

Pharma

Lec 22

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تقریغ + کتاب



Effect of The Site of Infection on Therapy: The Blood–Brain Barrier

- Capillaries with varying degrees of permeability carry drugs to the body tissues.
- the capillaries in the brain, which help to create and maintain the blood-brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules,

1. Lipid solubility of the drug:

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

2. Molecular weight of the drug:

- low molecular weight more ability to cross the BBB
- whereas compounds with a high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

میں مرکز لو صار (inflammation) بصعبه عبره بال (BBB)

ذکرہ
penicillin

ذکرہ

3. Protein binding of the drug:

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

- 4. **Susceptibility to transporters or efflux pumps:** Antibiotics that have an affinity for transporter mechanisms or do not have an affinity for efflux pumps have better CNS penetration.



Patient Factors

1. Immune system:

Antibiotic helps in Killing bacteria

immune system does the main Killing

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

2. Renal dysfunction

- Poor kidney function may cause accumulation of certain antibiotics.
- The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys, even with normal serum creatinine levels.

3. Hepatic dysfunction

- Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.

4. Poor perfusion

- Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that site of infection, making it more difficult to treat. Decreased perfusion of the gastrointestinal tract may result in reduced absorption, making attainment of therapeutic concentrations more difficult with enteral routes.



Patient Factors

— مثلاً (Meningitis) لها يؤثر على مريضه عمره أيام بختلافه لو أثر على مريضه كبير

5. Age: Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of agents such as chloramphenicol and sulfonamides. Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively. Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

ما ذكر اي مثال مدهودا بس افهموا الفكرة العامة

6. Pregnancy (Fetal toxicity)

Some antibiotics are teratogenic

— في ادوية ممكن تعبها (placenta) وتؤدي إلى تأثيرات على المولود بنسبة المؤثر (Teratogenic infector)

7. Risk factors for multidrug-resistant organisms:

- prior antimicrobial therapy in the preceding 90 days

(إذا المريض كانه ماخذ (Antibiotic) في آخر 3 شهور ريش؟ لأنه ممكن يكونه قتل أغلب البكتيريا وفضل نسبة قليلة اللي بتقدر تعمل (resistance) وتعاثر)

- hospitalization for greater than 2 days within the preceding 90 days

(المستشفى مكانه رئيسي لخلي البكتيريا المقاومة والمرضه اللي بتسببها (Nosocomial infection) ممكن يكلاحته بغرفه (ICU))

- 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

The Patient has immune deficiency disorder.

must not be given to pregnant women

CATEGORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	there is <u>No</u> antibiotic
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	



→ only one of the factors choosing
Cost of Therapy: Is It Important?

- Although choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, but:



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

Safety is more important than Cost



ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis.

Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections who require maintenance of higher serum concentrations of antimicrobial agents. In hospitalized patients requiring intravenous (IV) therapy, the switch to oral agents should occur as soon as possible. Switching patients from IV to oral therapy when clinically stable has been shown to decrease health care costs, shorten length of stay, and decrease complications from IV catheters.

However, some antibiotics, such as vancomycin and aminoglycosides, are poorly absorbed from the gastrointestinal (GI) tract and do not achieve adequate serum levels via oral administration.

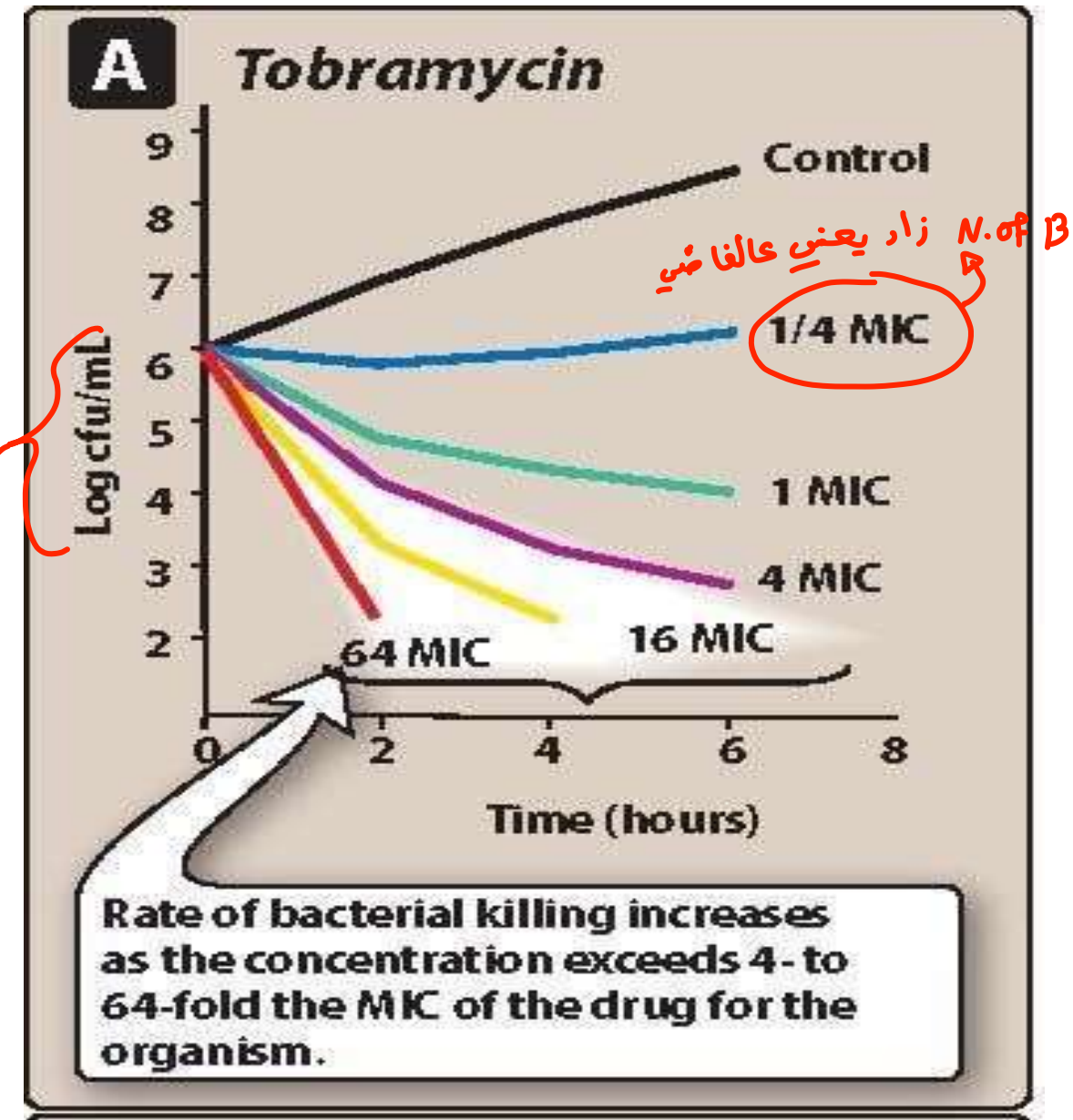
Determinants Of Rational Dosing

كل ما زاد التركيز زاد قتل البكتيريا وقلت البكتيريا

A. Concentration-dependent killing

- Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

Number of bacteria



aminoglycosides and daptomycin

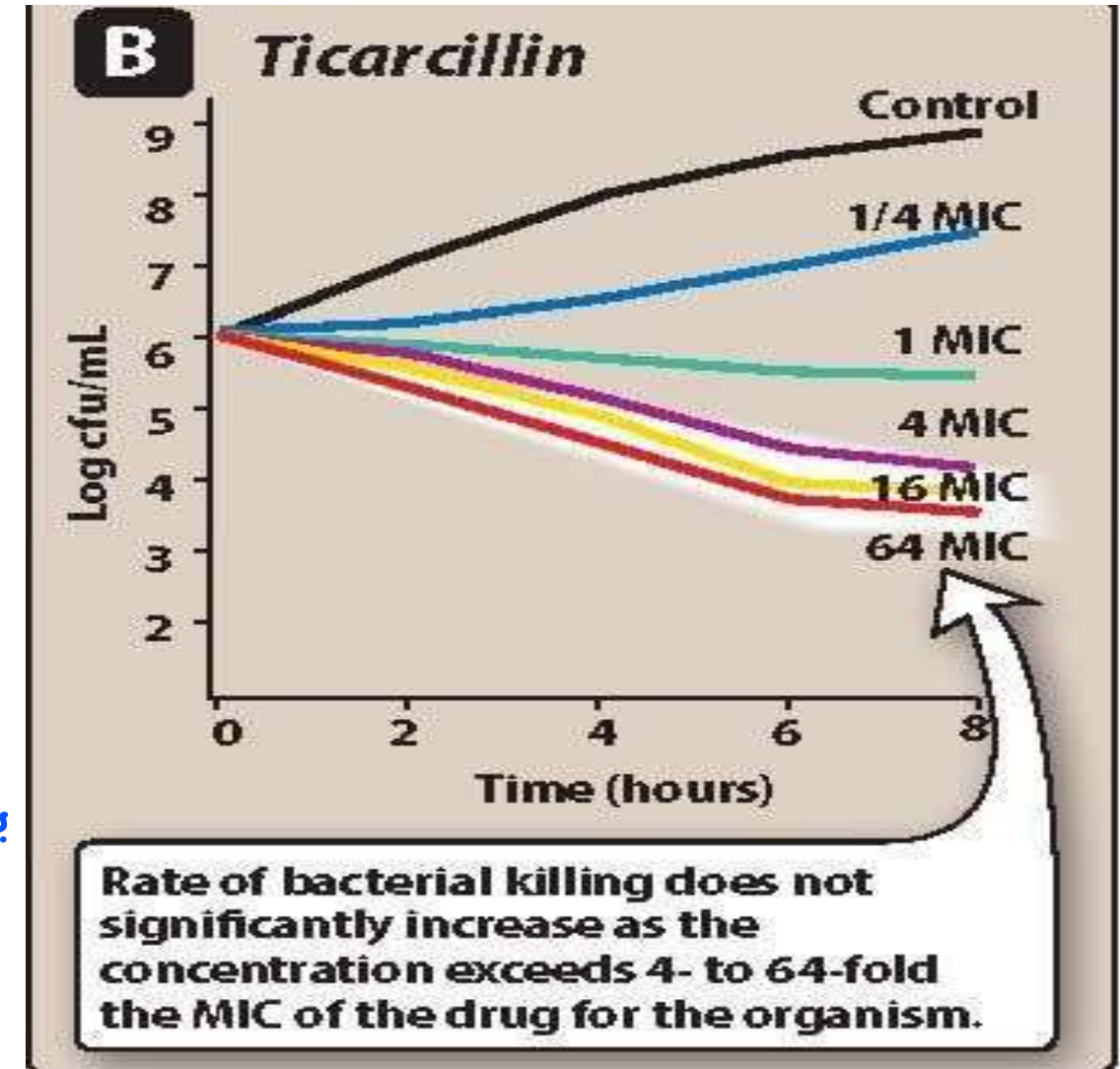
(single high dose for best treatment)

Determinants Of Rational Dosing

B. Time-dependent (concentration-independent) killing

-In contrast, glycopeptides, macrolides, clindamycin, and linezolid do not exhibit concentration-dependent killing .

The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC.



بنو سهل هونه لمح معين حتى لوزدنا الجرعة فارح نمو البكتيريا أو يتأثر معدل نموها

بنصير نعطى الدواء على جرعات متكررة عشانه يفضل موجود بالدم



The more the C_{max} is present, the more the bacteria are killed

لما يبدأ من الصفر زي هيك

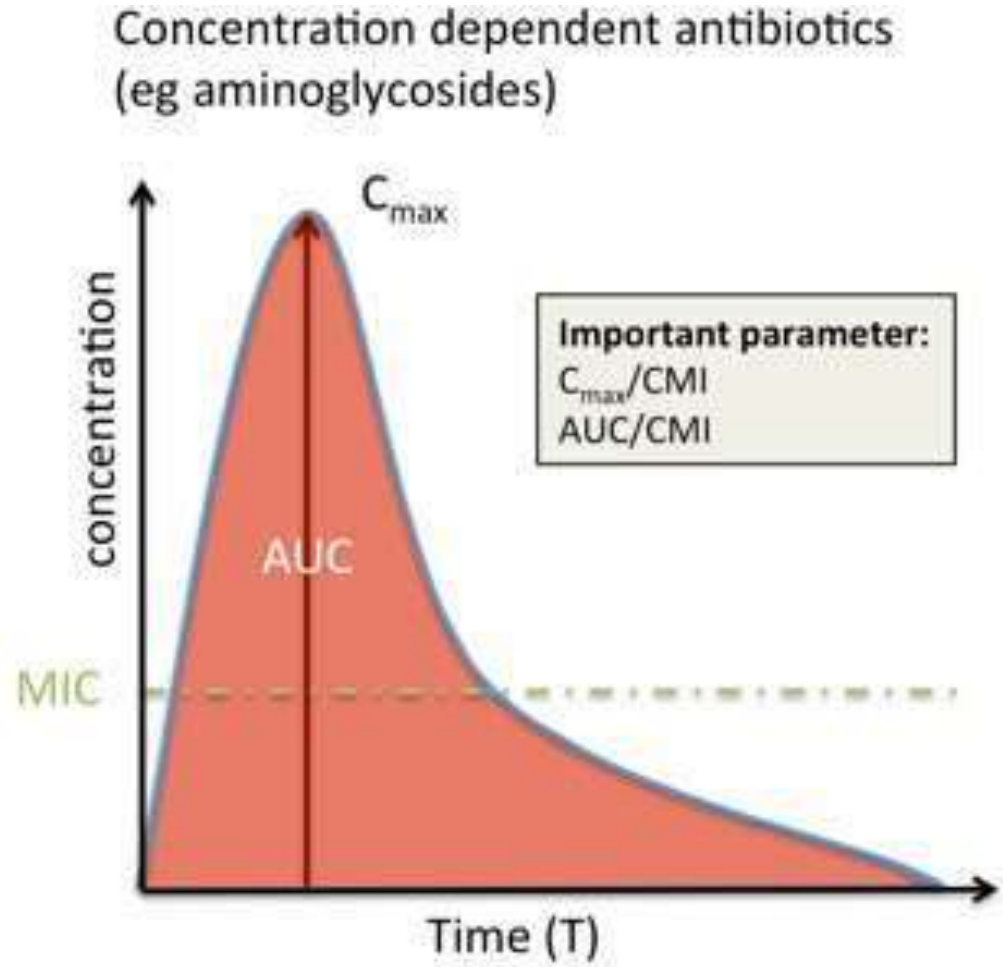
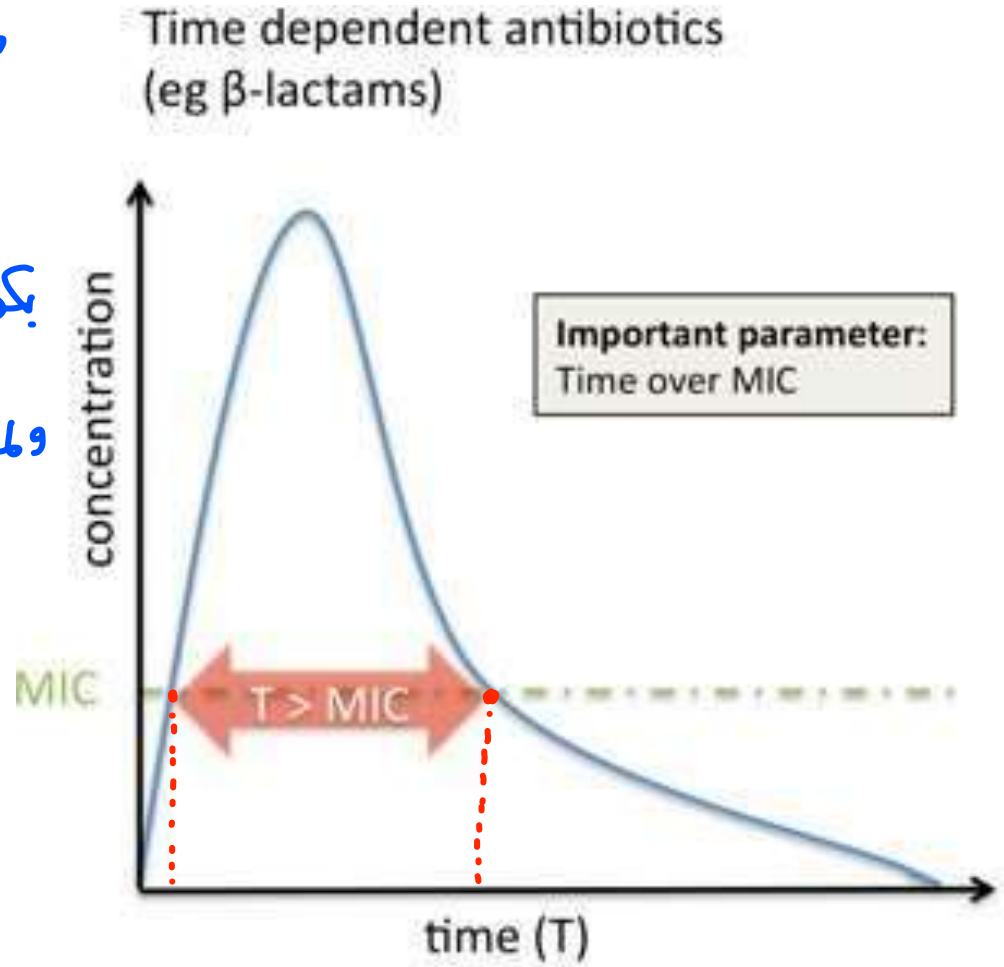


بكونه (oral)

ولما يبدأ من فوقه زي هيك



بكونه (IV)



AUC_{24}/MIC

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

Period of time where concentration of drug $> MIC$ should be for 50-60% of treatment time

وعشانه يفضل التركيز أعلى من الـ (MIC) دايضاً أعطى الدواء بتكرار على جرعات متكررة



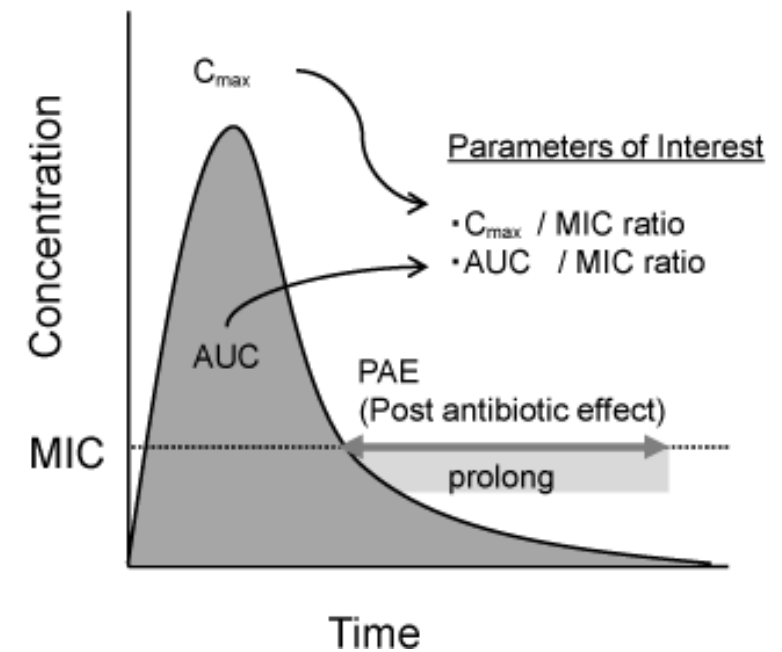
Determinants Of Rational Dosing

→ only in concentration-dependent

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

— حتى لو قل تركيز الدواء عن الـ (MIC) رح يضل شغال بس نركز أنه بس
Type(A)

Concentration-dependent antibiotics



- often require only one dose per day, particularly against gram negative bacteria.



Chemotherapeutic Spectra

عدد أنواع المضاد الحيوي الذي يقدر تأثيرها الـ (Anti biotic) وبناءً على هذا الكلام رح نصنف الـ (Anti biotics) إلى ٣ أنواع

- bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics.





Chemotherapeutic Spectra

Very limited range of bacterial coverage

• Narrow-spectrum antibiotics:

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

بسی نگو نه متاكد بين منہ اشى معيب بستخدمه

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

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

Other

Mycobacteria

T B



Chemotherapeutic Spectra

large range of bacterial coverage

• Extended-spectrum antibiotics:

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

Based on penicillin

بشغل على الـ (cell wall) اللي بكونه thick يعني (+)

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

بشمال كثير بكتيريا

• Broad-spectrum antibiotics:

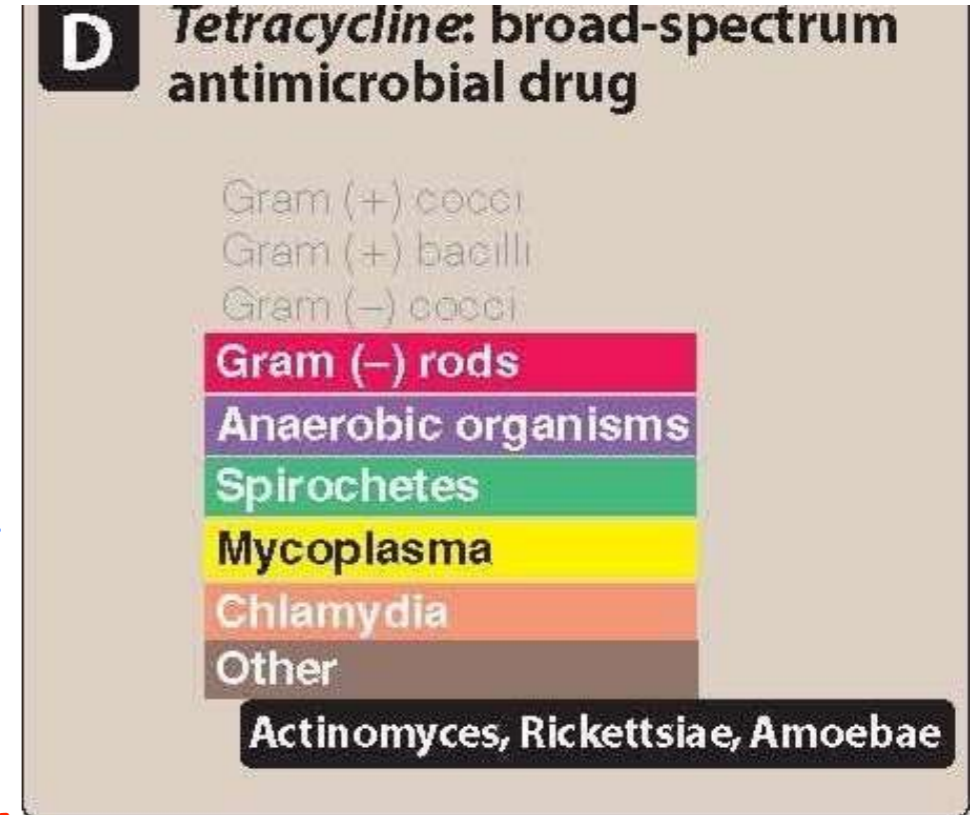
antibiotic that acts on both gram-positive and gram-negative bacteria

- ممكنه استخدمه بس اكونه متعجل وما في وقت هاد العلاج اسمه

(Empiric therapy). خيب ليش ما استخدمه على حلول؟! عشانه صبيبت:

- عشانه موضوع ال (resistance)

- عشانه ما أقضي على البكتيريا النافعة بالجسم (Normal flora)





Choose one single best (mostly)



Combinations of Antimicrobial Agents

- It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism.

A. Advantages of drug combinations:

$$1 + 1 = 3$$

- **synergism**: combination is more effective than either of the drugs used separately. متى استخدموا

- Unknown origin/empirical one for G+ve one for G-ve

- Organisms with variable sensitivity (TB) (بكتيريا تقاوم مضادات حيوية وصعب علاجها)

B. Disadvantages of drug combinations:

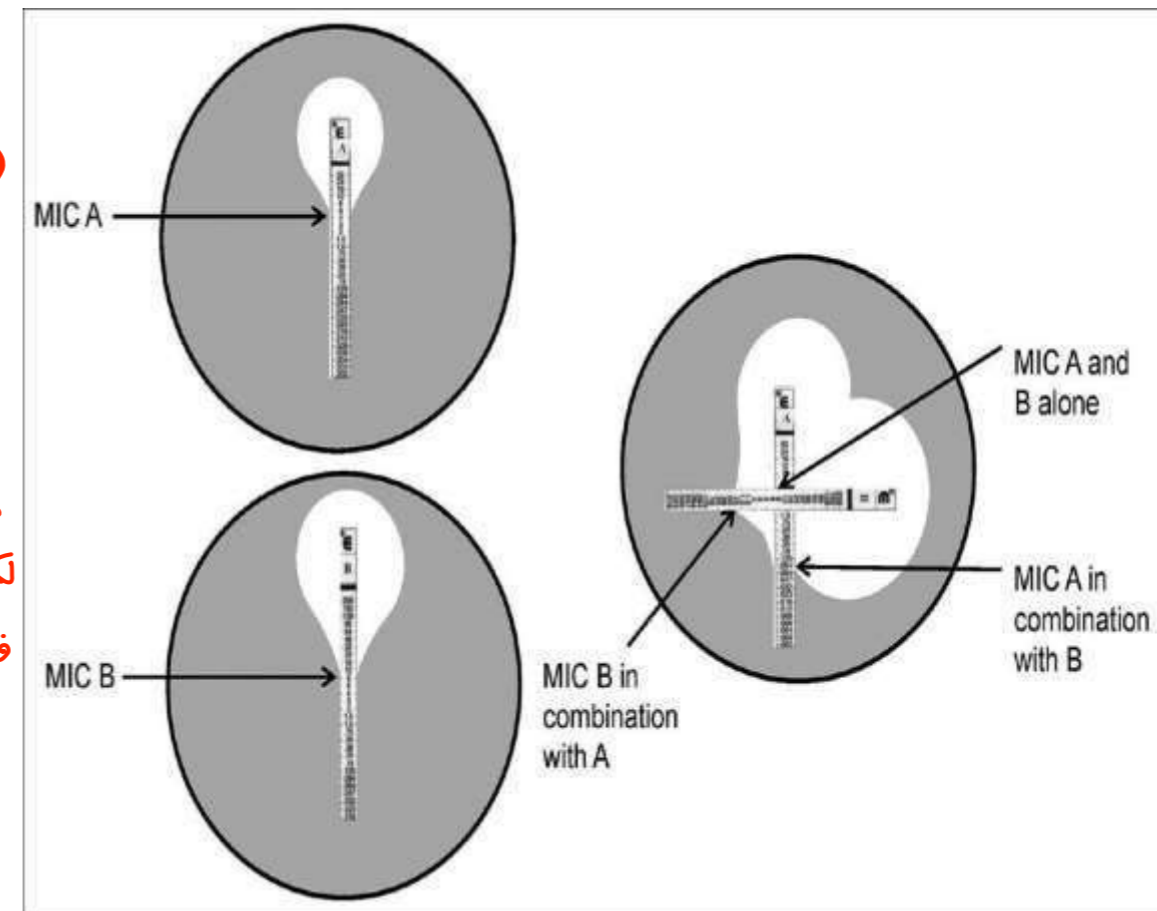
- Interference in the mode of action: bacteriostatic + bactericidal

- Selection pressure/antimicrobial resistance

ممكنه الـ (Bacteriostatic) تشبث البكتيريا

لكنه بدون قتل فينتجرب على (Bactericidal)

فلانزم بس نختار نختار نفس النوع





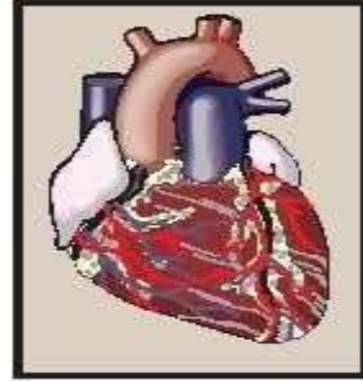
وقائية Prophylactic Use Of Antibiotics

بكونه ما عنده عدوى بكتيرية
لكنه بعطيه في هذه الحالات
لغرض الوقاية

"Prevention not treatment"

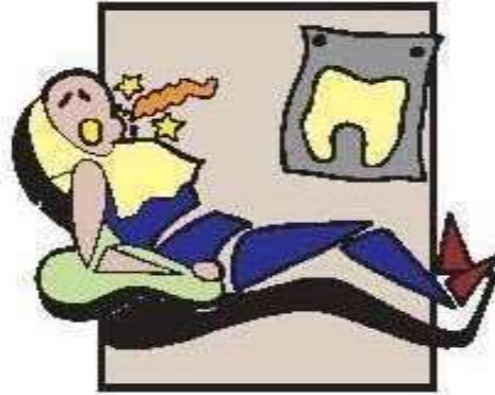
1

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



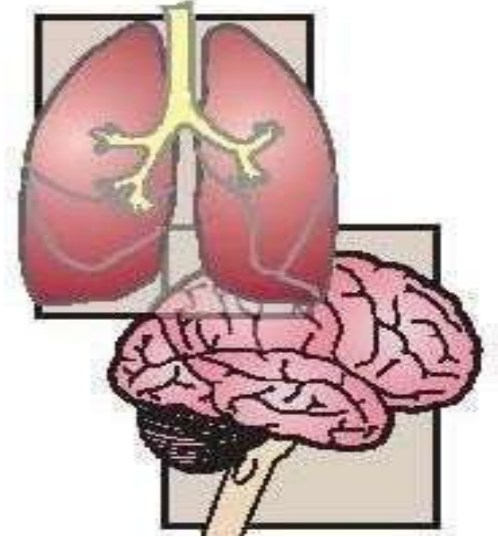
2

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



3

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



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.



✦ الأشفاء التي بروحوا على الحج أو العمرة 🙏❤️ بنعطيهم مضعوم ضد السعيا مع أنه ما يكونه عندهم بس عشان الوقاية



Complications Of Antibiotic Therapy

A. Hypersensitivity

-ranges from mild skin rash to life-threatening anaphylaxis

mild



Urticaria
Drug: penicillin

more severe



Red man syndrome
Drug: vancomycin

seen with rapid infusion

most severe



Steven-Johnson syndrome
Drug: penicillins, sulfa drugs

should never be rechallenged, not even for antibiotic desensitization.



Complications Of Antibiotic Therapy

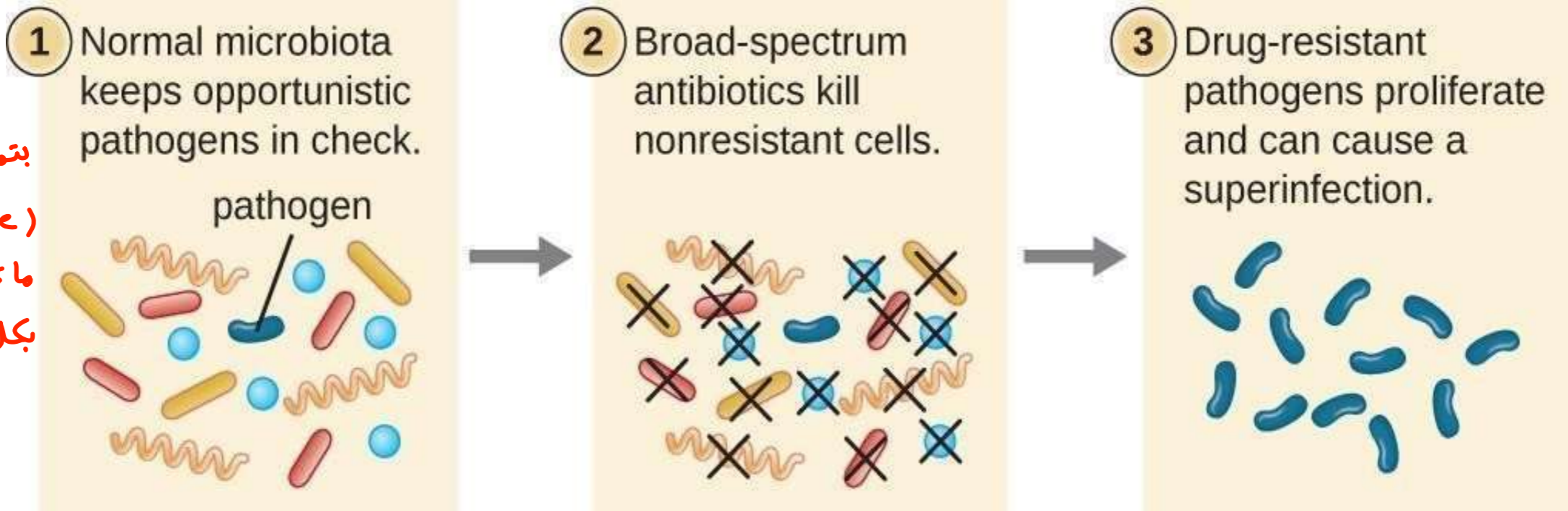
B. Direct Toxicity (كل (Amino acid) له (side effect) معين)

C. Superinfections: (أو كى ممكن يعالج المنطقة المصابة بس رح يؤدى منطقة أخرى غالباً يؤدى الـ (Normal flora) فيؤثر على (GIT))

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

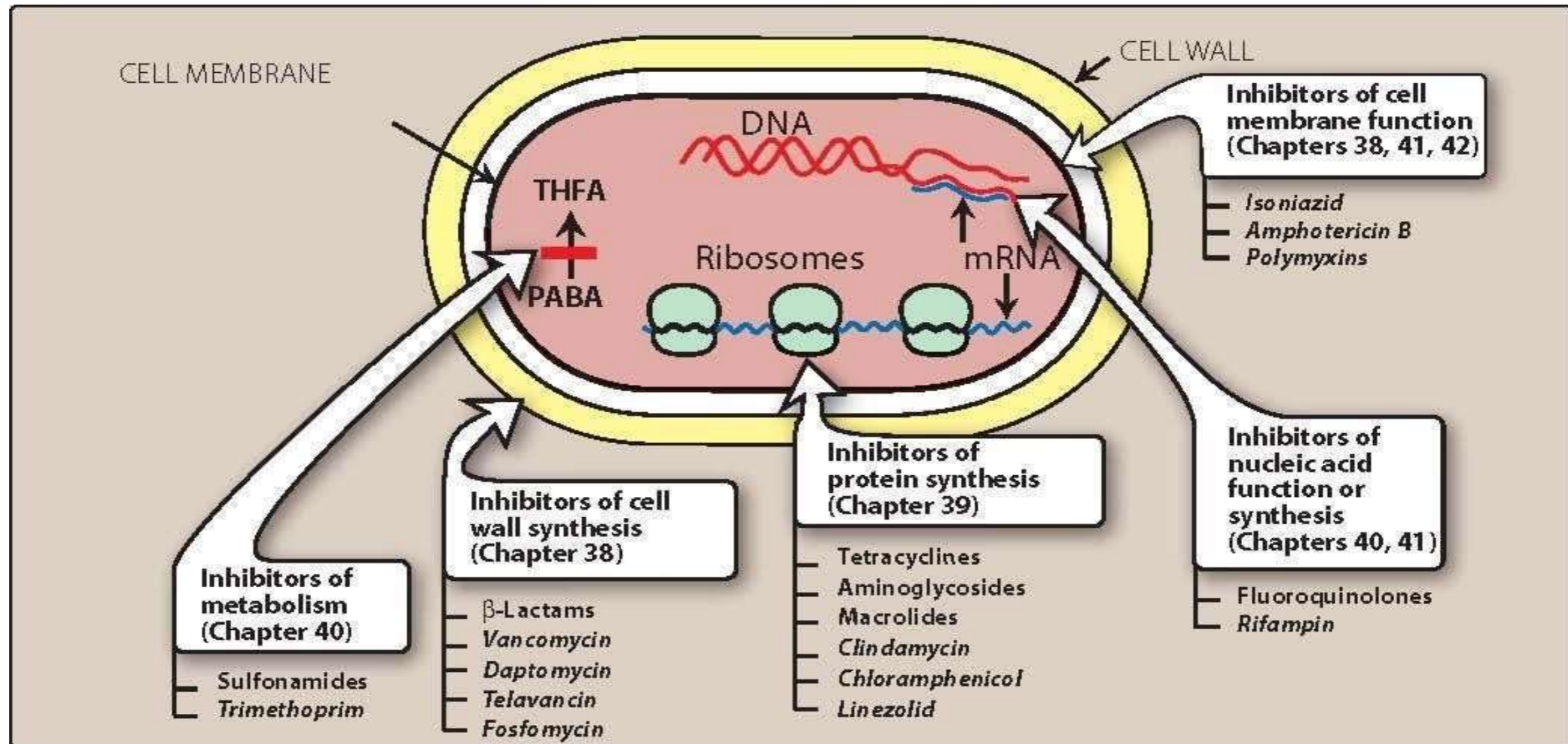
يحدث بسبب (Gastro intestinal infection)

((Normal flora))
بتمنع نمو وتكاثر الـ (Pathogene) ما تده رح ينمو (Pathogene) بكل أريحية





Sites Of Antimicrobial Actions



طَلَبُ الْعِلْمِ بِنَيْفِ