-dose/short-course therapy for genitourinary Chlamydia/Mycoplasma spp. infections. Clindamycin is used primarily for skin, soft tissue, bone and joint infections. Pharmacokinetics Macrolides • Variable bioavailability (intravenous and oral preparations available). deficiencies, interstitial nephritis and potentiation of aminoglycosidemediated kidney damage are also recognised (p. 122). Seizures and encephalopathy have been reported, particularly with high doses in the presence of renal insufficiency. Thrombophlebitis occurs in up to 5% of patients receiving parenteral β-lactams. Drug interactions Synergism occurs in combination with aminoglycosides in vitro. Ampicillin decreases the biological effect of oral contraceptives and the whole class is significantly affected by concurrent administration of probenecid, producing a 2–4-fold increase in the peak serum concentration. Penicillins Natural penicillins are primarily effective against Gram-positive organisms (except staphylococci, most of which produce a penicillinase) and anaerobic organisms. Strep. pyogenes has remained sensitive to natural penicillins worldwide. According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), the prevalence of non-susceptibility to penicillin in Strep. pneumoniae in Europe in 2014 varied widely from 0% (Cyprus) to 46.7% (Romania). Penicillinase-resistant penicillins are the mainstay of treatment for infections with Staph. aureus, other than MRSA. However, EARS-Net data from 2014 indicate that MRSA rates in Europe vary widely from 0.9% (Netherlands) to 56% (Romania). Aminopenicillins have the same spectrum of activity as the natural penicillins, with additional Gram-negative cover against Enterobacteriaceae. Amoxicillin has better oral absorption than ampicillin. Unfortunately, resistance to these agents is widespread (57.1% of E. coli Europe-wide in 2014, range 34.7–73%), so they are no longer appropriate for empirical use in Gram-negative infections. In many organisms, resistance is due to β-lactamase production, which can be overcome by the addition of β-lactamase inhibitors (clavulanic acid or sulbactam). Carboxypenicillins (e.g. ticarcillin) and

ureidopenicillins (e.g. piperacillin) are particularly active against Gram-negative organisms, especially Pseudomonas spp., which are resistant to the aminopenicillins. Beta-lactamase inhibitors may be added to extend their spectrum of activity (e.g. piperacillin–tazobactam). Temocillin is derived from ticarcillin; it has good activity against Enterobacteriaceae, including those that produce ESBL enzymes, but poor activity against Pseudomonas aeruginosa and Grampositive bacteria. Cephalosporins and cephamycins Cephalosporins are broad-spectrum agents. Unfortunately, their use is associated with CDI (p. 264). With the exception of ceftobiprole, the group has no activity against enterococci. Only the cephamycins have anti-anaerobic activity. All cephalosporins are inactivated by ESBL. Cephalosporins are arranged in ‘generations’ (Box 6.22). • First-generation compounds have excellent activity against Gram-positive organisms and some activity against Gram-negatives. • Second-generation drugs retain Gram-positive activity but have extended Gram-negative activity. Cephamycins (e.g. cefoxitin), included in this group, are active against anaerobic Gram-negative bacilli. • Third-generation agents further improve anti-Gramnegative cover. For some (e.g. ceftazidime), this is extended to include Pseudomonas spp. Cefotaxime and ceftriaxone have excellent Gram-negative activity and 6.22 Cephalosporins First generation • Cefalexin, cefradine (oral) • Cefazolin (IV) Second generation • Cefuroxime (oral/IV) • Cefaclor (oral) • Cefoxitin (IV) Third generation • Cefixime (oral) • Cefotaxime (IV) • Ceftriaxone (IV) • Ceftazidime (IV) Fourth generation • Cefepime (IV) Fifth generation (also referred to as ‘next generation’) • Ceftobiprole (IV) • Ceftaroline (IV)

122 • PRINCIPLES OF INFECTIOUS DISEASE are < 1 mg/L and 5–10 mg/L (7–10 mg/L with less sensitive organisms, e.g. P. aeruginosa), respectively. • For other aminoglycosides, consult local guidance. Adverse effects • Renal toxicity (usually reversible) accentuated by other nephrotoxic agents. • Cochlear toxicity (permanent) more likely in older people and those with a predisposing mitochondrial gene mutation. • Neuromuscular blockade after rapid intravenous infusion (potentiated by calcium channel blockers, myasthenia gravis and hypomagnesaemia). Spectinomycin Chemically similar to the aminoglycosides and given intramuscularly, spectinomycin was developed to treat strains of Neisseria gonorrhoeae resistant to β-lactam antibiotics. Unfortunately, resistance to spectinomycin is very common. Its only indication is the treatment of gonococcal urethritis in pregnancy or in patients allergic to β-lactam antibiotics. Quinolones and fluoroquinolones These are effective and generally well-tolerated bactericidal agents. The quinolones have purely anti-Gram-negative activity, whereas the fluoroquinolones are broad-spectrum agents (Box 6.23). Ciprofloxacin has anti-pseudomonal activity but resistance emerges rapidly. In 2014, European surveillance showed that resistance to fluoroquinolones in E. coli ranged between 7.8% (Iceland) and 46.4% (Cyprus). Quinolones and fluoroquinolones are used for a variety of common infections, including urinary tract infection and pneumonia, and less common problems like MDR-TB. Pharmacokinetics • Well absorbed after oral administration but delayed by food, antacids, ferrous sulphate and multivitamins. • Wide volume of distribution; tissue concentrations twice those in serum. • Good intracellular penetration, concentrating in phagocytes. Fig. 6.18 Dosing of aminoglycosides using the Hartford nomogram. The nomogram is used to determine the dose interval for 7 mg doses of gentamicin or tobramycin, using measurements of drug levels in plasma 6–14 hours after a single dose. Dose every 48 hours Dose every 36 hours Dose every 24 hours Hours since administration Concentration in plasma (μg/mL)

• Frequency of administration: erythromycin is administered 4 times daily, clarithromycin twice daily, azithromycin once daily. • High protein binding. • Excellent intracellular accumulation.

Lincosamides (e.g. clindamycin) • Good oral bioavailability. • Food has no effect on absorption. • Good bone/joint penetration; limited CSF penetration. Adverse effects • Gastrointestinal upset, especially in young adults (erythromycin 30%). • Cholestatic jaundice with erythromycin estolate. • Prolongation of QT interval can cause torsades de pointes (p. 476). • Clindamycin predisposes to CDI. Aminoglycosides and spectinomycin Aminoglycosides are effective mainly in Gram-negative infections and are therefore commonly used in regimens for intra-abdominal infection. Some aminoglycosides, e.g. amikacin, are important components of therapy for MDR-TB. Because they act synergistically with β-lactam antibiotics they are used in combinations to treat biofilm infections, including infective endocarditis and orthopaedic implant infections. They cause very little local irritation at injection sites and negligible allergic responses. Oto- and nephrotoxicity must be avoided by monitoring of renal function and drug levels and by use of short treatment regimens. Aminoglycosides are not subject to an inoculum effect (p. 120) and they all exhibit a post-antibiotic effect (p. 119). Pharmacokinetics • Negligible oral absorption. • Hydrophilic, so excellent penetration to extracellular fluid in body cavities and serosal fluids. • Very poor intracellular penetration (except hair cells in cochlea and renal cortical cells). • Negligible CSF and corneal penetration and may require intrathecal administration during neurosurgical infections. • Peak plasma levels 30 minutes after infusion. • Monitoring of therapeutic levels required. Gentamicin dosing • Except in certain forms of endocarditis, pregnancy, severe burns, end-stage renal disease and paediatric patients, gentamicin is administered at 7 mg/kg body weight. The appropriate dose interval depends on drug clearance and is determined by reference to the Hartford nomogram (Fig. 6.18). • In streptococcal and enterococcal endocarditis, gentamicin is used with a cell wall active agent (usually a β-lactam), to provide synergy. Commonly used doses are 1 mg/kg 2–3 times daily for enterococcal endocarditis and 3 mg/kg once daily for most strains of oral streptococci. Target pre- and post-dose levels are < 1 mg/L and 3–5 mg/L, respectively, when gentamicin is dosed 3 times daily. • When not used according to the Hartford regimen or for endocarditis, gentamicin is administered twice or 3 times daily at 3–5 mg/kg/day. Target pre- and post-dose levels

Adverse effects • Histamine release due to rapid vancomycin infusion produces a ‘red man’ reaction (rare with modern preparations). • Nephrotoxicity is rare but may occur with concomitant aminoglycoside use, as may ototoxicity. • Teicoplanin can cause rash, bronchospasm, eosinophilia and anaphylaxis. Lipopeptides Daptomycin is a cyclic lipopeptide with bactericidal activity against Gram-positive organisms (including MRSA and GRE) but not Gram-negatives. It is not absorbed orally, and is used intravenously to treat Gram-positive infections, such as soft tissue infections and Staph. aureus infective endocarditis. Daptomycin is not effective for community-acquired pneumonia. Treatment can be associated with increased levels of creatine kinase and eosinophilic pneumonitis. Polymyxins Colistin is a polymyxin antibiotic that binds and disrupts the outer cell membrane of Gram-negative bacteria, including P. aeruginosa and Acinetobacter baumannii. Its use has increased with the emergence and spread of multi-resistant Gram-negative bacteria, including CPEs. It can be administered by oral, intravenous and nebulised routes. Significant adverse effects include neurotoxicity, including encephalopathy, and nephrotoxicity. Folate antagonists These are bacteriostatic antibacterials (p. 109). A combination of a sulphonamide and either trimethoprim or pyrimethamine is most commonly used, which interferes with two consecutive steps in the metabolic pathway. Available combinations include trimethoprim/sulfamethoxazole (co-trimoxazole) and pyrimethamine with either sulfadoxine (used

to treat malaria) or sulfadiazine (used in toxoplasmosis). Co-trimoxazole is the first-line drug for Pneumocystis jirovecii infection, the second-line drug for treatment and prevention of B. pertussis (whooping cough) infection, and is also used for a variety of other infections, including Staph. aureus. Dapsone is used to treat leprosy (Hansen's disease) and to prevent toxoplasmosis and pneumocystis when patients are intolerant of other medications. Folinic acid should be given to prevent myelosuppression if these drugs are used long-term or unavoidably in early pregnancy. Pharmacokinetics • Well absorbed orally. • Sulphonamides are hydrophilic, distributing well to the extracellular fluid. • Trimethoprim is lipophilic with high tissue concentrations. Adverse effects • Trimethoprim is generally well tolerated, with few adverse effects. • Sulphonamides and dapsone may cause haemolysis in glucose-6-phosphate dehydrogenase deficiency (p. 948). • Sulphonamides and dapsone cause skin and mucocutaneous reactions, including Stevens–Johnson syndrome and 'dapsone syndrome' (rash, fever and lymphadenopathy). • Dapsone causes methaemoglobinaemia (p. 135) and peripheral neuropathy. Adverse effects • Gastrointestinal side-effects in 1–5%. • Rare skin reactions (phototoxicity). • Tendinitis and Achilles tendon rupture, especially in older people. • Central nervous system effects (delirium, tremor, dizziness and occasional seizures in 5–12%), especially in older people. • Reduces clearance of xanthines and theophyllines, potentially inducing insomnia and increased seizure potential. • Prolongation of QT interval on ECG, cardiac arrhythmias. • Ciprofloxacin use is associated with the acquisition of MRSA and emergence of C. difficile ribotype 027 (p. 264). Glycopeptides Glycopeptides (vancomycin and teicoplanin) are effective against Gram-positive organisms only, and are used against MRSA and ampicillin-resistant enterococci. Some staphylococci and enterococci demonstrate intermediate sensitivity or resistance. Vancomycin use should be restricted to limit emergence of resistant strains. Teicoplanin is not available in all countries. Neither drug is absorbed after oral administration but vancomycin is used orally to treat CDI. Pharmacokinetics Vancomycin • Administered by slow intravenous infusion, good tissue distribution and short half-life. • Enters the CSF only in the presence of inflammation and may require intrathecal administration during neurosurgical infections. • Therapeutic monitoring of intravenous vancomycin is recommended, to maintain pre-dose levels of > 10 mg/L (15–20 mg/L in serious staphylococcal infections). Teicoplanin • Long half-life allows once-daily dosing. Agent Route of administration Typical antimicrobial spectrum Quinolones Nalidixic acid Oral Enteric Gram-negative bacilli (not Pseudomonas aeruginosa) Fluoroquinolones Ciprofloxacin Norfloxacin Ofloxacin IV/oral Oral IV/oral/topical Enteric Gram-negative bacilli, P. aeruginosa, Haemophilus spp., 'atypical' respiratory pathogens* Levofloxacin (L-isomer of ofloxacin) IV/oral Haemophilus spp., Strep. pneumoniae, 'atypical' respiratory pathogens* Moxifloxacin Oral Strep. pneumoniae, Staph. aureus, 'atypical' respiratory pathogens*, Mycobacteria and anaerobes } 6.23 Quinolones and fluoroquinolones *'Atypical' pathogens include Mycoplasma pneumoniae and Legionella spp. Fluoroquinolones have variable activity against M. tuberculosis and other mycobacteria.

 H. influenzae, Strep. pneumoniae and N. meningitidis. It has a very broad spectrum of activity against aerobic and anaerobic organisms, spirochaetes, Rickettsia, Chlamydia and Mycoplasma spp. It competes with macrolides and lincosamides for ribosomal binding sites, so should not be used in combination with these agents. Significant adverse effects are 'grey baby' syndrome in infants (cyanosis and circulatory collapse due to inability to conjugate drug and excrete the active form in urine); reversible dose-dependent bone marrow depression in adults receiving high cumulative doses; and severe aplastic anaemia in 1 in 25 000–40 000 exposures (unrelated to dose, duration of therapy or route of administration).

Oxazolidinones Linezolid and tedizolid are examples and their good activity against Gram-positive organisms means they are often used to treat skin and soft tissue infections. They may also be used in infection caused by resistant Gram-positive bacteria, including MRSA and GRE. Administration can be intravenous or oral. Common linezolid adverse effects include mild gastrointestinal upset and tongue discoloration. Myelodysplasia and peripheral and optic neuropathy can occur with prolonged use. Linezolid has monoamine oxidase inhibitor (MAOI) activity, and co-administration with other MAOIs or serotonin re-uptake inhibitors should be avoided, as this may precipitate a ‘serotonin syndrome’ (p. 1199). Other antibacterial agents Fusidic acid This antibiotic, active against Gram-positive bacteria, is available in intravenous, oral or topical formulations. It is lipid-soluble and distributes well to tissues. Its antibacterial activity is, however, unpredictable. Fusidic acid is used in combination, typically with antistaphylococcal penicillins, or for MRSA with clindamycin or rifampicin. It interacts with coumarin derivatives and oral contraceptives. Nitrofurantoin This drug has very rapid renal elimination and is active against aerobic Gram-negative and Gram-positive bacteria, including enterococci. It is used only for treatment of urinary tract infection, being generally safe in pregnancy and childhood. With prolonged treatment, however, it can cause eosinophilic lung infiltrates, fever, pulmonary fibrosis, peripheral neuropathy, hepatitis and haemolytic anaemia so its use must be carefully balanced against risks. Fidaxomicin Fidaxomicin is an inhibitor of RNA synthesis, and was introduced for the treatment of CDI in 2012. In non-severe CDI it is noninferior to oral vancomycin and is associated with a lower recurrence rate. Its effectiveness has not been assessed in severe CDI. Fosfomycin Fosfomycin acts by inhibiting cell wall synthesis. It has activity against Gram-negative but also Gram-positive bacteria and can demonstrate in vitro synergy against MRSA when combined with other antimicrobials. It is used for treatment of urinary tract infections but can be employed in other situations against multi-resistant bacteria. Tetracyclines and glycylcyclines Tetracyclines Of this mainly bacteriostatic class, the newer drugs doxycycline and minocycline show better absorption and distribution than older ones. Many streptococci and Gram-negative bacteria are now resistant, in part due to their use in animals (which is banned in Europe). Tetracyclines are indicated for Mycoplasma spp., Chlamydia spp., Rickettsia spp., Coxiella spp., Bartonella spp., Borrelia spp., Helicobacter pylori, Treponema pallidum and atypical mycobacterial infections. Tetracyclines can also be used for malaria prevention. Pharmacokinetics • Best oral absorption is in the fasting state (doxycycline is 100% absorbed unless gastric pH rises) and absorption is inhibited by cations, e.g. calcium or iron, which should not be administered at the same time. Adverse effects • All tetracyclines except doxycycline are contraindicated in renal failure. • Dizziness with minocycline. • Binding to metallic ions in bones and teeth causes discoloration (avoid in children and pregnancy) and enamel hypoplasia. • Oesophagitis/oesophageal ulcers with doxycycline. • Phototoxic skin reactions. Glycylcyclines (tigecycline) Chemical modification of tetracycline has produced tigecycline, a broad-spectrum, parenteral-only antibiotic with activity against resistant Gram-positive and Gram-negative pathogens, such as MRSA and ESBL (but excluding Pseudomonas spp.). Re-analysis of trial data has shown that there was excess mortality following tigecycline treatment as opposed to comparator antibiotics, so tigecycline should be used only when there has been adequate assessment of risk versus benefit. Nitroimidazoles Nitroimidazoles are highly active against strictly anaerobic bacteria, especially Bacteroides fragilis, C. difficile and other Clostridium spp. They also have significant antiprotozoal activity against amoebae and Giardia lamblia. Pharmacokinetics • Almost completely absorbed after oral administration (60% after rectal administration). • Well distributed, especially to brain and CSF. • Safe in pregnancy. Adverse effects • Metallic taste (dose-dependent). • Severe vomiting if taken with alcohol – ‘Antabuse

effect’. • Peripheral neuropathy with prolonged use. Phenicols Chloramphenicol is the only example in clinical use. In developed countries its use tends to be reserved for severe and lifethreatening infections when other antibiotics are either unavailable or impractical, largely because of concerns about toxicity. It is bacteriostatic to most organisms but apparently bactericidal to

neurotoxicity); and paraminosalicylic acid (which causes rashes and gastrointestinal upset). Linezolid may also be used and has good CSF penetration, while meropenem with co-amoxiclav is occasionally chosen. New drugs developed for XDR-TB include delamanid and bedaquiline; their adverse effects include QT prolongation and cardiac arrhythmias. Their co-administration with other agents with a similar side-effect profile (e.g. fluoroquinolones) therefore requires careful risk assessment. Clofazimine Clofazimine is used against M. leprae and resistant strains of M. tuberculosis. Its mode of action may involve induction of oxidative stress and it is weakly bactericidal. Oral absorption is variable and it is excreted in the bile. Side-effects include gastrointestinal upset, dry eyes and skin, and skin pigmentation, especially in those with pigmented skin. Antifungal agents See Box 6.24. Antimycobacterial agents Isoniazid Isoniazid is bactericidal for replicating bacteria and bacteriostatic for non-replicating bacteria. It is activated by mycobacterial catalase-peroxidase (KatG) and inhibits the InhA gene product, a reductase involved in mycolic acid synthesis. Mutations in KatG or InhA result in isoniazid resistance, which was reported in 15% of cases of M. tuberculosis infection globally in 2013. Isoniazid is well absorbed orally and metabolised by acetylation in the liver. The major side-effects are hepatitis, neuropathy (ameliorated by co-administration of pyridoxine) and hypersensitivity reactions. Rifampicin Rifampicin inhibits DNA-dependent RNA polymerase and is bactericidal against replicating bacteria. It is also active in necrotic foci, where mycobacteria have low levels of replication, and is therefore important in sterilisation and sputum conversion. Resistance most often involves the β-subunit of RNA polymerase and most often occurs with isoniazid-resistant MDR-TB. Rifampicin is well absorbed orally. It is metabolised by the liver via the microsomal cytochrome P450 system and is one the most potent inducers of multiple P450 isoenzymes, so is subject to extensive drug–drug interactions. Common side-effects include hepatitis, influenza-like symptoms and hypersensitivity reactions. Orange discoloration of urine and body secretions is expected. Pyrazinamide The mechanism of action of pyrazinamide is incompletely defined but includes inhibition of fatty acid synthase and ribosomal trans-translation. Pyrazinamide is often bacteriostatic but can be bactericidal and is active against semidormant bacteria in a low-pH environment. Primary resistance is rare but MDR-TB strains are frequently pyrazinamide-resistant and intrinsic resistance is a feature of Mycobacterium bovis strains. Pyrazinamide is well absorbed orally and metabolised by the liver. Side-effects include nausea, hepatitis, asymptomatic elevation of uric acid and myalgia. Ethambutol Ethambutol is a bacteriostatic agent. It inhibits arabinosyl transferase, which is involved in the synthesis of arabinogalactan, a component of the mycobacterial cell wall. Resistance is usually seen when resistance to other antimycobacterial agents is also present, e.g. in MDR-TB strains. It is orally absorbed but, in contrast to the first-line agents described above, it achieves poor CSF penetration and is renally excreted. The major side-effect is optic neuritis with loss of red–green colour discrimination and impaired visual acuity. It can also cause hepatitis. Streptomycin Streptomycin is an aminoglycoside whose mechanism of action and side-effects are similar to those of other aminoglycosides. It is administered intramuscularly. Other antituberculous agents Second-line agents used in MDR or XDR strains (p. 116) include aminoglycosides (amikacin,

capreomycin or kanamycin) and fluoroquinolones (moxifloxacin or levofloxacin), discussed above. Other established second-line agents administered orally are cycloserine (which causes neurological side-effects); ethionamide or prothionamide (which are not active with InhA-gene-mediated resistance but have reasonable CSF penetration; their side-effect profile includes gastrointestinal disturbance, hepatotoxicity and Agent Usual route(s) of administration Clinically relevant antifungal spectrum Imidazoles Miconazole Econazole Clotrimazole Topical Candida spp., dermatophytes Ketoconazole Topical, oral Malassezia spp., dermatophytes, agents of eumycetoma Triazoles Fluconazole Oral, IV Yeasts (Candida and Cryptococcus spp.) Itraconazole Oral, IV Yeasts, dermatophytes, dimorphic fungi (p. 300), Aspergillus spp. Voriconazole Oral, IV Yeasts and most filamentous fungi (excluding mucoraceous moulds) Posaconazole Oral, IV Yeasts and many filamentous fungi (including most mucoraceous moulds) Isavuconazole Oral, IV Yeasts and many filamentous fungi (variable activity against mucoraceous moulds) Echinocandins Anidulafungin Caspofungin Micafungin IV only Candida spp., Aspergillus spp. (no activity against Cryptococcus spp. or mucoraceous moulds) Polyenes Amphotericin B Nystatin IV Topical Yeasts and most dimorphic and filamentous fungi (including mucoraceous moulds) Others 5-fluorocytosine Oral, IV Yeasts Griseofulvin Oral Dermatophytes Terbinafine Topical, oral Dermatophytes } } 6.24 Antifungal agents

 is similar. Lipid formulations of AmB are used in invasive fungal disease, as empirical therapy in patients with neutropenic fever (p. 1327), and also in visceral leishmaniasis (p. 282). Other antifungal agents Flucytosine Flucytosine (5-fluorocytosine) has particular activity against yeasts. When it is used as monotherapy, acquired resistance develops rapidly, so it should be given in combination with another antifungal agent. Adverse effects include myelosuppression, gastrointestinal upset and hepatitis. Griseofulvin Griseofulvin has been largely superseded by terbinafine and itraconazole for treatment of dermatophyte infections, except in children, for whom these agents remain largely unlicensed. It is deposited in keratin precursor cells, which become resistant to fungal invasion. Terbinafine Terbinafine distributes with high concentration to sebum and skin, with a half-life of more than 1 week. It is used topically for dermatophyte skin infections and orally for onychomycosis. The major adverse reaction is hepatic toxicity (approximately 1: 50 000 cases). Terbinafine is not recommended for breastfeeding mothers. Antiviral agents Most viral infections in immunocompetent individuals resolve without intervention. Antiviral therapy is available for a limited number of infections only (Box 6.25). Antiretroviral agents These agents, used predominantly against HIV, are discussed on page 324. Anti-herpesvirus agents Aciclovir, valaciclovir, penciclovir and famciclovir These antivirals are acyclic analogues of guanosine, which inhibit viral DNA polymerase after being phosphorylated by virus-derived thymidine kinase (TK). Aciclovir is poorly absorbed after oral dosing; better levels are achieved intravenously or by use of the prodrug valaciclovir. Famciclovir is the prodrug of penciclovir. Resistance is mediated by viral TK or polymerase mutations. Ganciclovir Chemical modification of the aciclovir molecule allows preferential phosphorylation by protein kinases of cytomegalovirus (CMV) and other β-herpesviruses (e.g. human herpesvirus (HHV) 6/7) and hence greater inhibition of the DNA polymerase, but at the expense of increased toxicity. Ganciclovir is administered intravenously or as a prodrug (valganciclovir) orally. Cidofovir Cidofovir inhibits viral DNA polymerases with potent activity against CMV, including most ganciclovir-resistant CMV. It also has activity against aciclovir-resistant herpes simplex virus (HSV) and varicella zoster virus (VZV), HHV6 and occasionally adenovirus, poxvirus, papillomavirus or polyoma virus, and may be used to treat these infections in immunocompromised hosts. Azole antifungals The azoles

(imidazoles and triazoles) inhibit synthesis of ergosterol, a constituent of the fungal cell membrane. Side-effects vary but include gastrointestinal upset, hepatitis and rash. Azoles are inhibitors of cytochrome P450 enzymes, so tend to increase exposure to cytochrome P450-metabolised drugs (p. 24). Imidazoles Miconazole, econazole, clotrimazole and ketoconazole are relatively toxic and therefore administered topically. Clotrimazole is used extensively to treat superficial fungal infections. Triazoles are used for systemic treatment because they are less toxic. Triazoles Fluconazole is effective against yeasts (Candida and Cryptococcus spp.) and has a long half-life (approximately 30 hours) and an excellent safety profile. The drug is highly water-soluble and distributes widely to all body sites and tissues, including CSF. Itraconazole is lipophilic and distributes extensively, including to toenails and fingernails. CSF penetration is poor. Because oral absorption is erratic, therapeutic drug monitoring is required. Voriconazole is well absorbed orally but variability in levels requires therapeutic drug monitoring. It is used mainly in aspergillosis (p. 596). Side-effects include photosensitivity, hepatitis and transient retinal toxicity. Posaconazole and isavuconazole are broad-spectrum azoles, with activity against Candida spp., Aspergillus spp. and some mucoraceous moulds. Isavuconazole is non-inferior to voriconazole in the management of invasive aspergillosis and may be considered as an alternative when voriconazole is not tolerated. Echinocandins The echinocandins inhibit β-1,3-glucan synthesis in the fungal cell wall. They have few significant adverse effects. Caspofungin, anidulafungin and micafungin are used to treat systemic candidosis, and caspofungin is also used in aspergillosis. Polyenes Amphotericin B (AmB) deoxycholate causes cell death by binding to ergosterol and damaging the fungal cytoplasmic membrane. Its use in resource-rich countries has been largely supplanted by less toxic agents. Its long half-life enables once-daily administration. CSF penetration is poor. Adverse effects include immediate anaphylaxis, other infusionrelated reactions and nephrotoxicity. Nephrotoxicity may be sufficient to require dialysis and occurs in most patients who are adequately dosed. It may be ameliorated by concomitant infusion of normal saline. Irreversible nephrotoxicity occurs with large cumulative doses of AmB. Nystatin has a similar spectrum of antifungal activity to AmB. Its toxicity limits it to topical use, e.g. in oral and vaginal candidiasis. Lipid formulations of amphotericin B Lipid formulations of AmB have been developed to reduce AmB toxicity and have replaced AmB deoxycholate in many regions. They consist of AmB encapsulated in liposomes (liposomal AmB, L-AmB) or complexed with phospholipids (AmB lipid complex, ABLC). The drug becomes active on dissociating from its lipid component. Adverse effects are similar to, but considerably less frequent than, those with AmB deoxycholate, and efficacy

cases of influenza, e.g. in intensive care units. It is now approved for use in adults in a number of countries. An intravenous formulation of zanamivir is also in development for critically ill patients. Laninamivir is approved as an intranasal formulation in Japan. Amantadine and rimantadine These drugs reduce replication of influenza A by inhibition of viral M2 protein ion channel function, which is required for uncoating (see Fig. 6.2). Resistance develops rapidly and is widespread, and amantadine and rimantadine should be used only if the prevalence of resistance locally is known to be low. They are no longer recommended for treatment or prophylaxis in the UK or USA, having been superseded by zanamivir and oseltamivir. However, they may still be indicated to treat oseltamivir-resistant influenza A in patients unable to take zanamivir (e.g. ventilated patients). Other agents used to treat viruses Antiviral agents used to treat hepatitis B and C virus are discussed on pages 875 and 878, and those used against HIV-1 are described on page 324.

Foscarnet This analogue of inorganic pyrophosphate acts as a non-competitive inhibitor of HSV, VZV, HHV6/7 or CMV DNA polymerase. It does not require significant intracellular phosphorylation and so may be effective when HSV or CMV resistance is due to altered drug phosphorylation. It has variable CSF penetration. Anti-influenza agents Zanamivir and oseltamivir These agents inhibit influenza A and B neuraminidase, which is required for release of virus from infected cells (see Fig. 6.2, p. 101). They are used in the treatment and prophylaxis of influenza. Administration within 48 hours of disease onset reduces the duration of symptoms by approximately 1–112 days. In the UK, their use is limited mainly to adults with chronic respiratory or renal disease, significant cardiovascular disease, immunosuppression or diabetes mellitus, during known outbreaks. Peramivir has been developed as a distinct chemical structure, which means that it retains activity against some oseltamivir- and zanamivir-resistant strains. It has poor oral bioavailability and has been developed as an intravenous or intramuscular formulation for treatment of severe Drug Route(s) of administration Indications Significant side-effects Antiretroviral therapy (ART, p. 324) Oral HIV infection (including AIDS) CNS symptoms, anaemia, lipodystrophy Anti-herpesvirus agents Aciclovir Topical/oral/IV Herpes zoster Chickenpox (esp. in immunosuppressed) Herpes simplex infections: encephalitis (IV only), genital tract, oral, ophthalmic Significant side-effects rare Hepatitis, renal impairment and neurotoxicity reported rarely Valaciclovir Oral Herpes zoster, herpes simplex As for aciclovir Famciclovir Oral Herpes zoster, herpes simplex (genital) As for aciclovir Penciclovir Topical Labial herpes simplex Local irritation Ganciclovir IV Treatment and prevention of CMV infection in immunosuppressed Gastrointestinal symptoms, liver dysfunction, neurotoxicity, myelosuppression, renal impairment, fever, rash, phlebitis at infusion sites Potential teratogenicity Valganciclovir Oral Treatment and prevention of CMV infection in immunosuppressed As for ganciclovir but neutropenia is predominant Cidofovir IV/topical HIV-associated CMV infections and occasionally other viruses (see text) Renal impairment, neutropenia Foscarnet IV CMV and aciclovir-resistant HSV and VZV infections in immunosuppressed Gastrointestinal symptoms, renal impairment, electrolyte disturbances, genital ulceration, neurotoxicity Anti-influenza agents Zanamivir Inhalation Influenza A and B Allergic reactions (very rare) Oseltamivir Oral Influenza A and B Gastrointestinal side-effects, rash, hepatitis (very rare) Peramivir IV, IM Amantadine, rimantadine Oral Influenza A (but see text) CNS symptoms, nausea Agents used in other virus infections* Ribavirin Oral/IV/inhalation Lassa fever (IV) RSV infection in infants (inhalation) Haemolytic anaemia, cough, dyspnoea, bronchospasm and ocular irritation (when given by inhalation) } 6.25 Antiviral agents *Antiviral agents used in viral hepatitis are discussed on pages 875 and 878. (AIDS = acquired immunodeficiency syndrome; CMV = cytomegalovirus; CNS = central nervous system; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IM = intramuscular; IV = intravenous; RSV = respiratory syncytial virus; VZV = varicella zoster virus)

128 • PRINCIPLES OF INFECTIOUS DISEASE Lumefantrine Lumefantrine is used in combination with artemether to treat uncomplicated falciparum malaria, including chloroquine-resistant strains. Its mechanism of action is unknown. Significant adverse effects are uncommon. Drugs used in trypanosomiasis Benznidazole Benznidazole is an oral agent used to treat South American trypanosomiasis (Chagas’ disease, p. 279). Significant and common adverse effects include dose-related peripheral neuropathy, purpuric rash and granulocytopenia. Eflornithine Eflornithine inhibits biosynthesis of polyamines by ornithine decarboxylase inhibition, and is used in West African trypanosomiasis (T. brucei gambiense infection) of the central nervous system. It is administered as an intravenous infusion 4 times daily, which may be logistically difficult in the geographical areas affected by this disease. Significant adverse effects are common and include convulsions,

gastrointestinal upset and bone marrow depression. Melarsoprol This is an arsenical agent, used to treat central nervous system infections in East and West African trypanosomiasis (T. brucei rhodesiense and gambiense). It is administered intravenously. Melarsoprol treatment is associated with peripheral neuropathy and reactive arsenical encephalopathy (RAE), which carries a significant mortality. Nifurtimox Nifurtimox is administered orally to treat South American trypanosomiasis (Chagas' disease). Gastrointestinal and neurological adverse effects are common. Pentamidine isetionate Pentamidine is an inhibitor of DNA replication used in West African trypanosomiasis (T. brucei gambiense) and, to a lesser extent, in visceral and cutaneous leishmaniasis. It is also prescribed in Pneumocystis jirovecii pneumonia. It is administered via intravenous or intramuscular routes. It is a relatively toxic drug, commonly causing rash, renal impairment, profound hypotension (especially on rapid infusion), electrolyte disturbances, blood dyscrasias and hypoglycaemia. Suramin Suramin is a naphthaline dye derivative, used to treat East African trypanosomiasis (T. brucei rhodesiense). It is administered intravenously. Adverse effects are common and include rash, gastrointestinal disturbance, blood dyscrasias, peripheral neuropathies and renal impairment. Other antiprotozoal agents Pentavalent antimonials Sodium stibogluconate and meglumine antimoniate inhibit protozoal glycolysis by phosphofructokinase inhibition. They are used parenterally (intravenous or intramuscular) to treat leishmaniasis. Adverse effects include arthralgia, myalgias, raised hepatic transaminases, pancreatitis and electrocardiogram changes. Severe cardiotoxicity leading to death is not uncommon. Ribavirin Ribavirin is a guanosine analogue that inhibits nucleic acid synthesis in a variety of viruses. It is used in particular in the treatment of hepatitis C virus but also against certain viral haemorrhagic fevers, e.g. Lassa fever, although it has not been useful against Ebola virus. Antiparasitic agents Antimalarial agents Artemisinin (qinghaosu) derivatives Artemisinin originates from a herb (sweet wormwood, Artemisia annua), which was used in Chinese medicine to treat fever. Its derivatives, artemether and artesunate, were developed for use in malaria in the 1970s. Their mechanism of action is unknown. They are used in the treatment, but not prophylaxis, of malaria, usually in combination with other antimalarials, and are effective against strains of Plasmodium spp. that are resistant to other antimalarials. Artemether is lipid-soluble and may be administered via the intramuscular and oral routes. Artesunate is water-soluble and is administered intravenously or orally. Serious adverse effects are uncommon. Current advice for malaria in pregnancy is that the artemisinin derivatives should be used to treat uncomplicated falciparum malaria in the second and third trimesters, but should not be prescribed in the first trimester until more information becomes available. Atovaquone Atovaquone inhibits mitochondrial function. It is an oral agent, used for treatment and prophylaxis of malaria, in combination with proguanil (see below), without which it is ineffective. It is also employed in the treatment of mild cases of Pneumocystis jirovecii pneumonia, where there is intolerance to co-trimoxazole. Significant adverse effects are uncommon. Folate synthesis inhibitors (proguanil, pyrimethamine–sulfadoxine) Proguanil inhibits dihydrofolate reductase and is used for malaria prophylaxis. Pyrimethamine–sulfadoxine may be used in the treatment of malaria. Quinoline-containing compounds Chloroquine and quinine are believed to act by intraparasitic inhibition of haem polymerisation, resulting in toxic build-up of intracellular haem. The mechanisms of action of other agents in this group (quinidine, amodiaquine, mefloquine, primaquine, etc.) may differ. They are employed in the treatment and prophylaxis of malaria. Primaquine is used for radical cure of malaria due to Plasmodium vivax and P. ovale (destruction of liver hypnozoites). Chloroquine may also be given for extra-intestinal amoebiasis. Chloroquine can cause a pruritus sufficient to compromise adherence to therapy. If used in long-term, high-dose regimens, it causes an irreversible retinopathy. Overdosage leads to

lifethreatening cardiotoxicity. The side-effect profile of mefloquine includes neuropsychiatric effects ranging from mood change, nightmares and agitation to hallucinations and psychosis. Quinine may cause hypoglycaemia and cardiotoxicity, especially when administered parenterally. Primaquine causes haemolysis in people with glucose-6-phosphate dehydrogenase deficiency (p. 948), which should be excluded before therapy. Chloroquine is considered safe in pregnancy but mefloquine should be avoided in the first trimester.

Ivermectin Ivermectin binds to helminth nerve and muscle cell ion channels, causing increased membrane permeability. It is an oral agent, used in Strongyloides infection, filariasis and onchocerciasis. Significant side-effects are uncommon. Niclosamide Niclosamide inhibits oxidative phosphorylation, causing paralysis of helminths. It is an oral agent, used in Taenia saginata and intestinal T. solium infection. Systemic absorption is minimal and it has few significant side-effects. Piperazine Piperazine inhibits neurotransmitter function, causing helminth muscle paralysis. It is an oral agent, used in ascariasis and threadworm (Enterobius vermicularis) infection. Significant adverse effects are uncommon but include neuropsychological reactions such as vertigo, delirium and convulsions. Praziquantel Praziquantel increases membrane permeability to Ca2+, causing violent contraction of worm muscle. It is the drug of choice for schistosomiasis and is also used in T. saginata, T. solium (cysticercosis) and fluke infections (Clonorchis, Paragonimus) and in echinococcosis. It is administered orally and is well absorbed. Adverse effects are usually mild and transient, and include nausea and abdominal pain. Pyrantel pamoate This agent causes spastic paralysis of helminth muscle through a suxamethonium-like action. It is used orally in ascariasis and threadworm infection. Systemic absorption is poor and adverse effects are uncommon. Thiabendazole Thiabendazole inhibits fumarate reductase, which is required for energy production in helminths. It is used orally in Strongyloides infection and topically to treat cutaneous larva migrans. Significant adverse effects are uncommon. Further information Websites cdc.gov Centers for Disease Control and Prevention, Atlanta, USA. Provides information on all aspects of communicable disease, including prophylaxis against malaria. dh.gov.uk UK Department of Health. The publications section provides current UK recommendations for immunisation. ecdc.europa.eu European Centre for Disease Prevention and Control. Includes data on prevalence of antibiotic resistance in Europe. gov.uk/government/organisations/public-health-england Public Health England. Provides information on infectious diseases relating mainly to England, including community infection control. idsociety.org Infectious Diseases Society of America. Publishes up-to-date, evidence-based guidelines. who.int World Health Organization. Provides up-to-date information on global aspects of infectious disease, including outbreak updates. Also has information on the ‘World Antibiotic Awareness Week’ campaign. Diloxanide furoate This oral agent is used to eliminate luminal cysts following treatment of intestinal amoebiasis, or in asymptomatic cyst excreters. The drug is absorbed slowly (enabling luminal persistence) and has no effect in hepatic amoebiasis. It is a relatively non-toxic drug, the most significant adverse effect being flatulence. Iodoquinol (di-iodohydroxyquinoline) Iodoquinol is a quinoline derivative (p. 128) with activity against Entamoeba histolytica cysts and trophozoites. It is used orally to treat asymptomatic cyst excreters or, in association with another amoebicide (e.g. metronidazole), to treat extra-intestinal amoebiasis. Long-term use of this drug is not recommended, as neurological adverse effects include optic neuritis and peripheral neuropathy. Nitazoxanide Nitazoxanide is an inhibitor of pyruvate–ferredoxin oxidoreductasedependent anaerobic energy metabolism in

protozoa. It is a broad-spectrum agent, active against various nematodes, tapeworms, flukes and intestinal protozoa. Nitazoxanide also has activity against some anaerobic bacteria and viruses. It is administered orally in giardiasis and cryptosporidiosis. Adverse effects are usually mild and involve the gastrointestinal tract (e.g. nausea, diarrhoea and abdominal pain). Paromomycin Paromomycin is an aminoglycoside (p. 122) that is used to treat visceral leishmaniasis and intestinal amoebiasis. It is not significantly absorbed when administered orally, and is therefore given orally for intestinal amoebiasis and by intramuscular injection for leishmaniasis. It showed early promise in the treatment of HIV-associated cryptosporidiosis but subsequent trials have demonstrated that this effect is marginal at best. Drugs used against helminths Benzimidazoles (albendazole, mebendazole) These agents act by inhibiting both helminth glucose uptake, causing depletion of glycogen stores, and fumarate reductase. Albendazole is used for hookworm, ascariasis, threadworm, Strongyloides infection, trichinellosis, Taenia solium (cysticercosis) and hydatid disease. Mebendazole is used for hookworm, ascariasis, threadworm and whipworm. The drugs are administered orally. Absorption is relatively poor but is increased by a fatty meal. Significant adverse effects are uncommon. Bithionol Bithionol is used to treat fluke infections with Fasciola hepatica. It is well absorbed orally. Adverse effects are mild (e.g. nausea, vomiting, diarrhoea, rashes) but relatively common (approximately 30%). Diethylcarbamazine Diethylcarbamazine (DEC) is an oral agent used to treat filariasis and loiasis. Treatment of filariasis is often followed by fever, headache, nausea, vomiting, arthralgia and prostration. This is caused by the host response to dying microfilariae, rather than the drug, and may be reduced by pre-treatment with glucocorticoids.

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