**Principles of use of antimicrobial drugs**

Although originally used for the treatment of established bacterial infections, antibiotics have proved useful in the prevention of infection in various high - risk circumstances; this applies especially to patients undergoing various surgical procedures where perioperative antibiotics have significantly reduced postoperative infectious complications. The advantages of effective antimicrobial chemotherapy are self - evident, but this has led to a significant problem in ensuring that they are always appropriately used. Prescribers face a dilemma: initial antimicrobial therapy must be effective against all likely infective organisms for the individual presentation, but excessive use of broad - spectrum agents contributes to the development and selection of drug - resistant organisms. Hence, anti – infective agents are the only class of drug where inappropriate use in one patient can jeopardize the efficacy of treatment in other individuals. Examples of inappropriate antimicrobial use include prescribing in situations where antibiotics are either ineffective, such as viral infections, or where the selected agent, its dose, route of administration or duration of use are inappropriate. Of particular concern is the unnecessarily prolonged use of antibiotics for surgical prophylaxis. Apart from encouraging super-infection by drug - resistant organisms, prolonged use is wasteful of health resources and unnecessarily increases the risk of adverse drug reactions. It should be remembered that these agents are also extensively used in veterinary practice and, to a diminishing extent, in animal husbandry as growth promoters. Thus, it is essential that the clinical use of these agents be based on a clear understanding of the principles that have evolved to ensure safe, yet effective, prescribing.

**Factors to consider**

**Susceptibility of infecting organisms:** Drug selection should be based on knowledge of its activity against infecting microorganisms. Selected organisms may be predictably susceptible to a particular agent, and laboratory testing is therefore rarely performed. For example, *Streptococcus pyogenes* is uniformly sensitive to penicillin. In contrast, the susceptibility of many Gram-negative enteric bacteria is less predictable and laboratory guidance is essential for safe prescribing. It can be seen that, although certain bacteria are susceptible *in vitro* to a particular agent, use of that drug may be inappropriate, either on pharmacological grounds or because other less toxic agents are preferred.

**Host factors:** *In vitro* susceptibility testing does not always predict clinical outcome. Host factors play an important part in determining outcome and this applies particularly to circulating and tissue phagocytic activity. Infections can progress rapidly in patients suffering from either an absolute or functional deficiency of phagocytic cells. This applies particularly to those suffering from various hematological malignancies, such as the acute leukemias, where phagocyte function is impaired both by the disease and also by the use of potent cytotoxic drugs which destroy healthy, as well as malignant, white cells. Under these circumstances it is essential to select agents that are bactericidal, as bacteriostatic drugs, such as the tetracyclines or sulphonamides, rely on host phagocytic activity to clear bacteria. Widely used bactericidal agents include the aminoglycosides, broad - spectrum penicillins, the cephalosporins and quinolones. In some infections the pathogenic organisms are located intracellularly within phagocytic cells and therefore remain relatively protected from drugs that penetrate cells poorly, such as the penicillins and cephalosporins. In contrast, erythromycin, rifampicin and the fluoroquinolones readily penetrate phagocytic cells. Legionnaires’ disease is an example of an intracellular infection and is treated with erythromycin with or without rifampicin.

**Pharmacological factors:** Clinical efficacy is also dependent on achieving satisfactory drug concentrations at the site of the infection; this is influenced by the standard pharmacological factors of ***absorption, distribution, metabolism and excretion***. If an oral agent is selected, gastrointestinal absorption should be satisfactory. However, it may be impaired by factors such as the presence of food, drug interactions (including chelation), or impaired gastrointestinal function either as a result of surgical resection or mal-absorptive states. Although effective, oral absorption may be inappropriate in patients who are vomiting or have undergone recent surgery; under these circumstances a parenteral agent will be required and has the advantage of providing rapidly effective drug concentrations. Antibiotic selection also varies according to the anatomical site of infection. Lipid solubility is of importance in relation to drug distribution. For example, the aminoglycosides are poorly lipid - soluble and although achieving therapeutic concentrations within the extracellular fluid compartment, penetrate the cerebrospinal fluid (CSF) poorly. Likewise the presence of inflammation may affect drug penetration into the tissues. In the presence of meningeal inflammation, β - lactam agents achieve satisfactory concentrations within the CSF, but as the inflammatory response subsides drug concentrations fall. Hence it is essential to maintain sufficient dosage throughout the treatment of bacterial meningitis. Other agents such as chloramphenicol are little affected by the presence or absence of meningeal inflammation. Therapeutic drug concentrations within the bile duct and gallbladder are dependent on biliary excretion. In the presence of biliary disease, such as gallstones or chronic inflammation, the drug concentration may fail to reach therapeutic levels. In contrast, drugs that are excreted primarily via the liver or kidneys may require reduced dosage in the presence of impaired renal or hepatic function. The malfunction of excretory organs may not only risk toxicity from drug accumulation, but will also reduce urinary concentration of drugs excreted primarily by glomerular filtration. This applies to the aminoglycosides and the urinary antiseptics nalidixic acid and nitrofurantoin, where therapeutic failure of urinary tract infections may complicate severe renal failure.

**Drug resistance:** Drug resistance may be a natural or an acquired characteristic of a microorganism. This may result from impaired cell wall or cell envelope penetration, enzymatic inactivation, altered binding sites or active extrusion from the cell as a result of efflux mechanisms. Knowledge of the local epidemiology of resistant pathogens within a hospital, and especially within high - dependency areas such as intensive care and hemodialysis units, is invaluable in guiding appropriate drug selection.

**Drug combinations:** Antibiotics are generally used alone, but may on occasion be prescribed in combination. Combining two antibiotics may result in synergism, indifference or antagonism. In the case of synergism, microbial inhibition is achieved at concentrations below that for each agent alone and may prove advantageous in treating relatively insusceptible infections such as enterococcal endocarditis, where a combination of penicillin and gentamicin is synergistically active. Another advantage of synergistic combinations is that it may enable the use of toxic agents where dose reductions are possible. For example, meningitis caused by the fungus *Cryptococcus neoformans* responds to an abbreviated course of amphotericin B when it is combined with 5 - flucytosine, thereby reducing the risk of toxicity from amphotericin B. Combined drug use is occasionally recommended to prevent resistance emerging during treatment. For example, treatment may fail when fusidic acid is used alone to treat *Staph. aureus* infections, because resistant strains develop rapidly; this is prevented by combining fusidic acid with flucloxacillin. Likewise, tuberculosis is initially treated with a minimum of three agents, such as rifampicin, isoniazid and pyrazinamide; again drug resistance is prevented, which may result if either agent is used alone. The most common reason for using combined therapy is in the treatment of confirmed or suspected mixed infections where a single agent alone will fail to cover all pathogenic organisms. This is the case in serious abdominal sepsis where mixed aerobic and anaerobic infections are common and the use of metronidazole in combination with either an aminoglycoside or a broad – spectrum cephalosporin is essential. Finally, drugs are used in combination in patients who are seriously ill and about whom uncertainty exists concerning the microbiological nature of their infection. This initial ‘blind therapy’ frequently includes a broad - spectrum penicillin or cephalosporin in combination with an aminoglycoside. The regimen should be modified in the light of subsequent microbiological information.

**Adverse reactions:** Regrettably, all chemotherapeutic agents have the potential to produce adverse reactions with varying degrees of frequency and severity, and these include hypersensitivity reactions and toxic effects. These may be dose - related and predictable in a patient with a history of hypersensitivity or a previous toxic reaction to a drug or its chemical analogues. However, many adverse events are idiosyncratic and therefore unpredictable. ***Hypersensitivity reactions*** range in severity from fatal anaphylaxis, in which there is widespread tissue edema, airway obstruction and cardiovascular collapse, to minor and reversible hypersensitivity reactions such as skin eruptions and drug fever. Such reactions are more likely in those with a history of hypersensitivity to the drug, and are more frequent in patients with previous allergic diseases such as childhood eczema or asthma. It is important to question patients closely concerning hypersensitivity reactions before prescribing, as it precludes the use of all compounds within a class, such as the sulphonamides or tetracyclines, while cephalosporins and carbapenems should be used only with caution in patients who are allergic to penicillin, because these agents are structurally related. They should be avoided entirely in those who have had a previous severe hypersensitivity reaction to penicillin. ***Drug toxicity*** is often dose - related and may affect a variety of organs or tissues. For example, the aminoglycosides are both nephrotoxic and ototoxic to varying degrees; therefore, dosaging should be individualized and the serum assayed, especially where renal function is abnormal, to avoid toxic effects and non – therapeutic drug concentrations. An example of dose - related toxicity is chloramphenicol - induced bone marrow suppression. Chloramphenicol interferes with the normal maturation of bone marrow stem cells and high concentrations may result in a steady fall in circulating red and white cells and also platelets. This effect is generally reversible with dose reduction or drug withdrawal.

**Superinfection:** Anti - infective drugs not only affect the invading organism undergoing treatment but also have an impact on the normal bacterial flora, especially of the skin and mucous membranes. This may result in microbial overgrowth of resistant organisms with subsequent superinfection. One example is the common occurrence of oral or vaginal candidiasis in patients treated with broad – spectrum agents such as ampicillin or tetracycline. A more serious example is the development of pseudomembranous colitis from the overgrowth of toxin - producing strains of *Clostridium difficile* present in the bowel flora following the use of clindamycin or broad - spectrum antibiotics, though any antimicrobial can precipitate this condition. *C. difficile* - associated diarrhea is managed by drug withdrawal and oral vancomycin, or oral/intravenous metronidazole. Intravenous immunoglogbulin is occasionally used in severe cases, and rarely, colectomy (excision of part or whole of the colon) may be necessary. Once established, *C. difficile* infection is transmissible, particularly in the hospital setting; isolation of symptomatic patients and strict observation of hygiene practices (e.g. hand washing) are therefore key in preventing outbreaks.

**Chemoprophylaxis:** An increasingly important use of antimicrobial agents is that of infection prevention, especially in relationship to surgery. Infection remains one of the most important complications of many surgical procedures, and the recognition that perioperative antibiotics are effective and safe in preventing this complication has proved a major advance in surgery. The principles that underlie the chemoprophylactic use of antibacterials relate to the predictability of infection for a particular surgical procedure, in terms of its occurrence, microbial aetiology and susceptibility to antibiotics. Therapeutic drug concentrations present at the operative site at the time of surgery rapidly reduce the number of potentially infectious organisms and prevent wound sepsis. If prophylaxis is delayed to the postoperative period, then efficacy is markedly impaired. It is important that chemoprophylaxis be limited to the perioperative period, the first dose being administered approximately 1 hour before surgery for injectable agents; for many procedures and operative sites, a single dose is now considered sufficient. Prolonging chemoprophylaxis beyond this period is not cost - effective and increases the risk of adverse drug reactions and superinfection. One of the best examples of the efficacy of surgical prophylaxis is in the area of large - bowel surgery. Before the widespread use of chemoprophylaxis, postoperative infection rates for colectomy were often 30% or higher; these have now been reduced to around 5%. Chemoprophylaxis has been extended to other surgical procedures where the risk of infection may be low but its occurrence has serious consequences. This is especially true for the implantation of prosthetic joints or heart valves. These are major surgical procedures and although infection may be infrequent its consequences are serious and on balance the use of chemoprophylaxis is cost - effective. Examples of chemoprophylaxis in the non – surgical arena include the prevention of pneumococcal infection with penicillin V in asplenia or patients with sickle – cell disease, and the prevention of secondary cases of meningococcal meningitis with rifampicin or ciprofloxacin among household contacts of an index case.