



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) دواء

Pharmaceutical Microbiology

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Antimicrobial → Drugs effective to eradicate microorganism

الركيزة هي هاد السلايد → من الحفظ

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.

ملاحظة هامة: *

Efficacy & Safety

أي دواء يجب فيه

To Kill the microbes

Drug should exhibit a Kind of selective

toxicity

سبب Selective toxicity هو اختلاف
الخلايا cell ناع Fungi الذي يتولى
human cell ناع وجوده عند ال human

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

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

Pr

2

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

لا الشخص - نوع من دكتور ويكتب Antibiotic و الدكتور ما
يكون قسمة Natural substances و هي هارت كلمة عامة لها ترمز
Natural & semisynthetic & Synthetic

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*
- 4. Resistance** by Microorganisms Not Easily Acquired. → *ما ينفذ البكتيريا تحمل أي مقاومة*
- 5. Long Shelf-life.** *(كل ما كانت البكتيريا لا تقاومه 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

No resistance
by microorganism

→ if it Kill microorganism or suppress it's growth, this bacteria should not produce any resistance

Long shelf-life
Antibiotic
يوجد فترة يجب التوقف عن استخدامه بفترة قصيرة بعد فتحه للأستعمال
يعني في فيا Powder لو تم حلها خلص يتم استعمالها وري ما تبقى

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) *هذا أوكي 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+. *فرضا Antibiotic سيم لـ G-ve و G+ve (Ampicillin)*

3. **Broad spectrum:** active against a wide variety of microbial species. (Tetracyclines, quinolones, Chloramphenicol)

يعطي G+ve و G-ve و Atypical bacteria, Mycoplasma

يعني هذا ال Spectrum يعطي Range كبير

The Spectrum of Activity

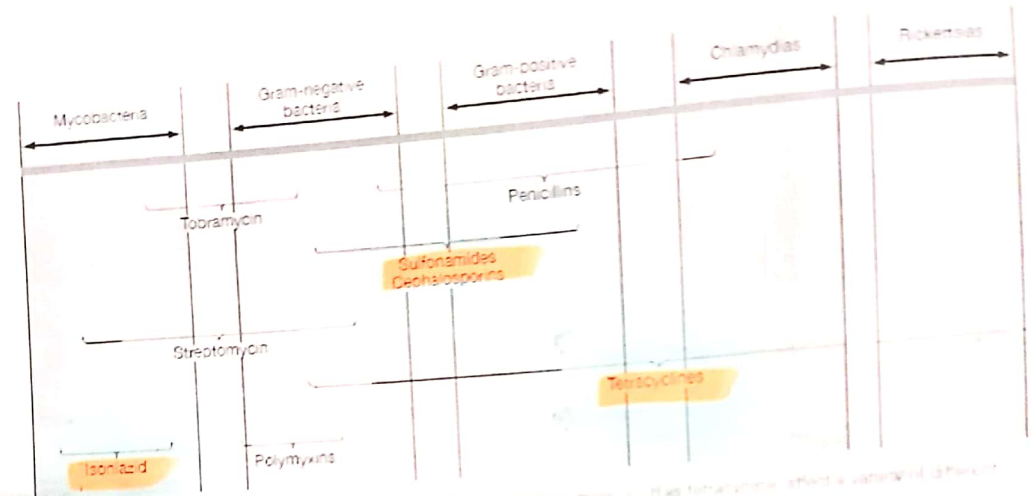


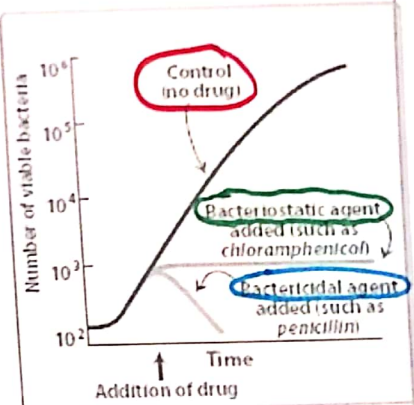
FIGURE 13.1 The spectrum of antibiotic activity. Broad-spectrum drugs, such as tetracyclines, affect a wide range of different organisms. Narrow-spectrum drugs, such as isoniazid, affect only a few specific types of organisms.

- 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 Chlamydiae & Rickettsiae so it is broad spectrum

Antimicrobial Action

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)**.

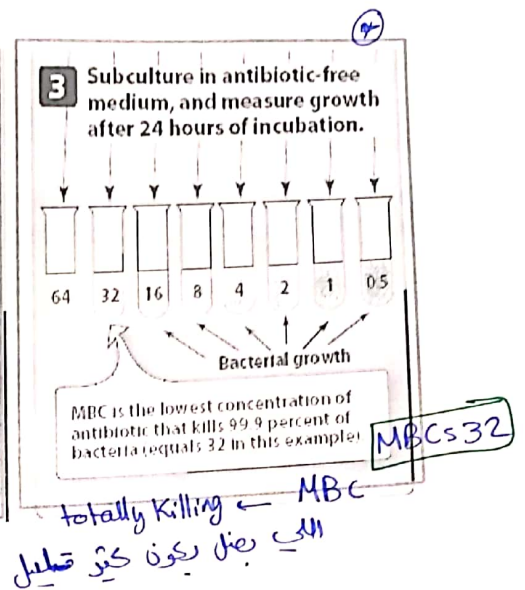
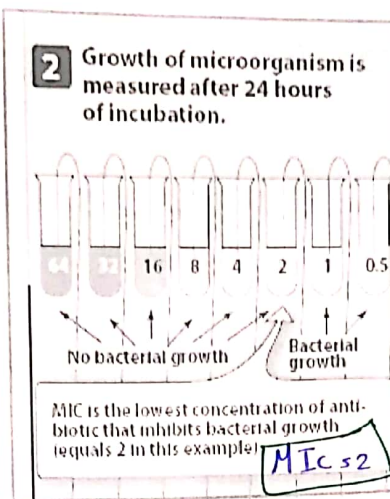
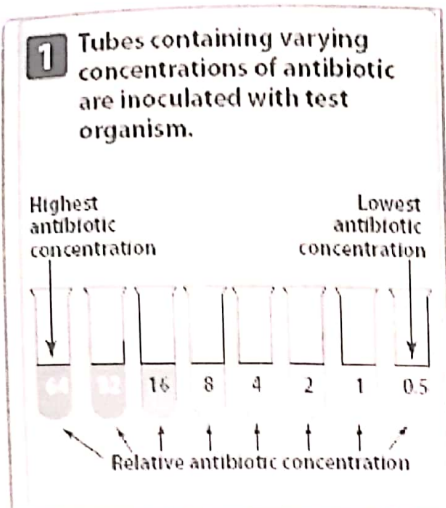


Bactericidal: Kill microorganisms (such as Penicillins and Aminoglycosides). This is determined in vitro by exposing a standardized concentration of organisms to a series of antimicrobial dilutions. The lowest concentration that kills 99.9% of the population is referred to as the **Minimum Bactericidal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

لو زرعنا عدد معين من Bacteria في Petri dish 6 حوصلا without any drug مع الوقت دة يزيد

ولن يكون اوتيل (Platuo Phase)

لكن لو استخدمت Chloramphenicol (Bacteriostatic agent) عدد البكتيريا سيعف (Bactericidal agent) لكن لو اعطيت Penicillin عدد البكتيريا سيعل لان سيعلم



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) وهاد

يعني بليست Bacteriostatic (كنى لا) Bactericidal بليست Bacteriostatic Concentration dependent
 Selection of 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 إنه نفس المرض

- ① Genetics → مرضى القول في أدوية لا يستطيعوا أخذها
- ② Age → في Antibiotic لا تغطي لمن هم أقل من 18 سنة
- ③ Immune Status
- ④ Allergy History of allergy
- ⑤ Gender → المرأة الحامل في Antibiotic لا تغطي لها
- 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 (تفحيط) 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 (مبيدات)

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

Produced by the fungi ← Penicillin
to Kill another organism (bacteria)

So Penicillin is antibiatic

* 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)

حساب مناعة المريض بقدر إعطائه Bacteriostatic أو Bactericidal
 لا مناعة المريض مناعة
 (compromise immune system)

MIC → The lowest concentration that inhibits the growth of organisms

لو دوا الـ $MIC = 20$ و دوا الـ $MIC = 40$

مين رح يكون more potent ؟ الى الـ $MIC = 20$

و هذا بتعرفه عن طريق Serial dilution مع شرحه تحت ↓

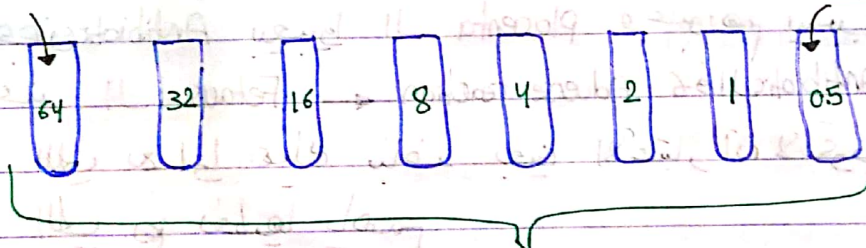
MBC → The lowest concentration that kills 99.9% of Population

Serial dilution

لتحديد و معرفة MIC & MBC

Highest antibiotic Concentration

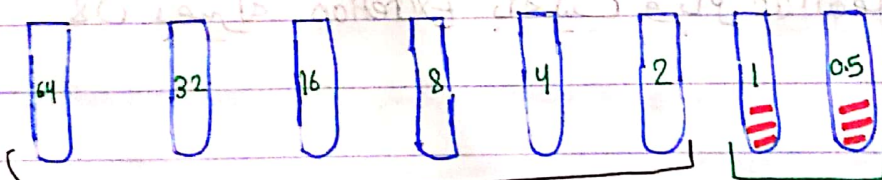
Lowest antibiotic Concentration



Relative antibiotic Concentration

24 hours of inc

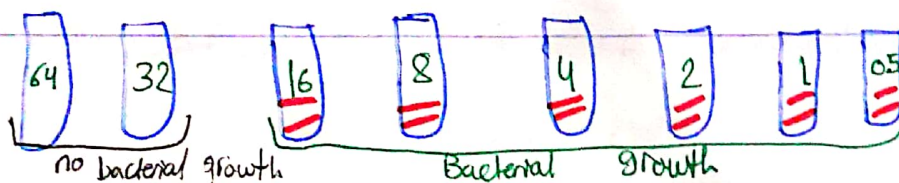
ينجي منقطع بعد



no bacterial growth

High bacterial growth

هنا هون لو بننا خدر MIC و MBC من الرسمه هي
 بين معنا ان $MIC \leq 2$ و ان 0.5 هو أقل تركيز من Antibiotic لتثبيط النمو البكتيري



لكن من هون نحدد $MBC \leq 32$ الى هو أقل 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 it's 3+ve or G+ve
[CSF من عينة من 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 Antibiotic
(abscess, obstruction). → 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 اقل غالي وافي رخيص

- ① Right drug
- ② in right rout
- ③ in right frequency
- ④ in right duration → Antibiotic

إذا كان عند المريض obstruction أو abscess (القالب الجلد أو حرقه) وفيه accumulation of dead cells بسبب Burns فتلا في Dead cells بغير barrier أو mold بعد أي عملية جراحية يصير في Abscess التي هو Pus secretion لازم اول نزل ال Pus ونظف الجرح ثم نعطى Antibiotic (الحزاع)

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 يعبر ويعبروا

لكن بعين لاء لأن دخولهم رح بسبب Adverse fetal reaction (سؤفات حادة)

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

- 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.

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

- 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

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

قتل الملاريا من infection سرية لانتشاره
 لما كانوا يسافروا بالبحر
 كانوا يافروا Antimicrobial medication
 causes

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 بس في 2 Factor بنا نبيه عندهم في مهم ::

① بعض Antibiotics يعبروا ال Placenta وعبورهم يسبب
عند ال Fetus ← Adverse reaction
اللي يعملوا هيك بناخذ بعين الاعتبار أن لانكون
اللي رجع نعطيهما باهم
Pregnancy women

② المرأة المرضعة لازم ما نعطيهما Tetracycline
لأن بصره Excretion بالحليب وبنات عن الطفل

- 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:- antimalarial medication

2 or more
antibody

الجمع ← Combination of
antibiotics

في استخدام 4

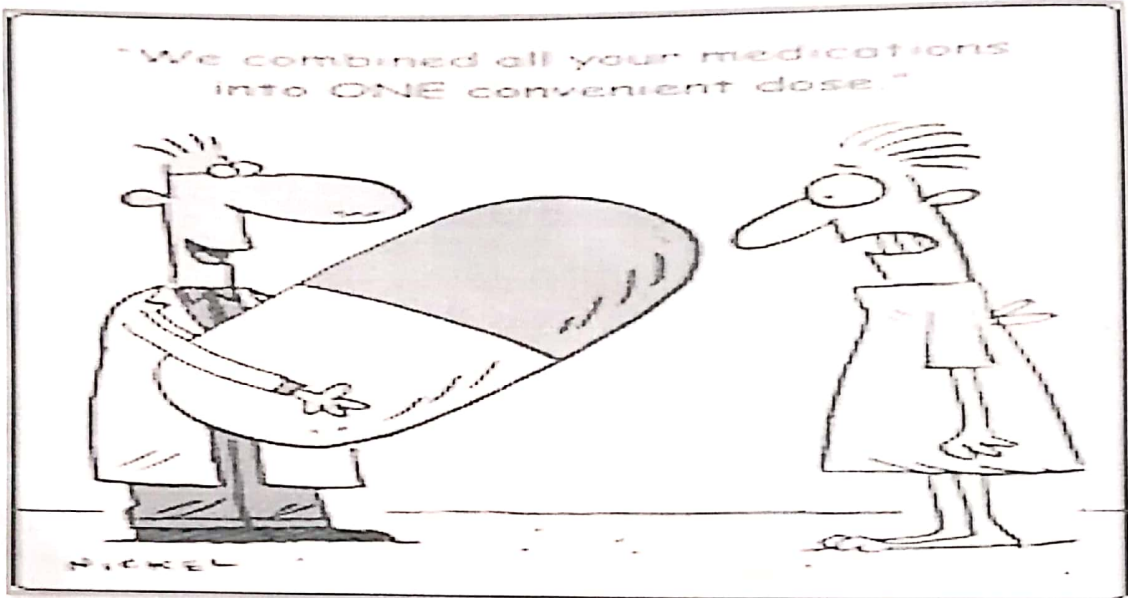
① increase drug efficacy

→ Advantages : ② Broaden spectrum (

③ Avoid drug resistance

Grave ل دواء
Grave ل دواء

Combination of antimicrobials



استخدام ال Combination يكون في حالات معينة ←
Patient critical illness و microorganism نوع ال infection و نوع ال
empiric therapy critical ill وينا نفعي

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

cell wall → Lactam و Aminoglycoside

Disadvantages:

1. Concomitant administration of a second agent is usually bacteriostatic and may interfere with the action of the first drug that is bactericidal

Synergistic effect $\rightarrow$ لا يكون الدواء الذي يستخدم معه Synergistic effect
Antagonist agent $\rightarrow$ لا يكون الدواء الذي يستخدم معه Antagonist agent

2. Suppression of normal flora, so give higher chance for opportunistic infection (superinfection).
3. Increased incidence of adverse reactions.
4. Highly cost

increase the risk of adverse effect
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 effect to induce an effect

دواء $\rightarrow$ Dose $\rightarrow$ لا يثبط أو يقتل البكتيريا $\rightarrow$ لا يثبط أو يقتل البكتيريا

Problems $\rightarrow$

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 medium
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:

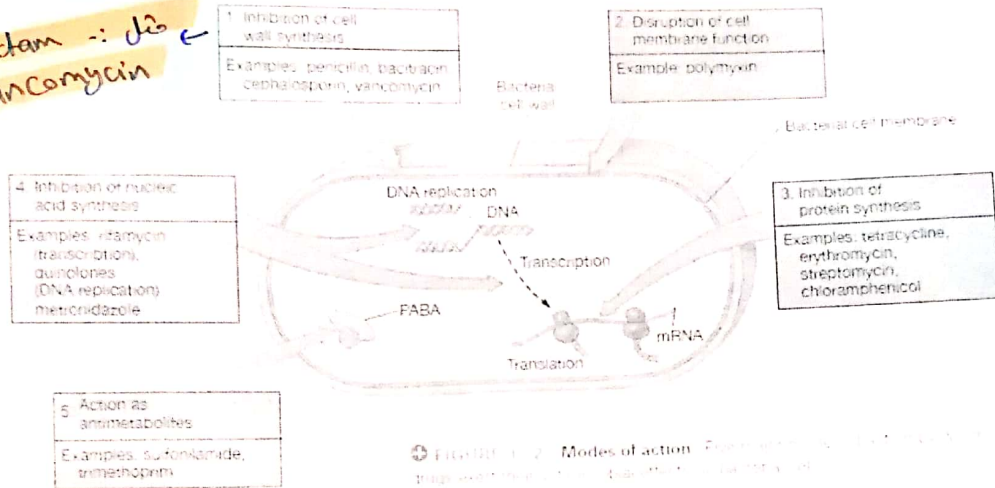
1. Inhibit cell wall synthesis will affect on Peptidoglycan
2. Inhibit protein synthesis will affect on RNA & ribosomes
3. Inhibit nucleic acid synthesis
4. Injury to plasma membrane
5. Inhibit synthesis of essential metabolites

Folic acid

is need for bacteria which are important for DNA & RNA synthesis

Mechanisms of Action of Antibacterial Drugs

B-lactam :- β -lactam
& Vancomycin



(there structure are like the same of substrate)

Antibacterial β -lactam
مستأنس β -lactam
receptor β -lactam

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

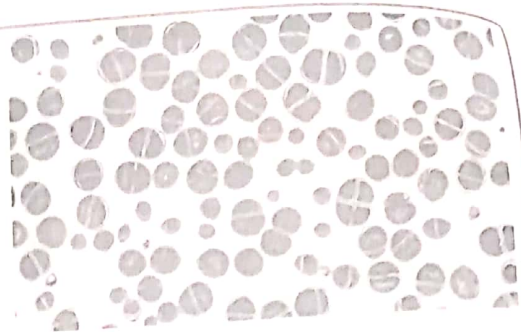
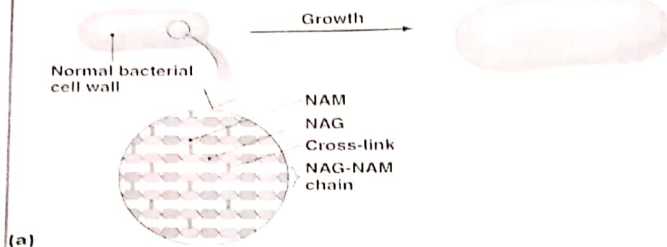
- Once bacteria is needed to divide, it will prepare its cell wall to be able for separation -

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

Link between subunits
(New NAM to old NAM)

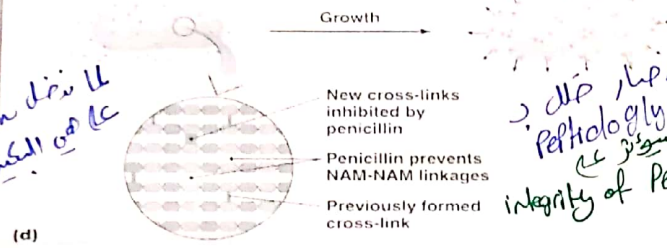
A bacterial cell wall is composed of a macromolecule of peptidoglycan composed of NAG-NAM chains that are cross-linked by peptide bridges between the NAM subunits.

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.

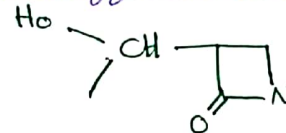


Penicillin يمنعNAM من الالتصاق

Penicillin يمنعNAM من الالتصاق
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 → Bactericidal

Cephalosporins

- Cefalexin
- Cefuroxime
- Cefotaxime
- Ceftriaxone

Cephalosporine → Cef

Monobactams

- Aztreonam

end with am

Carbapenems

- Meropenem
- Imipenem
- Doripenem
- Ertapenem

Penicillins

Narrow Spectrum

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

Broad Spectrum

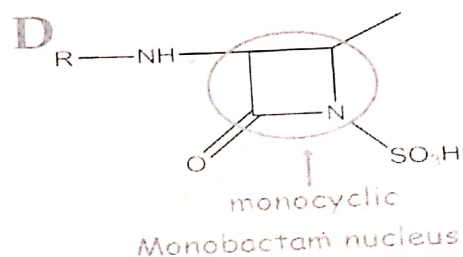
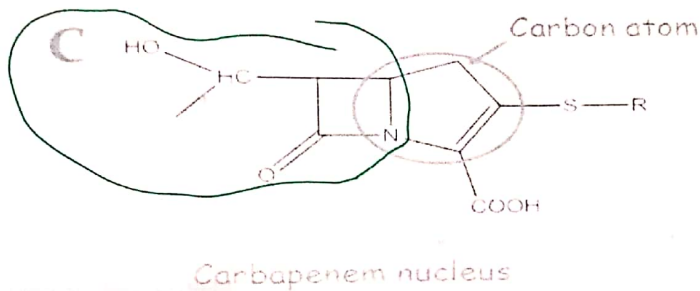
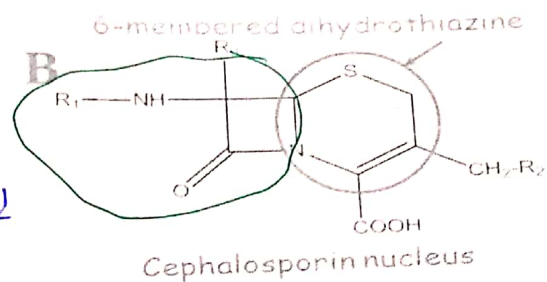
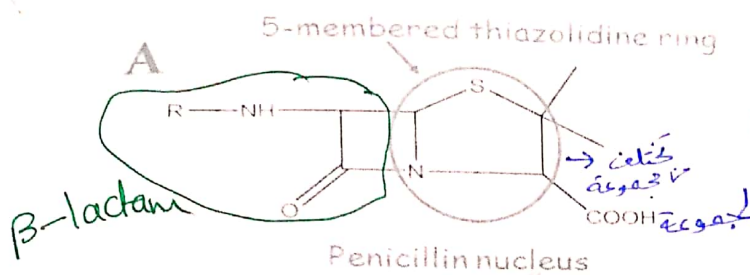
- Amoxicillin/Co-amoxiclav
- Ampicillin

Penicillin → Drug name end with icillin

Carbapenems → Drug name end with Penem

→ They share the Same β -lactam ring

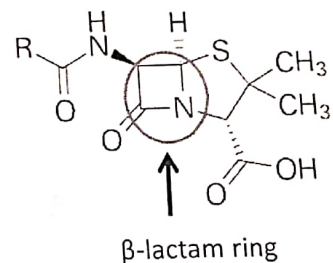
β -lactam antibiotics



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

Penicillins

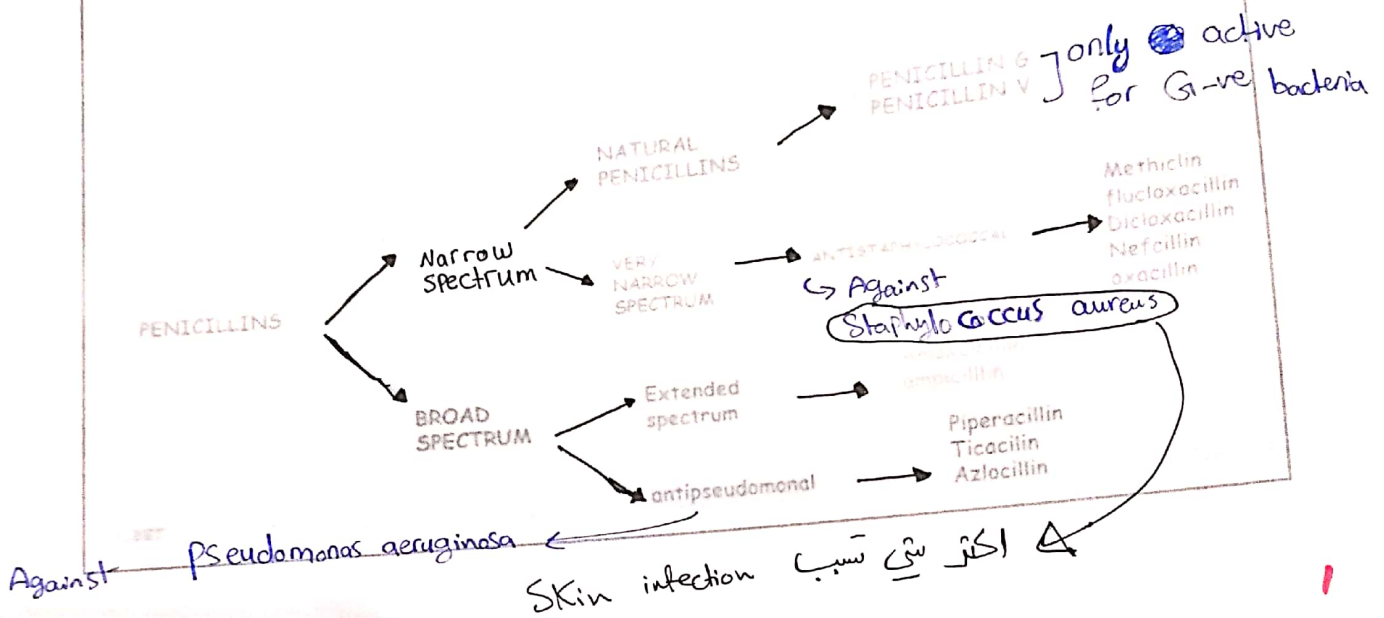
- Have β -lactam ring
- Bacteriocidal



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

مضاد حيوي واسع النطاق Bacteriocidal
يعني كير قوي مضاد ولا ضيق يكون wide spectrum

Classification of Penicillins



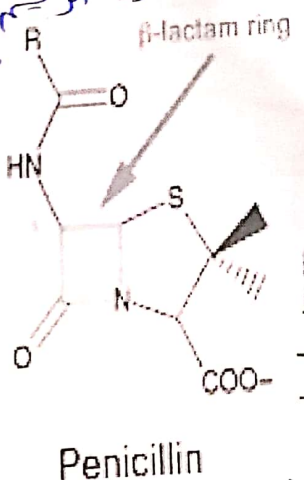
Some bacteria produce β -lactamase enzyme that breaks the critical β -lactam ring

Penicillin Resistance

β -lactam ring is very important for antibacterial drug

resistance في بكتيريا ←
to Penicillin
تقویر انزیم β -lactamase
فالتیابی

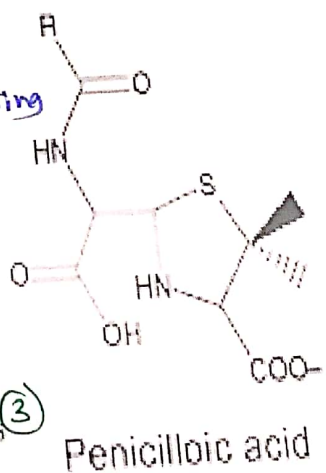
Drug will lose its activity



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
 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....

Ex. **Clavulanic acid**

- Suicide inhibitor -

Clavulenic acid
 ينخر و تقاومه البكتريا

Amoxicillin
 حتى يقوم

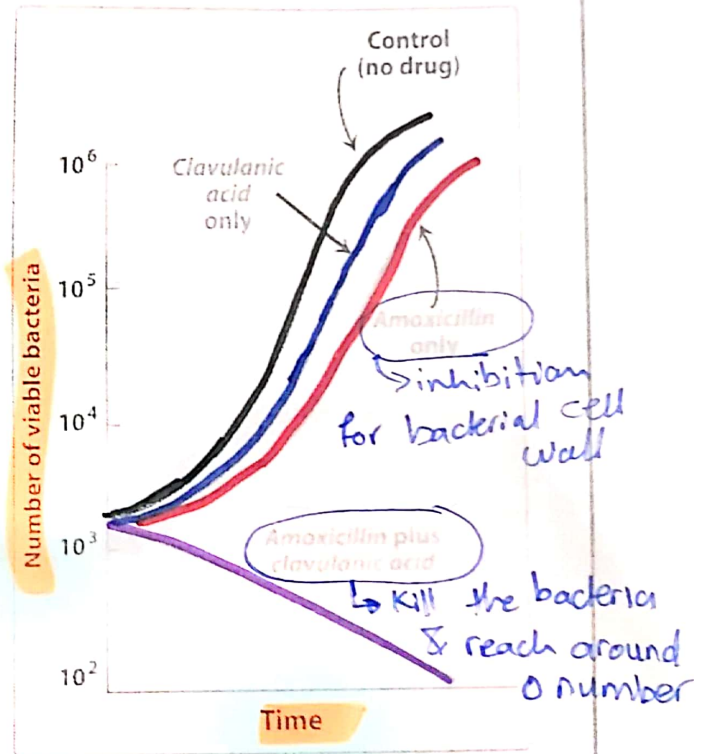
For example clavulanic acid Binds to beta-lactamase and competitively protects amoxicillin

*They potentiating amoxicillin against beta-lactamase producing bacteria.

* It is called "suicide inhibitor"

Addition of Clavulanic acid to amoxicillin
 Potentiate it's action

عززة
 من قبل
 inhibition
 - β -lactamase



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 نشأ المريف اذا عنده
Penicillin allergy

لو المريف تحسس من

Amoxicillin

ورمى اعطى Ampicillin

✓ There is cross-reactivity among all Penicillins

✓ Penicillins and cephalosporins ~5%

غالب لا نهم نفس المجموعة
Cross allergy يعني عند المريف 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

هبوط ضغط

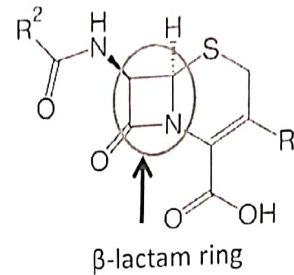
* المطلوب بالأساس جزء Suffix أو Prefix للدوا لتعرف
هو أي مجموعة

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 mangitla
ما بروج استخدمه Cephalosporine
ليس ؟ لأنه من ضمن الشقات
التي تزيلها ما تغطي Antibiotic
هو إنه تفتن وصوله Site of infection
و Cephalosporine لا يصل إلى CNS

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

- They are safe in Pregnancy & taking by lactating mother

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 يغطيه Cephalosporine

- Penicillins & cephalosporins exert their activity against growing bacteria

لو كان عننا Dormant bacteria

WHY???

Penicillin & Cephalosporine
ما راح يغطي Activity

لو استخدمنا مع Penicillin ال Bacteriostatic
يعني توقف نمو البكتيريا
لأنه حينئذ نمو البكتيريا وتكاثرها لأن بها طوي
نم قتلها

لأنهم يشغلوا على wall cell فهي بليش تشغلها هون
لأن حالة طور السكون ما بتفتح Peptidoglycan فهي لا
تكون متاحة

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 يعيق immune system
لأن: العمر الكبير أو مريض الكلى إلى باخدا Chemotherapy
أو immune suppressant ← ما يقدر يعطي له Bacteriostatic
لأن البكتيريا بفضل الجسم

③ لو استخدمنا penicillin مع Bacteriostatic شو رح يصير؟
رح يوقف نمو البكتيريا و رح توقف عمل Penicillin
لأنه مبني على نمو البكتيريا وتأثيرها لأنها بالطور يتم قتلها
لكن لو استخدمنا penicillin or cephalosporine بطور السكون
ما رح يعطي أي activity العلاج

Dormant stage

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
 لا يعمل ضد البكتيريا موجبة الجرام
 improper use
 Highly effective or Highly active
 resistance
 لا يكون في

Vancomycin

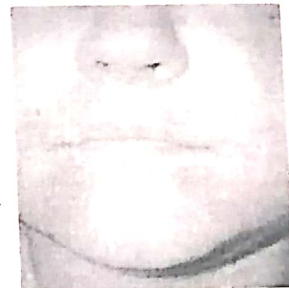
cell wall synthesis inhibitor (يسبب توقف دورة حياة البكتيريا)
 β -lactam inhibitor

- 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)

natural

Antistaphylococcal

في مجموعة من penicillin في
 في Chain في Staphylococcus aureus
 تطورت وصارت تقاوم penicillin فابتليت
 لتصبح له فئلاً 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

Demeclocycline
 Doxycycline
 Minocycline
 Tetracycline

MACROLIDES/KETOLIDES

Erythromycin
 Clarithromycin
 Azithromycin
 Roxithromycin

GLYCOSYCLINES

Gentamicin

AMINOGLYCOSIDES

Amikacin
 Gentamicin
 Neomycin
 Streptomycin
 Tobramycin

OTHERS

Chloramphenicol
 Clindamycin
 Linezolid
 Quasipristin, Dalbacin

main group

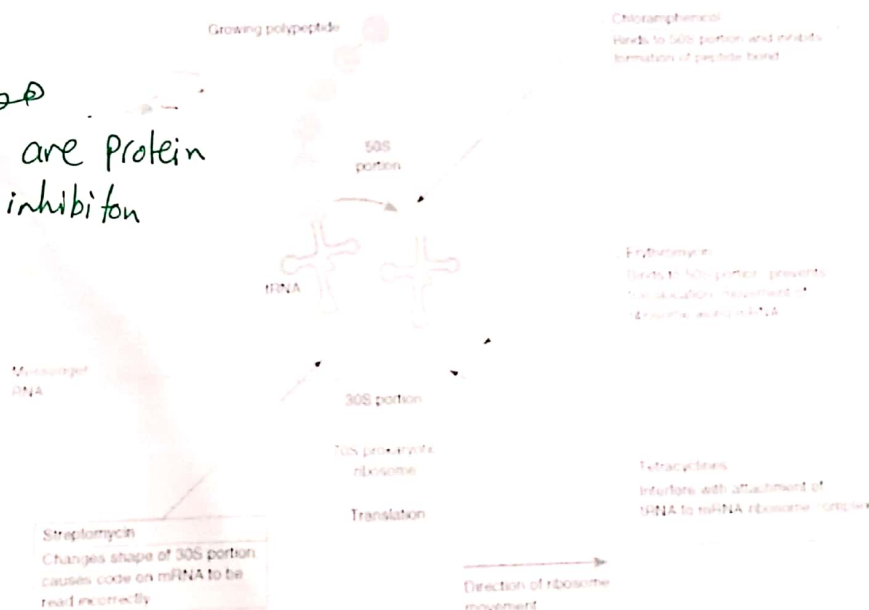
Classification of Protein Synthesis inhibitor

Tetracycline
 Glycylcycline
 Aminoglycosides
 Macrolides/Ketolides

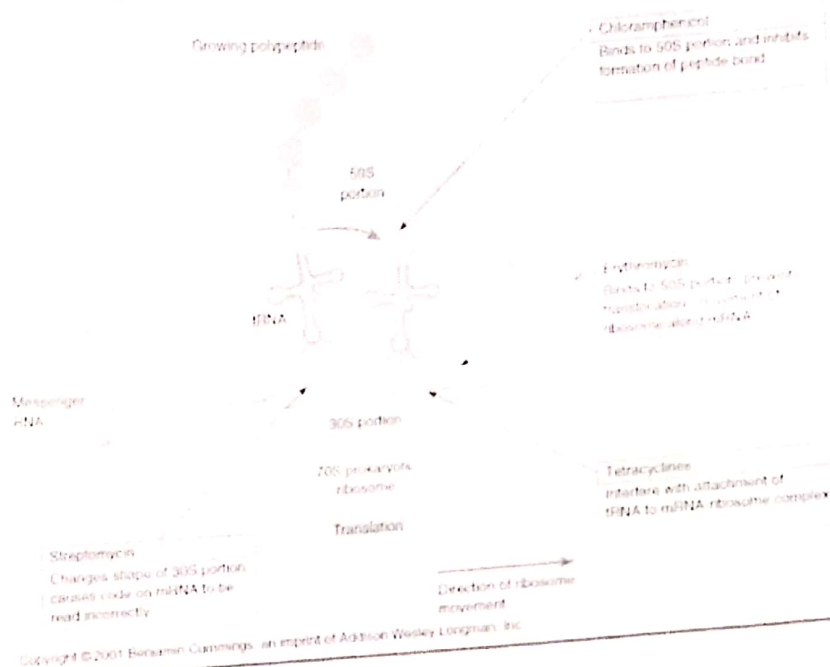
we are going to talk about them and about: Linezolid & Chloramphenicol which are Protein Synthesis inhibitor

protein synthesis inhibitors antibiotics

All of them are protein synthesis inhibitor



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 will not respond.

Aerobic, gram-negative bacteria
Anaerobic bacteria will not respond
for aminoglycoside

- Anaerobic bacteria are resistant.
- 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 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

that mean they
amino glycoside
derivatives

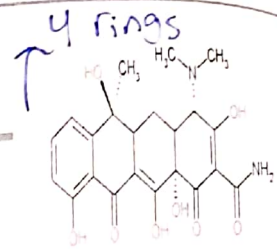
Pores سوراخ inhibition of cell wall synthesis پنیسیلین Penicillin

فہار مع ساءع Penetration الـ Aminoglycoside فبالل هو Synergistically effect

رابعي

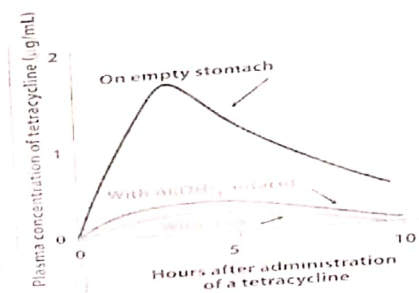
②

Tetracyclines



- Their names end in "cycline"
- Example: Doxy cycline → Doxydar اسمه 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 الحديد 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 يائي اسمه Alkylation
Tetracycline

وتجمل 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 يمكنه Deposition
في الأسنان

Brown teeth discoloration
Permanent

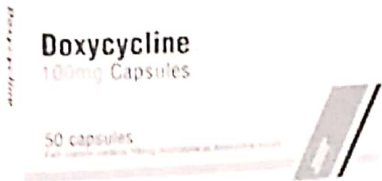
- Alteration in intestinal flora may result in Superinfection (overgrowth of nonsusceptible organisms such as Candida)

→ 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



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 الذين لديهم
Pencillin allergy
نحتاج إلى بديل
Macrolides

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

Immunomodulatory
Effect

لأنه ~~antibacterial~~ Anti-bacterial
وكان يحفز Control of releasing cytokines

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

عشان هذا أكثر
في بكتيريا
الأناتية

↓
it is a superinfection

بسبب Diarrhea ← يعني لو ارجع 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
نظام
exclude

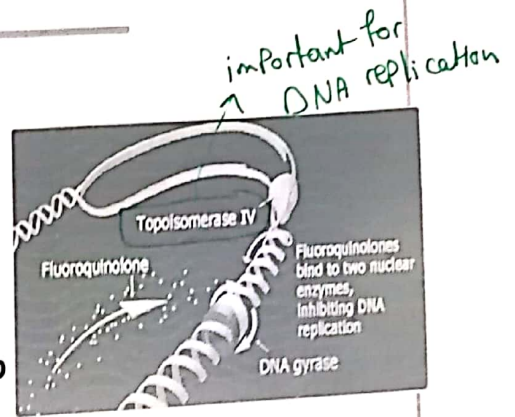
مخبر
نقص
فقدان
الصفائح
& RBC's
& WBC's

كأنه في مشكلة وقف استخدام Systemically بس

as eye drop & ointment ← as topical
adverse effect

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

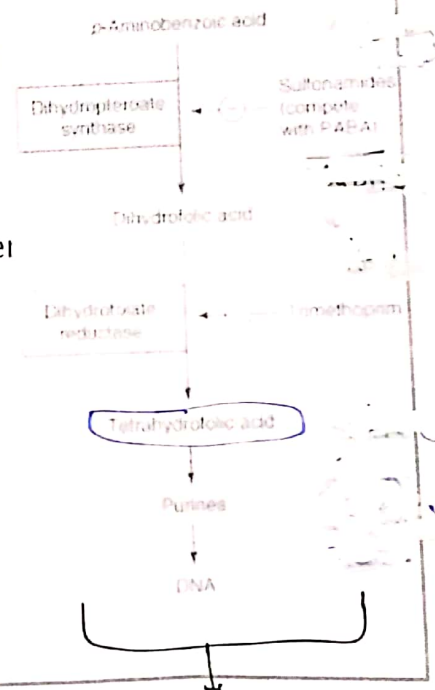


Fluoroquinones → Bind to topoisomerase & Cause inhibition of DNA gyrase
So inhibit DNA replication

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

Antimetabolites (7)

- DNA replication
- RNA synthesis
- 1st step of folic acid synthesis
- 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 ← **co-trimoxazole**

البكتيريا قادرة على تصنيع folic acid من substrate PABA

* **Sulfonamide** inhibit Dihydropteroate Synthase

* **Trimethoprim** inhibit Dihydrofolate reductase

الأحسن هو الجمع بين عمل
Sulfonamide + Trimethoprim
step 1+2 أنت
يعني أنت نأكل كل ال
Pathway

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

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 يزرعوا البكتيريا Agar Plate و Filter Paper يكون مشبعة بـ

Certain amount of antimicrobial agent

كل وحدة فيها Antibiotic Kirby-Bauer Method (diffusion test) أكثر Filter Paper

تحت ضوء 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.

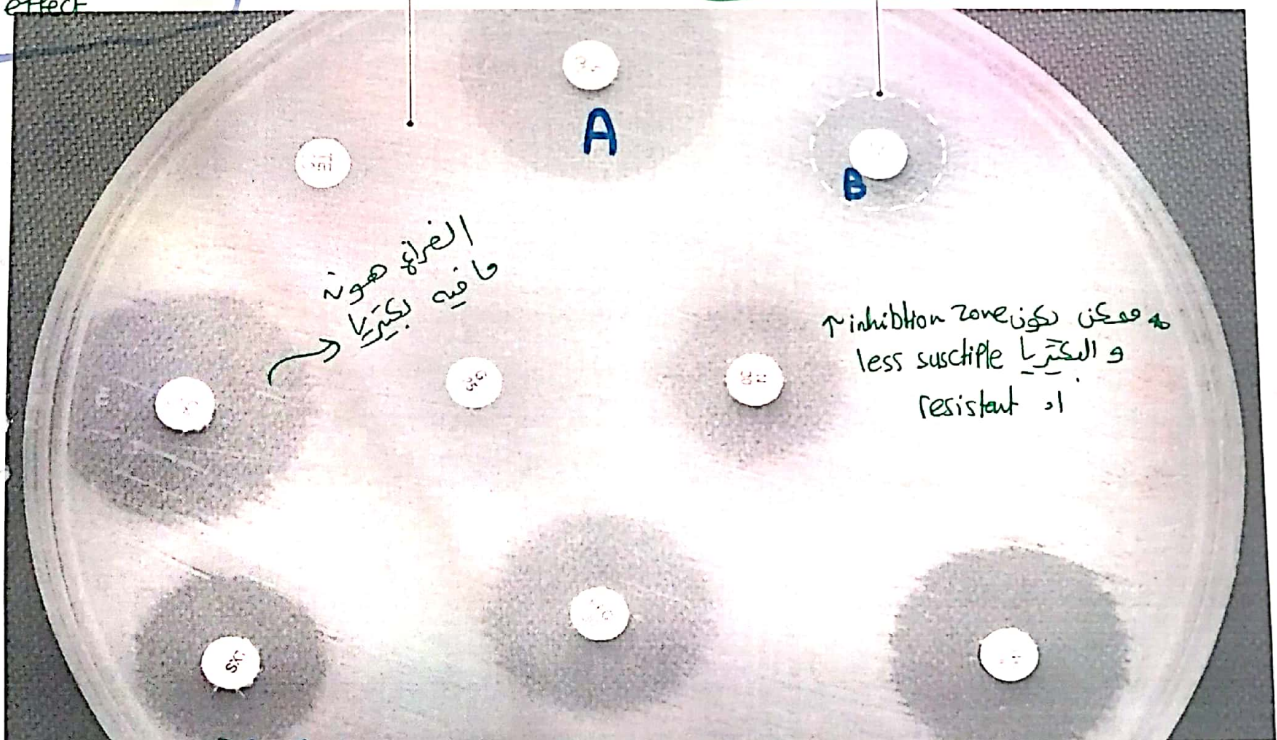
Although the inhibition zone give us a hint to know the antibiotic if effective or not regarding to it's diameter, however we should back to a reference table

نقطة عرقه • من كل Antibiotic و Inhibition Zone يعني Active

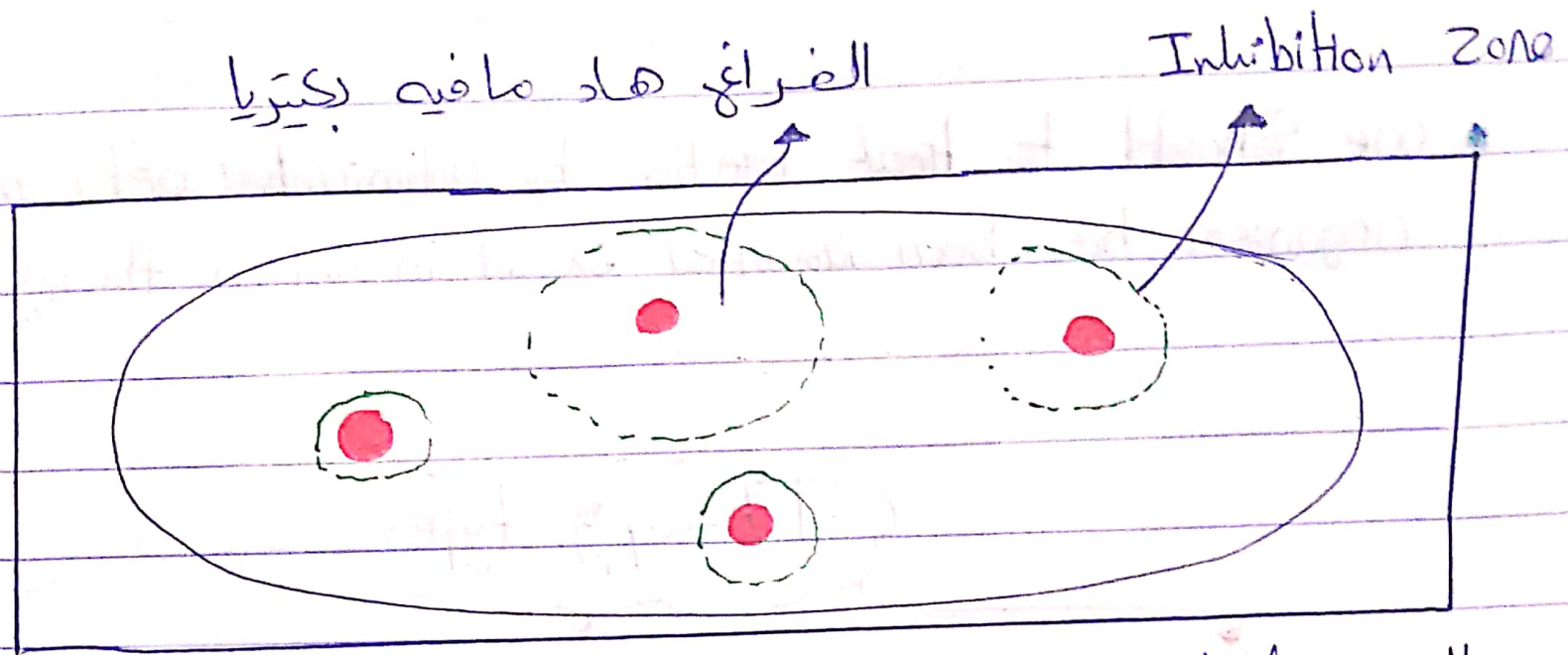
* ↓ Mw of antibody
So ↑ rate of diffusion
So ↑ effect

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

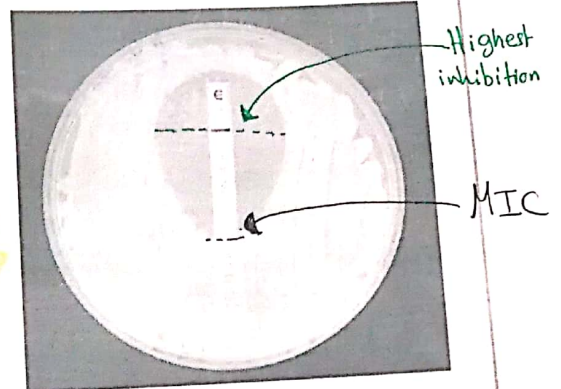
reference table

resistance	intermediate	Susceptible	↑ inhibition zone
Susceptible	لا	لا	لا

* ↓ 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.

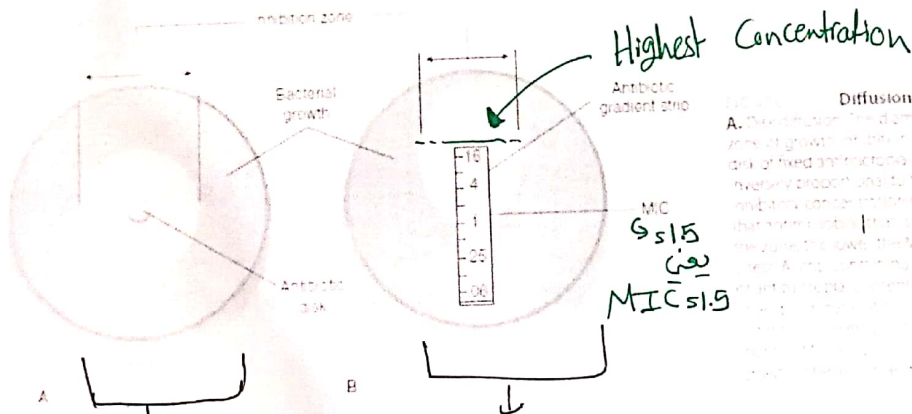


بكون في Plastic strip فيها Gradient of conc. of antibiotic

Strip بكون مدرجة

Diffusion tests

نوعها ٤ هذا يحتاج لقياس agar بكون
Plate
measurement of that bacteria resistant to this antibody



هذا بالمسطرة بقياس
inhibition zone

هون بقياس عن
Strip ببقية
Antibiotic فيها
واحد

بقياس هون بين بقياس
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. Counted 5 colonies and culture concentration is made serially

4. Plate amount of each serial dilution and count results of each dilution to calculate concentration of each dilution



Broth dilution method for measuring minimum inhibitory concentration of antibiotics

3. After overnight incubation, check tubes for growth. The MIC is the lowest concentration of antibiotic that prevents viable growth. In this example, the MIC is 0.4 mg/L

5. After overnight incubation, check cultures for growth. The MIC is the lowest concentration of antibiotic that prevents viable growth. In this example, the MIC is 0.4 mg/L

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 القِوة Turbid ← Tube لا يكون لال
There is Killing ← Clear كان لال
of bacteria