ANTIMICROBIAL AGENTS

- **Classification**
- **Resistance** ⇒ Withstand the destractive effect of drug by microorganisms.
- **Cross resistance** ⇒ Any Antibiotic that belong to a group and it's resistant to the bacteria, all the group would be the same.
- **Prevention of drug resistance**
  - How to stop the Resistance?

MASKING of an INFECTION

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

=> Ex=) Similar symptoms that got shut down temporarily by the short course of the drug.

2 infections عندي كانه ✗
واحد خفيت بس الدواء لفترة قصيرة
والثاني قوي . و لكن بجوز فس
الأعراض (القوي بيانيت) .
ولأنه الفترة قصيرة ، بقوي أخذ مقاومة
للدواء ، ليه؟ كانه بعزوني أستعمله لفترة أطول!

Example

- Short course streptomycin for trivial respiratory infection
- Tuberculosis masked

will reappear later
But in severe form!

Hypersenstivity reactions

- macropapular **rash** → red area w/ bruising in the center.
- urticarial rash → rash caused by wound
- fever
- bronchospasm
- vasculitis
- serum sickness → immune complex reaction
- exfoliative dermatitis → تقشير للطبقة العلوية من الجلد
- Stevens-Johnson syndrome ⇒ Serious disorders of skin and mucous membrane.
- **anaphylaxis**

Q) All the following are true, except?

Q) Which of the following is a hyper sensitivity reaction?

Drugs that cause Hypersenstivity reactions

(Adrenaline, corticosteroids, Antihistamine) given during severe Allergy reactions → Most important drugs that should be Available always.

- 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

Mostly caused be staphylococcus bacteria

Collection of pus in small zones

Inflammation of the vein, may cause thrombosis

why? Endothelial injury.

Systemic toxicity

- High therapeutic index – **safely**

- Lower therapeutic index –
  doses individualized & toxicity watched

  Aminoglycosides

  Tetracyclines

  Chloramphenicol

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

  Vancomycin

  Amphotericin B

Nutritional deficiency

- Prolonged use of Anti-Microbials alter intestinal flora (Microorganisms Naturally present in the gut)
- Intestinal flora synthesizes vitamin B complex & Vit K
- Utilized by man.
- **Vitamin Deficiency** ⇒ Net Result of Prolonged use of Antimicrobials

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

أنواع البكتيريا اللي ممكن تصيبني أثناء الـ Primary Infection.

WHY?????

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

  intestinal,

  upper respiratory

  & genitourinary tracts.

- **Removal of inhibitory influence of the normal flora** ⇒ due to prolonged use of Antimicrobial or Malnutrition.

- 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** ⇒ لأنه من بمكن الأدوية واسعة المدى, تأذي الـ Normal Flora.

Ex: Tetracyclines, Chloramphenicol

- Low with penicillins
- Incidence inc. with **prolonged administration**

- Pathogen selective agents i.e.

Ex → gram + or -

Narrow spectrum

Duration short

Selection of antimicrobial agent

الإختيار بحكيم

Judicious selection requires

- Clinical judgement &
- Detailed knowledge of Pharmacological properties of the antibiotic Suitable w/ the clinical symptoms and the kinetics of the patient or Not!
- As well as microbiological factors i.e. potential infecting microorganisms

like cidal or static!

- **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

Ex: gram(-)

obvious symptoms

guess

Narrow the options

Definitive therapy

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

Prophylactic therapy

⇒ Vaccines are an example!

- 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

Ex:

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

Factors affecting Antimicrobial Therapy

Depends on

- **Pharmacokinetic factors**
- **Host factors** ⇒ Patient

Q) what are the Pharmacokinetic factors?

- **Site of infection**, Ex: 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)

  لازم يوصل موقع الالتهاب تركيز قده او أعلى من الـMIC

  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**

Lower doses than Normal.

Renal failure: dose reduction Ex

Aminoglycosides, vancomycin Flucytosine

liver failure: Ex

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

مجموعة من الأدوية

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.** ← واحد فيكون يلغي الأعراض الجانبية للثاني.
- **To prevent emergence of resistance**

1 + 1 = 3 additive 1+1=2

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,** culture sensitivity
- **Clindamycin /metronidazole for anaerobes**
- **Single agent.** ⇒ one drug has all the specs needed.

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

↳ More powerful than what we expected to be.

- **Two bactericidal agents:**

killer

Additive if organism is sensitive to both

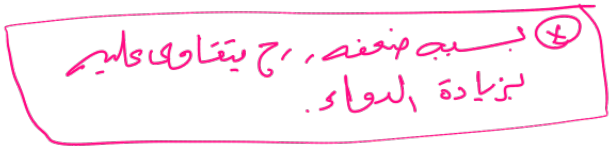
eg. Penicillin + streptomycin

Carbenicillin + gentamycin

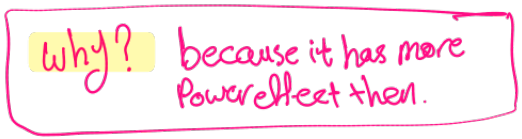
Rifampin + isoniazid

- **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** Ex: maybe both toxic!
- **Multiple drug resistance**
- **Increased cost**
- **Antagonism of antibacterial effect if bacteriostatic & bactericidal agents are given concurrently.** استغلو عكس بعض او ضد تأثير بعض

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.**

بحيث الأدوية
عالها ما بزبطلها مثال:
ممكن بحاجة لعملية جراحية!

- **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