Anti-Microbial Drugs

Lecture 1

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Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they've the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute.

**Selection of Antimicrobial Agents:**

- It requires knowledge of the followings:

**A. Identification of the infecting organism:**

- Characterization of the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram's stain, which is particularly useful in identifying the presence & morphologic features of microorganisms in body fluids that are normally sterile (CSF, pleural fluid, synovial fluid, peritoneal fluid & urine).

- However, it is generally necessary to culture the infective organism to arrive at a convulsive diagnosis & to determine the susceptibility of the bacteria to antimicrobial agents.
B. Empiric therapy prior to identification of the organism:

1. The acutely ill patient: acutely ill patient with infections of unknown origin e.g. a neutropenic patient or a patient with symptoms characteristics of meningitis require immediate treatment after specimens for laboratory analysis have been obtained but before the results of the culture are available.

2. Selecting a drug: broad spectrum therapy may be needed initially for serious infections when the identity of the organism is unknown or the site makes a poly-microbial infection likely.

- The choice of agents may also be guided by known association of particular organisms with infection in a given clinical setting, for example, a gram +ve coccus in the spinal fluid of a 40 year old patient is most likely to be S. pneumoniae, this organism is frequently resistant to penicillin G, & often requires treatment with a 3rd generation cephalosporin or vancomycin.

C. Determination of antimicrobial susceptibility of infective organisms:
Some pathogens, such as streptococcus pyogens & Neisseria meningitides, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram - ve bacilli, enterococci & staphylococcal species often show unpredictable susceptibility patterns to various antibiotics & require susceptibility testing to determine appropriate anti microbial therapy.
1. **Bacteriostatic versus bactericidal drugs:**
   - **Bacteriostatic drugs** arrest the growth & replication of bacteria at serum levels achievable in the patients thus limiting the spread of infection while the body's immune system attacks, immobilizes & eliminates the pathogens.
   - **Bactericidal drugs** kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, these agents are often the drugs of choice in seriously ill patient. It is possible for an antibiotic to bacteriostatic for one organism & bactericidal for another e.g. chloramphenicol is static agent gram–verods & is cidal against other organisms, such as *S. pneumoniae*.

2. **Minimum inhibitory concentration (MIC):** the **MIC is the lowest concentration of antibiotic that inhibits bacterial growth.**

3. **Minimum bactericidal concentration (MBC):** the **MBC is the minimal concentration of antibiotic that kills the bacteria.**
spectrum

Graph
D. Effect of the site of infection on therapy:

- The endothelial cells comprising the walls of the capillaries of many tissues have fenestrations (openings) that allow most drugs not bound by plasma proteins to penetrate. However, natural barriers to drug delivery exist in some tissues, such as the prostate, the vitreous body of the eye & the CNS. Of particular significance are the capillaries in the brain, which help create & maintain the blood brain barrier (BBB). This barrier is formed by the single layer of tileLike endothelial cells fused by light junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small & lipophilic.

- The penetration & concentration of an antibacterial agent in the CSF is particularly influenced by:

  1. Lipid solubility of the drugs: all compounds without a specific transporter must pass intracellularly from the blood to the CSF through 2 endothelial cell membranes. The lipid solubility of a drug is therefore a major determinant of its ability to penetrate into the brain e.g.: β-lactam antibiotics, such as penicillin, are ionized at physiological pH & have low solubility in lipids. They therefore have limited penetration through the intact blood brain barrier under normal circumstances.

  2. Molecular weight of the drug: compounds with a high molecular weight e.g.: vancomycin penetrates poorly into the brain, even in the presence of meningeal inflammation.
3. **Protein binding of the drug:** A high degree of protein binding of a drug in the serum restricts its entry into the CSF.

**E. Patient factors:** In selecting an antibiotic, attention must be paid to the condition of the patient.

1. **Immune system:** Antibacterial drugs decrease the microbial population (bactericidal) or inhibit further bacterial growth (bacteriostatic), but the host defense system must ultimately eliminate the invading organisms. **Alcoholism, diabetes, infection with the human immunodeficiency virus, malnutrition or advanced age can affect a patient's immune-competency, as can therapy with immunosuppressive drugs.** Higher than usual doses of bactericidal agents or longer course of treatment are required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function (10% or less than normal) causes accumulation in the body of antibiotics that ordinarily are eliminated by this route. This may lead to serious adverse effects unless drug accumulation is controlled by adjusting the dose or the dosage schedule of the antibiotic. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (e.g. erythromycin & tetracycline) are contraindicated in treating patients with liver disease.
4. Poor perfusion: decreased circulation to an anatomic area, such as the lower limbs of a diabetic, reduces the amount of antibiotic that reaches the area & makes infection difficult to treat.

5. Age: renal or hepatic elimination processes are poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of chloramphenicol & sulfonamides. Young children should not be treated with tetracycline, which affects bone growth.

6. Pregnancy: all antibiotics cross the placenta. Adverse effects to the fetus are rare, except for tooth dysplasia & inhibition of bone growth encountered with the tetracycline. Aminoglycosides should be avoided in pregnancy because of their ototoxic effect on the fetus.

7. Lactation: drugs administered to a lactating mother may enter the nursing infant via the breast milk.

F. Safety of the agent: many of the antibiotics, such as penicillins, are among the least toxic of all drugs, because they interfere with a site unique to the growth of microorganisms.

G. Cost of therapy: often, several drugs may show similar efficacy in treating an infection but vary widely in cost.
**Routes of Administration:**

- The oral route of administration is chosen for infections that are mild & can be treated on an outpatient basis.
- Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal tract & for treatment of patients with serious infections for whom it is necessary to maintain higher serum concentration of antimicrobial agents then can be reliably obtained by the oral route.

**Determinants Of Rational Dosing:** (important)

Rational dosing of antimicrobial agents is based on their pharmacodynamics as well as their pharmacokinetics properties.

A) **Concentration-dependent killing:**

- Certain antimicrobial agents, including aminoglycosides & fluoroquinolones, show significant increase in the rate of bacterial killing as the concentration of antibiotics increases from 4 to 64 fold the MIC of the drug for the infecting organism. Such drugs exhibit a concentration dependent killing.
- By contrast, β-lactams, macrolides & clindamycin don't exhibit this property. Their clinical efficacy is best predicted by the percentage of time their blood concentrations remain above the MIC. This effect is called time dependent killing.

B) **Post-antibiotic effect (PAE):** The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. Antimicrobials such as aminoglycosides & fluoroquinolones exhibit a long PAE (several hours). Antimicrobial drugs exhibiting a concentration-dependent killing and a long PAE often require only one dose per day.
Chemotherapeutic Spectra:

A. Narrow spectrum antibiotics: chemotherapeutic agents acting only on a single or a limited group of microorganisms e.g. isoniazid.

B. Extended spectrum antibiotics: antibiotics that are effective against gram +ve organisms & also against a significant number of gram –ve bacteria e.g. ampicillin.

C. Broad spectrum antibiotics: antibiotics that affect a wide variety of microbial species e.g. tetracycline & chloramphenicol.

Combinations of Antimicrobial Drugs: (important)

Antimicrobial combinations should be selected for one or more of the following reasons:

1. To provide broad spectrum empirical therapy in seriously ill patients.
2. To treat polymicrobial infections such as intraabdominal abscesses.
3. To decrease the emergence of resistant strained as in T.B.
4. To decrease dose related toxicity by using reduced doses of one or more components of the drug regimen.
5. To obtain enhanced inhibition or killing i.e. synergism e.g. β-lactams & aminoglycosides.

Note: 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.
Drug Resistance:

Occurs when bacterial growth is not stopped by the maximal level of the antibiotic that can be tolerated by the host.

A. Genetic alterations leading to drug resistance:

Resistance develops due to the ability of bacterial DNA to undergo spontaneous mutation or to move from one organism to another.

1. Spontaneous mutations of DNA: chromosomal alteration may occur by insertion, deletion or substitution of one or more nucleotide within the genome.

2. DNA transfer of drug resistance: of particular concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are usually encoded in extrachromosomal R-factors (resistance plasmids).

B. Altered expression of proteins in drug resistant organisms:

1. Modification of target sites: alteration of an antibiotic's target site through mutation can confer organismal resistance to one or more related antibiotics.

2. Decreased accumulation: decrease uptake or increased efflux of an antibiotic can confer organismal resistance, because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism.

3. Enzymatic inactivation: the ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic inactivating enzymes include β-lactamases, acetyl transferases & esterases.
Prophylactic Antibiotics:

Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections. Some of these are:

2. Pretreatment of patients undergoing dental extractions that have implanted prosthetic devices, such as artificial heart valves, to prevent seeding of the prosthesis. Patients with rheumatic valvular dysfunction are also pretreated.
3. Prevention of tuberculosis or meningitis among individuals who are in close contact with infected patients.
4. Treatment prior to certain surgical procedures e.g. bowel surgery, joint replacement and some gynecologic interventions to prevent infections.
5. Treatment of the mother with zidovudine to protect the fetus in case of an HIV-infected, pregnant woman.

Complications of Antibiotic Therapy: (important)

1. Hypersensitivity reactions to antimicrobial drugs or their metabolic products.
2. Direct toxicity affecting cellular processes in the host by high serum levels of certain antibiotics.
3. Super infections: drug therapy, particularly broad spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal & genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.
Classification of Antimicrobial Drugs: