Principles of antibiotic therapy

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Key points

The aminoglycosides and fluoroquinolones exhibit 'concentration-dependent killing' and so higher doses are associated with greater efficacy.

β-Lactams, erythromycin, clindamycin, and linezolid demonstrate 'time-dependent killing' and therefore duration above minimum inhibitory concentration is more important.

The accuracy of self-reported drug allergy is poor and should be critically assessed.

Successful prophylactic antibiotic use depends on the patient being at high risk of infection, the likely infecting organisms and their susceptibilities should be known, and prophylaxis should only be administered at the time of risk.

Four main factors drive microbial resistance—excess antibiotic usage, incorrect use of broad-spectrum agents, incorrect dosing, and non-compliance.

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Historical perspective

Microsopy

Although the use of 'magnifying glasses' was recorded in the first century AD by Pliny the elder, the forerunner of the modern microscope was only developed in 1590 when a pair of Dutch spectacle makers, Zaccharias Jannsen and his son, discovered that pairing lenses allowed objects to be magnified. Galileo, on hearing of this discovery, experimented and outlined the science of lenses and produced a focusing magnifier. Another Dutchman, Antonie van Leeuwenhoek (1632–1723), produced microscopes with up to 270× magnification and as a result was the first to see and describe bacteria.

Bacteria

Abu Ali ibn Sina, a Persian polymath, was the first to propose the presence of bacteria in 1020, when he described the presence of 'foul, earthly foreign bodies'. Other noted Muslim scholars, Ibn Khatima and Ibn-al-Khotib, also proposed that infectious diseases were caused by contagious entities, after the event of the Black Death in al-Andalus (modern Andalucia) in the fourteenth century.

After van Leeuwenhoek's work, Louis Pasteur demonstrated that fermentation is due to microorganisms, and with Robert Koch proposed the 'germ theory of disease'. Koch (1843–1910) can be considered the father of modern microbiology. His work with tuberculosis proved the germ theory and for this he received the Nobel Prize. His criteria for testing the pathogenesis of infective disease, *Koch's postulates*, are still in use today.

Gram's staining was developed by Hans Christian Gram in 1884 and first used to discriminate between pneumococci and klebsiellae.

Antibiotics

The ancient Chinese, Greeks, and Egyptians are all known to have used moulds and plants to treat infection. Throughout history, infectious diseases have been treated with a variety of herbal remedies, such as quinine, which has long been used as a remedy for malaria.

In modern times, the first discovery was by Ernest Duchesme, describing the antibacterial properties of *Penicillium* spp. in 1897. This was followed by Fleming's work in 1928. The first true antibiotic was Salvarsan, a treatment for Syphilis, discovered by Paul Ehrlich after his work on arsenic and other metallic compounds in Germany, 1909. His ideas of exploiting the affinity of certain dyes for bacteria led to the development of the first commercially successful broad-spectrum antibiotics—the sulphonamides. Gerhard Domagsk, a pathologist, discovered these in the Bayer laboratories in 1932.

Pharmacology of antibiotic agents

Antibiotics can be defined as pharmacological agents that selectively kill or inhibit the growth of bacterial cells, while having little or no effect on the mammalian host. Bacteriostatic antibiotics prevent further replication of bacteria, and therefore rely on an intact immune system to clear the infection, whereas bactericidal antibiotics kill the bacteria. The use of a bactericidal agent is mandatory when treating infective endocarditis since the bacteria are protected from host immune functions within valve vegetations. Cidal activity can sometimes be achieved by a combination of antibiotics. A good example is in treatment of enterococcal endocarditis with the use of a combination of penicillin and an aminoglycoside. On their own, penicillins are bacteriostatic against enterococci and aminoglycosides are inactive.

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Pharmacokinetics and pharmacodynamics

The relationships between pharmacokinetic (PK), pharmacodynamic (PD), and microbiological parameters are increasingly used to predict microbiological and clinical outcome. PK refer to absorption, metabolism, distribution, and elimination, whereas PD refer to the effects of the drug on the body or organism.

After a bolus or short, rapid infusion, the peak concentration of an agent depends on the dose and the initial volume of distribution (central compartment in most multi-compartmental models). The rate of decline of drug concentrations after that depends on the rates of redistribution, metabolism, or renal clearance. Most antibiotics are eliminated via the kidneys—by either glomerular filtration or tubular secretion—and thus should be used with caution in patients with impaired renal function to prevent accumulation.

Particular caution is required with the aminoglycosides, as the toxic effects are closely related to the intracellular concentration. Elimination closely parallels the creatinine clearance, and thus the latter has been successfully incorporated in nomograms used to determine dosing interval.

PK–PD parameters most commonly measured include the peak concentration (the highest concentration in the reference compartment, usually serum), minimum inhibitory concentration (MIC), and the area under the concentration–time curve at steady state over 24 h (AUC). Other parameters including protein binding and post-antibiotic effect should also be taken into consideration. Using PK–PD indices of peak/MIC, time/MIC, and AUC/MIC, antibiotics can be divided into three groups, with some overlap. These indices have important consequences for optimal dosing strategies and are correlated with clinical outcome in human and animal experiments.[1]

The aminoglycosides and fluoroquinolones exhibit 'concentration-dependent killing' with peak concentration/MIC and AUC/MIC being the parameters that best correlate with efficacy. These antibiotics also exhibit a prolonged antibiotic effect after the serum level decreases below the MIC for the particular organism. Higher doses result in greater efficacy and once-daily dosing for aminoglycosides maximizes the peak concentration/MIC. Different ratios have been found to be efficacious for different drug–bug combinations. For example, for fluoroquinolones, the optimal AUC/MIC ratio for successful treatment of *Streptococcus pneumoniae* is 25–35, whereas ratios >100 may be required for successful treatment of Gram-negative bacilli. Higher AUC/MIC ratios are also less likely to be associated with development of resistance.

β-Lactams, erythromycin, clindamycin, and linezolid demonstrate 'time-dependent killing' with time/MIC being the most important index for efficacy. Thus, for these agents, the proportion of time above MIC is the most important parameter.

AUC/MIC correlates best with efficacy for azithromycin, tetracyclines, glycopeptides, and quinupristin–dalfopristin.

Adverse reactions

Hepatic, renal dysfunction

Most adverse reactions to antibiotics (such as rashes, diarrhoea, nausea and vomiting, and headache) are relatively minor. The carbapenems can be associated with transient increases in liver transaminases, which resolve after the cessation of therapy. The aminoglycosides can cause permanent nephrotoxicity (tubular damage) and ototoxicity if intracellular accumulation occurs. Nephrotoxicity has also been described at levels thought to be safe.[2] The aminoglycosides are commonly used in patients with sepsis and renal hypoperfusion, both of which are independent risk factors for renal dysfunction, and so it can be difficult to determine the primary cause of toxicity. Once-daily dosing regimens have been proposed to reduce side-effects.

Allergic reactions

Of the antibiotic agents, allergic reactions are most common with β-lactams. It is important to remember that the accuracy of self-reported drug allergy is poor, as patients frequently confuse recognized side-effects [such as gastrointestinal (GI) effects], non-immunologic drug rashes, or the original presenting disorder, for allergy. Also, allergic reactions to antibiotics in the 1950s and 1960s were commonly caused by contaminants not present in modern formulations.

Reliance on inaccurate reports may result in the use of sub-optimal antibiotic regimens against life-threatening infections. A careful and critical drug allergy history is thus important.

With increasing antibiotic resistance, it is now more important than ever to be able to use the full armamentarium. Recent work has tried to define the true allergy rates and incidence of cross-reactivity. In one study, the true allergy rate was 33% if an allergy was documented in the medical notes, whereas it was only 7% when based on self-reporting. In penicillin allergic patients, the incidence of cross-reactivity to other β-lactam agents (including cephalosporins and carbapenems) is of the order of 10%.

Resistance

Antibiotic resistance is not a new problem—the first clinical examples were described shortly after the introduction of sulphonamides in 1935 and penicillin in 1941. In 1946, ~14% of *Staphylococcus aureus* cultures were resistant, but by 1948 only 20% of *Neisseria gonorrhoeae* isolates were sensitive to sulphonamides.

The concept of resistance is often considered in all or nothing terms, but some bacteria may not be inhibited adequately by drug concentrations that are safely achievable at the affected body site. For example, penicillin remains effective for the treatment of pneumonia, but not meningitis, caused by pneumococci with intermediate susceptibility to penicillin.

Antibiotic resistance may be intrinsic or acquired. Intrinsic resistance arises if the drug target is not present in the bacterium's

metabolic pathways or if the antibiotic cannot enter the bacterium due to impermeability. Hence, β-lactam agents with activity against the bacterial cell wall have no effect against mycoplasma, small bacteria that lack a cell wall. Resistance may be acquired either by mutation or by transfer of genetic material from resistant to susceptible organisms. Mutations occur frequently with rifampicin and fusidic acid; hence, these agents should be used in combination with another antibiotic for treatment of infection. Transfer of genetic material occurs via plasmids and transposons (small molecules of DNA that are distinct from the bacterial chromosome), bacteriophages, or direct conjugation between bacterial cells.

Whatever the method of acquisition of resistance, the spread of successful clones of resistant bacteria continue to cause clinical problems. Examples include the spread of epidemic strains of methicillin-resistant *S. aureus* in hospitals and resistant tuberculosis (TB) in the community.

Niederman[3] has defined four main factors driving microbial resistance—excess antibiotic usage, incorrect use of broad-spectrum agents, incorrect dosing, and non-compliance.

Principles of prescribing

Prophylaxis

Successful prophylactic antibiotic use depends on three principles. The individual patient should be at high risk of infection, the likely infecting organisms and their susceptibilities should be known, and prophylaxis should only be administered at the time of risk. An example is the management of contacts of a case of meningococcal meningitis, who should be offered chemoprophylaxis at the time of greatest risk of developing the infection (rifampicin or ciprofloxacin is commonly used). Lengthy prescriptions, such as before and after surgery, provide no additional protection and may promote selection of resistant organisms.

Surgical chemoprophylaxis

Surgical chemoprophylaxis depends on the type of procedure to be performed and these have been subdivided as follows:[4]

(i) clean: those that do not open body cavities and are not associated with inflamed tissue;
(ii) clean-contaminated: involve the opening of body cavities, for example, the GI or GU tract;
(iii) contaminated: procedures involving acute inflammation or visible wound contamination;
(iv) dirty: operations performed in the presence of pus, a previously perforated viscus or open injuries that are >4 h old.

There is a corresponding increase in risk of bacterial contamination and subsequent infection through the classes. For clean operations, such as thyroidectomy, prophylaxis is generally not recommended since infection within this group should be prevented by attention to strict asepsis and good surgical technique. In contrast, large bowel surgery is associated with heavy levels of bacterial contamination and postoperative infection rates are much higher. Alternative strategies of prophylaxis such as bowel sterilization by the use of poorly absorbed oral antibiotics have been abandoned. Therefore, prophylaxis depends on reducing faecal bacterial load by mechanical means and the administration of systemic antibiotics active against aerobic and anaerobic organisms. These should be administered at induction to ensure adequate antibiotic levels at the start of surgery, in accordance with local or national guidelines.[5]

Patients who are having foreign materials implanted have a higher risk of infection and may require chemoprophylaxis. In orthopaedic procedures, skin commensals are commonly implicated in peri-prosthetic infections.

Infective endocarditis occurs in individuals at risk of developing endocardial vegetations caused by anatomical abnormalities, prosthetic valves, or sequelae of rheumatic fever. Procedures that cause a transient bacteraemia, usually cleared by the reticulo-endothelial system, may result in endocarditis in at-risk patients. The UK National Institute of Clinical Excellence has recently produced evidence-based guidelines for prophylaxis against infective endocarditis.[6] Prophylaxis is not recommended for dental procedures or procedures of the upper and lower GI, genitourinary (GU), and respiratory tracts when there is no evidence of infection at the site of the procedure.

In certain circumstances, long-term prophylaxis is appropriate. Patients with repeated urinary tract infections, often as a result of anatomical abnormalities, can be given permanent courses of trimethoprim or nitrofurantoin which are successful because they are excreted at high concentrations through the urinary tract. The use of prophylaxis against ventilator-associated pneumonia is more controversial. Although there is strong evidence of benefit for selective decontamination of the digestive tract,[7] this is not widely practised because of fear of development of resistant organisms.

Treatment of existing infections

Choice of empirical therapy

An initial clinical assessment allows the pathology to be defined and a reasonable estimate of the likely infecting organism. For example, community acquired pneumonias in immunocompetent hosts are usually caused by a relatively small pool of organisms which includes *S. pneumoniae*. Other important clinical factors include the severity of illness, immune status of the patient and other co-morbidities, and infected prosthetic implants such as joint replacements or prosthetic valves. Infections associated with prosthetic materials are more difficult to eradicate without first removing the device.

Before commencing antibiotic therapy, it is vitally important to obtain appropriate samples for culture. Once antibiotics have been administered, culture and sensitivity information is difficult to obtain, as the responsible organism may not proliferate in the laboratory. Suspected cases of meningitis are an exception to this

rule. A first dose of antibiotic should be given as soon as the diagnosis is considered, as it has been demonstrated that delays before the administration of antibiotics increase the risk of mortality.

Broad spectrum vs *narrow spectrum*

Broad-spectrum antibiotics such as β-lactam/β-lactamase inhibitor combinations (co-amoxiclav and piperacillin–tazobactam), third-generation cephalosporins, quinolones, and carbapenems are useful for initial empirical therapy in critically ill patients. They allow a greater range of pathogens to be covered, but should be altered to a more targeted therapy once culture and susceptibility reports are available. Broad-spectrum agents are more likely to lead to selection of resistant organisms, including fungi, and some agents, particularly third-generation cephalosporins and quinolones have the propensity to cause antibiotic-associated diarrhoea. Narrow-spectrum agents (e.g. penicillin, trimethoprim and flucloxacillin) are preferred, where possible, as they are less likely to provoke the development of resistance and are less likely to be associated with *Clostridium difficile*.[8]

Route of administration

The route of administration of the drugs to be used is determined by the site and severity of the infection. For example, mild impetigo affecting a small area of skin can be treated by short-term topical antibiotic preparations. Choice of oral or i.v. therapy will depend on the drug levels required at the site of infection, the potential for absorption from the GI tract, and the severity of the disease process. I.M. therapy is rarely used. Ciprofloxacin has good bioavailability when taken enterally, and results in similar blood levels and AUC values compared with i.v. administration (absorption may be reduced by antacid use). Parenteral administration may be required for severe life-threatening infections, or where the oral route is not available.

Duration of treatment

Antibiotics should be continued until resolution of the infection is achieved. This can be judged by means of a clinical assessment, for example, improvements in gas exchange, resolving pyrexia, decreasing secretions, and resolution of infiltrates on the chest X-ray in ventilator-associated pneumonias. This clinical information is often supplemented with laboratory data such as decreasing white cell counts and C-reactive protein assays. The duration of therapy required varies enormously between different anatomical sites and organisms. An uncomplicated lower urinary tract infection will resolve after 3 days of antibiotic therapy, whereas patients with infective endocarditis will require many weeks of treatment. The recommendation for pulmonary TB is for 6 months of quadruple therapy.[9]

Microscopy and culture

Early microbiological information can be obtained by microscopy of appropriate body fluid samples, for example, blood, urine, or cerebrospinal fluid. A count of white blood cells, red blood cells, or epithelial cells according to sample type allows an assessment of inflammation and sample quality, whereas Gram's staining allows a rapid division of bacteria into two large groups, Gram-positive and Gram-negative, based on the properties of their cell walls. Further subdivision into cocci and bacilli in conjunction with knowledge of the clinical setting can allow a reasonable assumption of the likely organism type, thus providing an early opportunity for the selection of empirical antibiotic therapy. For example, the isolation of Gram-positive diplococci from blood cultures of a patient with lobar pneumonia leads one to suspect that the likely organism is *S. pneumoniae*.

Bacterial culture is integral to microbiological practice, since it enables empirical treatments to be refined to agents that may be less toxic, cheaper, or more effective. Cultures also allow the local microbiological flora to be described and antibiotic susceptibilities to be performed—this can subsequently improve the accuracy of empirical or prophylactic regimes as the bacteria that cause particular infections and their susceptibilities vary among regions and hospitals. Non-culture techniques, including nucleic acid amplification tests, are increasingly being performed to identify bacteria and their resistance genes. The results are more rapid than traditional culture but they are more expensive and require technical expertise.

Susceptibility tests

Disc diffusion tests are performed using standard agar plates inoculated with the target bacteria at a concentration to achieve semi-confluent growth of bacteria on the agar. Discs with known antibiotic concentrations are applied to the agar plate and incubated in standard conditions for 18–24 h. Interpretation of susceptibility is determined by comparing the diameter of the zones of inhibition around the antibiotic disc with published data for susceptible and resistant organisms. Broth and agar dilution methods use a standardized amount of organism incubated in doubling dilutions of culture media in standard conditions for 18–24 h. The lowest concentration at which no growth occurs is referred to as the MIC. Automated and semi-automated susceptibility testing machines use broth dilution techniques to determine susceptibility. The gradient or E-test technique uses a pre-defined gradient of antibiotic within a plastic strip. This is applied onto an agar plate inoculated with the test organism and incubated. This test gives an accurate MIC comparable with agar or broth dilution tests and is technically less demanding. This is an alternative to agar or broth dilution MICs and is used in the laboratory to determine the MIC of a resistant organism determined by disc diffusion or to determine an MIC when treating difficult infections, for example, endocarditis or pneumococcal meningitis.

Antibiotic assays

Antibiotic serum levels are performed for several reasons. It can be performed in order to prevent the development of toxic levels,

to ensure that levels are therapeutic, or to assess compliance with drug regimes (predominantly TB treatment courses).

Assays can be 'chemical', simple measures of the drug concentration in plasma, to ensure efficacy and avoid toxicity. This is commonly performed during aminoglycoside therapy. Alternatively, they can be more complex 'microbiological assays' or 'back-assays' in which samples of a patient's plasma containing the administered antibiotics are combined with standardized concentration of the infecting organism. Although this allows a direct assessment of the efficacy of the antibiotic dose, these assays are rarely performed because results are inconsistent and difficult to interpret.

Conclusion

A greater understanding of the role of PK and PD parameters allows for greater efficacy in the use of current antibiotics and may reduce the development of resistance. Reductions in the amount of overall antibiotic use, greater use of narrow-spectrum agents, and ensuring compliance with therapy may also reduce the development of resistance.

The accuracy of self-reported allergy is low and critical allergy history taking is essential to allow the use of the most appropriate antibiotic. The use of routine chemoprophylaxis should be considered carefully with reference to recognized guidelines. Appropriate use of the microbiology laboratory is central to correct antibiotic usage and guides the use of correct agents and dosage to ensure efficacy and avoid toxicity.

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Please see multiple choice questions 7–9