



اللهم وفقني في دراستي، ونور بالكتاب بصري، وشرح به
صدري، واستعمل به بدني، واطلق به لساني، وقوّ به عزمي
بحولك وقوتك، فإنه لا حول ولا قوة إلا بك يا أرحم الراحمين

كل ما في السلايدات مطلوب حفظه و الملخصات
المذكورة في الملف هي وسيلة لتسهيل ربط المعلومات و
تضمن ملاحظات حكتها الدكتورة

وفقكم الله...

Antimicrobials Therapy

ميكروب (microb) دند

Pharmaceutical Microbiology

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Antimicrobial → Drugs effective to eradicate microorganism

الركيزة دى هاد السلايد → مش للحفظ

History of antimicrobial drugs

Introduction

- The discovery of Antimicrobial drugs have successfully controlled the majority of bacterial, parasitical, fungal infections during the last 80 years or more.
- Sulfonamide 1934, Penicillin G 1941 (from Penicillium notatum), followed by Aminoglycosides (Streptomycin, Kanamycin, 1946, from soil bacteria - Actinomyces).
- At present more than 100 antimicrobial drugs of different classes are available for use in humans.
- Clinically effective antimicrobial agents should exhibit selective toxicity toward the bacterium and not the host, few side effects and good pharmacokinetics.

ملحوظات مهمة مطلوبة :-

Efficacy & Safety

لأي دوا دهنا فيه :-

To Kill the microbes

Drug should exhibit a Kind of selective

toxicity

سبب selective toxicity هو اختلاف
ال wall cell تاع Fungi الذي كيتوي
عن chitin و عمر وجوده عند ال human

(that mean:- active against microorganism
alone & has less activity
against human cell)

Chemotherapy agent لا تستخدم فقط للتجرب عن علاج الكائنات
الكيميائية وإنما لأي علاج تستخدم فيه Chemical substances

Pr

Antihypertensive drugs considered as chemotherapy

يعني

Definition

- **Chemotherapeutic agent (drug):** any **chemical substance** used in medical practice
- **Antimicrobial chemotherapy:** the utilization of chemical substances to treat **microbial infections**
- **Antibiotic:** chemical substances **produced** by **microorganisms** that inhibit the growth or destroy other microorganisms when used at low concentration. Such as Penicillin
- Although the definition of **antibiotic** indicates natural substances, many antimicrobial compounds that are **semisynthetic** (e.g. some β -lactams) or **synthetic** (e.g. sulfonamides & quinolones) are still called antibiotics in common practice

الشخص يفرق بين دكتور وصيدلي Antibiotic
Natural substances هي مخرطة كذا عامة هي تفرز
Synthetic & semisynthetic & natural

Properties of Ideal Antimicrobial Agents

1. Selective toxicity:

- **The drug should harm the microbe without significant harm on the host.** This means the **toxic dosage level** (the dose that causes damage to the host) should be much higher than the **effective therapeutic dosage level** (the dose needed to destroy the microbe).

لازم يكون TD اكبر من ED بكثير

- To evaluate toxicity of the drug, **chemotherapeutic index** is used: the ratio between toxic dose & effective dose

1) **Toxic dosage** → The dose that causes damage to the host

2) Therapeutic index $= \frac{TD_{50\%}}{ED_{50\%}} = \frac{\text{Toxic dose in 50\% of the population}}{\text{Effective dose in 50\% of the population}}$

3) **effective therapeutic dosage** → The dose needed to destroy the microbe

Properties of Ideal Antimicrobial Agents

2. **Nonallergenic.** The agent should not elicit an allergic reaction in the host. *Some of antibiotic causes allergic response such as:- Penicillin or B-lactam*
3. **Stability:** maintenance of a constant, therapeutic concentration in blood and tissue fluids → *Constant therapeutic concentration* *الحافظ على التركيز العلاجي*
4. **Resistance** by Microorganisms Not Easily Acquired. → *ما ينفذ البكتيريا تحمل أي مقاومة*
5. **Long Shelf-life.** *(كل ما كانت البكتيريا لا مقاومة كل ما كان أفضل)*
6. **Reasonable Cost.** → *Hope & request of any patient*

Ideal antimicrobial agent

Non allergic: not Produce any allergic response

Stable: it should maintain therapeutic effect at certain *storage* & certain temperature

Long shelf-life
بعض Antibiotic
يوجد فترة حجب التوقف عن استخدامه بفترة قصيرة بعد فتحه للزجاجات
يعني في فيلدا Powder لو تم حلها خلد يتم استخدامها وهي ما تبقى

No resistance
by microorganism
if it Kill microorganism or suppress its growth, this bacteria should not produce any resistance

The Spectrum of Activity

Spectrum: the range of microorganisms that a drug is effective against

1. **Narrow spectrum** antibiotic: active against single or limited group of M.O. (Isoniazid) *• فئله أوسى Antibiotic فعال فقط لـ E.coli*
2. **Extended spectrum** : is one that, as a result of chemical modification, affects additional types of bacteria, usually those that are gram-negative. active against types of bacteria G- & G+.
(Ampicillin) • فئله Antibiotic تستخدم لـ G+ve و G-ve
3. **Broad spectrum:** active against a wide variety of microbial species.
(Tetracyclines, quinolones, Chloramphenicol)

• بعض Atypical bacteria, Mycoplasma و G+ve و G-ve

يعني هذا ال Spectrum يغطي range كبير

The Spectrum of Activity

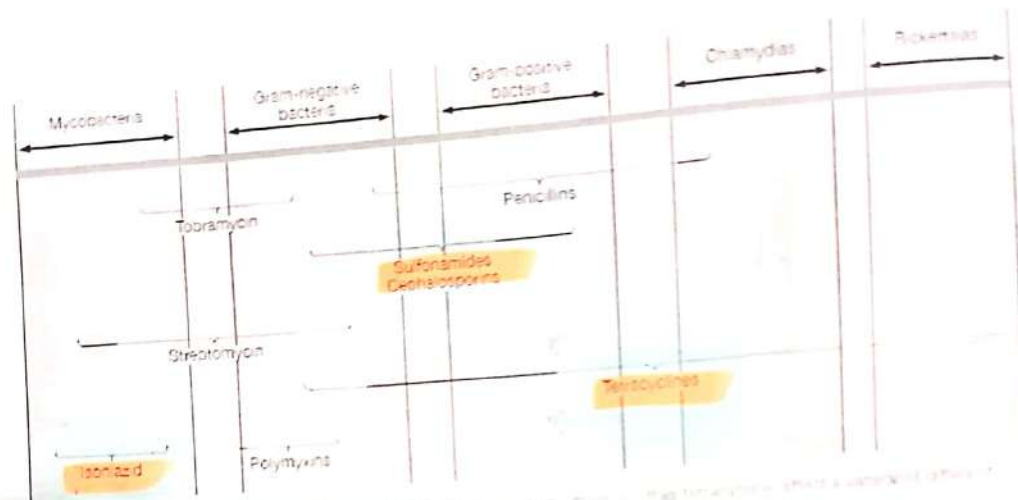


FIGURE 13.1 The spectrum of antibiotic activity. Each antibiotic drug is effective against a specific group of organisms. Narrow-spectrum drugs act on a small group of organisms, while broad-spectrum drugs act on a large group of organisms.

- Isoniazid → used for only Mycobacteria so it is Narrow Spectrum
- Sulfonamides & cephalosporins → used for G+ve & G-ve so it is extended spectrum
- Tetracyclines → used for G+ve & G-ve & A typical bacteria like Chlamydia & Rickettsia so it is broad spectrum

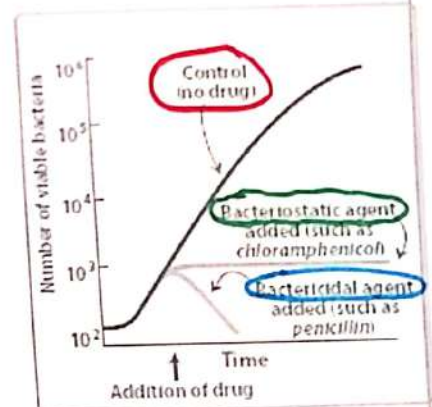
Antimicrobial Action

ملاحظة: حسب حالة المريض يشوف
ثوبيلش يعني من دايماً بيش ب

Bacteriostatic

Bacteriostatic: inhibit growth of microorganisms such as (Sulfonamides, Chloramphenicol and Tetracyclines). This is determined in vitro by testing a standardized concentration of organisms against a series of antimicrobial dilutions. The lowest concentration that inhibits the growth of the organism is referred to as the **Minimum Inhibitory Concentration (MIC)**.

Bactericidal: Kill microorganisms (such as Penicillins and Aminoglycosides). This is determined in vitro by exposing a standardized concentration of organisms to a series of antimicrobial dilutions. The lowest concentration that kills 99.9% of the population is referred to as the **Minimum Bactericidal Concentration (MBC)**.

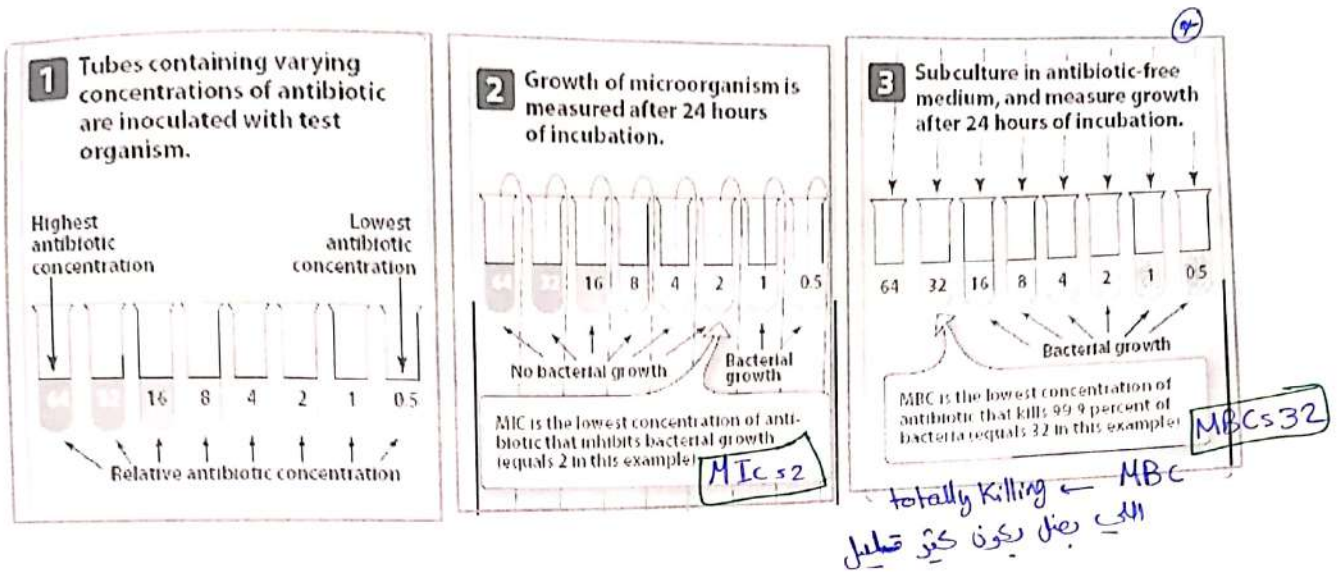


لو زرعنا عدد معين من Bacteria بي
Petri dish 6 ساعة without any drug
مع الوقت دج يزيو

ولنا يكون أوتيل
(Plateau Phase)

عدد البكتيريا سيبف (Bacteriostatic agent)
عدد البكتيريا سيبف لان
سيتاع

Chloramphenicol (Bacteriostatic agent)
Penicillin (Bactericidal agent)



Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

→ That's mean → Many of Antibiotic has either Bactericidal or Bacteriostatic effect (not both) وهذا

Concentration dependent
يعني بليست Bacteriostatic (كن لا)
Bactericidal بليست Bacteriostatic

Selection of
يعود لاختلاف mechanism of action
فقط واحد
Bactericidal أو Bacteriostatic

Agents



= Factors that is needed when we select antimicrobial agent?
يعني سبب اختلاف Drug من Patient ل Patient رغم انه نفس المرض

① Genetics → مثلاً: مرضى القولون في أدوية لا يستطيعوا أخذها

② Age → في Antibiotic لا تعطى لمن هم أقل من 18 سنة

③ Immune Status

⑤ Gender → المرأة الحامل في Antibiotic لا تعطى لها

④ History of allergy

⑥ Drug-Drug interaction

Microbiology

* what causes selective toxicity ?

هو اختلاف structure ال microorganism عن ال Human
فمثلاً ال Fungi يحتوي ال cell wall على Chitin
ولكن هو غير موجود عن الإنسان

لكن ال Selective toxicity لا تمنع ان يكون هناك Side effect

بسبب ال Adverse reaction فحينئذ يكون ال Adverse reaction
دعم ذلك .

* The better of drug to have a good Pharmacokinetics

- Good absorption so enhancing bioavailability
- Good distribution to reach the site of action
- Easily metabolized So do not produce toxic metabolite
which considered good & easily to eliminated or excreted
by the Kidney

Anti biotic

Antidot biology (مضاد حيوي)

Substances Produced by microorganism in which this
Substances are capable to inhibit or Kill another
microorganism once it used in certain doses

فمثلاً ← Penicillin Produced by the fungi
to Kill another organism (bacteria)
So Penicillin is antibiotic

* Antibiotic's Source is natural Compounds

but Some Cases are not natural

- Semisynthetic
- Synthetic

So, Antibiotics maybe

- natural e.g. Penicillin
- Semisynthetic e.g. Some β -lactams
- Synthetic e.g. Sulfonamides & Quinolones

- Classification of antibiotics according to spectrum :-

the range of microorganism that drug against it

Narrow spectrum :- used for limited group of microorganism

Extended spectrum :- result of chemical modification so affect additional types of bacteria

Broad spectrum :- Active against a wide variety

- Classification of antibiotics according to Action :-

Bacteriostatic :- Arrest or inhibit microorganism
(Tetracycline, Sulfonamides, Chloramphenicol)

Bactericidal :- Kill microorganisms
(Penicillins, Aminoglycosides)

حسب ملاحظة المريض نقرر إعطائه Bacteriostatic أو Bactericidal
 للملاحظة المرضية من ملاحظة (compromise immune system)
 Bacteriostatic أو Bactericidal
 للملاحظة المرضية من ملاحظة (compromise immune system)

MIC → The lowest concentration that inhibits the growth of organisms

لو دوا الـ 4 MIC = 20 و دوا الـ 40 MIC = 40
 من راج يكون more potent ؟ الـ 40
 وهذا يعرف عن طريق Serial dilution مع شرحه في آخر

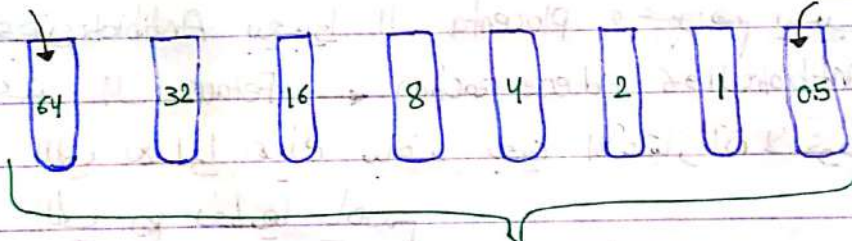
MBC → The lowest concentration that kills 99.9% of Population

Serial dilution

لتحديد ومعرفة MIC & MBC

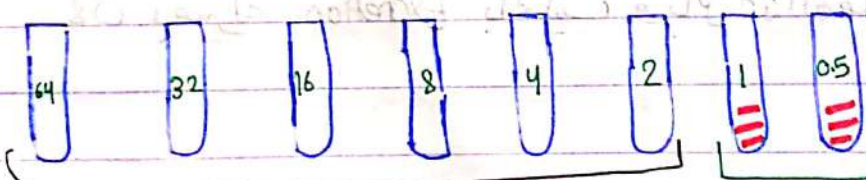
Highest antibiotic concentration

Lowest antibiotic concentration



Relative antibiotic concentration

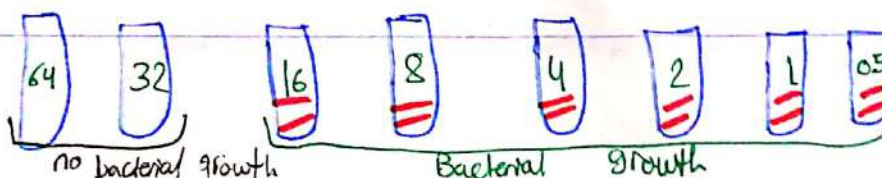
24 hours of inc. نتجى منقطع بعد



no bacterial growth

High bacterial growth

هنا هو لو بنينا خدر MIC و MBC من الرسمه هي
 بيين معنا ان MIC ≤ 2 لان هو اقل تركيز من Antibiotic لشيط النمو البكتيري



no bacterial growth

Bacterial growth

لكن
 من هو نحدد MBC ≤ 32
 الي هو اقل تركيز Antibiotic يقتل 99.9% من البكتيريا

* For sure before we starting any ...
1) making a diagnosis that we have infection

2) identify the site of infection
3) take specimen of infection to determine if its 3+ve or G+ve
[CSF ناض عينة من CSF] meningitis

4) identify the causative microorganism

1- Making the diagnosis :

- ✓ To be sure that the patient is suffering from an bacterial infection. → infection
- ✓ Know the site of infection (GI, RT, UT).
- ✓ Take the required specimen from the patient. (blood, CSF, mid stream urine, ear swap, vaginal discharge)
- ✓ Identify the organism.

2- Remove the pathological barrier to cure (abscess, obstruction).
[حاجز دوائى للمضاد للميكروبات] Antibiotic
→ to increase the effectiveness of treatment

3- Select the best drug : So that it reach site of infection in the therapeutic conc.

- Drug properties: PK, TI. selecting will be depending on Patient factors
- Optimum dose & frequency & drug safety
- the most appropriate route of administration

4- The cost of therapy.
[في اوقاتنا وايضا رخيص]

- لازم متنبه يكون عندي :
- ① Right drug
 - ② in right rout
 - ③ in right frequency
 - ④ in right duration
- من الخطأ عدم تغطية ال Antibiotic

إذا كان عند المريض obstruction أو abscess (القهار بالدار أو حرقه) وفيه accumulation of dead cells بسبب Burns مثلا وفعلا Dead cells تعتبر Barrier أو mold بعد أي عملية جراحية يصير في Abscess التي هو Pus secretion (الخراج) لازم أول نزيل ال Pus ونظف الجرح ثم نغطي Antibiotic

5- Patient factors:

1. Immune system.
2. Renal dysfunction. → will lead to drug accumulation & So drug toxicity
3. Hepatic dysfunction. → lead to growth bacteria that is resistant to this antibody
4. Poor perfusion.
5. Age.
6. Pregnancy.
7. Lactation. → She should avoid taking tetracycline, it will excreted in milk and affect on the baby
8. Concomitant medication.
9. Allergy.

* Pregnancy → Placenta Antibiotic نطعم ويعبروا

لكن بعضهم لازم لأن دخولهم رح بسبب Adverse fetal reaction (سؤفات حادة)

When we start healing infection :-

- ① For Sure before we starting antibiotic we should
 - make sure the patient is suffering from bacterial infection
 - Know site of infection
 - Take Specimen of the patient
 - Identify the organism
- ② Remove the pathological barrier to cure to increase the effectiveness of treatment in cases of abscess and obstruction
- ③ Select the best drug by determining:-
 - optimum dose & frequency
 - The most appropriate route of administration
- ④ The cost of therapy
- ⑤ Patient factors (9 factors are mentioned in previous slides)
 - لكن سن في 2 Factor بنا سنه عنهم في مهم :-
 - ① بعض Antibiotics يعبروا ال Placenta وعبورهم يسبب Adverse reaction ← Fetus عند ال Antibiotic
اللي يعملوا هيك بناخذ بعين الاعتبار ان لانكون Pregnancy women اللي ربح نعطها باهم
 - ② المرأة المرضعة لازم ما نعطها Tetracycline لان بصره Excretion بالحليب وبنار عن الطفل

Once we identify the organism we select the treatment
 لكن في Some cases we give the antibiotic before we identify the organism - Some exception

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established.

However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

* meningitis cancer patient should take the antibiotic before identify the organism
 immediate empiric therapy

مثل مريض
 meningitis
 ضاعته ضعيفة
 فيكون ما يتكون
 الضو وحرارة
 عالية مباشرة
 ببطء Antibiotic
 وسحب عينه
 CSF لان العينه يتطول بها 3 ايام

In empiric therapy we give either antibiotic has broad spectrum or combination

Empiric therapy: is treating the patient without knowing the causative organisms & their sensitivity test. because we can't wait!

Immediate administration of the drug prior to identification of bacteria and sensitivity test. (or the specimens is obtained but lab result not available)

Definitive therapy

treating exactly the causative agent depending on its sensitivity test (done after receiving the results of test)

identify the microorganism then give the treatment

Prophylactic therapy: وقاية

Used drugs to prevent an infection rather than to treat, to maintain health and prevent the spread of disease.

give the treatment before the occurrence of infection

مثل الملاريا من infection سريعة الانتشار
 لما كانوا يسافروا بالبحر
 كانوا ياتخذوا Antimalarial medication
 causes

- We should to treat infection by antimicrobial **after** the organism has been identified except in empiric therapy

Therapy types

Empiric therapy

- Treat patient without know causative agent
(Treat infection **before** know the causative agent)

- Combination or broad spectrum is given

Definitive therapy

- Treat patient after know causative agent

Prophylactic therapy

- Treatment to prevent an infection
as in:- antimicrobial medication

2 or more
antibody

Combination of
antibiotics

use 4

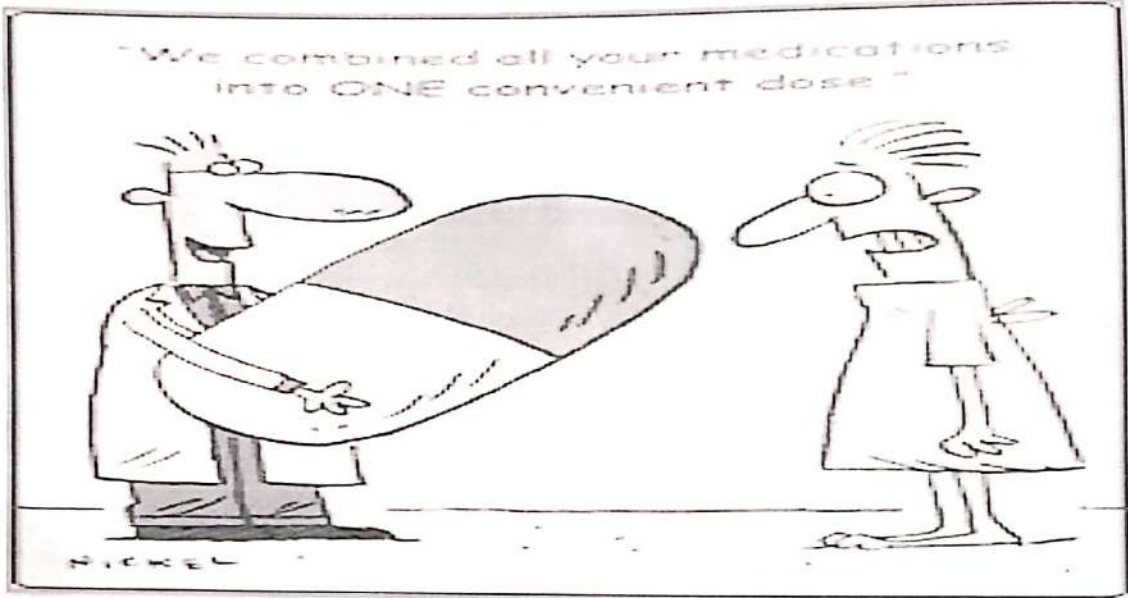
① increase drug efficacy

Advantages : ② Broaden spectrum (

③ Avoid drug resistance

Gr+ve & Gr-ve

Combination of antimicrobials



To control certain infections ← Combination
Patient critical illness & microorganism
empiric therapy

Advantages

1. To delay or avoid the development of resistance.

(Ex. Tuberculosis)

→ need combination of drugs to treat it

2. To broaden the spectrum of activity. (Mixed infection, severe unknown infection,).

because it is highly resistant

3. To obtain potentiation (synergistic effect).

Ex: -B-lactams and aminoglycosides in endocarditis. Penicillin + Aminoglycosides

2 separate IV bolus injection, with time interval to avoid interaction.

- Co-trimoxazole.

Aminoglycosides

inhibition of protein

Synthesis in bacteria

β -lactam

inhibition the cell wall

Penetration

Aminoglycoside

cell wall →

Disadvantages:

1. Concomitant administration of a second agent is usually bacteriostatic and may interfere with the action of the first drug that is bactericidal • مع إعطاء الدواء معاً يكون تأثيره بكتريوساتيك وقد يتداخل مع تأثير الدواء الأول الذي يكون بكتريسيدي

Antagonist agent لا اوقات میں (کون) Synergistic effect کے ساتھ ملا کر Synergistic effect

2. Suppression of normal flora, so give higher chance for opportunistic infection (superinfection).

3. Increased incidence of adverse reactions. *increase the risk of adverse effect*

4. Highly cost

because once the antibiotic is broad spectrum, the patient is exposed to another infection because antibiotic (broad spectrum) may kill the normal flora.

when? once we identified the infection & the causative microbe
 & give drug in right route & frequency & dose & duration

Using of antimicrobial? yes!

Problems with antimicrobial agents

→ but using antibiotic associated with some problems :-

1. Drug resistance. (the major problem)

(if the maximal level of that antibiotic that can be tolerated by the host does not halt bacterial growth).

- ## 2 Drug-drug interaction

- ### 3. Adverse effects.

note

Drug tolerance:-

The therapeutic dose is ~~not~~ effective to induce an effect

جهاز Dose II
Inhibit or Kill bacteria

مسئله ال Problems :-

mistake in Proper drug

mistake in selected drug dose

mistake in right frequency

mistake in drug combination

multiple factor will increase the drug resistance

Note Prebiotic → nutrient or food
Probiotic → normal flora itself

Problems with antimicrobial agents

3. Adverse effects

Dose related

a. Hypersensitivity: (not dose related)

e.g. Penicillin, cephalosporin.

b. Toxic effect (dose related)

High serum levels of certain antibiotics may cause Direct toxicity / Organ toxicity

e.g. Aminoglycosides (ototoxicity)

c. Superinfections:

Play important role in Patient immune mechanism

alterations of the growth of normal flora of intestine, genitourinary tracts.

Respiratory tract

Appearance of a new infection while treating an original infection (multiply C.difficile).

→ Antimicrobial that is characterized by wide therapeutic index can alter growth of normal flora in intestine or genitourinary system or respiratory system

Clindamycin pleural infection → can alter normal flora growth so Patient susceptible to superinfection

Mechanisms of Action of Antibacterial Drugs

Antimicrobial drugs affect various bacterial cellular targets:

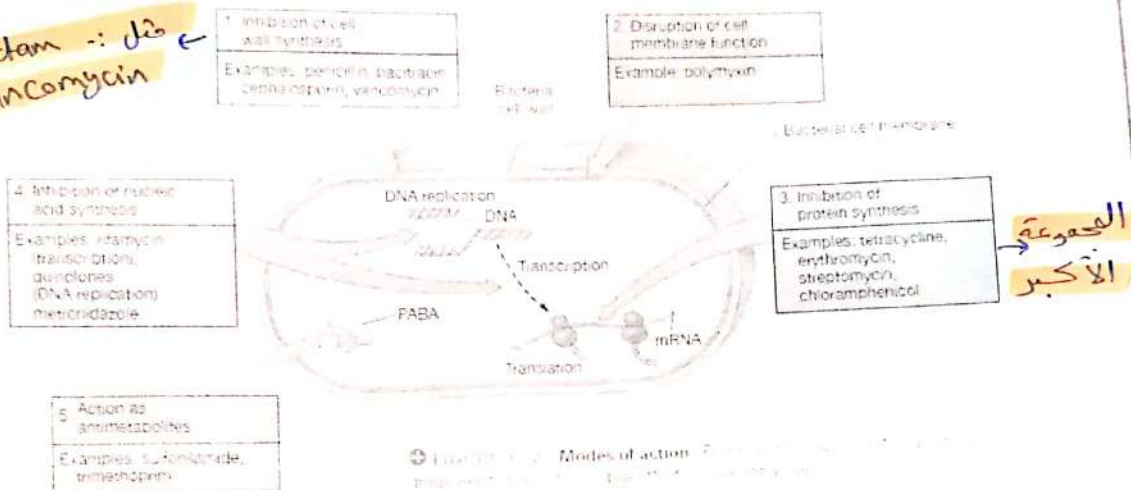
1. Inhibit cell wall synthesis will affect on Peptidoglycan
2. Inhibit protein synthesis will affect on RNA & ribosomes
3. Inhibit nucleic acid synthesis
4. Injury to plasma membrane
5. Inhibit synthesis of essential metabolites

Folic acid is need for bacteria

which are important for DNA & RNA synthesis

Mechanisms of Action of Antibacterial Drugs

B-lactam :- β -lactam
& Vancomycin



(these structure are like the same of substrate)

Competition

Antibacterial
receptor

Inhibition of Cell Wall Synthesis

β -Lactam Drugs

- The main group of AB that act on bacterial cell wall is the 'beta lactams'; so called due to presence of a β -lactam ring.
- Irreversibly inhibit enzymes involved in the final steps of cell wall synthesis
- These enzymes mediate formation of peptide bridges between adjacent stands of peptidoglycan (cross link, PBPs)
- Drug binds to enzyme, competitively inhibits enzymatic activity
- β -lactam drugs include: Penicillins, Cephalosporins, Carbapenems and Monobactams

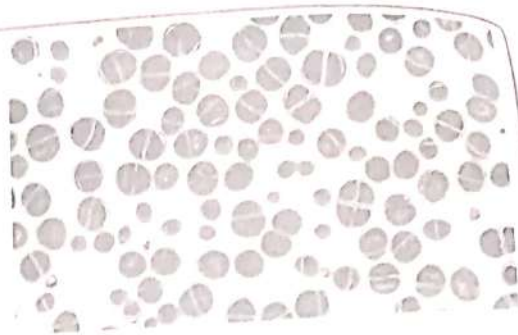
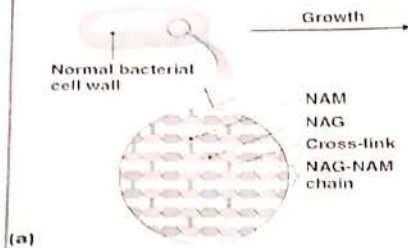
- Once bacteria is needed to divide, it will prepare its cell wall to be able for separation.

- Subunits needed in cell wall synthesis :- N-acetyl glucose amine

Link between subunits
(New NAM to old NAM)

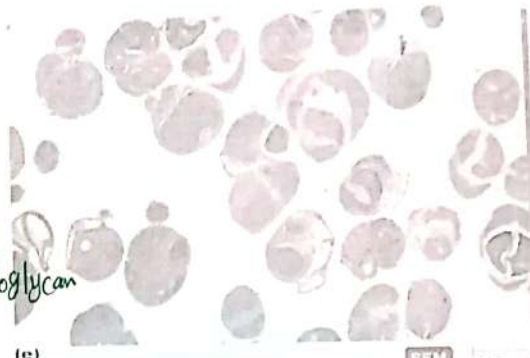
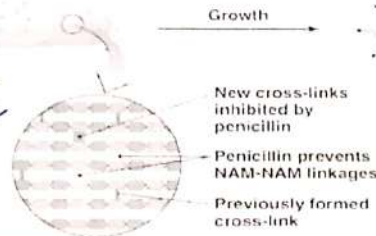
A bacterial cell wall is composed of a macro molecule of peptidoglycan composed of NAG-NAM chains that are cross-linked by peptide bridges between the NAM subunits.

New NAG and NAM subunits are inserted into the wall by enzymes, allowing the cell to grow. Normally, other enzymes link new NAM subunits to old NAM subunits with peptide cross-links.



Penicillin interferes with the linking enzymes and NAM subunits remain unattached to their neighbors. However, the cell continues to grow as it adds more NAG and NAM subunits.

The cell bursts from osmotic pressure because the integrity of peptidoglycan is not maintained.

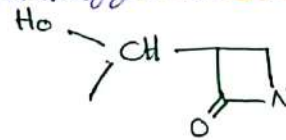


Penicillin disrupts the cell wall

New cross-links inhibited by penicillin
Penicillin prevents NAM-NAM linkages
Previously formed cross-link
integrity of Peptidoglycan

Penicillin interferes with linking enzymes so new cross links will be inhibited by penicillin & penicillin will prevent NAM-NAM linkage & material of bacteria will go out & affect on integrity of peptidoglycan so cell bursts so penicillin is bactericidal

β -Lactams Antibiotics



β -Lactams $\rightarrow$ Bactericidal

Cephalosporins

- Cefalexin
- Cefuroxime
- Cefotaxime
- Ceftriaxone

Cephalosporine $\rightarrow$ Cef

Monobactams

- Aztreonam

end with am

Carbapenems

- Meropenem
- Imipenem
- Doripenem
- Ertapenem

Penicillins

Narrow Spectrum

- Benzylpenicillin (Penicillin G)
- Phenoxymethylpenicillin (Pen V)
- Flucloxacillin

Broad Spectrum

- Amoxicillin/Co-amoxiclav
- Ampicillin

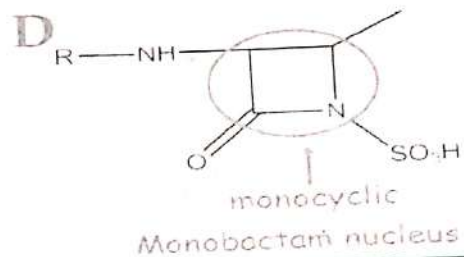
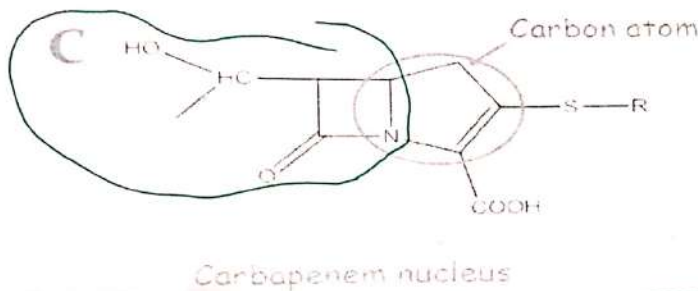
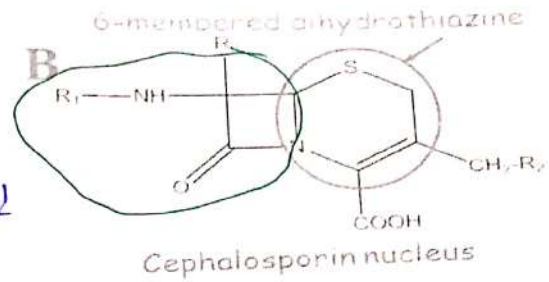
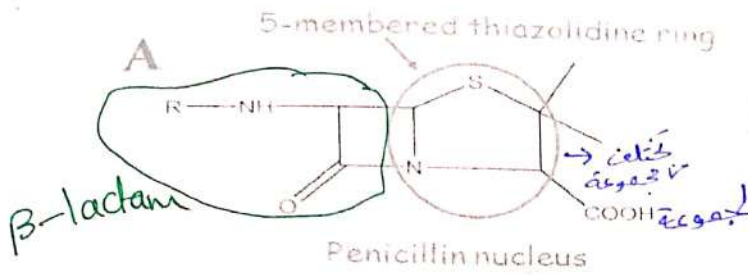
Penicillin $\rightarrow$ Drug name end with icillin

Carbapenems $\rightarrow$ Drug name end with Penem

→ They share the Same β -lactam ring

β -lactam antibiotics

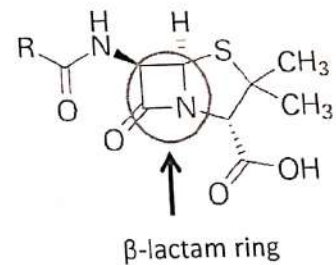
bio 11 for Structure 11



* β -lactam ring is so important for antibiotic action, if it is destroyed the antibiotic will lose its activity

Penicillins

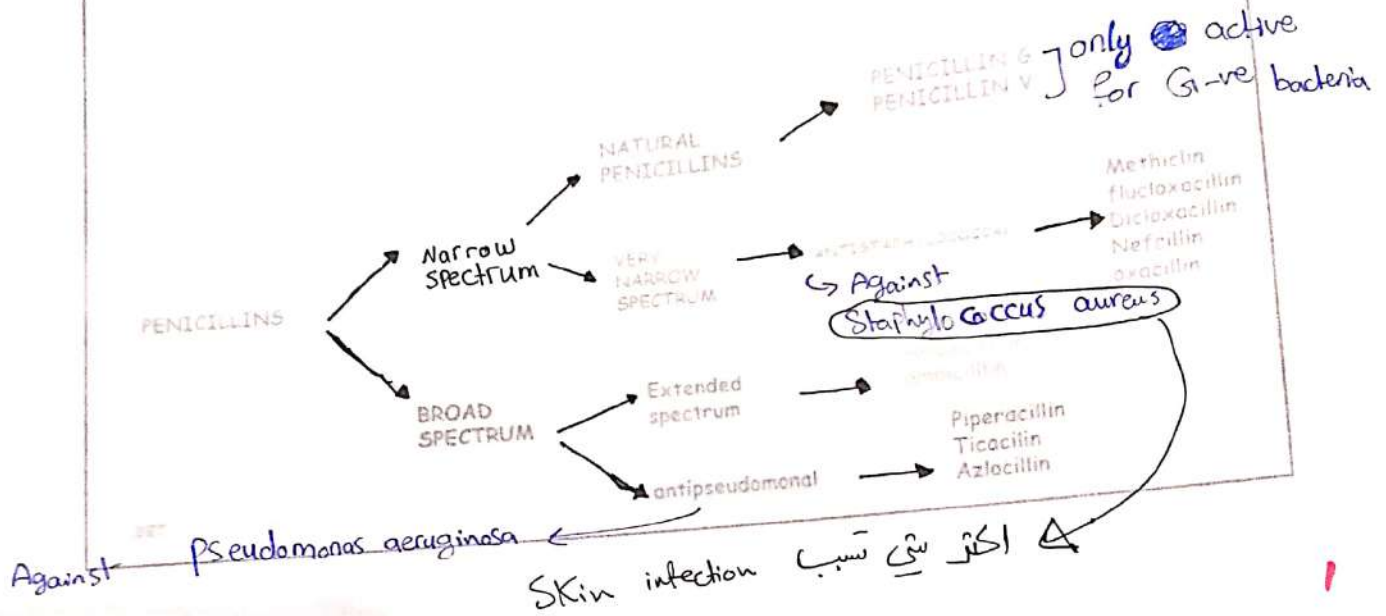
- Have β -lactam ring
- Bacteriocidal



- Their official names usually include or end in "cillin"

مضاد حيوي واسع النطاق Bacteriocidal
يكون wide spectrum

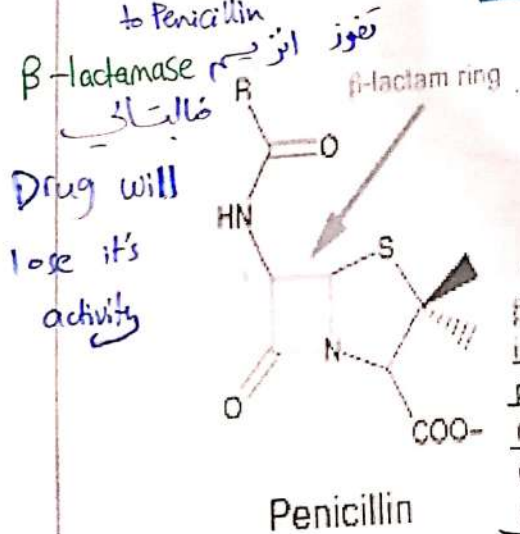
Classification of Penicillins



Some bacteria produce β -lactamase enzyme that breaks the critical β -lactam ring

Penicillin Resistance

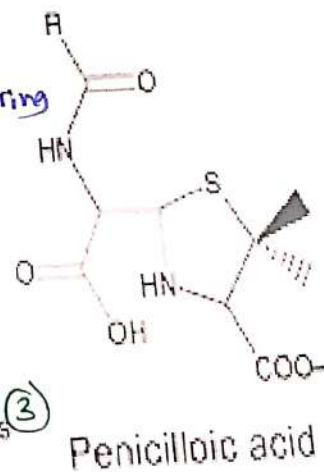
β -lactam ring is very important for antibacterial drug



Degrade the β -lactam ring

β -lactamase

① β -lactamase breaks a bond in the β -lactam ring of penicillin to disable the molecule. Bacteria with this enzyme can resist the effects of penicillin and other β -lactam antibiotics.



it has no antibacterial effect ← **فم حل المسألة ← تم تطوير دوا**
 it is only β lactamase inhibitor

B-lactamase inhibitors

Substance **don't** have antibacterial activity but they have the ability to **inhibit** the B-lactamase enzyme....

- Suicide inhibitor -

Ex. **Clavulanic acid**

Clavulenic acid **يعني يتحرر و تقاومه البكتريا**

Amoxicillin **حتى يقوم بحد**

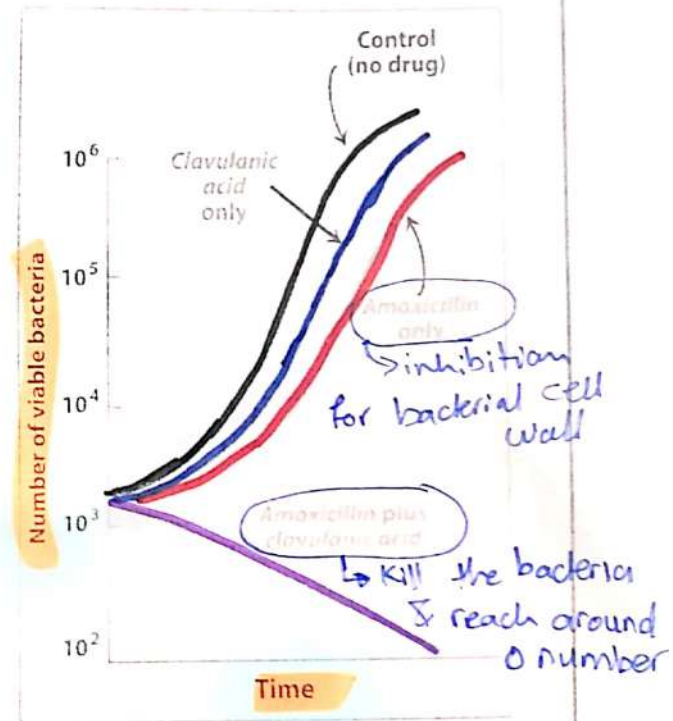
For example clavulanic acid Binds to beta-lactamase and competitively protects amoxicillin

*They potentiating amoxicillin against beta-lactamase producing bacteria.

* It is called "suicide inhibitor"

عززة من قبل inhibition β -lactamase

Addition of Clavulanic acid to amoxicillin Potentiate it's action



Black line → Bacteria has not been treated so with time there is still a bacterial growth

Blue line → number of bacteria decreases a little bit, but there is no anti bacterial effect (very weak)

Red line → number of bacteria decreases more & more

Purple line → Best result

Penicillins adverse effects

- Allergy to penicillins is rare among children but occurs in 1 to 10% of adults.

أكثر Adverse effect من Penicillins هو Allergy

- Mild: rash

- Severe: anaphylaxis & death

هم دائماً نشأه المرض اذا عنده
Penicillin allergy

✓ There is cross-reactivity among all Penicillins

لو المرضي تحسس من

Amoxicillin

✓ Penicillins and cephalosporins ~5%

وربعه اعطاه Ampicillin

غلط لأنهم نفس المجموعة
Cross allergy يعني عند المرضي يكون في

5% حساسية من Penicillin & cephalosporin

- Penicillins are generally nontoxic, but large doses can have toxic effects on the kidneys, liver, and central nervous system

Anaphylactic shock → ~~acute~~ acute sever ~~situation~~ situation

↳ acute sever situation associated by:- Bronchoconstriction & Vasodilation
& this may induce death

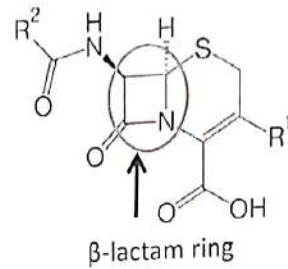
* المطلوب بالأساس Prefix أو Suffix هو أي مجموعة

Cephalosporins

- Different generations (1st, 2nd, third and fourth.) 5th
- Bactericidal medications

- Safe in general

- 1st and 2nd generation drugs are not used for CNS Infections



- They are recognised by the inclusion of "cef" or "ceph"

يعني لو واحد عنده Bacterial meningitis ما بروج استعمله Cephalosporine
لأنه من ضمن الشغل
Antibiotic
هو إنه زعن ومنه
Site of infection

- they tend to be more resistant than Penicillins to β -lactamases

- They are safe in pregnancy & taking by lactating mother

CNS cephalosporine لا يدخل إلى

Cephalosporins

- Since cephalosporins are structurally similar to penicillins, 4-15% of patients who are allergic to penicillins are also allergic to cephalosporins

المريض الذي عنده Penicillin allergy

ما يخطيه Cephalosporine

- Penicillins & cephalosporins exert their activity against growing bacteria

لو كان عنده Dormant bacteria
Penicillin & Cephalosporine
ما راح يعطي activity

WHY???

لو استخدمنا مع Penicillin ال Bacteriostatic
يعني توقف نمو البكتيريا
لأنه حينئذ نمو البكتيريا وتكاثرها لأنها لم تقتل

لأنهم يشغلوا مع wall cell فهي بيكس شغلها
لأن حالة طور السكون ما بتفتح Peptidoglycan فهي لا
تكون مضطربة

Notes

- ① We can't use bacteriostatic & Penicillin because bacteriostatic will arrest growth of bacterial cell wall which is the target of Penicillin in treatment so this combination will antagonize or interfere negatively with penicillin action

② مهم نتذكر أن Bacteriostatic يعتبر مع immune system
لأن: العمر الكبير أو مريض الكلى الذي يأخذ Chemotherapy
أو immune suppressant ← ما يقدر يعطي له Bacteriostatic
لأن البكتيريا تنقل بحسبه

③ لو استخدمنا Penicillin مع Bacteriostatic شو رجع يسير؟
رج يوقف شو البكتيريا ورج يوقف عمل Penicillin
لأنه مبين على نمو البكتيريا وتكاثرها لأنها بالطور يتم قتلها
لكن لو استخدمنا Penicillin or cephalosporine لبكتيريا بطور السكون
Dormant stage ما رجع يعطي أي activity العلاج

Other β -lactam antibiotics:

- Monobactam/Aztreonam ⁽³⁾ (has a narrow spectrum)
 - Against Gram-negative bacteria,
 - poor against gram positive
- Carbapenem (Imipenem, Meropenem) ⁽⁴⁾ Bactericidal
 - A group of β -lactams that are highly resistant to β -lactamases
 - Active against G+ve & G-ve bacteria including *Pseudomonas aeruginosa* & *Enterococcus* Extended Spectrum

هذا الدواء فعال ضد البكتيريا سالبة الجرام فقط
 ضعيف ضد البكتيريا موجبة الجرام
 مجموعة من البنسلينات التي مقاومة لمضادات β -lactamase
 فعالة ضد البكتيريا موجبة وسالبة الجرام بما في ذلك *Pseudomonas aeruginosa* و *Enterococcus*
 Highly effective or Highly active
 الـ resistance من البكتيريا

Vancomycin

cell wall synthesis inhibitor (مضاد لبناء جدار الخلية)
 β -lactam inhibitor

- is a large, complex molecule produced by the soil actinomycete *Streptomyces orientalis*.
- It can be used to treat infections caused by methicillin-resistant staphylococci and enterococci. It is also the drug of choice against antibiotic-induced pseudomembranous colitis
- Vancomycin is fairly toxic, causing hearing loss and kidney damage
- Red man syndrome (red rash)



Antistaphylococcal في مجموعة من penicillin في
 في Chain في Staphylococcus aureus
 تطورت وصارت مقاومة penicillin ففقدت
 نجيب له فلياً للعلاج بـ Vancomycin

Cause of red man syndrome → Vancomycin Cause rapid histamine release
 mediator that Cause
 vasodilation & generalized allergic reaction

Human Protein $\rightarrow$ 80 s
 Bacterial Protein $\rightarrow$ 70 s } give good selectivity

Protein Synthesis Inhibitors

① Dose dependent
 ② Depend on microorganism

- These drugs act on bacterial (70S) ribosomes
- Since bacterial ribosomes (30S+50S=70S) are different than animal ribosomes (60S+40S=80S), these antibiotics have good selectivity
- They are bacteriostatic agents except aminoglycosides which are bactericidal at high concentrations

CLASSIFICATION OF PROTEIN SYNTHESIS INHIBITORS

TETRACYCLINES	MACROLIDES/KETOLIDES
Doxycycline	Erythromycin
Oxytetracycline	Clarithromycin
Misocycline	Clindamycin
Tetracycline	Chloramphenicol

GLYCOCYCLES	OTHERS
Glycylcyclines	Linezolid
Aminoglycosides	Quinupristin, Galfopristin
Amikacin	
Gentamicin	
Neomycin	
Streptomycin	
Tobramycin	

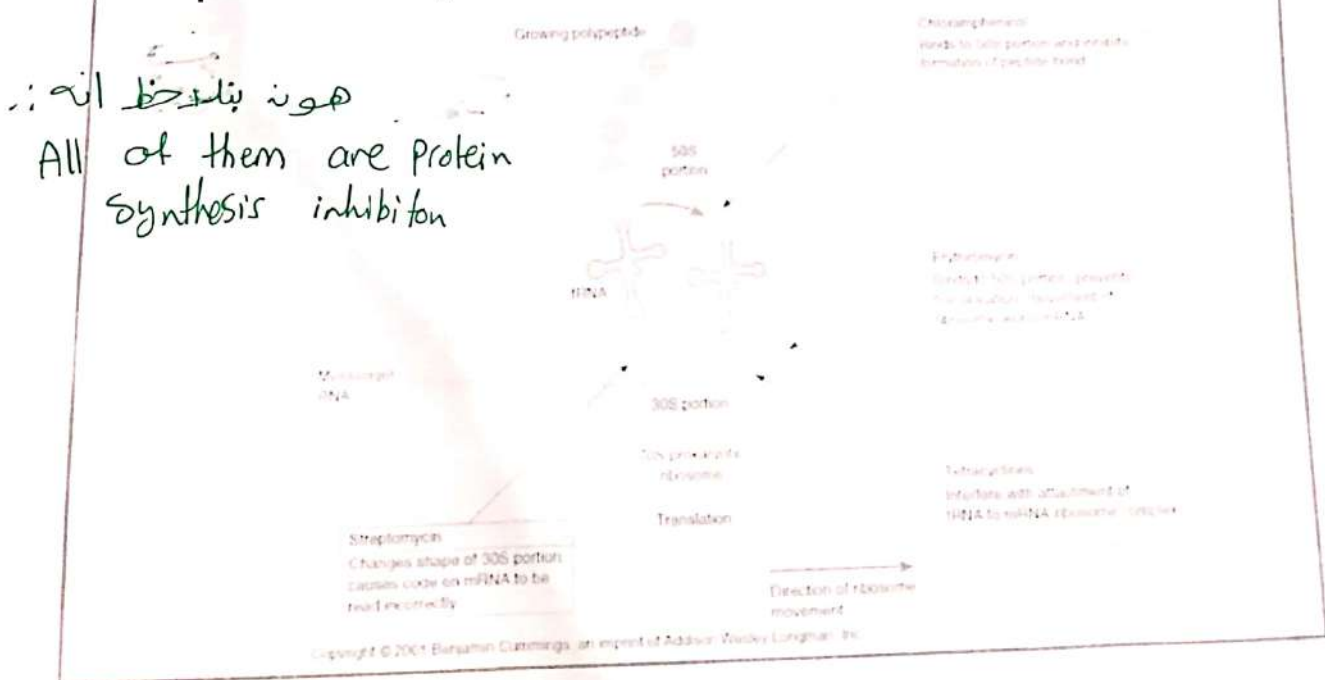
main group

Classification of Protein Synthesis inhibitor

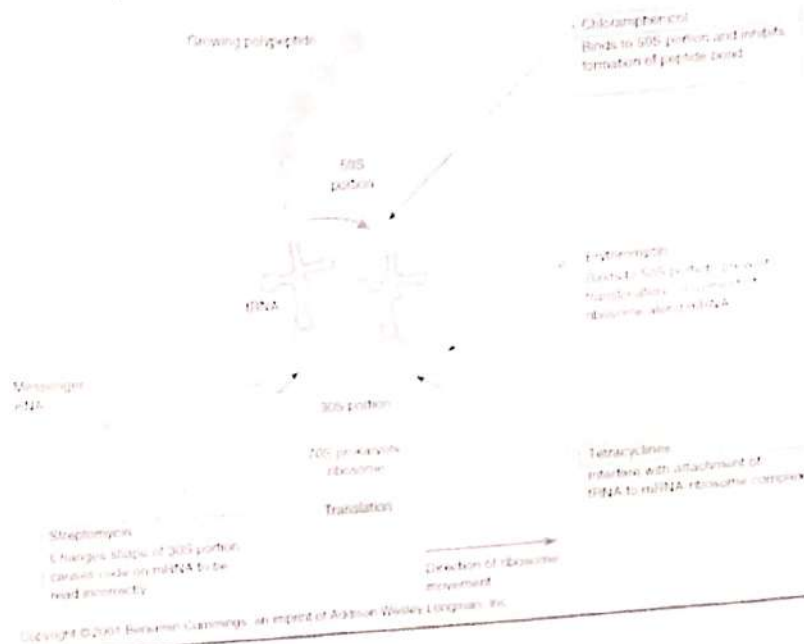
- Tetracycline
- Glycylcycline
- Aminoglycosides
- Macrolides / Ketolides

we are going to talk about them and about: **Linezolid & Chloramphenicol** which are Protein Synthesis inhibitor

protein synthesis inhibitors antibiotics



protein synthesis inhibitors antibiotics



Aminoglycosides Bactericidal

- Antibacterial spectrum of aminoglycosides varies with the type of antibiotic.
- All aminoglycosides are active against aerobic, gram-negative bacteria.
- Anaerobic bacteria are resistant. *Anaerobic bacteria will not respond for aminoglycoside*
- Aminoglycosides are transported across the bacterial membrane into cytoplasm by an OXYGEN dependent actively transport process. Therefore they have no activity against anaerobic bacteria.

- Have "mycin" or "micin" suffixes—e.g.: Gentamicin, Tobramycin *that mean they are aminoglycoside derivatives*
- An important property of aminoglycosides is their ability to act synergistically with other drugs—an aminoglycoside and another drug together often control an infection better than either could alone

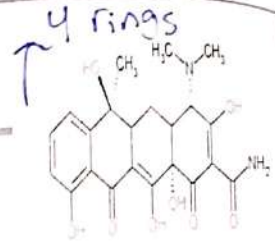
Penicillin inhibition of cell wall synthesis

Penetration Aminoglycoside Synergistically effect

رابعي

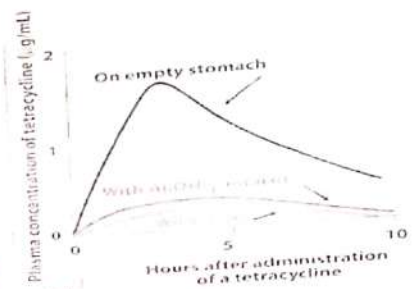
②

Tetracyclines



- Their names end in "cycline"
- Example: Doxycycline → Doxydar اسم التجاري هو
- They are absorbed from the GIT and hence can be administered orally
- Tetracyclines form complexes with calcium & become inactive, therefore milk & dairy products should not be taken with them. → Drug-Drug interaction

مثل الحديد والبيض و Dairy Product
التي تحتوي على Calcium أو الحماة التي تحتوي على iron
أو Iron Supplement أو Calcium supplement أو antacid
التي فيها Al^{+3} أو Mg^{+2} أو Ca^{+2} (يعني العناصر التي
سكنها $+2$ or $+3$)
مع ترتبط مع Tetracycline يأتي اسمه Alkylation
Tetracycline



inhibition of
Tetracycline absorption

Tetracyclines → it Can cross the placenta & reach fetus

- Due to their binding with calcium, they also cause teeth discoloration & abnormal bone formation so they are usually contraindicated during the second half of pregnancy or for children under the age of 8.

Contraindicated

Calcium لا Tetracycline
Deposition
في الأسنان

Brown teeth discoloration
Permanant

- Alteration in intestinal flora may result in Superinfection (overgrowth of nonsusceptible organisms such as Candida)

when there is a Chronic use of tetracycline

Kill Normal flora

Tetracycline will not be given to
→ Children under 8 years
→ Pregnancy women
→ lactating women

Doxycycline
100mg Capsules

50 capsules



Macrolides

▪ Generally bacteriostatic

▪ Their names end in "romycin" and mostly in "thromycin"

▪ E.g. Erythromycin, Clarithromycin

• They are active against most G+ve bacteria: Streptococci, Pneumococci, Staphylococci & also Mycoplasma.

• Macrolides have variable activity against G-ve bacteria

▪ Macrolides main use is for penicillin resistant infections & as alternative to penicillin for patients allergic to them

الأشخاص التي عندهم
Pencillin allergy
نحب إعطائهم
Macrolides

Azithromycin من هي المجموعة كان من أول البروتوكولات
المستخدمة في علاج Corona viruse

Immunomodulatory
effect

لأنه إلى ~~antimicrobial effect~~ Control of releasing cytokines
رغم إنه Antibacterial وكان يحفز

Lincosamides ⁽⁴⁾

- Bacteriostatic agents
- Include clindamycin & lincomycin.
- Clindamycin is used to treat Bacteroids & other anaerobic bacteria
- Also used for G+ve cocci (except Enterococci) and in topical preparations for acne
- Clindamycin also has antiprotozoan activity (i.e. toxoplasmosis)
- Long term use of clindamycin causes pseudomembranous colitis due to toxins from Clostridium difficile

عائنه هيا اكل
في بكتريا كاترق
الانسان

↓
it is a superinfection

بسبب Diarrhea ← يعني لو ايس مريض بعاني من Diarrhea

- we should
- ① Stop the medication
 - ② replace fluid & electrolyte loss
 - ③ Treat this superinfection

Chloramphenicol ⁽⁵⁾

- It is a bacteriostatic agent
- It has a broad spectrum of activity excluding Pseudomonas & Enterococcus
- But it has serious side effects such as aplastic anemia and bone marrow suppression which could be fatal because of RBC's deficiency synthesis
- Therefore, its use is considered as a last choice when other effective agents are unavailable
- Among its main uses is to treat typhoid fever & meningitis for patients who are allergic to cephalosporins & penicillins

بسبب نقص الدم
نفسا فيف ال
exclude

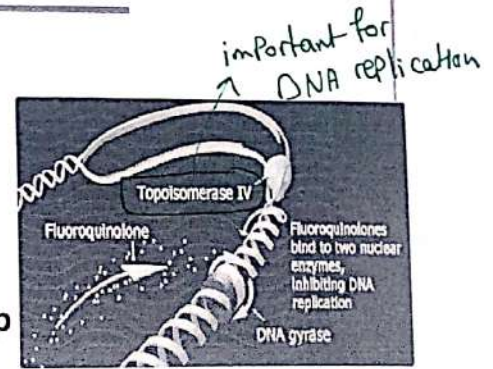
مريض
نقص الدم
فيل ال
Platelet
& RBC's
& WBC's

كمان في الحسنة وقف استعماله Systemically بس

as eye drop & ointment ← as topical موجود
adverse effect لا يسبب هذه

Inhibitors of Nucleic Acid Synthesis (6)

- Quinolones are a group of synthetic antibiotics that act by inhibiting DNA gyrase (the enzyme which unwinds DNA double helix preparing it to replication) thus inhibiting DNA synthesis.
- The basic drug of this group is nalidixic acid, but the majority of drugs in clinical use belong to the subgroup **fluoroquinolones** such as ciprofloxacin, norfloxacin.
- They are active against **both G+ve & G-ve bacteria** (including *Pseudomonas aeruginosa*)
- Used mainly for traveler's diarrhea & urinary tract infections caused by bacteria that are resistant to other antibiotics



Fluoroquinones → Bind to topoisomerase & Cause inhibition of DNA gyrase
So inhibit DNA replication

→ Similar to tetracycline so we can't use them in pregnancy & lactating women & children less than 8 years

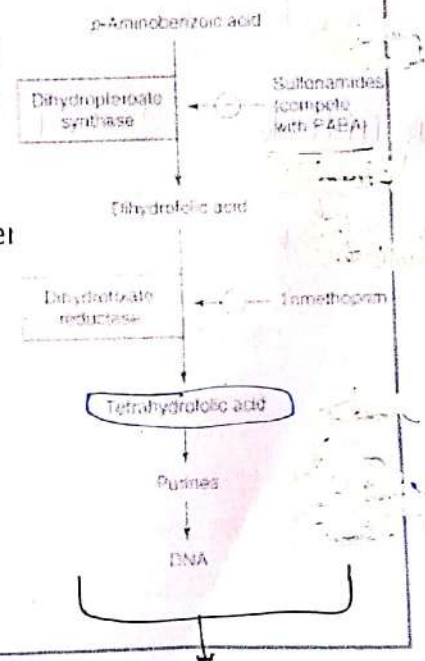
Antimetabolites (7)

DNA replication, RNA synthesis, Diet is folic acid

- The **sulfonamides**, or **sulfa drugs**, bacteriostatic agents
- They act by competitive inhibition to the enzyme that acts on para amino benzoic acid (PABA) needed for folic acid synthesis
- Folic acid is important for synthesizing nucleic acids & other metabolic products.
- Sulfonamides are chemically similar to PABA.

- Sulfamethoxazole is usually given in combination with trimethoprim which inhibits another enzyme in the pathway of folic acid synthesis
- This combination drug is called **co-trimoxazole**

sulfamethoxazole & Trimethoprim



البكتيريا قادرة على تصنيع folic acid من substrate PABA

Sulfamethoxazole & Trimethoprim → Synergistic effect
علاج أكثر فاعلية

* **Sulfonamide** inhibit Dihydropteroate Synthase

* **Trimethoprim** inhibit Dihydrofolate reductase

الأحسن هو الجمع بين عمل
Sulfonamide + Trimethoprim
step 1+2 حتى تحصل على
Pathway يعني أنت نأكل كل الـ

وهذا كان بدوا
Co-trimoxazole

folic acid synthesizing

P-aminobenzoic acid

Dihydropteroate Synthase

(not active form of folic acid) Dihydrofolic acid

Dihydrofolate reductase

(Active form of folic acid) Tetrahydrofolic acid

Purines

DNA

[Note] P-aminobenzoic acid = PABA

Antimicrobial agent

is classified according to microorganism they act against :-

- Antibacterial (against bacteria)
- Antifungal (Against Fungi)
- Antiviral (Against virus)

but

if we classified bacteria according to **mechanisms**

- Inhibit cell wall synthesis
- Inhibit Protein synthesis
- Inhibit nucleic acid synthesis
- Injury to plasma membrane
- Inhibit synthesis of essential metabolite

Folic acid

it is important for bacteria to synthesis DNA & RNA

Sulfonamide suppress folic acid synthesis

Antiprotozoal agents

- Drugs used to treat infections caused by protozoa. Protozoa are unicellular animal like organisms.

- Examples: giardia, amoeba, plasmodium, leishmania, toxoplasma

Cause

Entamoeba histolytica

Kind of it Species

Cause

Malaria

Cause

Toxoplasma gondii

Clostridium difficile → Aerobic bacteria responsible to cause Pseudomembranous colitis

* Anaerobic bacteria responsible to cause:-
→ Joint infection
→ Oral Cavity infection
→ Intraabdominal abscess
→ Gingivitis التهاب اللسان

Antiprotozoal agents

Nidazole الأسم الجاري أو الدواء الأردني

- Metronidazole (Falgyl®): causes breakage of DNA strands thus inhibit nucleic acid synthesis in Protozoa
- Effective against intestinal infections ^① caused by parasitic ^② Giardia & amoebas. Also it is effective against anaerobic ^③ bacteria (responsible for intraabdominal abscess, peritonitis, joint infections, gingivitis) & Clostridium difficile.
- It is effective in treating Trichomonas infections, which typically cause a vaginal discharge and itching.
- Used as part of multidrug regime for peptic ulcer against Helicobacter pylori

Other antiprotozoal drugs مع مقارنة أكثر في Metronidazole سيرة Antibacterial effect لأنه

→ Metronidazole can be used to treat even Protozoal infection or bacterial infection

فلو نرتب معلومات السليمة اللي فوقه ↑

Metronidazole اسمه التجاري إما :-
① Flagyl

الاسم التجاري (أرذني) Nidazole ②

How metronidazole works?

Via break DNA Strands so it inhibit nucleic acid synthesis

metronidazole is effective against what?

① intestinal infection, caused by parasitic Giardia & amoebas

② Anerobic bacteria, which cause :-

- Joints infection
- Oral cavity infection
- Intrabdominal abscess
- peritonitis
- Gingivitis

③ Clostridium difficile

→ Aerobic bacteria responsible to cause

pseudomembranous colitis which is most common as secondary infection due to overgrowth of

Clostridium difficile — why?

once we use a broad spectrum antibiotic we kill the normal flora, enhance the chance of Clostridium difficile growth in intestine so it will cause diarrhea & abdominal Pain.

④ Vaginal infection

↳ Caused by Trichomonas infections

* Metronidazole is part of multidrug regime for peptic ulcer against Helicobacter Pylori (H Pylori)

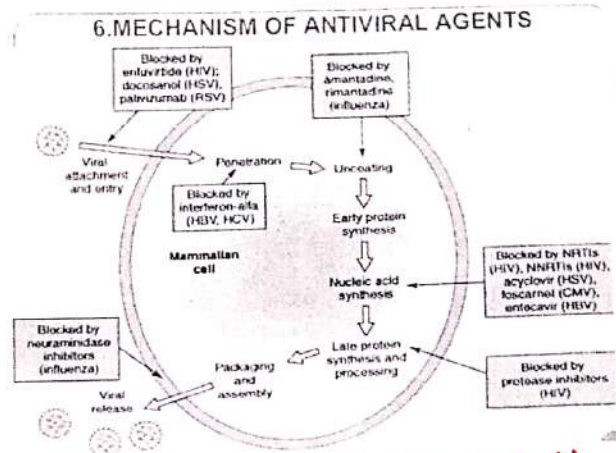
بكتريا هيليكوباكتر
Peptic ulcer سبب

Antiviral agents in general they are limited

The difficulty in finding antiviral drugs is that the drug should attack viruses inside cells without affecting host cell.

- Antiviral agents act by interfering on some phase of viral replication but they don't kill viruses.

Therefore, latent non replicating viruses can't be destroyed.



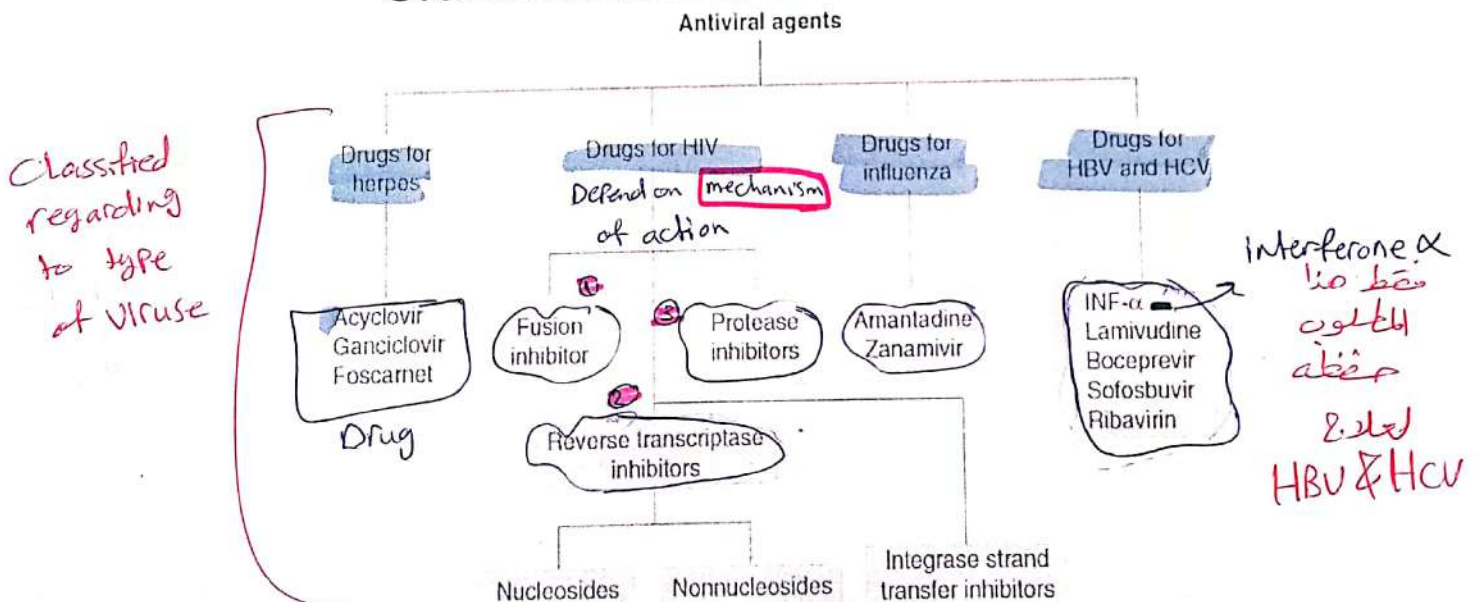
* Remember the cycle of the virus:-

- 1 Attachment
- 2 Penetrate the host cell
- 3 Synthesis new nucleic acid
- 4 Assembly of newly synthesized cell
- 5 Release new virions from the cell

المسألة بالذات هو :-
 1 Viruses 100% dependent on host cell for its metabolism, mean that is intracellular parasites

وذلك هو صعوبة العلاج
 Difficulty of toxicity treatment

Classification of antiviral agents

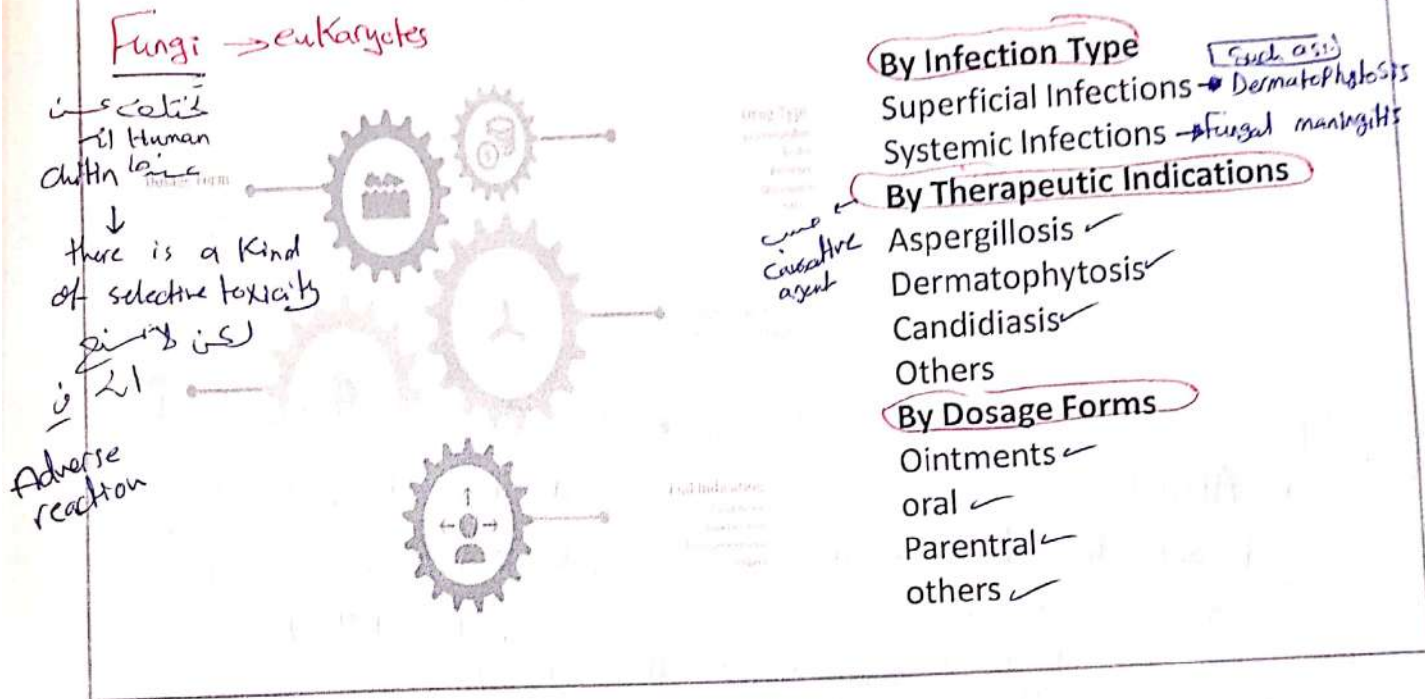


Interferone α
 لا يعمل
 على
 HBV & HCV

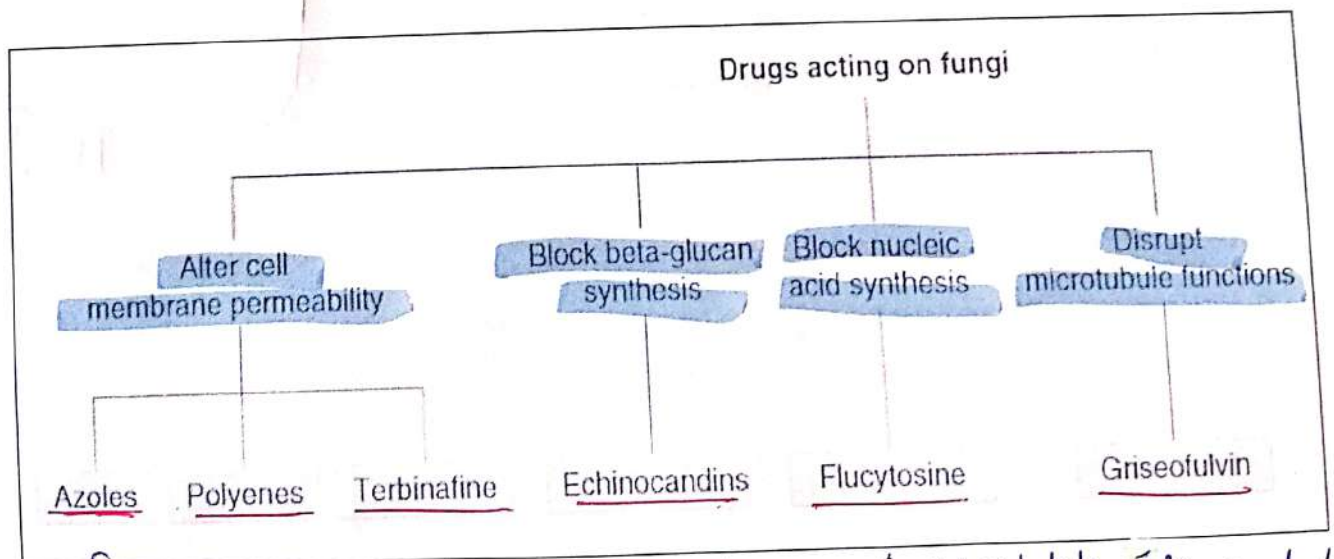
To Kill viruse we maybe:

- ① Supress viral attachment
- or ② Block viral uncoating which heal assembly
- or ③ Block nucleic acid synthesis in virus
- or ④ Block Proteases enzyme → needed for protein synthesis
- or ⑤ Block the release of virion by neuroamidase inhibitor
new Viruses

Antifungal Drugs



Antifungals are selectively toxic to fungi because they interact with or inhibit the synthesis of ergosterol, a sterol unique to fungal cell membranes.



- β glucan is needed in cell wall

- nucleic acid is needed for DNA replication

- microtubule is needed in mitosis & cell division

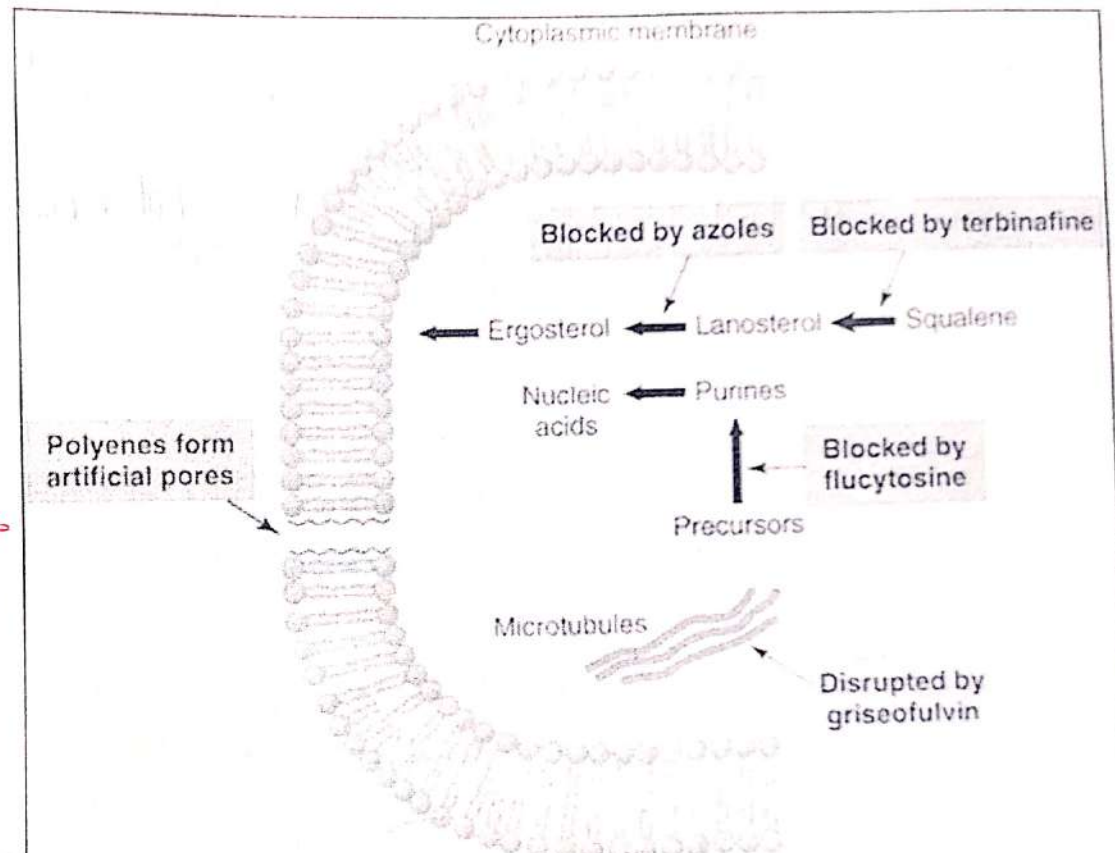
Mechanisms of antifungals

Cytoplasmic membrane is target

Block ergosterol synthesis
cell wall
Azoles target

Lanosterol is a source
of ergosterol

lanosterol Block
Terbinafine target



Block ergosterol by Azoles
Lanosterol by Terbinafine
nucleic acid synthesis by Flucytosine
microtubules function by Griseofulvin

LABORATORY TESTING OF ANTIMICROBIAL SUSCEPTIBILITY

- Drug efficacy determined based on clinical and laboratory parameters
- Antibiotic sensitivity testing or antibiotic susceptibility testing is the measurement of the susceptibility of bacteria to antibiotics. It is used because bacteria may have resistance to some antibiotics.
- Drug efficacy can be measured by susceptibility testing including:

1. Kirby-Bauer Method (diffusion test)
2. Broth dilution test
3. E-test

by
using
these
3 parameters:-

Test Agar Plate → البكتيريا
 يكون مشبعة
 Filter Paper
 Plate
 Certain amount of antimicrobial agent
 كل وحدة فيها Antibiotic
 أكثر Filter Paper
 Kirby-Bauer Method (diffusion test)
 over light

- In diffusion testing (often called the Kirby-Bauer technique), the inoculum is seeded onto the surface of an agar plate, and filter paper disks containing defined amounts of antimicrobials are applied.
- The antimicrobial diffuses into the medium to produce a circular gradient around the disk. After incubation overnight, the size of the zone of growth inhibition around the disk can be used as an indirect measure of the MIC of the organism.
- The diameters of the zones of inhibition obtained with the various antibiotics are converted to "susceptible," "intermediate," or "resistant" categories by referring to a table.

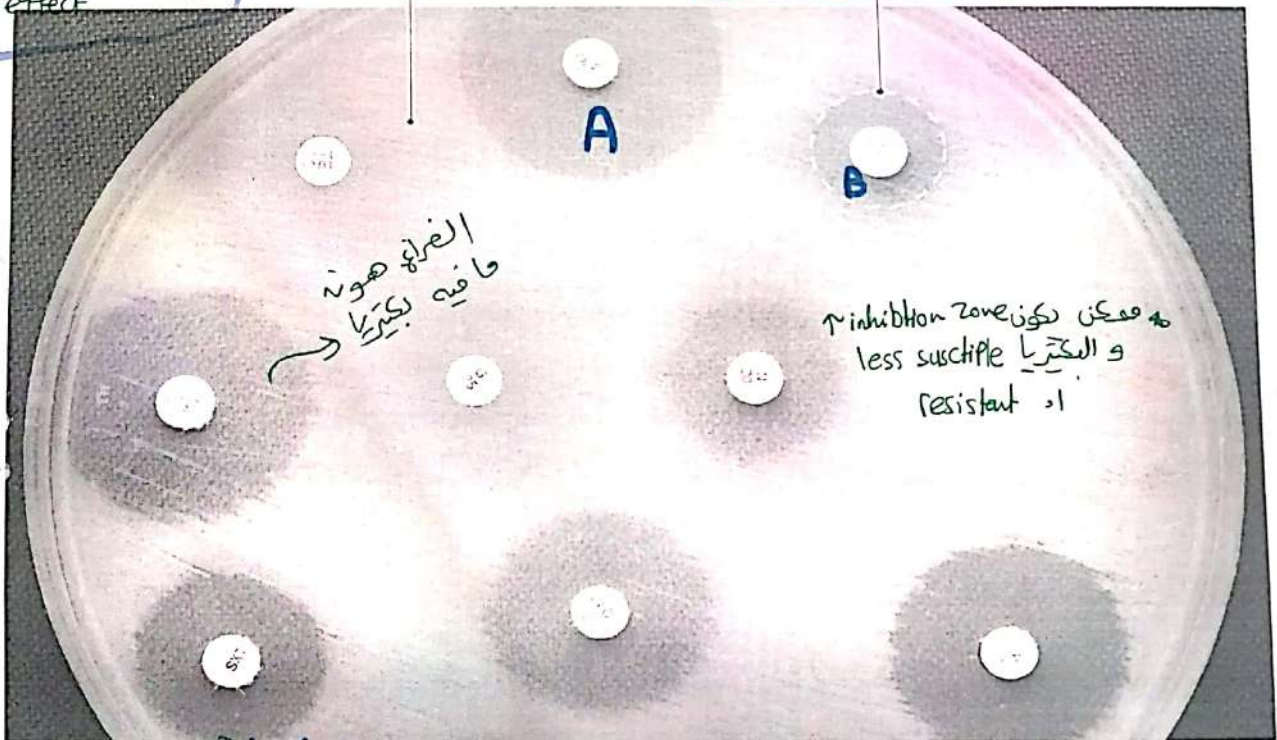
Although the inhibition zone give us a hint to know the antibiotic if effective or not regarding to it's diameter, however we should back to a reference table

Active يعني Inhibition Zone
 Antibiotic كل
 منطقة

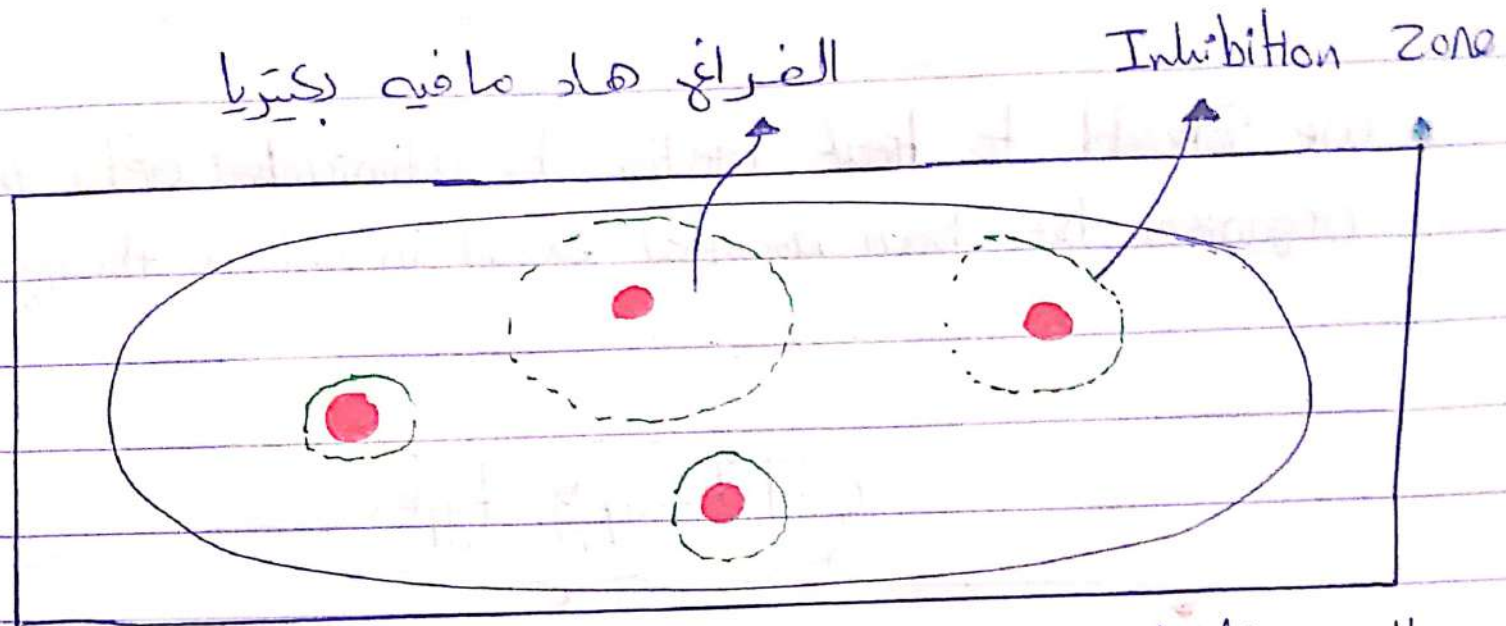
↓ Mw of antibody
 So ↑ rate of diffusion
 So ↑ effect

Bacterial lawn

Zone of inhibition



A has more efficacy than B



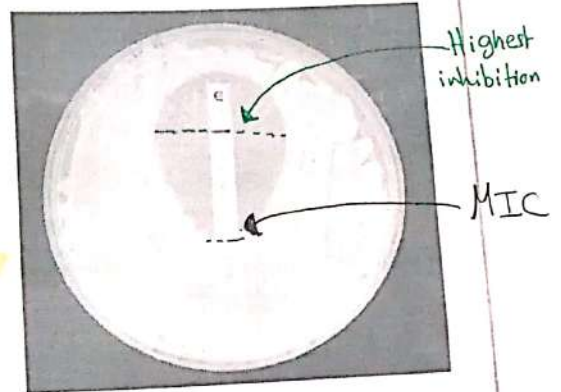
* Although the inhibition zone give us a hint to know the antibody if effective or not regarding to it's diameter, however we should back to a reference table

reference table | Diameter of antibody
 resistance | intermediate | susceptible
 Susceptible | ↑ inhibition zone

* ↓ M.w of antibody : ↑ rate of diffusion : ↑ effect

E(epsilometer) test

- A newer version of the diffusion test, called an **E(epsilometer) test** uses a **plastic strip containing a gradient of concentration of antibiotic**.
- Printed on the strips are concentration values, allowing the laboratory technician to directly read off the minimum concentration needed to inhibit growth.

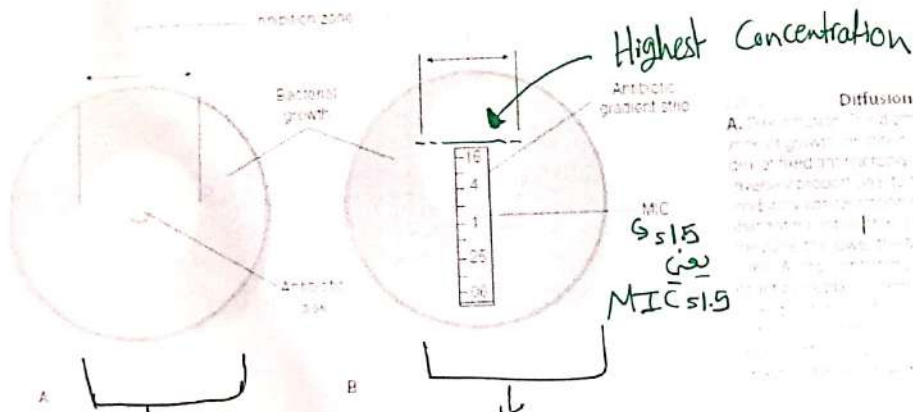


بكون في Plastic strip فيها Gradient of conc. of antibiotic

Strip بكون مدرجة

Diffusion tests

نزرع بكتريا في agar plate
نوعها، هذا يحتاج لنقل
measurement of that bacteria resistant to this antibody



هذا بالمسطرة بنقيس
inhibition zone

هون بنقيس عن
Strip طريق
فيها Antibiotic
واحد

القياس هون بين بنقيس
Diameter ال
طابقه نشوف فيها
MIC ال

To determine
MIC & MBC

← Broth dilution test

- ① Quantitative subculture of the clear tubes in the broth dilution test and
- ② comparison of the number of viable bacteria at the beginning and end of the test.

5u → MBC

1. Obtain isolated colonies of bacterial strain to test



2. A standard 500 µl volume of bacteria is added to each tube.

3. The standard amount of bacteria is added to each tube.



Broth dilution method for measuring minimum inhibitory concentration of antibiotics

4. After overnight incubation, check cultures for growth. The MIC is the lowest concentration of antibiotic that prevents visible growth. In this example, the MIC is 0.0625 mg/L.

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There is certain concentration of bacteria in each tube
(by serial dilution) & we should have one standard tube
contain only antibiotic & another standard tube contain only
bacteria

Bacterial growth في القى Turbid ← Tube لا يكون ال
There is Killing ← Clear كان
of bacteria