Pharmacology

Subject :

Lec no :

Done By :

وَقُل رَّبِّ زِدْنِي عِلْمًا

ملاحظات الدكتور
أول المحاضرة

Principles of Antimicrobial Therapy

..All the drugs are chemicals.
..The antimicrobial and anticancer therapy are usually classified as chemotherapy.

..Antimicrobial Chemotherapies : are designed to kill micro organisms that causes infections. These drugs change the humanity by increasing the life expectancy.

"Before many years,the first cause of death was microbial INFECTIONS. But now it is not"

*Nowadays, the causes of death are : Cardiovascular diseases, Cancers(due to increasing in life expectancy) and Car Accidants.

number one

Group of chemic al drugs to kill cancers

Before We Discuss Chemotherapy.....

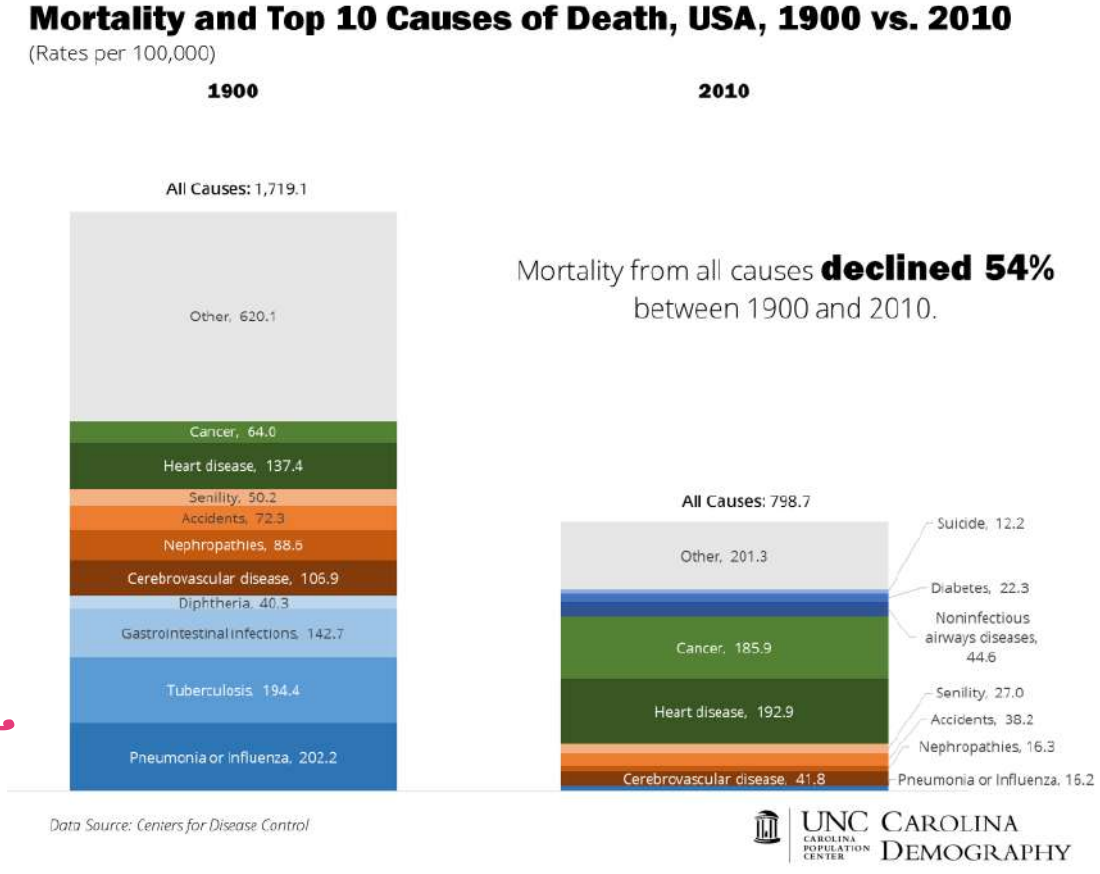
THINGS TO DO	THINGS NOT TO DO
• Engage in discussion	• Side talk
• Ask a question, always raise your hand	• Ask your friend on something
• Use your phone to look for information	• Keep your phone on ringtone mode
• Attend all classes	• Come late to classroom (later than 10 minutes of beginning)
• Participate in quizzes	• Cheat

How Did Antibiotics Change The World?

كان زمان بسبب الـ infection

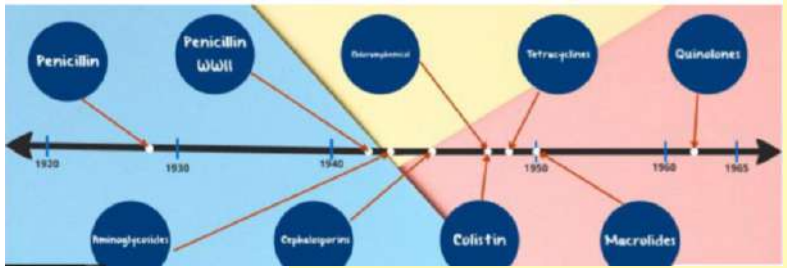
- **Life expectancy**: 47 years to 78 years (Western countries)
- **Major cause of death**: communicable diseases to non-communicable diseases

من مُعدي ← إلى غير مُعدي



أخذنا فصل شوي في محاضرة دكتورة هالة رقم (17) ←

The Story of Penicillin

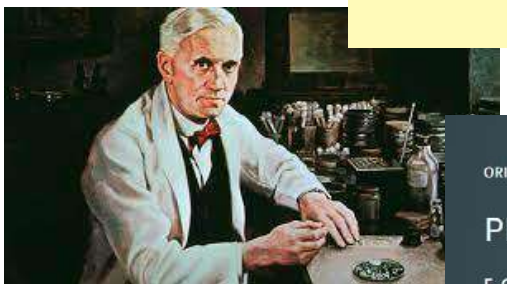


*The first Antibiotic was discovered is Penicillin. (Fungi product)

*It was discovered by an accidant(بالصدفة).

*On returning to his lab after a month-long holiday in 1928, Scottish doctor Alexander Fleming discovered that a culture of the bacteria staphylococcus aureus, which he had been experimenting with, had been destroyed by a mould growing in his petri dishes. Fleming had discovered the first antibiotic, which he called penicillin. The drug has saved countless lives, especially in that time, extensive injuries was spread around because of the World War 1. Many people befoe this discovery were injured and die because of the infection.

كانت فترتها الحرب العالمية الأولى



ORIGINAL ARTICLES | VOLUME 236, ISSUE 6104, P226-228, AUGUST 24, 1940

PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

E. Chain, Ph.D. Cambridge • H.W. Florey, M.B. Adelaide • A.D. Gardner, D.M. Oxford, F.R.C.S. • N.G. Heatley, Ph.D. Cambridge • M.A. Jennings, B.M. Oxford • J. Orr-Ewing, B.M. Oxford • et al. Show all authors

Published: August 24, 1940 • DOI: https://doi.org/10.1016/S0140-6736(01)08728-1

*After that, Chain and Florey from Oxford shared a paper which describes penicillin as a chemotherapy (it was not shared by Alexander Fleming). They search for anti-microbial agents. They did an experiment on 8 mice that were infected from Bacteria, 4 of them took the penicillin so they were recoverd after 2 days . And the other 4 died .

From the book :

*In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

لحد جواب السؤال تحت

Overview

Selective Toxicity:

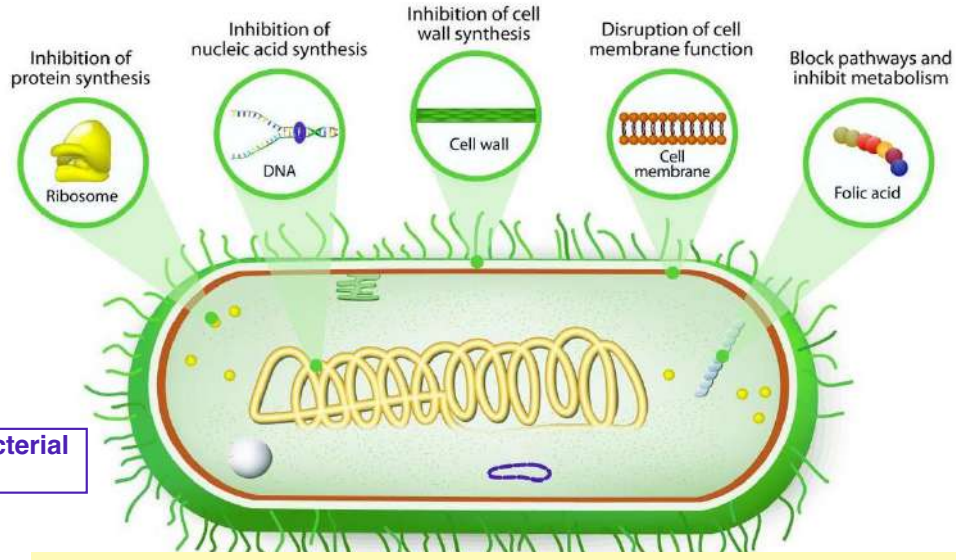
"The ability of an agent to injure or kill an invading microorganism without harming host cells"

[+Minimal effect of toxicity*

Mean that's antibiotic target bacterial with minimal effect on human

Is it absolute?

selective toxicity من ناحية



Anticancer drug << Antimicrobial drug

*Anticancer drugstargets cancer cells and the normal cells also→no selective toxicity.

مثال

One of the reasons of this selectivity is the presence of we usually target the cell wall of the bacteria).

Volters Kluwer

ناخد مثال صناعة البروتين بين ال eukaryotic و ال prokaryotic هل في فرق؟ اكيد ، (على سبيل المثال ال ribosome مختلف في كل وحدة ،،بس لا يعتبر completely different)،، بس نيجي لل cell wall يختلف بين الاثنين ال bacteria have cell wall الي كان من (peptideglycan) بينما ال human cells without cell wall ،،فلما نعمل drug بدنا نكون حريصين نستهدف ال cell wall حتى نعمل kill bacteria effectively with minimal toxicity

Selection of Antimicrobial Agent

هسا انت بس تروح على صيدلية وتسأل الصيدلاني كم نوع antibiotics عندك ؟ رح تلاقي انواع كثير توصل لل hundreds ، طب كيف بدي اعرف انو واحد اختار للمريض؟عنا selection group بدنا نعرفها حتى اختار على اساسها ال best choice

What needs to be known?

- The organism's identity
- The organism's susceptibility to a particular agent
- The site of the infection
- Patient factors
- The safety of the agent
- The cost of therapy

Resistance ~~residents~~ مهمه نعرف هاد المصطلح لانو عندي كثير

Treatment of CNS infections different than treatment of lung infections just because pharmacokinetic factors

↳ لما تكون وحيي بين دوبين عندهم نفس الفعالية بس واحد رخيص وواحد غالي حين رح تختار؟ اكيد الرخيص

Identification of The Infecting Organism

How?

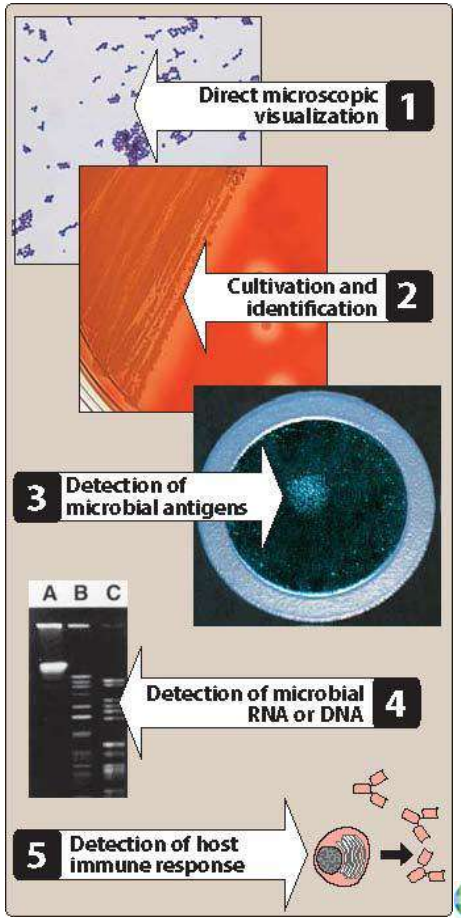
1) **Gram stain**: ↔ + / - shape
   - presence of microorganisms in sterile body fluids. How ? ⟶ لـCSF زي sterile مفروض يكون some of fluid فيه اخد عينة والاقي فيها بكتيريا بعرف انو فيها infections
   - morphologic features ↳ shape

2) **Culture**:
   - diagnosis
   - antibiotic susceptibility

3) **Microbial antigens**
   - DNA, RNA, etc

4) **Host immune markers**

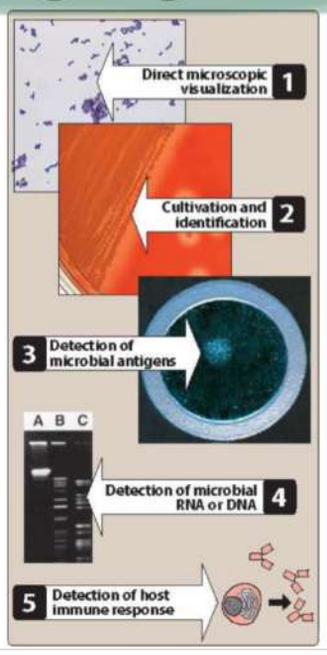
gram +/-
aerobic / anaerobic
typical / atypical



1

Identification of The Infecting Organism

- **Gram stain:** gram + / gram –
  - presence of microorganisms in sterile body fluids.
  - morphologic features
- **Culture:**
  - diagnosis
  - antibiotic susceptibility
- **Microbial antigens** Ex: PCR TEST
  - DNA, RNA, etc
- **Host immune markers**



*in the case of bacterial infection, we have multiple tests to do, to identify which type of bacteria we are dealing with.

*The simplest test and most straight forward test is gram staining → we take a sample from the suspected site of the infection and stain it with gram stain . Keep in mind that many of body compartment should be free from bacteria (sterile), for example blood (sepsis) , urine (urinary tract infection) , pericardium fluid , plural fluid and CSF, serum, synovial fluid. And we can determine the morphological features of the organism (cocci – bacilli – rods etc.)

*If you want to exactly determent the organism to initiate proper antimicrobial therapy you must do cell culture -> which is a gold standard test to diagnose bacterial infections.

IMPORTANT NOTE: gram staining do not tell you the exact microorganism but it defiantly tell you whether it is gram positive or gramnegative bacteria.

Culturing (not immediate tests) they take from 48 – 72 hours depending on microorganism, so in the sever or critical cases first we take a swap from the patient for culture and we start giving the patient antibiotic before the result .

طبعا انا باخد العينة من المريض قبل ما ابلش العلاج و قبل ما اعطية اي مضاد حيوي لأتأكد انه العلاج بناسبه او لا، في الحالات الحرجة و الطارئة ببدأ اعطيه الteatment حسب my experience و بنفس الوقت لازم اعمل culture

We use broad-spectrum antibiotics that recover a wide range of bacteria

بس ما تنسوا ضروري ضروري نوخد sample و نعمل culture

اكيد طارح اسئلة هالقد لحالة مثلاً عندها ساعات معدودة للحياة

هون في طالب سأل ليه ما بقدر أتوقع نوع البكتيريا من الاعراض الي عند المريض ؟

* منقول من تفريغ جهينة *

هسا في كم نقطة حكاهم الدكتور سهلين ما فيهم اشي جديد (بس للاحتياط حأكتبه) :

*أنا كطبيب بعرف انه الlung infection بالمنطقة الفلانية 4-6 انواع بكتيريا بسببوه

و بعرف ال anti-microbial susceptability بهاي المنطقة بالعالم

الي الدكتور بده ايانا نعرفه الآتي :

Resistence differs from one region in the world to others

هسا عنا بالارد ن مثلا كثير مناخد مضاد حيوي حتى لو يكون السبب فايروس وحكالك الدكتور ما بدك مضاد رح تلاقي المريض ما يرد ويروح يشتري من الصيدلية مضاد فهاد الايشي عمل عنا height microbial resistance(وهاد مش ايشي جيد)

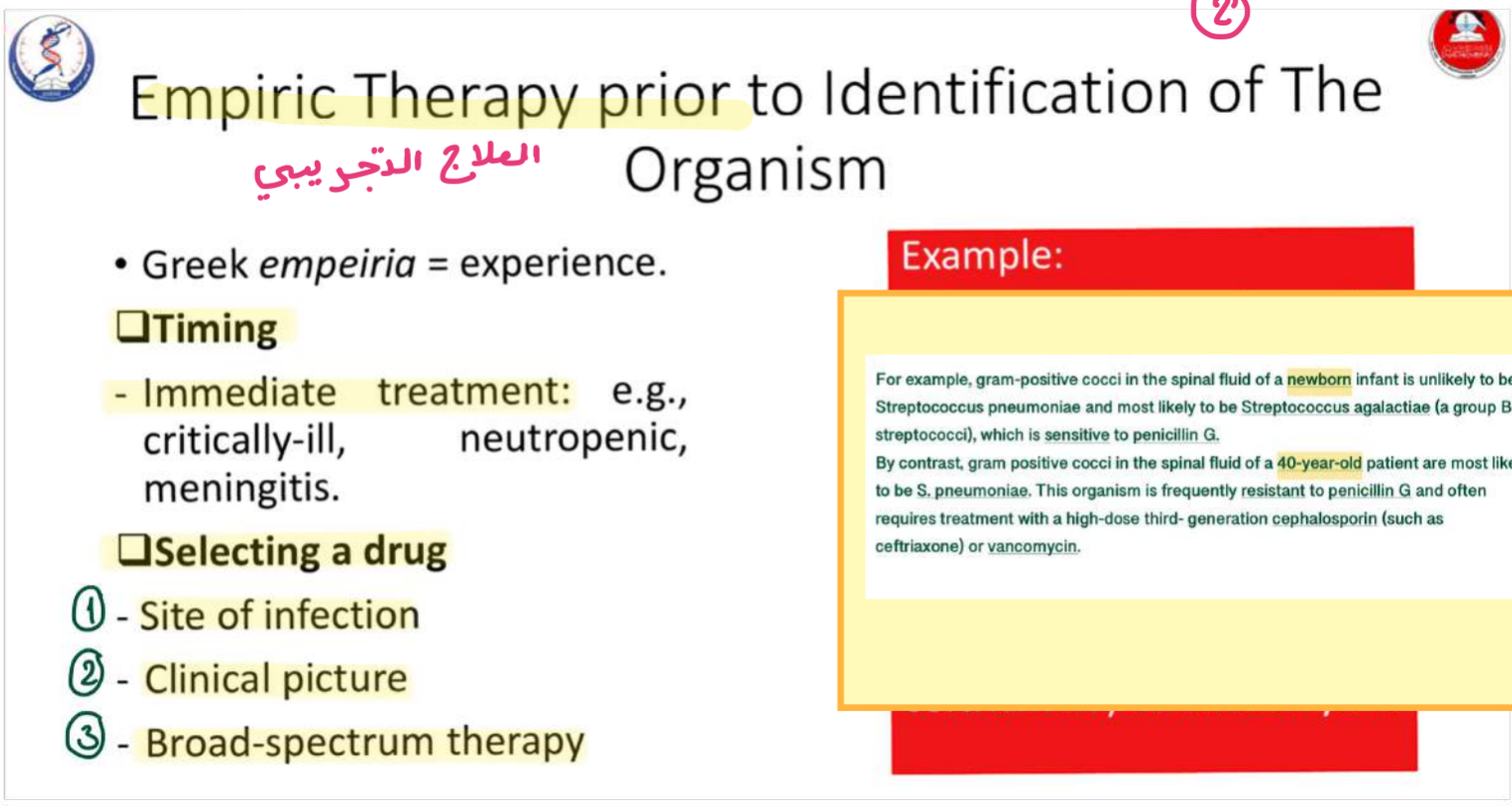
*مثال تاني : لو مريض مصاب ب meningitis، و حالته طارئة ؛ انا كطبيب لازم اكون عارف انه الadult حيكون مصاب بوحدة من هدول البكتيريتيين :

Neisseria meningitidis or streptococcus pneumonia

لهيك حأعطيه treatment يكون بستهدف هدول البكتيرتيتين

و لو كان هاد المريض عمره 24 يوم. ، انا كطبيب لازم اكون فاهم و عارف انه في بكتيريا تانية انتقلت للرضيع عبر birth canal و هي Listeria monocytogenes و الي تعتبر Gram Posetive لهيك بعطي هاد المريض دواء تاني يكون بستهدف هاي البكتيريا

* السلايد إلي تحت من تفريغ جهينة موضحينو بطريقة سهلة .



From the book :

*Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established.in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

*Empirical Treatment :empiric therapy is to start the treatment without knowing the actual cause of infection before you have the result of bacterial cell culture .Treatment given based on experience.

*Timing: Acutely ill patients with infections of unknown origin for example:

1. neutropenic patient (infections due to a reduction in neutrophils).
2. patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord) require immediate treatment.

*Selecting a drug: Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital or community acquired).

Broad-spectrum therapy may be indicated initially when the organism is unknown. The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting.

← بعدما توصلولهون شوف الـ box فوق

Determining Antimicrobial Susceptibility of Infective Organisms

Minimum inhibitory concentration Vs minimum bactericidal concentration to determine the efficacy of the antimicrobial drug.

- Predictable vs unpredictable susceptibility
- The susceptibility of a microorganism to a drug can be experimentally determined

تعريف

the lowest concentration of an antimicrobial that will inhibit the visible bacterial growth in culture

Minimum inhibitory concentration

MIC

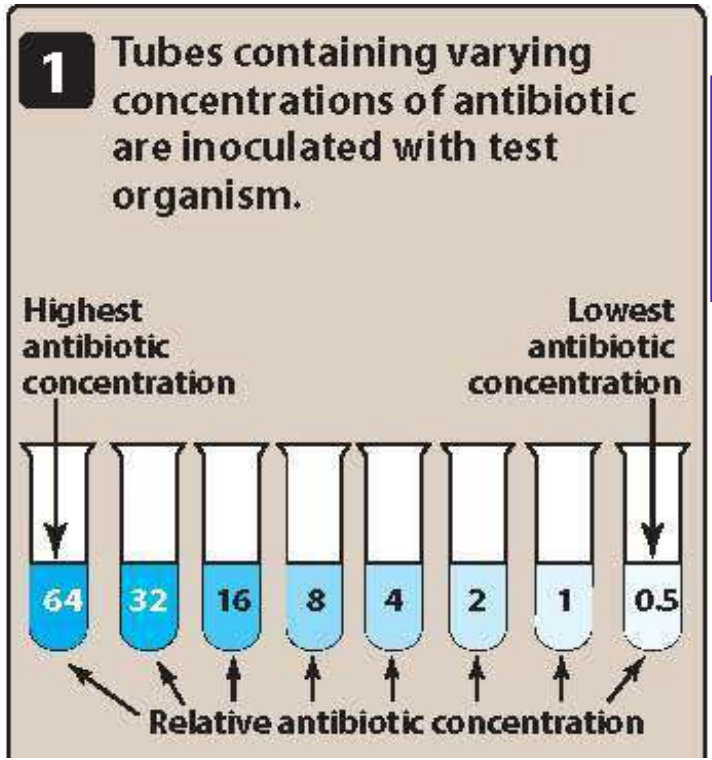
minimum bactericidal concentration

MBC

معنى visible:يعني اذا انا اجيت ازرع بكتيريا في culture شفتها بعيني هاد visible growth بس مش بالضرورة اذا انا ما شفتها يعني مافي بكتيريا لانو (البكتيريا microscopic)،،فا المهم انو ال visible growth هو العامل المحدد في MIC

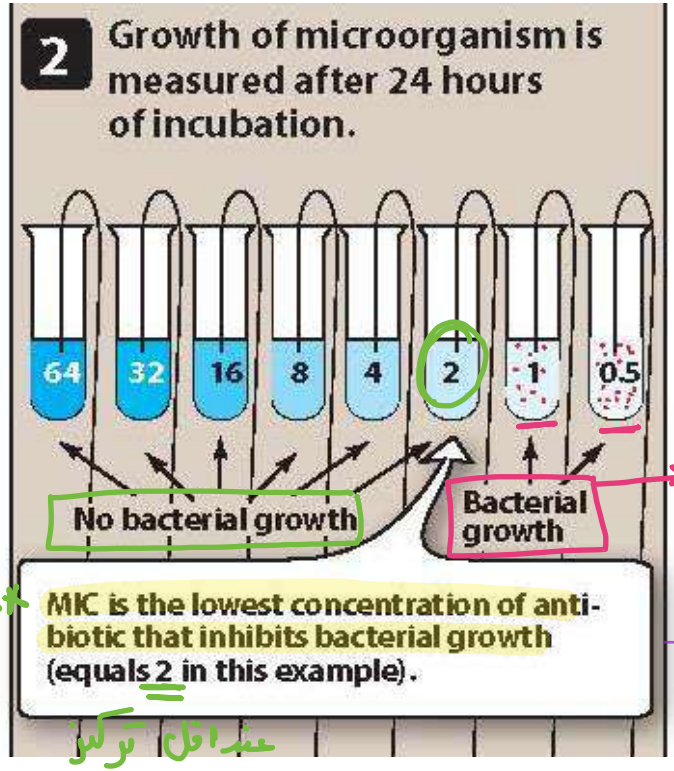
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

لنفرض واحد عندو Pain in urination



١)اخذت عينة من مريض من البول
٢)زرعتهم في test tubes كلهم في نفس التركيز
٣) At the same time solutions in the test tubes will have increase concentrations of antibiotic of choice
٤)تركتهم يوم كامل

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



هسا بعد ما نرجع مفروض البكتيريا بوجود ال antibiotic(وانت عارف انو في كل test tube فيه fixed amount of antibiotics)؟ المفروض ما الاقي بكتيريا بس شو التجربة بينتلي

هون البكتيريا قادر اشوفها بعيني

هسا السؤال هل انت متأكد انو مافي بكتيريا في ٢؟ او٤؟او حتى ٦٤ ؟ الجواب انو ممكن يكون في بس انا لازم اجرب وأتأكد

بطلت اشوفها

in → Lowest Concentration prevent bacteria to growth

MIC وهاد هو

عند اقل تركيز

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

*Usually, MBC > MIC
Means that we need high doses of antibiotic to kill bacteria than doses that inhibit the growth of bacteria.

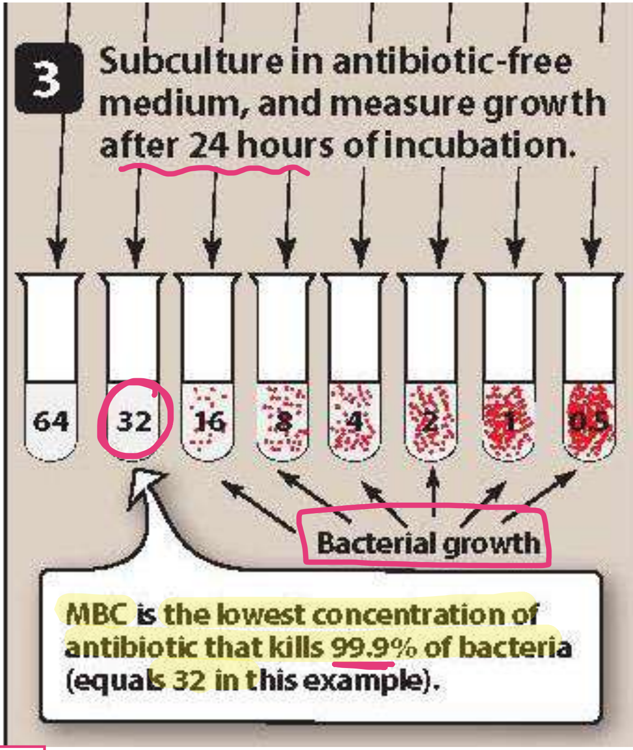
*Drug that has low MBC means that we need small dose concentration to kill bacteria
*So drugs with small MBC is more effective than drugs with high MBC.
*Drugs with small MIC are more potent than drugs with higher MIC.

2. LD_{50}: The **dose** that **kills 50%** of animals. lower LD_{50} → more toxic. The dose used should not exceed 10% of the estimated LD_{50}.

← دايماً منغلط بالامتحان
الجرعة الكبيرة مش معناها
انها Toxic ، معناها
التي تعدت من ال ED_{50}

تذكيو بمحاضرة ١٥
لدكتور شريف

نفهمها من سؤال : ال antibiotic A
MIC تاعتو 0.5 ،، antibiotic B ال MIC
الو 0.7 (on the same
organisms) مين more potent ؟0.5
هو ال more potent ،،



هون الي عملناه ١) اخدنا عينة من كل تيوب فوق

٢)حطيناها في تيوب جديد مافيه antibiotics
* اذا ال antibiotics موت البكتيريا مفروض لما اخد عينة واعمللها growth ما تظهر ،،،، بسس لو ال antibiotics عمل inhibitions to growth يعني ما صار (completely kill) واجيت وزرعتها في new culture شو مفروض يصير ؟ مفروض يصير growth of bacteria

Note: The MBC is rarely determined in clinical practice due to the time and labor requirements.

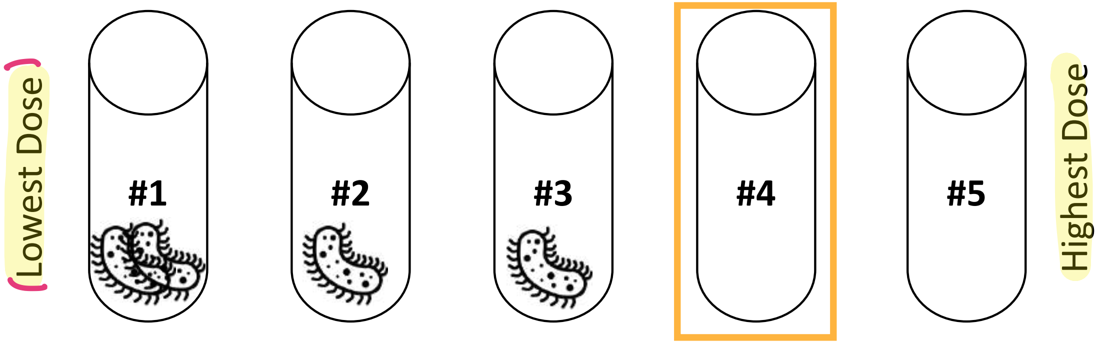
Tareq Saleh ©

لـ بتاخد وقت طويل

Wolters Kluwer

Practice Question

- You have 5 tubes and want to do 5 dilutions of antibiotic X on the growth of E.coli. Tubes 4-5 do not have growth, but tubes 1-3 have visible growth, the tube with the MIC would be?



من ال antibiotic

التركيز الاقل ← بطلت قادرة اشوف البكتيريا

حيون ي حققت شرطين

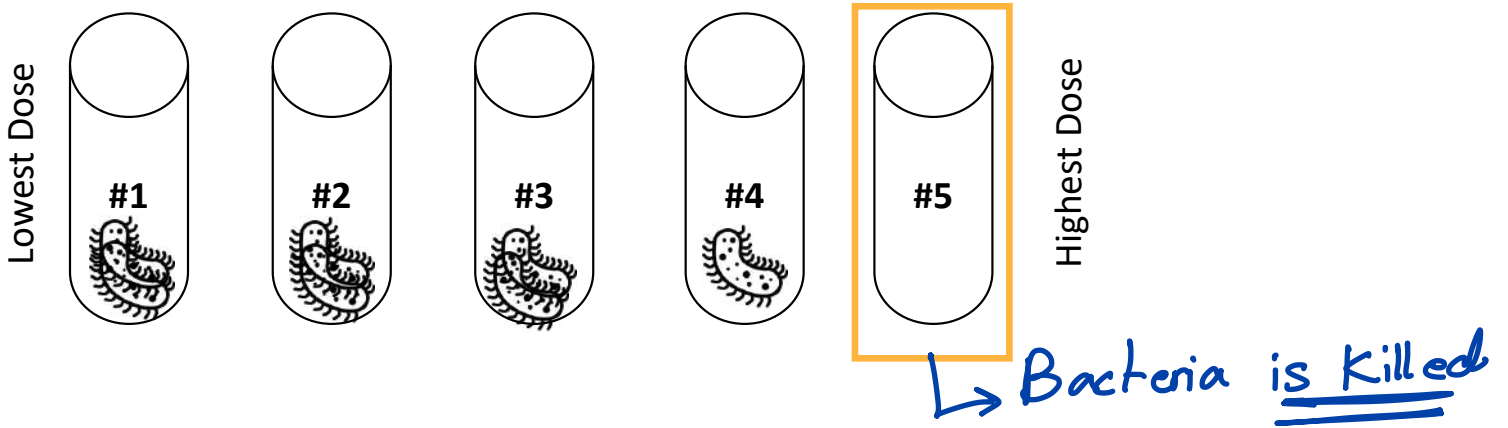
بدي عين MBC ؟
← بقدرش اعرف
لازم اخذ عينة وازرعها
في وسط بدون ال antibiotic

Tareq Saleh ©

Wolters Kluwer

Practice Question

- Subcultures of the last 5 tubes gave the following results. Which tube has MBC?



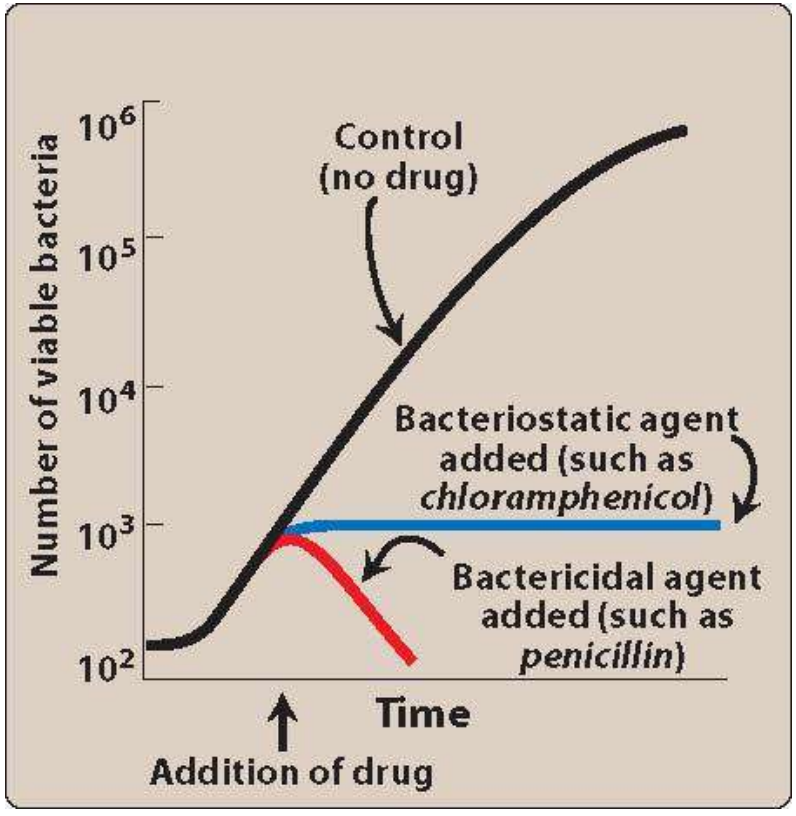
مشكلتي مع البكتيريا نموها سريع جداً
أسرع من قدرة جسمي
على المواجهة

Bacteriostatic vs Bactericidal

- **Bacteriostatic**: arrests the growth/replication of a microorganism

bacteriostatic" means that the agent prevents the growth of bacteria (i.e., it keeps them in the stationary phase of growth

- **Bactericidal**: kills bacteria (kill ≥ 99.9%)



cidal → قاتل
وبين قاشغتها

هسا هون بدنا نحدد هاد ال antibiotics هل ال mechanism تاعو Bacteriostatic او Bactericidal

اول شي شو الفرق بينهم ؟
ال bacteriostatic هو مثبط لنمو البكتيريا وحط تحتها خطوووط انو مش قاتل يعني المضاد الحيوي الي بشتغل بهاي الطريقة فا بحقق شغلتين ١) بوقف نموها حتى يتغلب عليها جهازي المناعي او ٢) فترة بقائها في الجسم تكون قليلة كم ساعة ومع تثبيط نموها تقتل حالها بنفسها

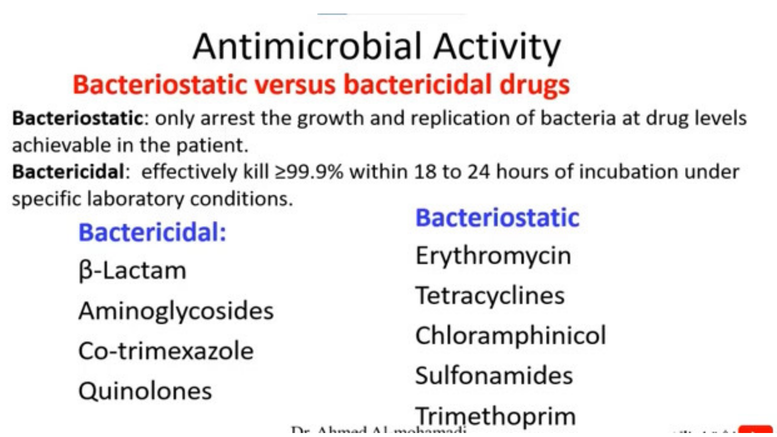
← زي ال antibiotic الي بثبط ال protein synthesis او / Metabolizem للبكتيريا

بالنسبة لل bactericidal فهو قاتل للبكتيريا

← مرات مضاعفة الجرعة بتحول ال antibiotic الي قاتل (المضادات الي بتثبط ال protien.S) + في مجموعات من الأدوية

*most cell wall inhibitors → bactericidal effect
*Protein synthesis inhibitors → bacteriostatic effect

بس للتوضيح ←



Antimicrobial Activity

Bacteriostatic versus bactericidal drugs

Bacteriostatic: only arrest the growth and replication of bacteria at drug levels achievable in the patient.
Bactericidal: effectively kill ≥99.9% within 18 to 24 hours of incubation under specific laboratory conditions.

Bactericidal:	Bacteriostatic
β-Lactam	Erythromycin
Aminoglycosides	Tetracyclines
Co-trimexazole	Chloramphinicol
Quinolones	Sulfonamides
	Trimethoprim

Dr. Ahmad Al-mohamadi

Bacteriostatic vs Bactericidal

But…

- ❑Classification is too simplistic
- ❑Microorganism-dependent
- ❑Similar efficacy for clinical infections

from the book

*** this classification may be too simplistic + microorganism - dependent because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another.**

For example, linezolid is bacteriostatic against Staphylococcus aureus and enterococci but is bactericidal against most strains of S. pneumoniae.