Principles of Antimicrobial therapy

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Antimicrobial agents are chemical substances that can kill or suppress the growth of microorganisms.

Antibiotics are soluble compounds that are derived from certain microorganisms and that inhibit the growth of other microorganisms.

Antimicrobial agents provide the most dramatic examples of the advances of modern medicine.

Many infectious diseases once considered incurable and lethal are now amenable to treatment with a few pills.

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings.
Antimicrobial drugs are effective in the treatment of infections because of their *selective toxicity*; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host.

However, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.
Types of infection and their treatment

- Bacterial infections - *antibacterial* that can be *bacteriostatic* (they inhibit the growth susceptible bacteria) or bactericidal (they kill susceptible bacteria).

- Fungal infections - *antifungal*

- Mycobacterial infections - *antimycobacterial*

- Helminthiasis - *antihelminthic*

- Protozoal infections - *antiprotozoal*

- Viral infection - *antiviral*
- **Minimum inhibitory concentration (MIC):** the lowest concentration of antibiotic that inhibits bacterial growth.
- **Minimum bactericidal concentration (MBC):** is the lowest concentration of antimicrobial agent that results in a 99.9 percent decline in colony count after overnight broth dilution incubations.

Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.
SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing:

- 1) the organism’s identity.
- 2) the organism’s susceptibility to a particular agent.
- 3) the site of the infection.
- 4) patient factors e.g. age, weight, pregnancy, hepatic and renal status, etc.
- 5) the safety of the agent.
- 6) the cost of therapy.

However, some patients require empiric therapy (umbrella therapy)—that is, immediate administration of drug(s) prior to bacterial identification and susceptibility testing.
Organism’s identity

- Characterizing the organism is central to selection of the proper drug.
- It is essential to obtain a sample culture of the organism prior to initiating treatment.

Determining antimicrobial susceptibility of infective organisms

- After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy.
Effect of the site of infection on therapy: 
*The blood-brain barrier*

- Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated.

- Lipid solubility of the drug: lipid-soluble drugs, such as chloramphenicol and metronidazole, have significant penetration into the CNS.

- Molecular weight of the drug: high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

- Protein binding of the drug.
Patient factors

- Attention must be paid to the condition of the patient.
- For example, the status of the patient’s immune system, kidneys, liver, circulation, and age must be considered.
- In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.
Safety of the agent

- Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs because they interfere with a site unique to the growth of microorganisms.

- Other antimicrobial agents (for example, chloramphenicol) are less microorganism specific and are reserved for life-threatening infections because of the drug’s potential for serious toxicity to the patient.
Cost of therapy

- Often several drugs may show similar efficacy in treating an infection, but vary widely in cost.
- Standard treatment of Helicobacter pylori includes various combinations of two or three antimicrobial agents along with a proton pump inhibitor.
- Figure illustrates relative cost of some drugs used for the treatment of peptic ulcers caused by H. pylori.
- It also demonstrates that a triple therapy regimen including clarithromycin is significantly more expensive than the bismuth subsalicylate based quadruple therapy.
The oral route of administration is chosen for infections that are mild and is favourable for treatment on an outpatient basis.

In patients requiring a course of i.v therapy initially, the switch to oral agents should occur as soon as possible.

However, some antibiotics, such as vancomycin, the aminoglycosides, and amphotericin B, are so poorly absorbed from the GIT that adequate serum levels cannot be obtained by oral administration.

Parenteral administration is used for drugs that are poorly absorbed from the GIT and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents than can be reliably obtained by the oral route.
Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism and elimination of the drug by the body).

1- Concentration-dependent killing: Certain antimicrobial agents, including aminoglycosides, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism.
2-Time-dependent (concentration-independent) killing: By contrast, β-lactams, glycopeptides, macrolides, clindamycin, and linezolid do not exhibit this concentration-dependent property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill.

Dose-dependent killing effect is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC.
3-Postantibiotic effect

The postantibiotic effect (PAE) is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

To measure the PAE of an antibiotic, a test culture is first incubated in antibiotic-containing medium and then transferred to antibiotic-free medium.

The PAE is defined as the length of time it takes (after the transfer) for the culture to achieve log-phase growth.

Antimicrobial drugs exhibiting a long PAE (several hours) often require only one dose per day.
CHEMOTHERAPEUTIC SPECTRA

1-Narrow-spectrum antibiotics
Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. E.g., *isoniazid* is active only against mycobacteria.

2-Extended-spectrum antibiotics
Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, ampicillin is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria.
3-Broad-spectrum antibiotics

- Drugs such as *tetracycline* and *chloramphenicol* affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics.

- Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection of an organism such as Clostridium difficile, *the growth of which* is normally kept in check by the presence of other microorganisms.
COMBINATIONS OF ANTIMICROBIAL DRUGS

- It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism.

- This strategy:
  1. reduces the possibility of superinfection.
  2. decreases the emergence of resistant organisms.
  3. minimizes toxicity.

- However, situations in which combinations of drugs are employed do exist.
- For example, the treatment of tuberculosis benefits from drug combinations.
A. Advantages of drug combinations:
1- To provide broad coverage (when the infection is due to more than one organism).
2- To provide synergism (when organisms are not effectively eradicated with a single agent alone)
3- For initial therapy (when the patient is seriously ill and the results of culture are pending).
4- To prevent emergence of resistance as in treatment of tuberculosis.

B. Disadvantages of drug combinations:
1- Antagonism (A number of antibiotics act only when organisms are multiplying. Thus, co-administration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.
2- An increase in the number or severity of adverse effects.
3- Increased cost.
DRUG RESISTANCE

- Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.

- Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to vancomycin.

- Some of these bacterial strains may even become resistant to more than one antibiotic.

- The emergence of bacteria that are resistant to several drugs is the major cause of failure in the treatment of infectious diseases.

- Overuse and inappropriate use of antibiotics has fueled a major increase in prevalence of multidrug-resistant pathogens, leading some to speculate that we are nearing the end of the antibiotic era.
Mechanism of drug resistance:

A- Genetic alterations leading to drug resistance
   1- Spontaneous mutations of DNA
   2- DNA transfer of drug resistance

B- Altered expression of proteins in drug-resistant organisms
   1- Modification of target sites
   2- Decreased accumulation
   3- Enzymatic inactivation
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Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoroquinolones.

β-Lactams enter gram-negative cells through porin channels. *Enterobacter* is largely resistant to cephalosporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.

Tetracycline was effective against gynecologic infection due to *Bacteroides*, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.

β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. *Neisseria gonorrhoeae* is now largely resistant to *penicillin* because of penicillinase activity.
PROPHYLACTIC ANTIBIOTICS

- Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections.

- Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.

- The duration of prophylaxis should be closely observed to prevent unnecessary antibiotic exposure.
COMPLICATIONS OF ANTIBIOTIC THERAPY

A. Hypersensitivity
- Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur.
- For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity
- High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host.
- For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the hair cells of the organ of Corti.

C. Superinfections
- Drug therapy (with broad-spectrum antimicrobials or combinations of agents) can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms. These infections are often difficult to treat.
Antimicrobial drugs can be classified in a number of ways:

1) by their chemical structure (e.g. β-lactams or aminoglycosides).
2) by their mechanism of action (e.g., cell wall synthesis inhibitors).
3) by their activity against particular types of organisms (e.g., bacteria, fungi, or viruses).