**Lec. 2**

**III. ROUTE OF ADMINISTRATION**

**The oral route of administration is chosen for infection that are mild and can be treated on an outpatient basis. In patients requiring a course of intravenous therapy initially, the switch to oral agents occurs as soon as possible. However, some antibiotics, such as vancomycin,the aminoglycosides, andamphotericin B , are so poorly absorbed from the gastrointestinal tract that adequate serum levels cannot be obtained by oral administration. Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents that can be reliably obtained by the oral route.**

**IV. DETERMINATS OF RATIONAL DOSING**

**Rational dosing of antimicrobial agents is based on their pharmacodynamics ( the relationship of drug concentrations to antimicrobial effects ) as well as their pharmacokinetic properties ( the absorption, distribution, and elimination of the drug by the body ) . Three important properties that have a significant influence on the frequency of dosing are concentration – dependent killing, time – dependent killing, and postantibiotic effect.**

**V. AGENTS USED IN BACTERIAL INFECTIONS**

The table below is a summary of thetypes or classes of antibiotics and their properties including their biological source, spectrum and mode of action.

**Classes of Antibiotics and their Properties**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Chemical class** | **Examples** | **Biological source** | **Spectrum (effective against)** | **Mode of action** |
| **Beta-lactams (penicillins and cephalosporins)** | Penicillin G, Cephalothin | *Penicillium notatum* and *Cephalosporium* species | Gram-positive bacteria | Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly |
| **Semisynthetic beta-lactams** | Ampicillin, Amoxicillin |  | Gram-positive and Gram-negative bacteria | Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly |  | |
| **Clavulanic Acid** | Augmentin is clavulanic acid plus Amoxicillin | *Streptomyces clavuligerus* | Gram-positive and Gram-negative bacteria | Inhibitor of bacterial beta-lactamases |  |
| **Monobactams** | Aztreonam | *Chromobacterium violaceum* | Gram-positive and Gram-negative bacteria | Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly |  |
| **Carboxypenems** | Imipenem | *Streptomyces cattleya* | Gram-positive and Gram-negative bacteria | Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly |  |
| **Aminoglycosides** | Streptomycin | *Streptomyces griseus* | Gram-positive and Gram-negative bacteria | Inhibits translation (protein synthesis) |  |
|  | Gentamicin | *Micromonospora* species | Gram-positive and Gram-negative bacteria esp. *Pseudomonas* | Inhibits translation (protein synthesis) |  |
| **Glycopeptides** | Vancomycin | *Amycolatopsis orientalis* (formerly designated *Nocardia orientalis*) | Gram-positive bacteria, esp. *Staphylococcus aureus* | Inhibits steps in murein (peptidoglycan) biosynthesis and assembly |  |
| **Lincomycins** | Clindamycin | *Streptomyces lincolnensis* | Gram-positive and Gram-negative bacteria esp. anaerobic *Bacteroides* | Inhibits translation (protein synthesis) |  |
| **Macrolides** | Erythromycin, Azithromycin | *Streptomyces erythreus* | Gram-positive bacteria, Gram-negative bacteria not enterics, *Neisseria, Legionella, Mycoplasma* | Inhibit translation (protein synthesis) |  |
| **Polypeptides** | Polymyxin | *Bacillus polymyxa* | Gram-negative bacteria | Damages cytoplasmic membranes |  |
|  | Bacitracin | *Bacillus subtilis* | Gram-positive bacteria | Inhibits steps in murein (peptidoglycan) biosynthesis and assembly |  |
| **Polyenes** | Amphotericin | *Streptomyces nodosus* | Fungi (*Histoplasma*) | Inactivate membranes containing sterols |  |
|  | Nystatin | *Streptomyces noursei* | Fungi (*Candida*) | Inactivate membranes containing sterols |  |
| **Rifamycins** | Rifampicin | *Streptomyces mediterranei* | Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis* | Inhibits transcription (bacterial RNA polymerase) |  |
| **Tetracyclines** | Tetracycline | *Streptomyces* species | Gram-positive and Gram-negative bacteria, Rickettsias | Inhibit translation (protein synthesis) |  |
| **Semisynthetic tetracycline** | Doxycycline |  | Gram-positive and Gram-negative bacteria, Rickettsias *Ehrlichia*, *Borrelia* | Inhibit translation (protein synthesis) |  |
| **Chloramphenicol** | Chloramphenicol | *Streptomyces venezuelae* | Gram-positive and Gram-negative bacteria | Inhibits translation (protein synthesis) |  |
| **Quinolones** | Nalidixic acid | synthetic | Mainly Gram-negative bacteria | Inhibits DNA  replication |  | |
| **Fluoroquinolones** | Ciprofloxacin | synthetic | Gram-negative and some Gram-positive bacteria (*Bacillus anthracis*) | Inhibits DNA replication |  | |
| **Growth factor analogs** | Sulfanilamide, Gantrisin, Trimethoprim | synthetic | Gram-positive and Gram-negative bacteria | Inhibits folic acid metabolism (anti-folate) |  | |
|  | Isoniazid (INH) | synthetic | *Mycobacterium tuberculosis* | Inhibits mycolic acid synthesis; analog of pyridoxine (Vit B6) |  | |
|  | para-aminosalicylic acid (PAS) | synthetic | *Mycobacterium tuberculosis* | Anti-folate |  | |

**VI. CHEMOTHERAPEUTIC SPECTRA**

**A. Narrow – spectrum antibiotics**

**Chemotherapeutic agents acting only on a single or a limited group of microoganisms are said to have a narrow spectrum. For example,isoniazid is active only against mycobacteria.**

**B. 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.**

1. **Broad – spectrum antibiotics**

**Drugs such as tetracycline and chloramphenicol affect a wide variety of microbial species. Administration of broad – spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate superinfection of an organism such as *Candida albicans*.**

**VII. COMBINATIONS OF ANTIMICROBIL DRUGS**

1. **Advantages of drug combinations**

**Certain combinations of antibiotics, such as ß–lactams and aminoglycosides , show synergism ; that is , the combination is more effective than either of the drugs used separately**

**B. Disadvantages of drug combinations**

**For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effect of penicillins and cephalosporins .**

**VIII. DRUG RESISTANCE**

**A. Genetic alterations leading to drug resistance**

**Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another  
( Fig. 4) .**

**Fig. 4: Genetic bacterial resistance.**

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

**2. DNA transfer of drug resistance : Resistance properties are usually encoded in extrachromosomal R factors ( resistance plasmids). In fact most resistance genes are plasmid mediated traits   
can become incorporated into host bacterial DNA.**

**Plasmids may enter cells by processes such as transduction   
(phage mediated), transformation, or bacterial conjugation.**

**B. Altered expression of proteins in drug – resistant organisms**

**Drug resistance may be mediated by a variety of mechanisms, such as a lack of or an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, of presence of antibiotic – inactivating enzymes  
( Fig. 5 )**

**1. modification of target sites :**

***S. pneumoniae* resistance to ß-lactam antibiotics involves alterations   
in one or more of the major bacterial penicillin binding proteins, resulting is decreased binding of the antibiotic to its target .**

**2. Decreased accumulation:**

**Decreased uptake or increased efflux of an antibiotic can confer resistance , because the drug is un able to attain access to the site of its action in sufficient concentrations to injure or kill the organism .**

**3. Enzymic inactivation:**

**Examples of antibiotic–inactivating enzymes include:**

1. **ß- lactamases ( ʺpenicillinasesʺ ) that hydrolytically inactivate the ß- lactam ring of penicillins , cephalosporins , and related drugs.**
2. **acetyltransferases that transfer an acetyl group to the antibiotic , inactivating cloramphenicol or aminoglycosides.**
3. **esterases that hydrolyze the lactone ring of macrolides .**

**Fig. 5: Drug resistance.**

**IX. 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 .**

**X. SITES OF ANTIMICROBIAL ACTIONS**

**Antimicrobial drugs can be classified in a number of ways. these include**

**1) By their chemical structure (for example, ß- lactams or aminoglycosides ) ,**

**2) By their mechanism of action ( for example , cell wall synthesis inhibitors ) (Fig. 6), or**

**3) By their activity against particular types of organisms (for example, bacteria, fungi, or   
viruses).**

**Fig. 6: Sites of action of antibiotics.**