INTRODUCTION TO CHEMOTHERAPY

Infection and inflammation module

Theme : fever and infection .(week 3)

By Dr Ayesha Jamil

Define basic terms like,

- **chemotherapy**
- **antibiotics**
- **antimicrobial**
- **chemoprophylaxis**
- **MBC,MIC**
- **Empirical therapy**
- **Post-antibiotic effect**
- **Bacteriostatic antimicrobials**
- **Bactericidal antimicrobials**

Explain advantages of drug combinations

Describe various mechanisms of bacterial resistance against antibiotics.

Differentiate between concentration and time dependent killing with examples.

Classify antimicrobials on the basis of mechanism of action (MOA)

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings

Chemotherapy

It is the treatment of infectious diseases and malignancy with drugs to destroy microorganisms or cancer cells with minimal damage to the host tissues.

The infection may be due to

Bacteria

Virus

Fungi

Protozoa

Helminthes.

Antibiotics

They are chemical substances obtained from micro-organisms that kill or suppress the growth of other micro-organisms at very low concentration.

Anti-microbials Agents (AMA)

They are synthetic agents as well naturally obtained drugs that target micro-organisms invading the host.

Chemoprophylaxis

Chemoprophylaxis is the administration of anti-microbial drugs to prevent the impending infection. The most ideal time to do chemoprophylaxis is

- **before the organism enters the host body**

or

- **before the development of signs and symptoms of the disease.**

Selection of anti-Microbial agents

1) the organism's identity,
2) the organism's susceptibility to a particular agent,
3) the site of the infection,
4) patient factors,
5) the safety of the agent,
6) the cost of therapy

Identification of the infecting organism

Gram staining

Culture

Definitive identification of the infecting organism may require other laboratory techniques, such as detection of

Microbial antigen

Microbial DNA

Microbial RNA

Detection of an inflammatory or host immune response to the microorganism.

Empirical Therapy

Definition

Immediate administration of drug prior to bacterial identification and susceptibility testing

Timing

Determinants of drug Selection

Infection site

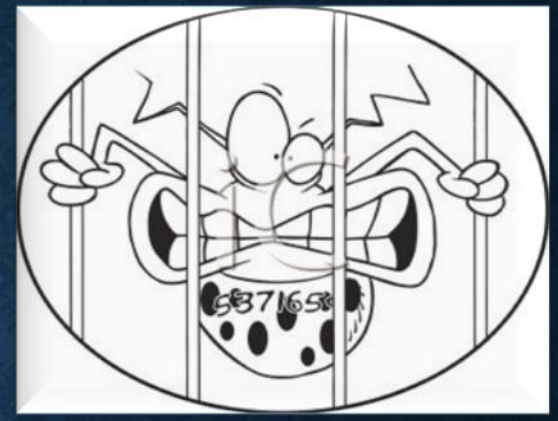
patient history

Prediction of susceptibility of infective organisms

Gram positive organisms have predictable susceptibility

Gram negative organisms often have unpredictable susceptibility

Bacteriostatic Antimicrobials



Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens

Bactericidal Antimicrobials

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 patients

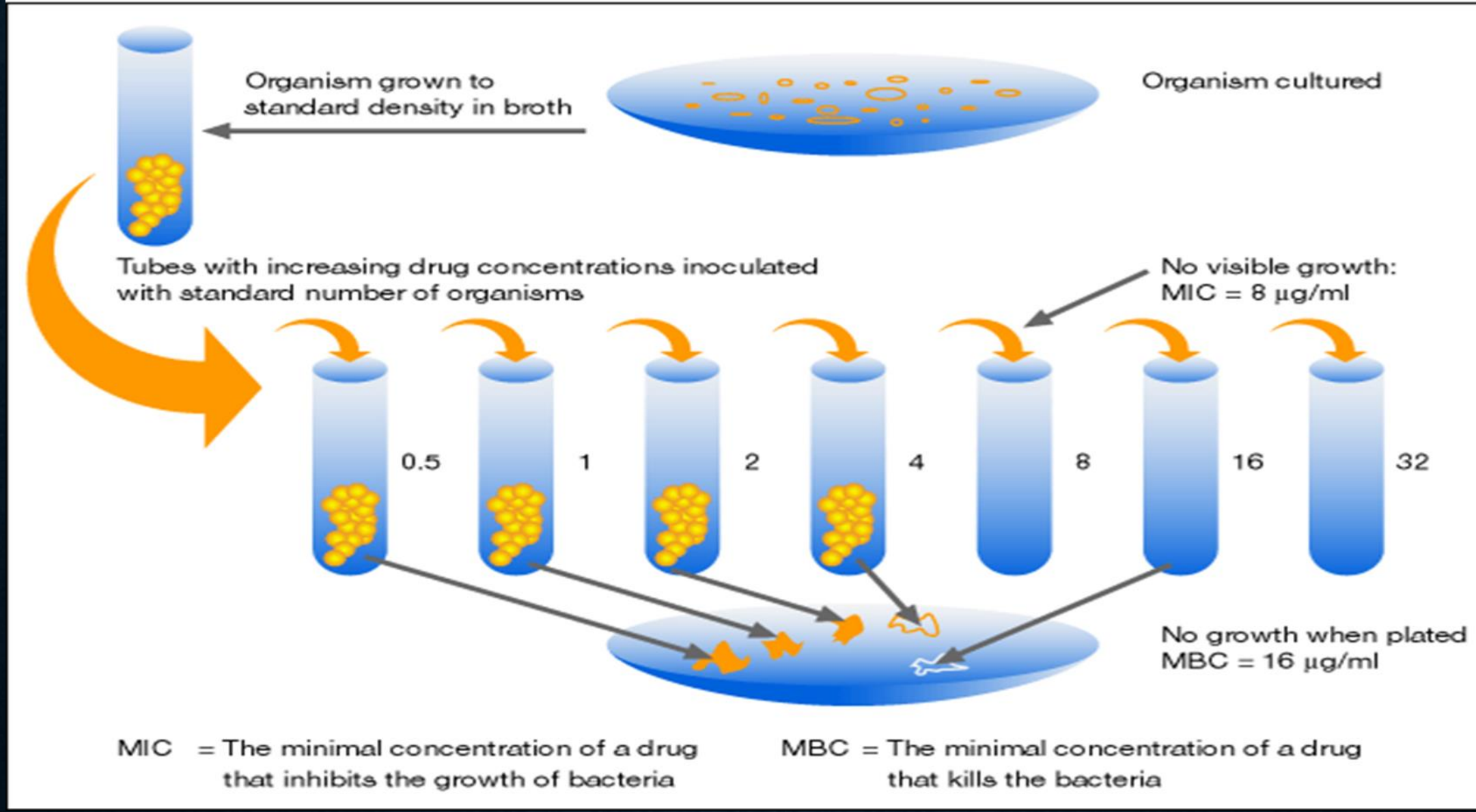
Minimum inhibitory concentration (MIC)

It is the lowest concentration of antibiotic that inhibits bacterial growth.

Minimum Bactericidal concentration (MBC)

It is the minimum concentration of antibiotic that kills the bacteria under investigation

Determination of MIC (here: broth ditution test)



MIC = The minimal concentration of a drug that inhibits the growth of bacteria

MBC = The minimal concentration of a drug that kills the bacteria

Effect of the site of infection on therapy (Blood Brain Barrier)

The capillaries in the brain create and maintain the blood-brain barrier.
This barrier is formed by the single layer of tile-like endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules.

Entry depends upon

- Lipid solubility
- Molecular weight
- Protein binding

Patient factors

- Immune system
- Renal dysfunction
- Hepatic dysfunction
- Poor perfusion
- Age
- Pregnancy
- Lactation

Safety of the agent

penicillin's, are among the least toxic of all drugs, because they interfere with a site unique to the growth of microorganisms. *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

Determinants of rationale dosing

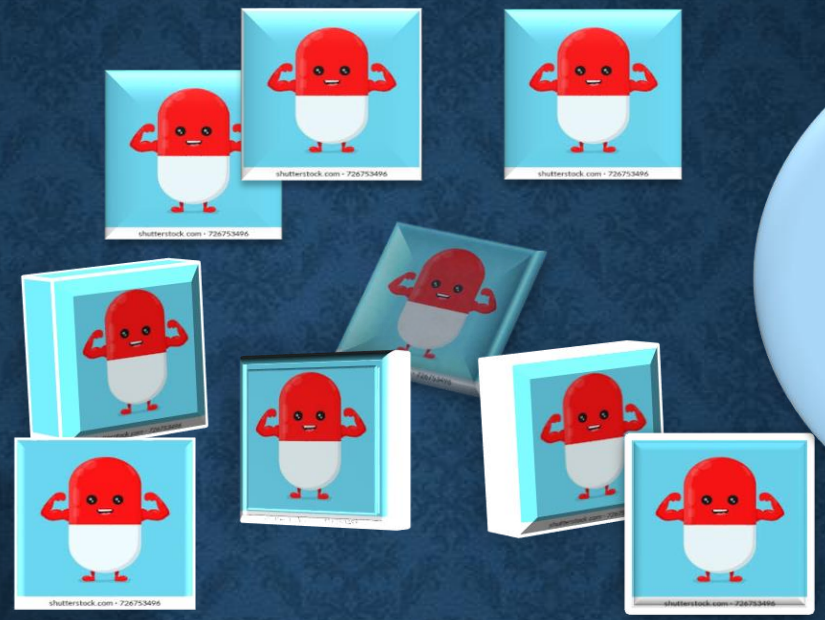
Rational dosing of antimicrobial agents is based on their pharmacodynamics as well as their pharmacokinetics of the drugs.

concentration-dependent killing

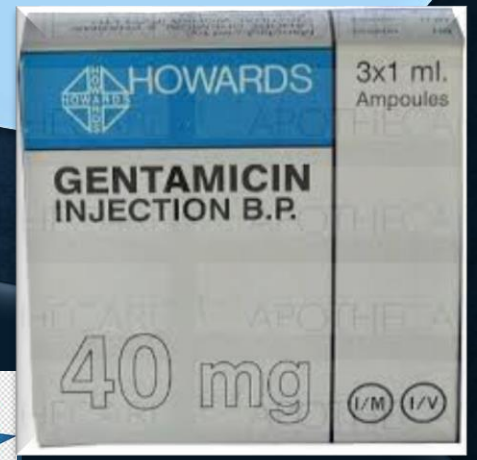
time-dependent killing,

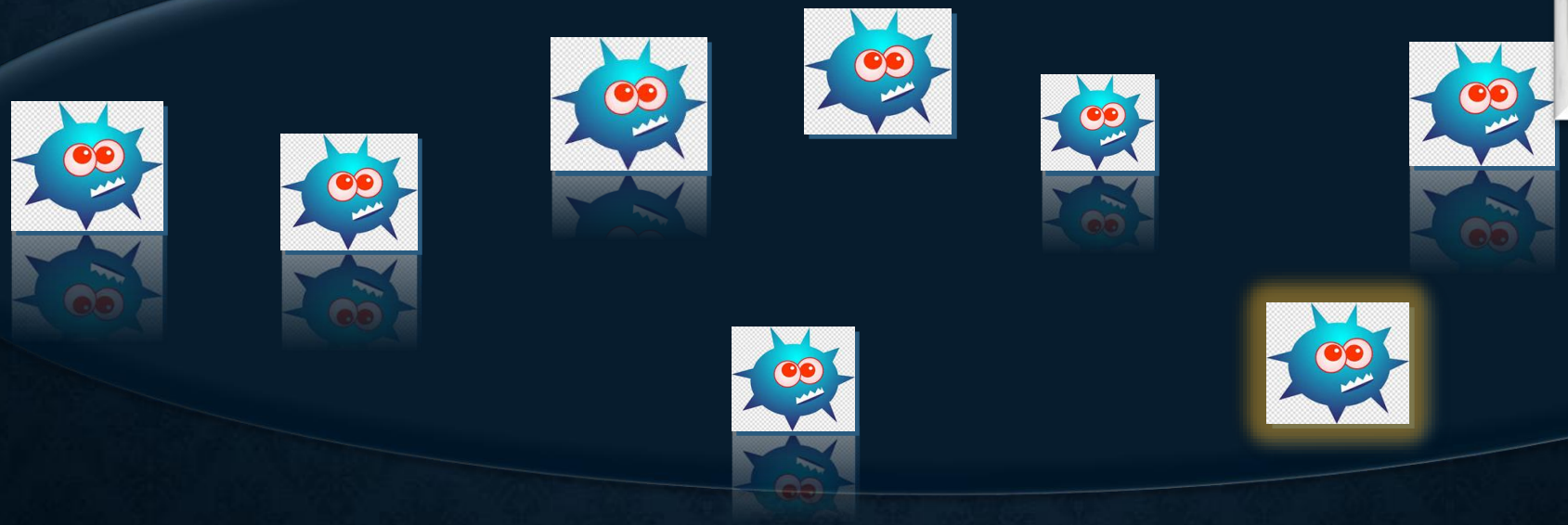
Post-antibiotic effect

Concentration-dependent killing

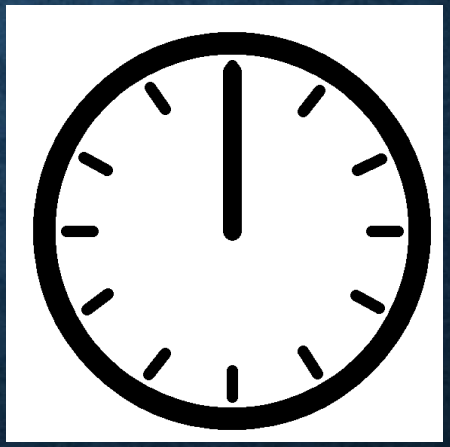


aminoglycosides show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC..





Time-dependent (concentration-independent) killing



The clinical efficacy of antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC.

Post Anti-Biotic effect

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

Drug combinations Advantages

To broaden the antibacterial spectrum.

To prevent dose dependent toxicity.

To increase the antibacterial activity. (synergism)

In severe infections when the etiology is not known, empirical therapy is given.

To prevent the emergence of resistant strains i.e, Multi Drug Therapy is used.

To reduce the duration of therapy.

Drug Combination Disadvantages

bactericidal+bacteriostatic action of the first will be interfered with by the second drug.

sometimes there will be increased toxicity

Increased cost.

DRUG RESISTANCE

- Bacteria are said to be resistant if dose of drug that can be barely tolerated and beyond which toxic effects will be produced cannot halt bacterial growth.

Some bacteria are inherently resistant to antibiotics .

Some initially are sensitive but later due acquire resistance due to spontaneous mutations as well as due to selection.

- There are two types of resistances.
- **Genetic alteration leading to drug resistance.**
- **Altered expression of proteins in drug- resistant organisms**

Genetic Alterations Leading To Drug Resistance.

Spontaneous mutations of DNA;
insertion, deletion or substitution of one or more nucleotides within the genome.

DNA transfer of drug
most resistance genes are plasmid mediated, 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

Altered expression of proteins in drug-resistant organisms

Modification of target sites:, *S. pneumoniae* resistance to β-lactam antibiotics involves alterations in one or more of the major bacterial *penicillin*-binding proteins,

Decreased accumulation
Decreased uptake or increased efflux of an antibiotic can confer resistance (-lactam antibiotics, tetracyclines, and *chloramphenicol)*

Enzymatic inactivation) **β-lactamases (penicillinases**

Types of Antibiotics (Based on their mode of action)

Bacteriostatic Antibiotics

- Tetracyclines
- Spectinomycin
- Sulphonamides
- Macrolides
- Chloramphenicol
- Trimethoprim

Bactericidal Antibiotics

- Penicillins
- Cephalosporins
- Fluoroquinolones (Ciprofloxacin)
- Glycopeptides (Vancomycin)
- Monobactams
- Carbapenems

Classification: Mode of action

- Cell wall synthesis inhibitors
  - Beta-lactams (penicillins, cephalosporins, aztreonam, imipenem)
  - Poly-peptides (bacitracin, vancomycin)
- Protein synthesis inhibitors
  - Aminoglycosides
  - Tetracyclins
  - Macrolides
  - Chloramphenicol
  - Clindamycin
- Inhibitors of essential metabolites (folate)
  - Sulfonamides
  - Trimethoprim
- Injury to plasma membrane
  - -polymyxin B
  - - mystatin
  - - amphotericin B
  - - miconazole
- Inhibition of nucleic acid replication and transcription
  - - Quinolones
  - - Rifampin


Thank
You