



Pharmacology

Subject :

Lec no : 22

Done By : Raneem Azzam

وَقُلْ رَبِّ زِدْنِي عِلْمًا



Effect of The Site of Infection on Therapy: The Blood-Brain Barrier (BBB)

هون ال antibiotic
 زي يوزي أي drug
 يعني نفس pharmacokinetic
 يطبقوا عليه

1. Lipid solubility of the drug:

- Lipid-soluble drugs e.g., chloramphenicol and metronidazole
- low-lipid-soluble drugs: e.g., penicillin
- meningitis

2. Molecular weight of the drug:

- low molecular weight more ability to cross the BBB

3. Protein binding of the drug:

- amount of free (unbound) drug not the total amount of drug

4. uncharged

✗ ال antibiotic فابقي يكون هو
 ال most effective لازم الجمع
 عن pharmacokinetic properties
 الي تسحله يدخل لا بتتيريا

* drugs that have high lipid solubility can readily cross the blood-brain barrier.
 * Chloramphenicol and metronidazole are high lipid soluble drugs which means that they can easily cross the BBB.
 * Penicillin has a high molecular weight, and it exist in a charged (ionized, polar) form at the physiological pH, this means that penicillin cannot cross the BBB. Penicillin is not used to treat infections in the CNS.

*** THERE ARE SOME EXCEPTIONS*
 patients with severe meningitis infection (which is usually caused by bacterial infection) have increased permeability through BBB → drugs that are usually cannot cross BBB in this case can cross it. for new born

*compounds with a high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

Other factors : susceptibility to transporters or efflux pump

← ملاحظات من تفريغ جهرية هي تذكير لى أخذنا سابقاً



Patient Factors

* Antibiotics helps in killing bacteria but immune system does the main killing function

1. Immune system:

- host defense system must ultimately eliminate the invading organisms.
- factors influencing immunocompetence: alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, immunosuppressive drugs.

having a normal immune response

منبهات مناعة

2. Renal dysfunction

3. Hepatic dysfunction

4. Poor perfusion

advanced age can affect a patient's immunocompetence, as can immunosuppressive drugs. (High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.)

كيف نعطيهم ال antibiotic
سهول انفس :-

2. Renal dysfunction

ما ننسى انو ال kidney بتعمل دور كثير مهم في ال elimination (الشخص الطبيعي في جرعة معينة بتضل بالجسم وبتخلص منها بعد وقت محدد بس الي عندو مشاكل ما بقدر اعطيه نفس الجرعة لانو ما منتخلص منو بنفس rate، ممكن يقلب تراكمول toxicity، لازم اكون حريص)

خلي عندك بعين الاعتبار انو kidney Some of antibiotics make damage، يعني لو عنا مريض بعمل Dialysis وال بيست antibiotics بعمل kidney damage هل بنفع اعطيه؟ اكد لا

3. Hepatic dysfunction

worked on Metabolism +
نفس
غلاة ال kidney +

- * Most of the drugs including many antibiotics are metabolized in the liver.
- * Patients with liver dysfunction need for dose adjustment.

+ site of
detoxification

4. Poor perfusion

بحكي عن important concept in pharmacokinetics وهي ال drug delivery
لانو شو هي ال way of distribution؟ ال bloody هو ال main way، طب لو ال target organ عندو poor perfusion مش رح تعمل complications sureeeeeeeeeee? in antibiotics treatment

- * Certain tissues of the body are not optimally perfused by blood (blood supply) such as tissues that are very distant from the heart (lower limbs for example).
- * Treatment of an infection in the lower extremities will be more difficult.
- * Diabetes mellitus interferes with proper vascularization (perfusion) of tissue.
- * Diabetic foot: chronic infection in the lower extremities that is very difficult to treat, and it remains for prolonged period of time.

حتى الدكتور حكي لو مريض سكري انجرح برجله سهل يصاب ب infection و صعب يتعالج منه

→ site of infection }
+ perfusion of }
that site }
كتر صهين
for antimicrobial works



قسّموا درجات فن X ← A على حسب ال risk



Patient Factors

حكيها فيها قبل

5. Age

* There are different protocols for treatment of diseases between adults and children.
* Some antibiotics that are very effective for treatment of certain infections in adults should not be given to children.

6. Pregnancy

7. Risk factors for multidrug-resistant organisms:

Geographic factors

- prior antimicrobial therapy in the preceding 90 days
- hospitalization for greater than 2 days within the preceding 90 days
- current hospitalization exceeding 5 days
- high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms)
- immunosuppressive diseases and/or therapies

main challenge الي مناجرها

CATEGORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins Aztreonam Clindamycin Erythromycin Azithromycin Metronidazole Nitrofurantoin Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	Chloramphenicol Fluoroquinolones Clarithromycin Trimethoprim Vancomycin Gentamicin Trimethoprim-sulfamethoxazole
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except gentamicin)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

ما يرد عن الدراسات ولكن ال risk سار في المقتر يعني احتمال ال كور متزال تحاشا

ممنوع تعطيها لأي امرأة حامل

مشكلة مافين ولا Drug

6. Pregnancy

- * Many drugs are able to cross the placental barrier (teratogenic effect) . If the drug is associated with high toxicity, it can harm the fetus resulting in life threatening or malforming toxicities.
- * Drugs are classified according to their toxicity on the fetus into 5 categories: (A, B, C, D, X)
- * Category A is the safest... there is no completely safe antibiotic.
- * Category B has reasonable safety ... e.g: penicillin
- * As we go down in the categories, the drugs are toxic.
- * Tetracycline and aminoglycosides are completely contraindicated during pregnancy. We can only use them in cases of severe infection in the pregnant woman.

يعن ممكن يكون عند المريضة كل شي تمام بس تطلع حامل فا خطة العلاج اكيدهم تختلف

هيهون ال
patient factor
حدو نوع antibiotic

7. Risk factors for multidrug-resistant organisms:

- * Certain classes of bacteria become resistant to wide variety of antibiotics. Ex: amoxicillin in Jordan.
- * Certain patients are at risk of developing multi-drug resistant bacteria.
- * These factors include:
 - 1) If the patient received antibiotic therapy in the last three months. If the patient has treated by antibiotic therapy and 99% of the bacteria are killed, the remaining 1% of the bacteria will develop resistance to that antibiotic and grow during the last three months.
 - 2) Hospitalization
 - * The hospital is a place for acquiring resistant bacteria.
 - * Nosocomial infection: acquired during hospitalization.
 - * Nosocomial infections are most likely to be caused by microorganisms that are highly resistant to therapy.



Cost of Therapy: Is It Important?

Factor ← عشق ال
الوحيد الي بتدخل

لا تنسى ان حينا فوقه

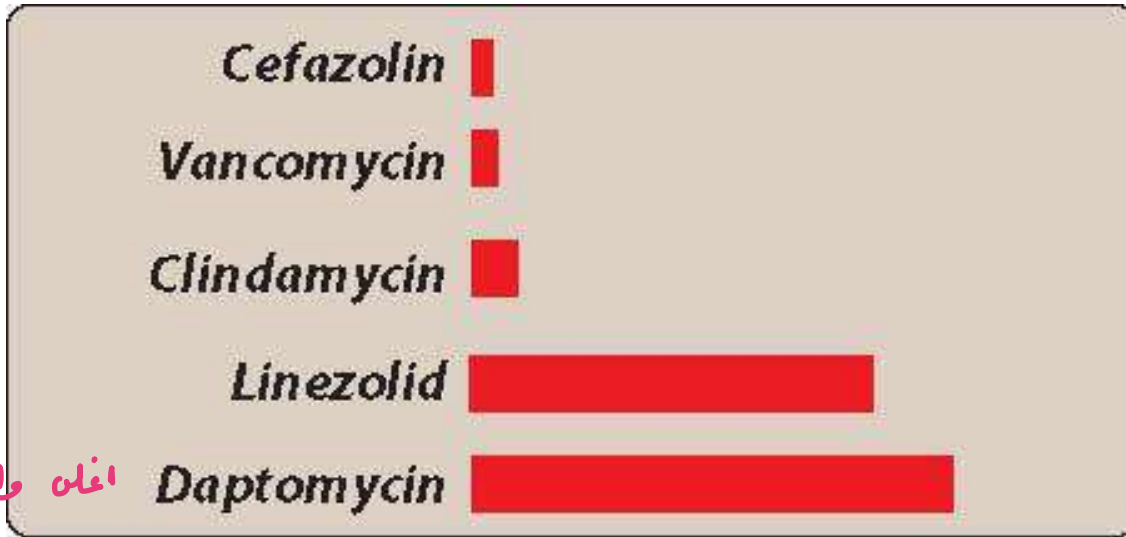
حداد ال factor بتدخل

بسه اكون صغيرة بين

أدوية عندنا same effect

أو ماشابه

:- حين بختار



Anti MRSA
drug
الادوية
المرتبة ←

اغلن واحد

Relative cost of some drugs used for the treatment of Staphylococcus aureus.

+ لوبري أحلولوية
بين سافت و cost
مين اختار؟ سافت

- 1) choice the most potent
 - 2) the most bacteria specific antibiotic based on type of bacteria
 - 3) the most suited of the patient factors
 - 4) the cheapest
- في مكان



Determinants Of Rational Dosing

A. Concentration-dependent killing

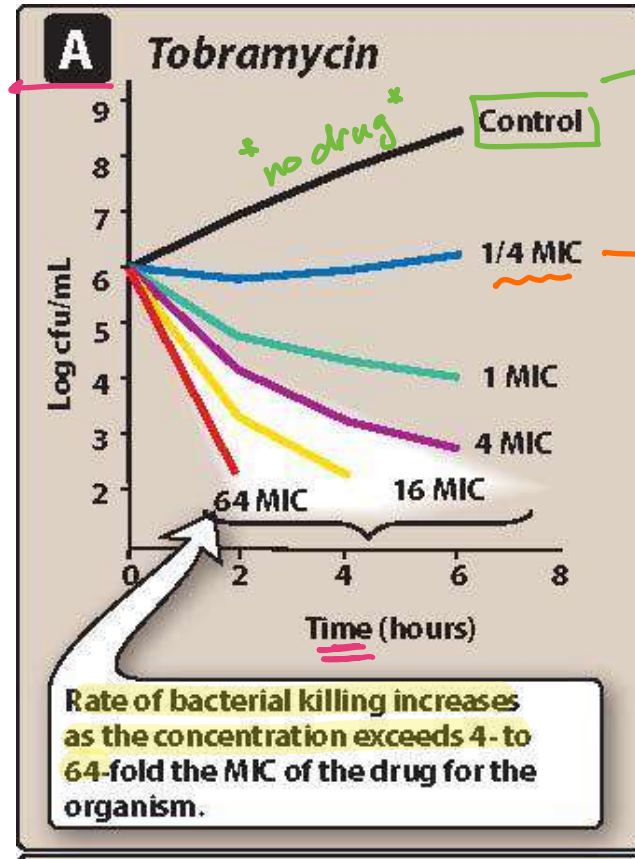
As you increase the dose of antibiotics you expect more bacterial kill
 بالتالي الموضوع معتمد على concentration

MIC ← ربع الكمية لا
 Mic ← اربع اضعاف = 4

❖ Drugs with concentration-dependent killing are usually effective if given at one to two doses per day.

The best choice: once or twice per day with single high safety concentration doses

Number of bacteria



المقارنة على هواه
 وقت البكتريا مع الوقت مقارنة مع ال control



Determinants Of Rational Dosing

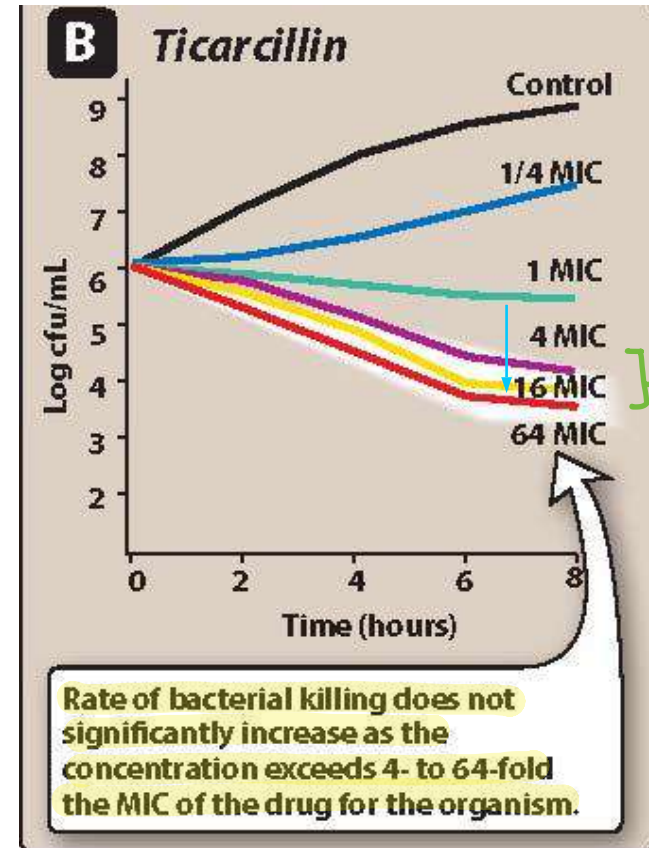
B. Time-dependent (concentration-independent) killing

❖ If the concentration of the antibiotic is increased, a limit of response will be reached (so increasing the concentration will not further increase the killing of the bacteria).

❖ In these antibiotics, the important factor to determine the efficacy of the drug and how many times do you give the dose to the patient is TIME.

❖ These drugs depends on the time that the drug is available in the plasma above the minimal inhibitory concentration (MIC).

❖ These drugs are given more frequently (multiple doses in the day) in order to maintain the drug concentration in the plasma above the minimal inhibitory concentration for 50% - 60% of the time.



↓ small effect

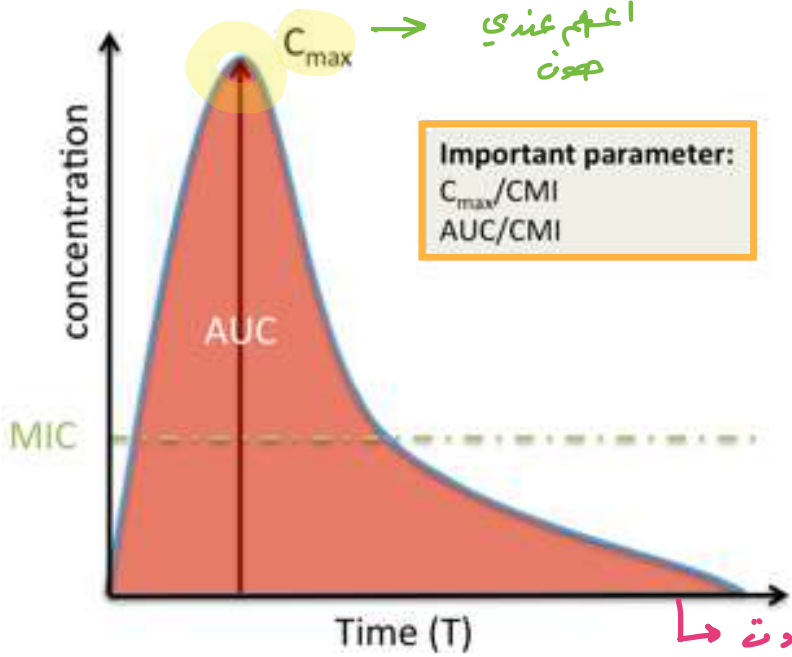
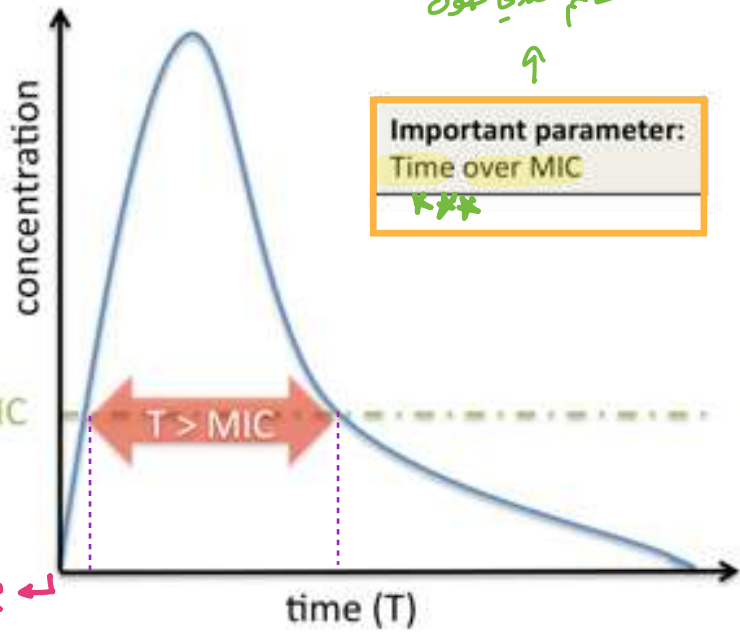
كل ما ازيد
الدose
عابلا حفظ
فوق / تغير
كبير

سبب
 حو
 Metabolism
 ...

Time dependent antibiotics
 (eg β -lactams)

Concentration dependent antibiotics
 (eg aminoglycosides)

انا حو ما بصين C_{max}
 بصين ال C يفضل
 اعلان MIC
 حتى يفضل فيه
 effect



له بينما هاد كيفة بدي
 از يداو effect حقه؟
 عن كويت اهل
 محافظا مان $MIC < C$
 من خلال frequency dose
 خلال اليوم

هاد النوع كل مازدت
 ال dose بزياد effect

MIC: minimum inhibitory concentration
 C_{max} : peak concentration
 AUC: «rea under the curve»

The period of time when the concentration is higher than MIC which should be for 50%-60% of treatment



Determinants Of Rational Dosing

Concentration-dependent **وجوده بس في**

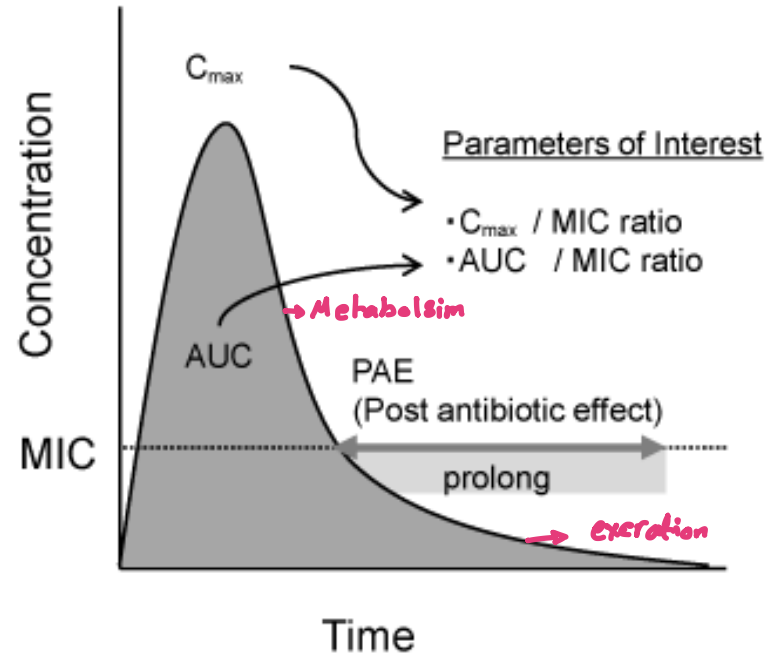


C. Postantibiotic effect = persistent suppression of microbial growth that occurs **after levels of antibiotic have fallen below the MIC**

اغلب الادوية بس يدخلو في مرحلة ال **metabolism or excretion** ب وقف تأثيرها ولكن بعض ال **antibiotic** بضل تأثيرها و **still killing bacteria**

حتى لو طلع من ال **system** وال **blood** لسا الو تأثير + ال **duration** تاعتو اطول مشان هيك هو غالباً ال **concentration depended** ، هاد برضوا يعزز فكرة انه يعطي **one height dose**

Concentration-dependent antibiotics



من جينته ↑

❖ Even if the concentration of the drug is **below the minimal inhibitory concentration**, it is able to exert the **antimicrobial effect** for prolonged period of time.



تابع ل فوق لو سألتك مين
 احسن ال
 concentration
 dependent or time
 dependent مين
 بتختار؟ فش واحد احسن
 من الثاني كل واحد شكل
 يدك تعرف تتعامل معاهم



Chemotherapeutic Spectra

A Medically important micro-organisms

- Gram (+) cocci
- Gram (+) bacilli
- Gram (-) cocci
- Gram (-) rods
- Anaerobic organisms
- Spirochetes
- Mycoplasma
- Chlamydia
- Other

antibiotic cover every مافي
 single type of bacteria

له بس فيه ايلي بتأثر على
 مساحة واسعة من
 البكتريا



Chemotherapeutic Spectra

type 1 =

Narrow-spectrum antibiotics:

Chemotherapeutic agents acting only on a single or a limited group of microorganisms.

ال** advantage الي الو انو بآثر على نوع واحد من البكتريا فما بطلعو resistant
+ ما بآثر على ال normal flora بالجسم

B **Isoniazid: narrow-spectrum antimicrobial drug**

- Gram (+) cocci
- Gram (+) bacilli
- Gram (-) cocci
- Gram (-) rods
- Anaerobic organisms
- Spirochetes
- Mycoplasma
- Chlamydia

Other

Mycobacteria

work on it →

* مثل ال TB مين البكتريا الحسبي

Mycobacterium tuberculosis



Chemotherapeutic Spectra

في التقييية
Basel اجت
on penicilline

دواعي استخدامها
تكون عم برحاي عن
low gram (+)
low gram (-)

type 2

• Extended-spectrum antibiotics:

antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria

C Ampicillin: extended-spectrum antimicrobial drug

- Gram (+) cocci
 - Enterococci
- Gram (+) bacilli
 - Listeria monocytogenes*
- Gram (-) cocci
- Gram (-) rods
 - Escherichia coli*
 - Haemophilus influenzae*
 - Proteus mirabilis*
 - Salmonella typhi*
- Anaerobic organisms
- Spirochetes
- Mycoplasma
- Chlamydia
- Other



Chemotherapeutic Spectra

- ① ← كديس لما يكون عندي أكثر
- من type of infection
- ② ← او لما اكون عنش عارف

use in empirical treatment

type

• Broad-spectrum antibiotics:

antibiotic that acts on both gram-positive and gram-negative bacteria

مش انو يشتغل على الكل لالا، يشتغل على wide range

- *risk of multi drug resistant
- *kill the normal flora

D Tetracycline: broad-spectrum antimicrobial drug

- Gram (+) cocci
- Gram (+) bacilli
- Gram (-) cocci
- Gram (-) rods**
- Anaerobic organisms**
- Spirochetes**
- Mycoplasma**
- Chlamydia**
- Other**

Actinomyces, Rickettsiae, Amoebae

هسا لو خيرتك مين احسن تستخدم one antibiotic ولا multiple antibiotics ؟
 الافضل انو نستخدم واحد حتى اقلل من ال risk of resistance + يكون قلت من
 adverse of effects لو استخدمت ادوية متعددة



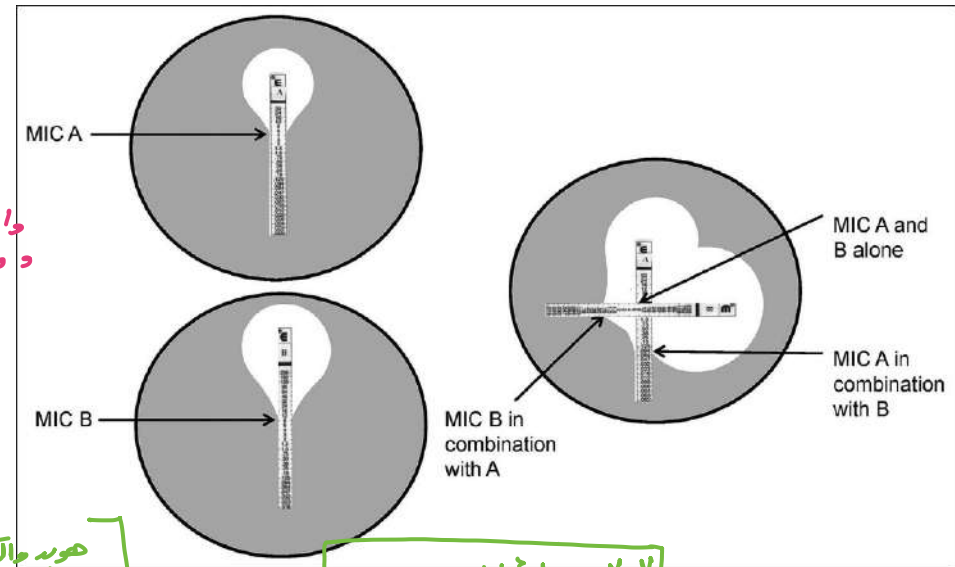
Combinations of Antimicrobial Agents

A. Advantages of drug combinations:

- **synergism:** $1 + 1 = 3$
- Combination is more effective than either of the drugs used separately.
- Unknown origin/empirical → (Gram +) دواء يفتحي (Gram -) دواء
- Organisms with variable sensitivity

B. Disadvantages of drug combinations:

- Interference in the mode of action: **bacteriostatic + bactericidal** → هوند دالتاكو يالمشروو fast to growth حتى يقتلها
- selection pressure/antimicrobial resistance



* + فالأفضل استخدم cidal + cidal

D.A → Give the chance of bacteria resistance to develop



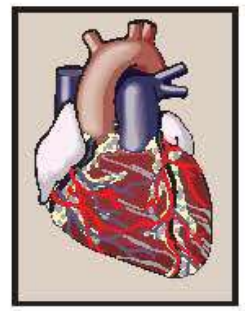
في عننا rule وهي اني اعطي ال antibiotic
 بس يصير في infection من بكتيريا
 ،ولكن بقدر اعطيه للوقاية في بعض الحالات



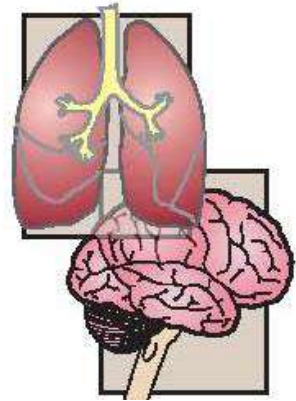
Prophylactic Use Of Antibiotics

"Prevention not treatment"

1
 Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.



3
 Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.

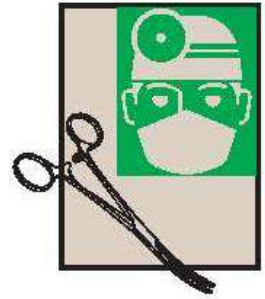


له الب يوروجعنا الحج فنلاً
 بعضوهم مضار

2
 Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.



4
 Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



بس تخلع سنك عند الدكتور شو اول شي بتطلبو analgesic
 antibiotic + drug لازم يوصفلك



Complications Of Antibiotic Therapy

A. Hypersensitivity

-ranges from mild skin rash to life-threatening anaphylaxis

اللي يكون عنده
حساسية من مضاد
معين مستحيل ارجع
اعطي اياه



Urticaria

Drug: penicillin

Mild



Red man syndrome

Drug: vancomycin

Sever



Steven-Johnson syndrome

Drug: penicillins, sulfa drugs

*Very sever sever
sever*

+ rare

*→ loss of Temperature
control + Fluid
→ shock → Death*



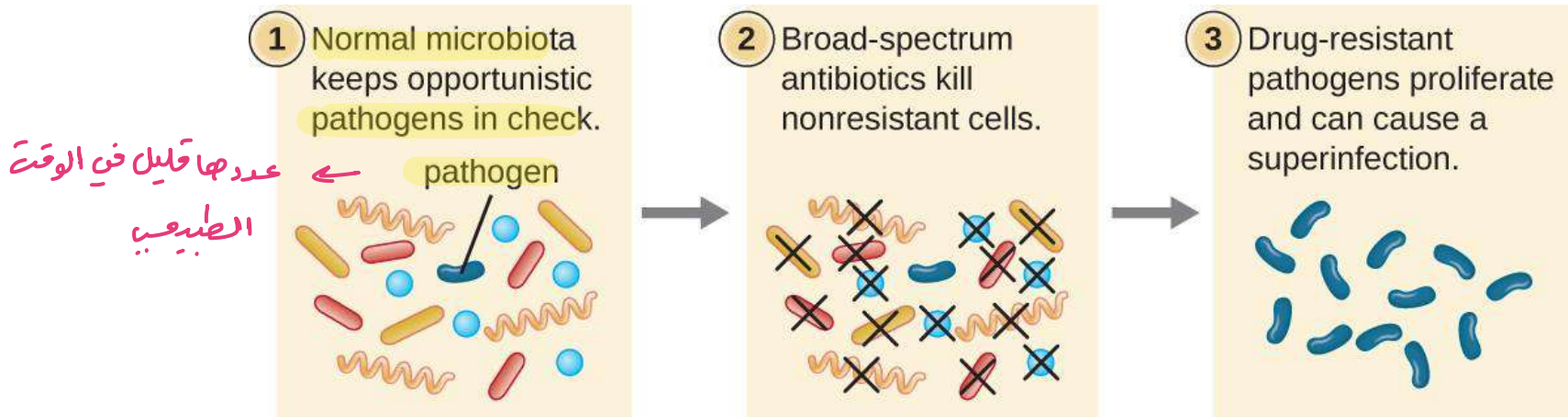
Complications Of Antibiotic Therapy

B. Direct Toxicity → *مثلاً For Liver or kidney*

C. Superinfections:

- mainly with broad-spectrum agents
- Overgrowth of opportunistic organisms

يعني انت عم بتعالج مريض باستخدام ال antibiotic بس بالغلط عم بتضيف infection ، كيف يعني ؟
 نرجع لل broad spectrum و بتعالج واحد عندو pneumonia باستخدام broad، هو good بس احنا حكينا انو ال borad (doesn't only infect the pathogenic bacteria ال normal flora ممكن كمان يخرّب ال beneficial bacteria وخليت منها ال harmful والي هي بتعمل فهون انت بتكون قتلت ال resistant)





Sites Of Antimicrobial Actions

from Ameera

* في بعض الـ Pathogenes موجودين بكمية قليلة مع الـ normal flora لكنها ضارطة
 فاذا أخذ المريف antibiotic وقتلها الـ flora ، يتيسر تكاثر الـ Pathogenes
 و تعمل ضرر كبير
 - فمثلاً انك بتكون بتعالج بالرة
 و بعد ايام همار عندك Infection
 بال gut

3 Drug-resistant pathogens proliferate and can cause a superinfection.

