

PRESCRIBING ANTIMICROBIALS: GENERAL PRINCIPLES

Chapter

1

The rational use of antimicrobials is a key element in developing a successful strategy against the development of resistance to antimicrobials. The physician should establish the need and the reason for therapy, select the appropriate antimicrobial agent, and then decide on the optimum dose and dosing interval, duration, as well as route of administration.

There are several reasons why aiming for appropriate antibiotic use makes sense:

- To cure or prevent infections using the best agent available in the shortest time and with the least side effects.
- To minimise the emergence and spread of resistant microorganisms, commonly called 'microbes'. Preventing the emergence of resistance and the dissemination of resistant microorganisms will also reduce costs.
- To provide healthcare services at a reasonable cost.

GENERAL PRINCIPLES IN CHOOSING AN ANTIMICROBIAL AGENT

- Antimicrobial drugs should be chosen according to the known or suspected pathogen and its susceptibility pattern. Choose the most effective agent with the narrowest spectrum according to antimicrobial stewardship principles.
- The efficacy of alternative agents should be considered.
- Drug side effects, interactions and individual conditions of the patient such as pregnancy, immunosuppression or renal impairment should be taken into account.
- After efficacy and toxicity issues, cost considerations are important.
- The likelihood of patient compliance should be considered.

ASPECTS WHICH DESERVE SPECIAL CONSIDERATION WHEN PRESCRIBING ANTIMICROBIAL AGENTS

NEED FOR REPRESENTATIVE SPECIMEN COLLECTION BEFORE STARTING THERAPY

It is important to obtain adequate and representative specimens from all potentially infected sites prior to the initiation of antimicrobial therapy, if possible. Appropriate antimicrobial therapy is based on definitive identification of pathogenic organisms which typically requires culture of the organism. Once antimicrobial therapy has been started, cultures are often rendered sterile, even though viable organisms may remain in the host. It is also important to avoid or minimise contamination by surface contaminants and commensals when collecting specimens.

INITIAL EMPIRIC CHOICE (I.E. AN INFORMED GUESS) BASED ON THE MOST LIKELY PATHOGENS AND SUSCEPTIBILITIES

In most cases, it may be impossible to determine the exact nature of the infecting organisms before instituting antimicrobial therapy. Initial therapy must therefore be empiric, and to make a rational choice from the many antimicrobial agents currently available, the clinician must be able to predict or 'guess' the infecting microorganism(s) and their antimicrobial susceptibility. In these cases, the use of 'bacteriological statistics', i.e. an awareness of those microorganisms most likely to cause infection in a given clinical setting, in conjunction with local antibiotic resistance patterns, may be particularly helpful in choosing an empiric antimicrobial agent.

SUBSEQUENT NEED TO ADJUST ANTIMICROBIAL THERAPY IN VIEW OF LABORATORY RESULTS

Since different organisms vary in their susceptibility to antimicrobial agents, it is imperative to have some means of determining the antimicrobial susceptibility of the infecting organism(s). Once the pathogen has been isolated, it can be subjected to susceptibility testing.

The commonly used disc-diffusion method is relatively simple to perform and is the method most widely employed. It provides semi-quantitative or qualitative data about the susceptibility of a given organism to a given agent. The qualitative assessment of susceptibility is generally categorised as sensitive or resistant; however, some laboratories also report an intermediate category.

Quantitative data is also provided by methods that incorporate serial dilutions of antimicrobials in agar-containing or broth culture media. The lowest concentration of the antimicrobial agent which inhibits visible growth after an 18 to 24 hour incubation period is known as the minimal inhibitory concentration (MIC).

Testing the ability of the cultured pathogen to grow at a critical concentration (chosen to distinguish between sensitive and resistant bacteria) or not, is a modification known as 'breakpoint' testing. A modification of the classical MIC test, the E-test, uses the diffusion of a continuous concentration gradient of an antimicrobial agent from a plastic strip into an agar medium to yield quantitative measurements of antimicrobial susceptibility.

MONITORING THERAPEUTIC RESPONSE

In many patients, it is possible to monitor the therapeutic response on clinical grounds alone. Therefore the subsidence of fever, the return of well-being, and the disappearance of both local and systemic signs of infection in the patient all signify an appropriate response. In most cases no further formal monitoring is necessary.

An apparent failure to respond clinically may be due to either the ineffectiveness of the antimicrobial agent(s) because of resistance or an inappropriate route of administration or dose, or to other reasons, e.g. a localised infection that requires surgical drainage, or a superinfection. Careful reassessment is recommended when considering changes to antimicrobial therapy.

MEASURING LEVELS FOR ANTIBIOTICS WITH A NARROW THERAPEUTIC/TOXIC RATIO

For antibiotics such as the aminoglycosides and vancomycin, the measurement of their concentrations in serum/plasma or other body fluids is often useful to avoid excessive levels which are associated with toxicity, yet to ensure that adequate (therapeutic) levels are achieved, especially in patients with impaired renal function, and in patients for whom long courses of either aminoglycosides or vancomycin are anticipated.

PHARMACOKINETIC PROPERTIES OF ANTIBIOTICS

Knowledge of the pharmacokinetic and pharmacodynamic properties of antibiotics is imperative in choosing the correct antibiotic and correct dose.

DEFINITIONS

Pharmacokinetics is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion.

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects.

In order for antibiotics to exert their bactericidal or bacteriostatic activity, a few important principles pertain:

- Microbiological activity – the antibiotic must bind to a specific binding site where it renders its effect (e.g. ribosome or penicillin-binding protein).
- Concentration of the antibiotic at the site of the infection is important (the higher the concentration, the more binding sites are occupied on/in the bacterial cells).
- The antibiotics also have to remain at these binding sites for a sufficient period of time.
- Minimum inhibitory concentration (MIC): This concentration represents the minimum amount of the drug that must come into contact with the bacteria in order for the antibiotic to work.

CLINICALLY SPEAKING, TWO DISTINCT GROUPS OF ANTIBIOTICS ARE RECOGNISED:

- **Time-dependant antibiotics:** (penicillins, cephalosporins, carbapenems, macrolides/azalides). The time that the antibiotic exceeds the MIC is crucial in predicting the effectiveness of the antibiotic. Concentrations of members of this group of antibiotics are required to be above the MIC for at least 50% of the dosing interval. If the bacterium is more resistant, the MIC is higher with subsequent reduction in the time that the antibiotic concentration exceeds the MIC and therefore higher dosages or alternative administration in the case of parenteral antibiotics may be required. In this regard, the exact role of continuous or prolonged infusions of β -lactam antibiotics in treating severe infections remains unclear, but increasing evidence is emerging that suggests potential benefits. This applies particularly if patients are in intensive care, are severely ill and are infected with bacteria with high MICs. Reduced variability in achieving steady-state concentrations and a greater chance of achieving target levels have been demonstrated. Alternatively, more frequent dosing of time-dependant antibiotics in this setting has been proposed.
- **Concentration-dependant antibiotics:** (quinolones, aminoglycosides). The more the antibiotic concentration exceeds the MIC, the more killing will take place (irrespective and independent of the time the concentration exceeds the MIC). For this group of antibiotics a ratio of concentration: MIC of 10 is required. This implies that a dose regimen should be chosen which results in a serum or tissue concentration of at least 10 times the MIC. Failure to achieve this concentration at the site of infection will lead to clinical and bacteriological failure and is likely to induce resistance to the entire class of antibiotic. In addition, the pharmacodynamic indices, 'peak/MIC' and '24 hours AUC/MIC', are major determinants of activity for these agents. These ratios show that giving the fluoroquinolones and aminoglycosides by once-a-day administration is attractive from a pharmacodynamic point of view. Thus the high peak levels obtained after short infusion dosing or high exposures during 24 hours cause the most rapid killing of the infecting pathogen. In this regard, for fluoroquinolones a 24 hour AUC/MIC of more than 100 has been proposed for most pathogens.

DURATION OF THERAPY

There is no ready means of determining the optimal duration of therapy. The site of infection, the pathogen involved, pharmacodynamics of the selected antimicrobial therapy, response to treatment and toxicity of the regimen should be evaluated. Duration should be as short as possible in accordance with antimicrobial stewardship principles.

For surgical prophylaxis, the use of antimicrobials beyond 24 hours is usually not indicated.

ROUTE OF ADMINISTRATION

It is a common practice to treat serious infections with parenteral antimicrobial agents. Since the rate of absorption from muscle depends on local perfusion and may be erratic following intramuscular injection, intravenous administration is preferred for treating life-threatening infections.

In certain clinical settings, sequential or 'switch' therapy is preferred. This is the practice of limiting the use of parenteral antibiotics to the early stages of infection and then switching to oral agents for the remaining duration of treatment. This approach is beneficial both clinically (early discharge, reduced risk of nosocomial infection, improved quality of life, etc.) and economically. In general, the following are widely accepted criteria for switching to oral therapy:

- Improvement in the clinical status of the patient.
- Improvement in the laboratory findings of infection such as a decrease in leucocyte count, C-reactive protein and procalcitonin.
- Absence of a life-threatening infection or severe immunosuppression, as well as any other medical situation necessitating parenteral therapy (need for high tissue concentrations, any gastrointestinal condition resulting in reduced absorption).

ANCILLARY MEASURES

There are other approaches to managing infections in addition to antibiotics. These include removal of foreign bodies, relief of obstruction and drainage of any abscesses. As a result of poor delivery of the antimicrobial agent into an abscess, drainage is a prerequisite for a successful outcome of the infection.

The presence of a foreign body at the site of infection may reduce the effectiveness of the antimicrobial agent. The foreign body acts as a nidus around which organisms may grow where the host's defences are ineffective and antibiotics are unable to penetrate. Intravascular devices and other foreign bodies may become coated by a layer of 'slime' (biofilm) produced by the infecting microorganism. This biofilm acts as a protective shield against host defences and antimicrobial agents. In cases of inadequate response, removing the foreign body may be the only effective option.