ANTIMICROBIAL AGENTS

- **Classification**
- **Resistance**
- **Cross resistance**
- **Prevention of drug resistance**

MASKING of an INFECTION

- Short course treats one infection
- Another infection is masked initially
- Does not manifest
- Manifests later in severe form

Example

- Short course streptomycin for trivial respiratory infection
- Tuberculosis masked

Hypersenstivity reactions

- macropapular **rash**
- urticarial rash
- fever
- bronchospasm
- vasculitis
- serum sickness
- exfoliative dermatitis
- Stevens-Johnson syndrome
- **anaphylaxis**

Drugs that cause Hypersenstivity reactions

- **Penicillins**
- **Cephalosporins**
- **Sulphonamides.**

- **Local Irritancy**
- **Systemic toxicity**

  High therapeutic index

  Lower therapeutic index

  Very low therapeutic index

Local Irritancy

- Gastric irritation
- Pain & abcess at site of i.m inj.
- Thrombophlebitis i.v

Systemic toxicity

- High therapeutic index – **safely**

- Lower therapeutic index –
  doses indivisualized & toxicity watched
  - Aminoglycosides
  - Tetracyclines
  - Chloramphenicol

- Very low therapeutic index
- **used in conditions, no available alternative**

  Vancomycin

  Amphotericin B

Nutritional deficiency

- Prolonged use alter intestinal flora
- Intestinal flora synthesizes vitamin B complex & Vit K
- Utilized by man.
- **Vitamin Deficiency**

Superinfections

- **Appearance of bacteriological & clinical evidence of a new infection during the chemotherapy of a primary one.**

  (common & dangerous)

Microorganisms resp. for new infection :

Enterobacteriaceae

Psuedomonas

Candida & other Fungi

WHY?????

- **Alteration in the normal microbial population of the**

  intestinal,

  upper respiratory

  & genitourinary tracts.

- **Removal of inhibitory influence of the normal flora**

- Normal flora contributes to host defence - antibacterial substances, **bacteriocins** which inhibit pathogenic microorganisms.
- Pathogen has to compete with the normal flora for essential nutrients
- Lack of competition may allow even **nonpathogenic component** of flora to predominate & invade

- More complete the suppression of body flora, greater the chances of developing superinfections.
- Common with **Broad spectrum/extended spectrum antibiotics**

  Tetracyclines, Chloramphenicol
- Low with penicillins
- Incidence inc. with **prolonged administration**

- Pathogen selective agents i.e.

Narrow spectrum

Duration short

Selection of antimicrobial agent

Judicious selection requires

- Clinical judgement &
- Detailed knowledge of Pharmacological properties of the antibiotic
- As well as microbiological factors i.e. potential infecting microorganisms

- Emperical therapy
- Definitive therapy
- Prophylactic or preventive therapy

Emperical therapy

- Infecting microorganism is unidentified
- Antibiotic must cover all the likely pathogens. Combination therapy/Single broad spectrum agent is employed
- Requires knowledge of infecting microorganisms
- Clinical picture suggests the likely microorganism

Definitive therapy

- Culture sensitivity is done
- Once the infecting microorganism is identified Definitive antimicrobial therapy is instituted
- Narrow spectrum

Prophylactic therapy

- Preventing the setting of an infection
- Suppressing contacted infection before it becomes clinically manifest
  - Prophylaxis against specific infections

    Tuberculosis INH (susceptible contacts of open cases)
  - Prevention of infection in high risk situations

  Eg: immunocompromised host, surgical prophylaxis, catheterization, dental extraction,

Factors affecting Antimicrobial Therapy

Depends on

- **Pharmacokinetic factors**
- **Host factors**

Pharmacokinetic factors

- **Site of infection**, Infection in CSF-BBB
- **Concentration** - site of infection

  Minimal drug concentration achieved at the infected site (should be approximately equal to the MIC for the infecting organism)

  Concentration should inhibit microorganisms, simultaneously it should be below the level toxic to human beings.
- **Route of administration**
- **Plasma protein binding**

Factors affecting Antimicrobial Therapy

- **Dose & dosing frequency**

  Constant antibacterial activity,

  rather than peaks & trough.

- **Mechanism of drug metabolism**

  Renal failure: dose reduction

  Aminoglycosides vancomycin Flucytosine

  liver failure:

  Erythromycin Metronidazole Chloramphenicol

Factors affecting Antimicrobial Therapy

- **Host Defences**

  Immunity intact - Bacteriostatic Agents

  Impaired immunity - Bactericidal Agents

Factors affecting Antimicrobial Therapy

- Local factors

  Pus, pH, anaerobic conditions,
- Age
- Genetic factors
- Pregnancy & lactation
- Drug allergy

Therapy with combined AMA's

Justified

- **Broaden the spectrum**

  For emperical therapy

  Treatment of polymicrobial (mixed) infections
- **To enhance antimicrobial activity i.e. synergism for a specific infection**
- **To reduce severity or incidence of adverse effects.**
- **To prevent emergence of resistance**

Therapy with combined AMA's

- **For emperical therapy**
  - **Bacterial diagnosis not known**
  - **Gram +ve, Gram –ve, Anaerobic**
  - **Till culture senstivity report**
- **Treatment of polymicrobial (mixed) infections**
  - **Bronchiectasis, UTI, Peritonitis, Abcesses, bed sores.**
  - **Aerobic + anaerobic organisms both**

Therapy with combined AMA's

- 2/more AMA have to be used to cover the pathogens.
- Drugs chosen : C/S, Bacteriological diagnosis, Senstivity pattern,
- Clindamycin /metronidazole for anaerobes
- Single agent.

Therapy with combined AMA's

To achieve synergism:

When two antimicrobials of different classes are used together

Their can be synergism (supra-additive)

additive

antagonism

- **Two bacteriostatic agents: Additive**

  eg. combination of tetracyclines, chloramphenicol, erythromycin

Exception, Sulphonamide + Trimethoprim **Supraadditive / synergism**

- **Two bactericidal agents:**

Additive if organism is sensitive to both

eg. Penicillin + streptomycin

Carbenicillin + gentamycin

Rifampin + isoniazid

- **Combination of bacteriostatic with bactericidal agents: Synergistic / Antagonistic**
- **If organism sensitive to cidal drug- response to the combination is equal to the static drug given alone**
  - **Apparent antagonism**
  - **Cidal drugs act on rapidly multiplying bacteria.**
  - **Static drug retards multiplication**

- If the organism has low senstivity to the cidal drug – **synergism** may be seen.

- Wherever possible, synergistic combinations may be used to treat infections that are normally difficult to cure.

Therapy with combined AMA's

To reduce severity or incidence of adverse effects.

- Possible **if combination is synergistic** so that doses can be reduced
- Needed with AMA's with **low safety margin,** which when used alone in effective doses produce unacceptable toxicity e.g.
  - Amphotericin B + Rifampin / minocycline
  - Amphotericin B + flucytosine

- **To prevent emergence of resistance**
  - **If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12} bacilli will be resistant to both.**
  - **Chances of relapse will be less**
  - **Chronic infections needing prolonged therapy eg: Tb, Leprosy, H.pylori, HIV etc.**

Therapy with combined AMA's

Disadvantages

- **Risk of toxicity**
- **Multiple drug resistance**
- **Increased cost**
- **Antagonism of antibacterial effect if bacteriostatic & bactericidal agents are given concurrently.**

Antibiotic misuse

- **Treatment of untreatable infections**
  - Viral : measles, mumps, self-limiting.
- **Improper dosage**
  - Wrong frequency, excessive/sub-therapeutic
- **Inappropriate reliance on chemotherapy alone**
  - Abcesses, necrotic tissue/foreign body,
  - Pneumonia, empyema
    - Surgical drainage + AMA
- **Lack of adequate bacteriological information.**

- **Lack of adequate bacteriological information.**
  - **Bacterial cultures, Gram stains too infrequent**
  - **Drug prescription based on habit**
  - **Dosage employed routine rather than indivisualized :**

    Microbiological information

    Clinical situation

- Improper selection of drug
  - dose
  - route
  - or duration of treatment
- Treatment begun too late
- Poor host defence

Failure of chemotherapy

- Failure to take adjuvant measures, pus drainage of empyma, abcesses etc
- Treatment of untreatable infections
- Presence of dormant or altered organisms

Thank u