Athar Batch

Pharmacology

Lecture: 26

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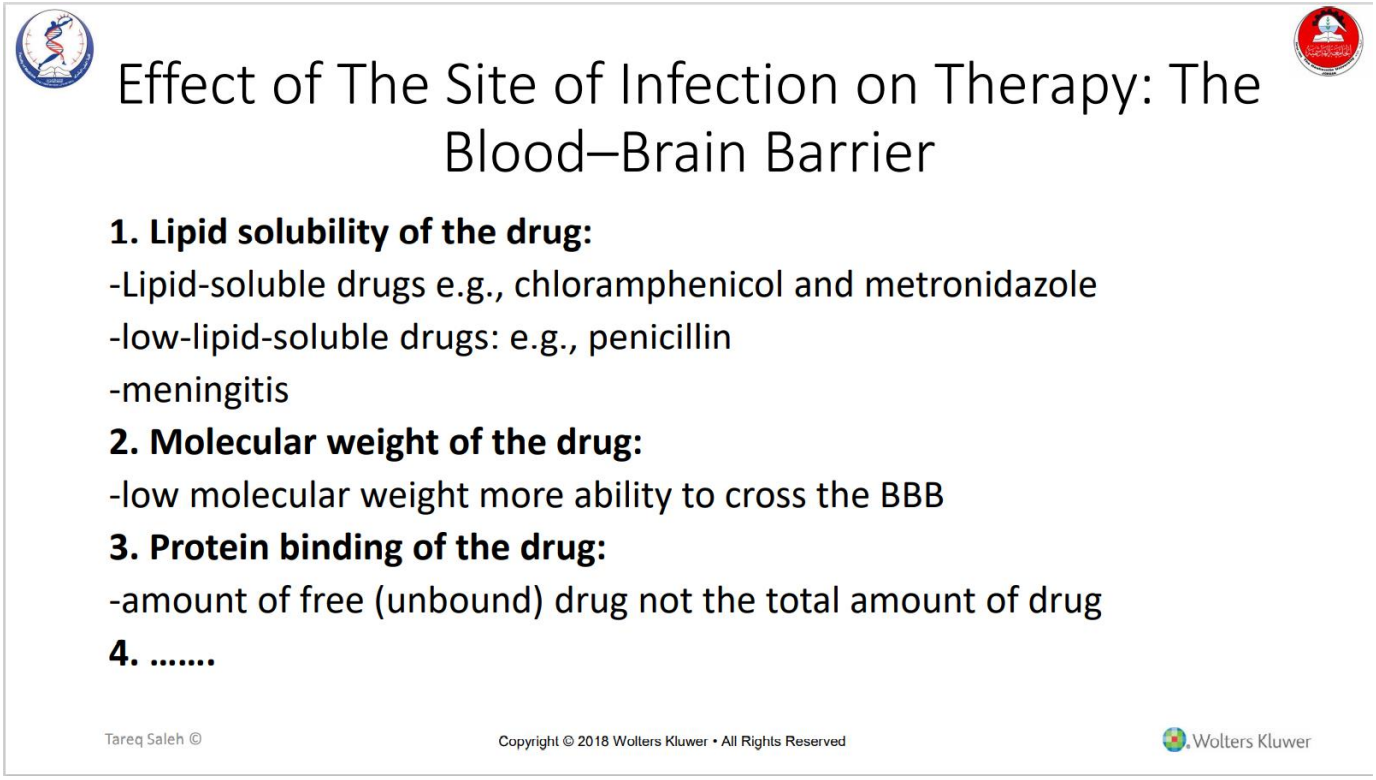
النادي الطبي

LECTURE 2- DR. TAREQ



- The passage of the drug to the CNS is governed by the blood-brain barrier.
- Blood-brain barrier is mainly constructed by endothelial cells that line the cerebral capillaries that are held together by tight junctions.
- In case of bacterial infection in the CNS (like meningitis, infection of the brain, infections in spinal cord), this requires the use of an antibiotic that can cross the blood-brain barrier.
- Several factors that affect the ability of the drug to cross the BBB:

1) The lipid solubility of the drug:

- 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…

2) Molecular weight of the drug:

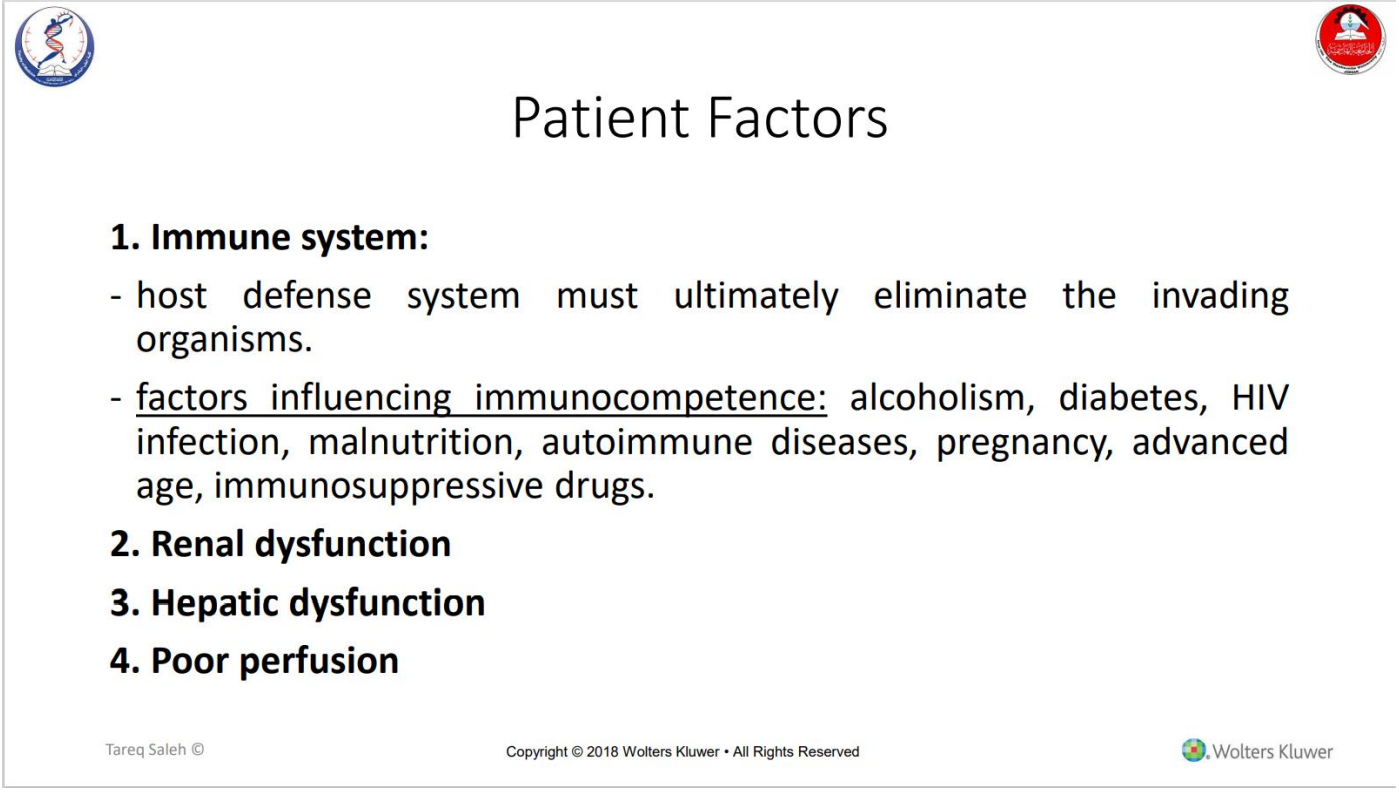
- Drugs with low molecular weight can cross the blood-brain barrier more easily.

3) Protein binding of the drug:

- The active form of the drug is the drug that is not bound to plasma proteins.

- Drugs that circulate in the plasma in the bound form, the plasma proteins bound drugs are inactive → cannot penetrate membranes and go to other body compartments.

4) Other factors (susceptibility to transporters or efflux pumps… من الكتاب)



- Antibiotics that can treat the bacterial infections in the lab (experimental setting) will be given to the patient. There are many individual factors that play an important role in how the antibiotic drugs exert their effect on human.
- Patient factors:

1) The status of the immune system

- The main function of the immune system is to remove foreign or pathogenic organisms.
- The antibiotics only help the immune system to eradicate the infection.
- Immunocompromised patients (have weak immune system) struggle with the bacterial infections. Those patients need to use higher doses of the antibiotic and for prolonged periods.

2) Renal functions

- Antibiotics are cleared from the body through the kidney into the urine.
- Patients with kidney diseases or renal dysfunction require dose adjustment of the antibiotic drug that is cleared by kidney. يعني نقلل الجرعة اللي بالعادة بنعطيها للمرضى اللي ما عندهم امراض بالكلية مشان ما يتراكم الدوا في الجسم
- Some antibiotics are not cleared by the kidney

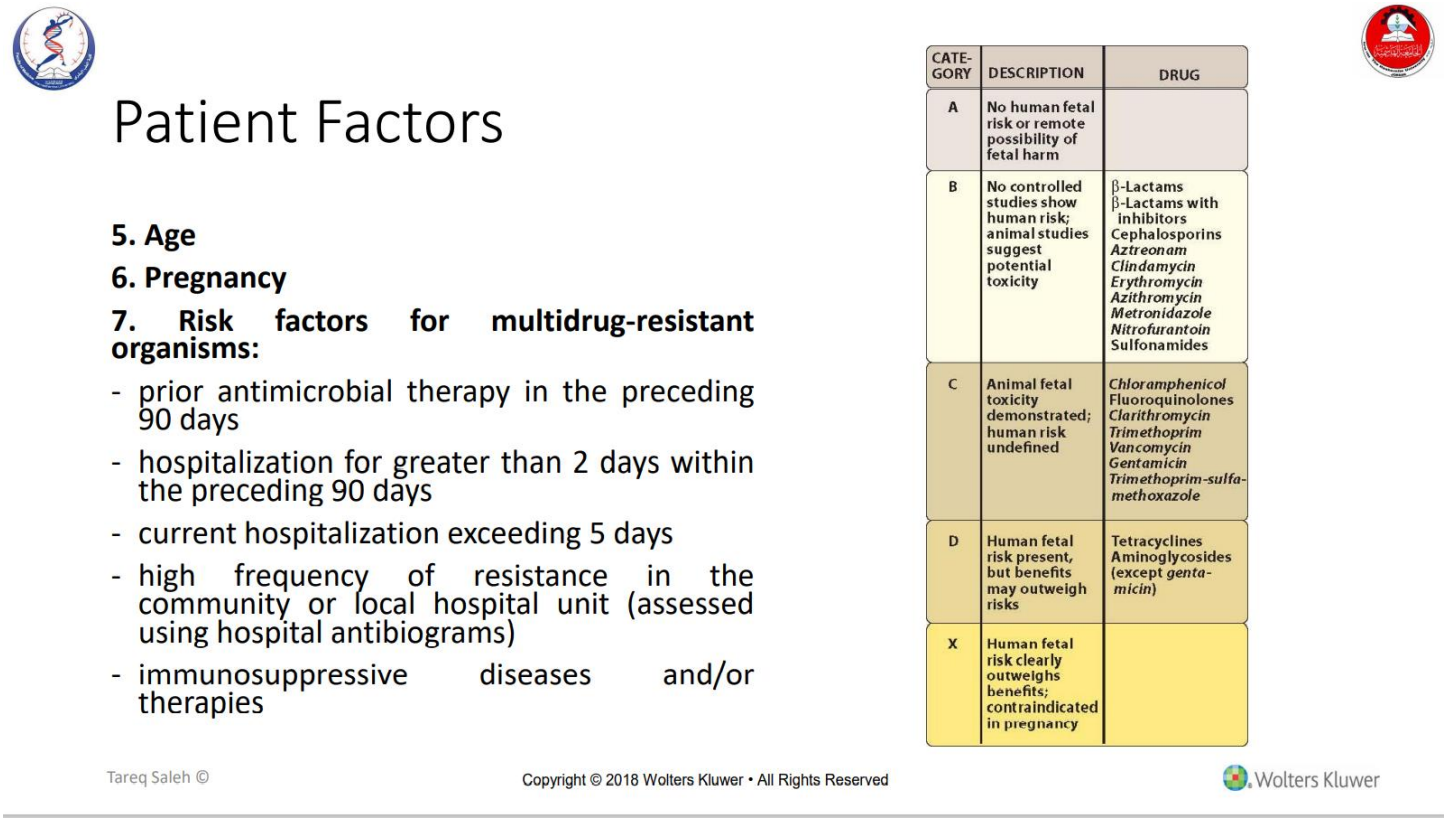
3) Liver function

- Most of the drugs including many antibiotics are metabolized in the liver.

- Patients with liver dysfunction need for dose adjustment.

4) Perfusion

- Certain tissues of the body are not optimally perfused by blood (blood supply) such as tissues that are very distant from the heart (lower limps 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.



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.
- Tetracycline, for example, precipitate in bones (binds to calcium very heavily) → interference with bone growth. So tetracycline is contraindicated to be given to children.
- With age, the number of the functional nephrons is decreased → elderly patients have minimal renal function → nephrotoxic or renal eliminated drugs are not used in elderly patients.

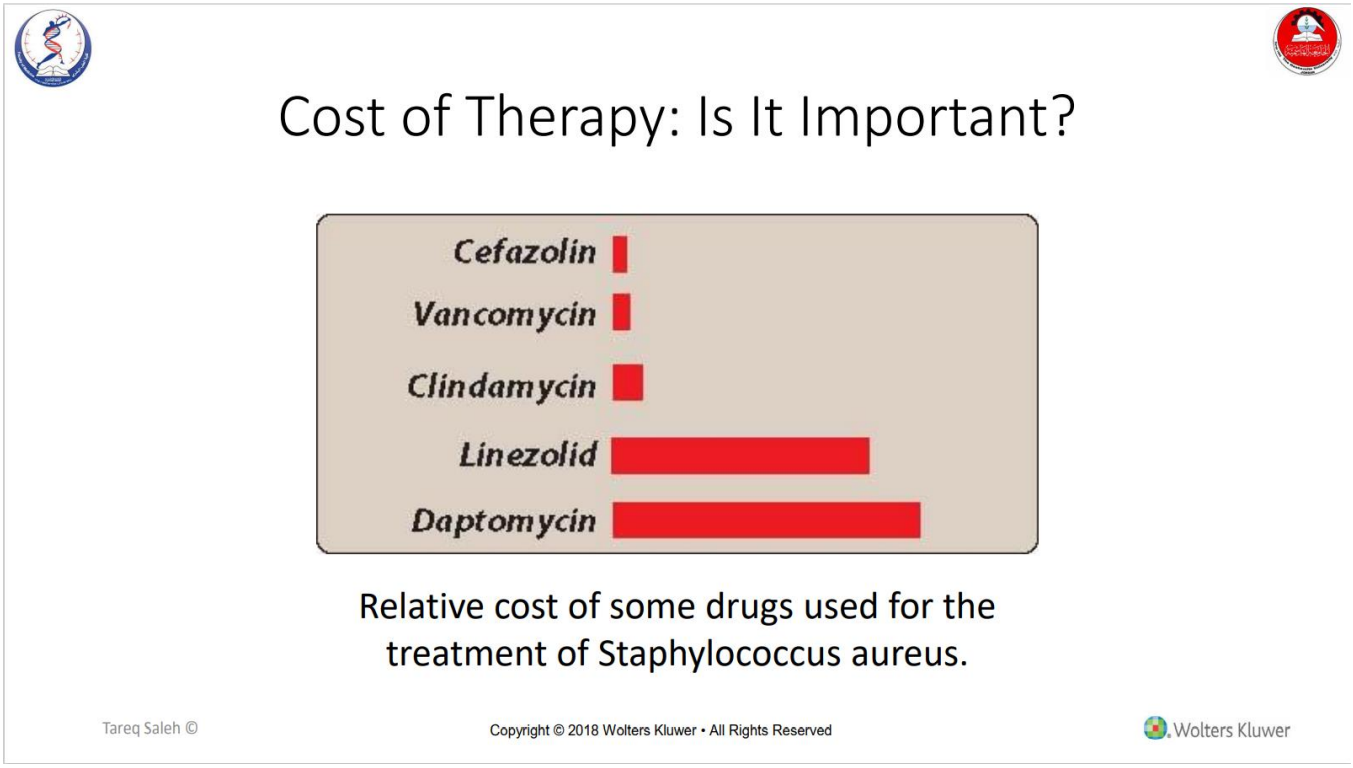
6) Pregnancy

- Many drugs are able to cross the placental barrier. If the drug is associated with high toxicity, it can harm the fetus resulting in life threating 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 drug toxicity
- Tetracycline and aminoglycosides are completely contraindicated during pregnancy. We can only use them in cases of severe infection in the pregnant woman.

7) Risk factors of multi-drug organisms

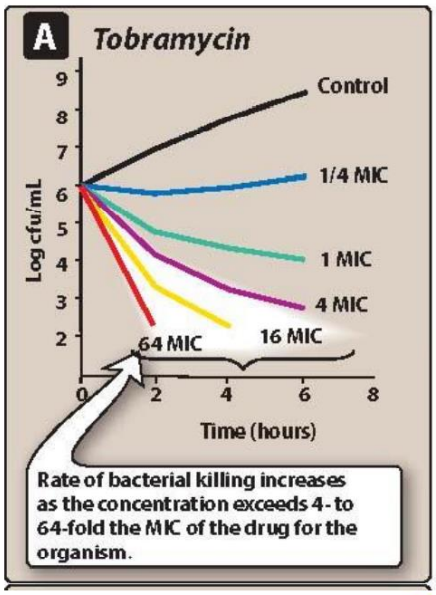
- Certain classes of bacteria become resistant to wide variety of antibiotics.
- Certain patients are at risk of developing multi-drug resistant bacteria.
- These factors include:
    1) If the patient received antibiotic therapy in the last three months. If the patient has treated by antibiotic therapy 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.



- Cafazolin, vancomycin, clindamycin, linezolid and daptomycin are all effective against MERSA, but they have different costs
- It is alaways adviced to use the cheapest drug of these effective drugs if there is not a need to use the expensive one (we have to choose the safest, cheapest, and the most effective antibiotic drug).

Determinants Of Rational Dosing

A. Concentration-dependent killing

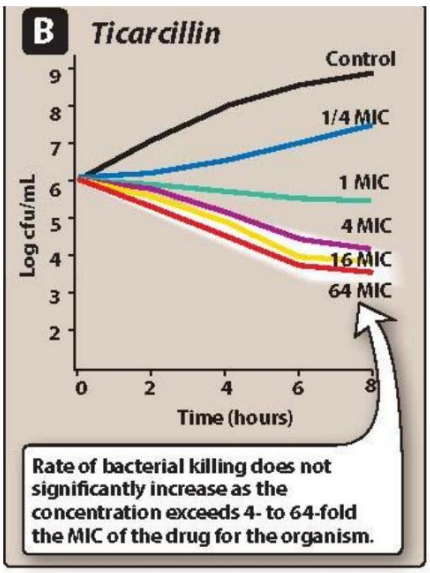


- How do we determine the best dosing of the antibiotic?
- It depends on three characteristics of antibiotics: their ability to exert concentration-dependent killing, Time-dependent killing or Postantibiotic effect or not.
- These factors depend on the pharmacodynamics and pharmacokinetics of the drug.
- Concentration-dependent killing:

  In the diagram above:
- Control sample: the sample of bacteria that is not exposed to an antibiotic.
- In control sample, the bacteria will continue to grow and form new colonies.
- If the bacteria is exposed to an antibiotic (let it be tobromycin for an example) in certain concentration, we will see that the number of bacterial cells starts reducing.
- As we increase the dose of antibiotic drug, we will get increased killing of the bacteria.
- Drugs with concentration-dependent killing are usually effective if given at one to two doses per day.

Determinants Of Rational Dosing

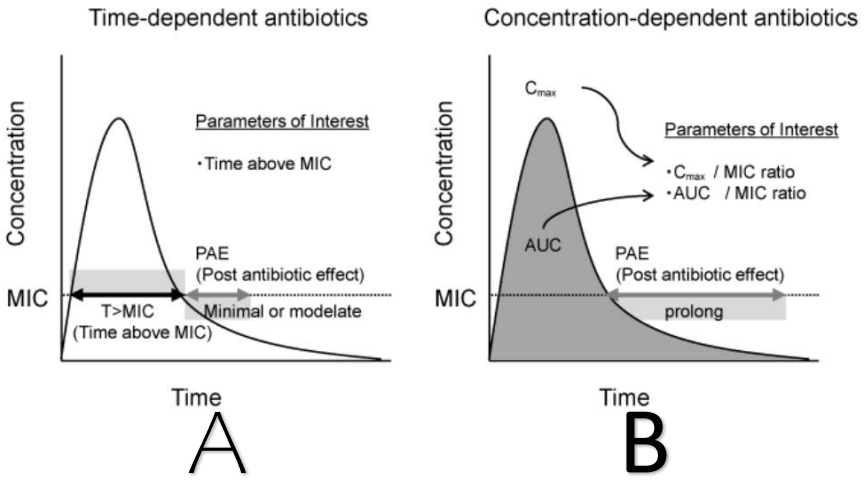
B. Time-dependent (concentration-independent) killing



- Time-dependent 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.
- 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.

Determinants Of Rational Dosing

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



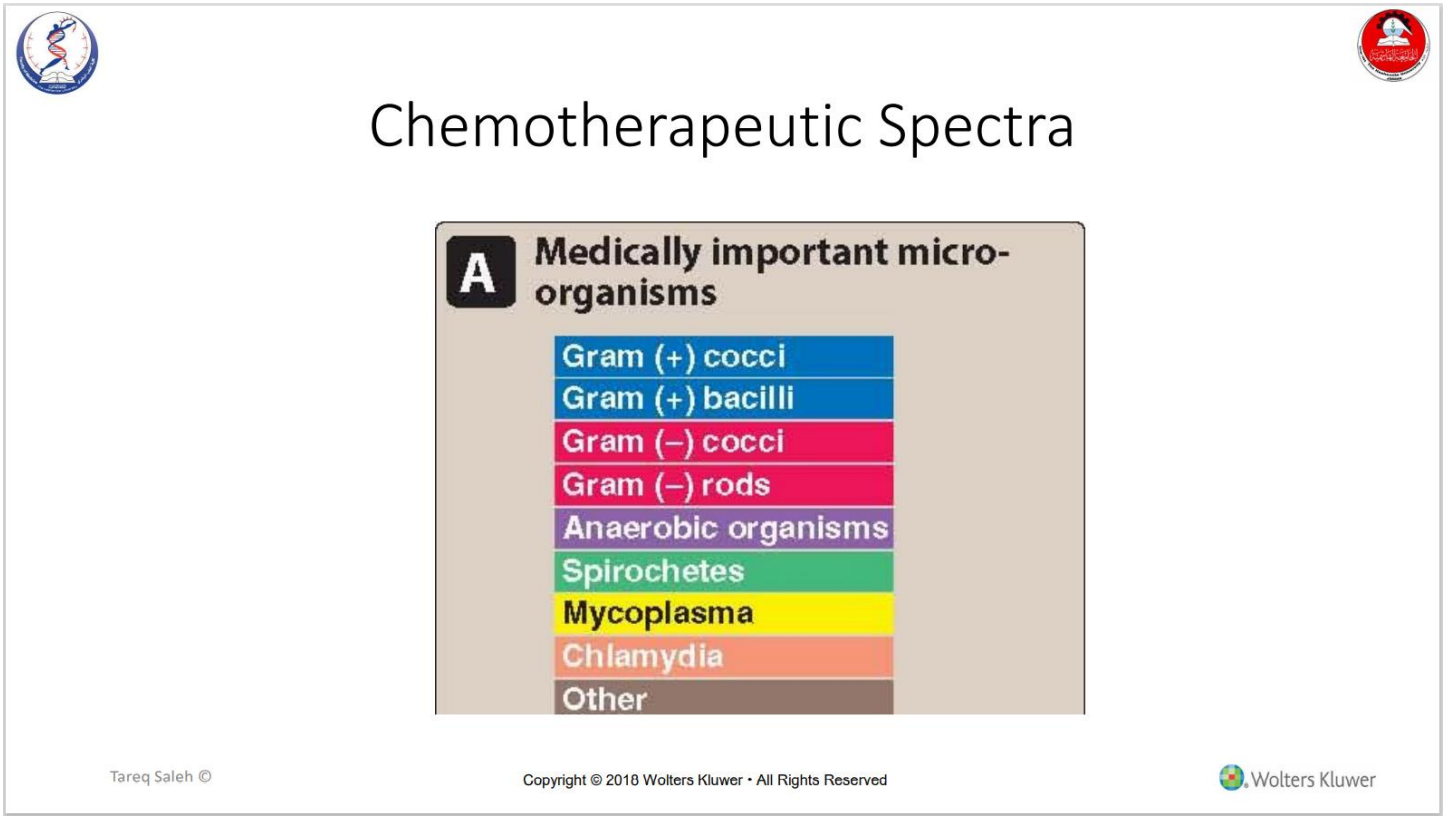
- Postantibiotic effect:
- Even if the concentration of the drug is below the minimal inhibitory concentration, it is able to exert the antimicrobial effect for prolonged period of time.

In the digram (B):

- The drug is concentration-dependent
- Let's say that is adminstrated through the oral route
- The drud is absorbed, so its level in the blood is going up until it reach the maximal concentration in the plasma
- Then the drug is undergoing metabolism and elimination until it falls below the minimal inhibitory concentration.
- The effect of the drug will remain for prolonged period of time.

In the diagram (A):

- Time-dependent
- The drug has minimal postantibiotic effect
- We need to contiue to provide the drug at multiple doses to keep the concentration of the drug in the plasma above MIC.

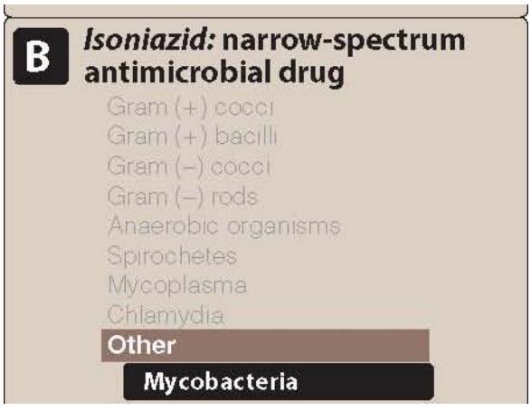


- Chemotherapeutic spectra: the bacterial species that are covered by certain antibiotic drug.
- There is no antibiotic that is effective against all types of bacteria.

Chemotherapeutic Spectra

- **Narrow-spectrum antibiotics:**

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

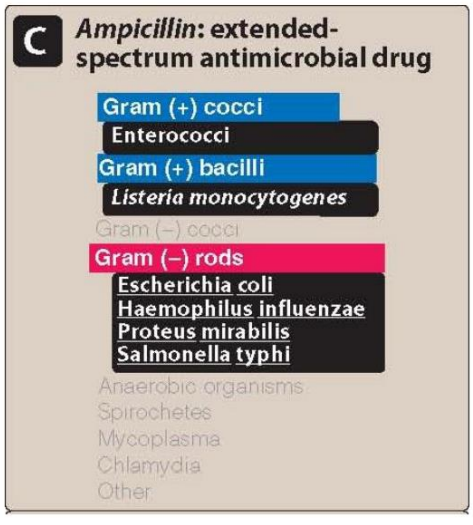


- We can classify antibiotics into:
  1) Narrow spectrum
  2) Extended spectrum
  3) Broad spectrum
- Broad spectrum:
- Effective against a limited group of bacteria, sometimes effective against single type of bacteria.
- Used when we are sure that certain type of bacteria caused the infection.
- Isoniazid: effective against one single type of bacteria (mycobacteria).

Chemotherapeutic Spectra

- **Extended-spectrum antibiotics:**

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

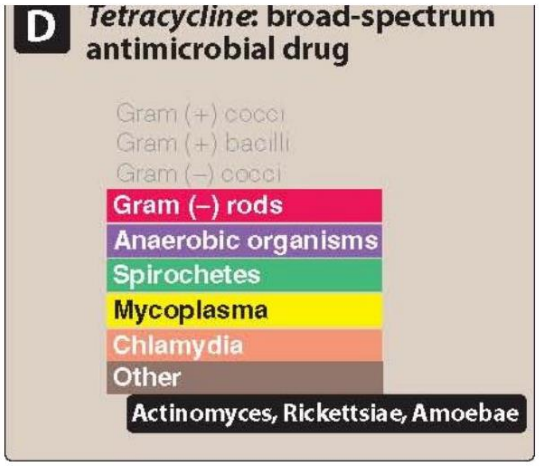


- Extended-spectrum antibiotics:
- Usually have larger bacterial coverage
- Cover the majority of gram-positive bacteria, also significant number of gram- negative bacteria

Chemotherapeutic Spectra

- **Broad-spectrum antibiotics:**

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



- Broad-spectrum antibiotics:
- Can cover a wide variety of bacteria.
- These antibiotics are highly effective
- Used in empirical treatment
- Why we use narrow-spectrum antibiotics while we have broad-spectrum antibiotics??
- Broad-spectrum antibiotics cover wide variety of bacteria including normal flora → causing super infections.
- Risk of resistance

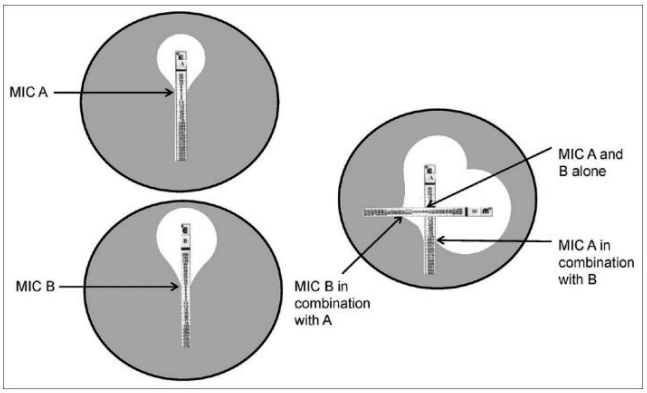
Combinations of Antimicrobial Agents

A. Advantages of drug combinations:

- **synergism**: combination is more effective than either of the drugs used separately.
- Unknown origin/empirical
- Organisms with variable sensitivity

B. Disadvantages of drug combinations:

- Interference in the mode of action: bacteriostatic + bactericidal
- selection pressure/antimicrobial resistance

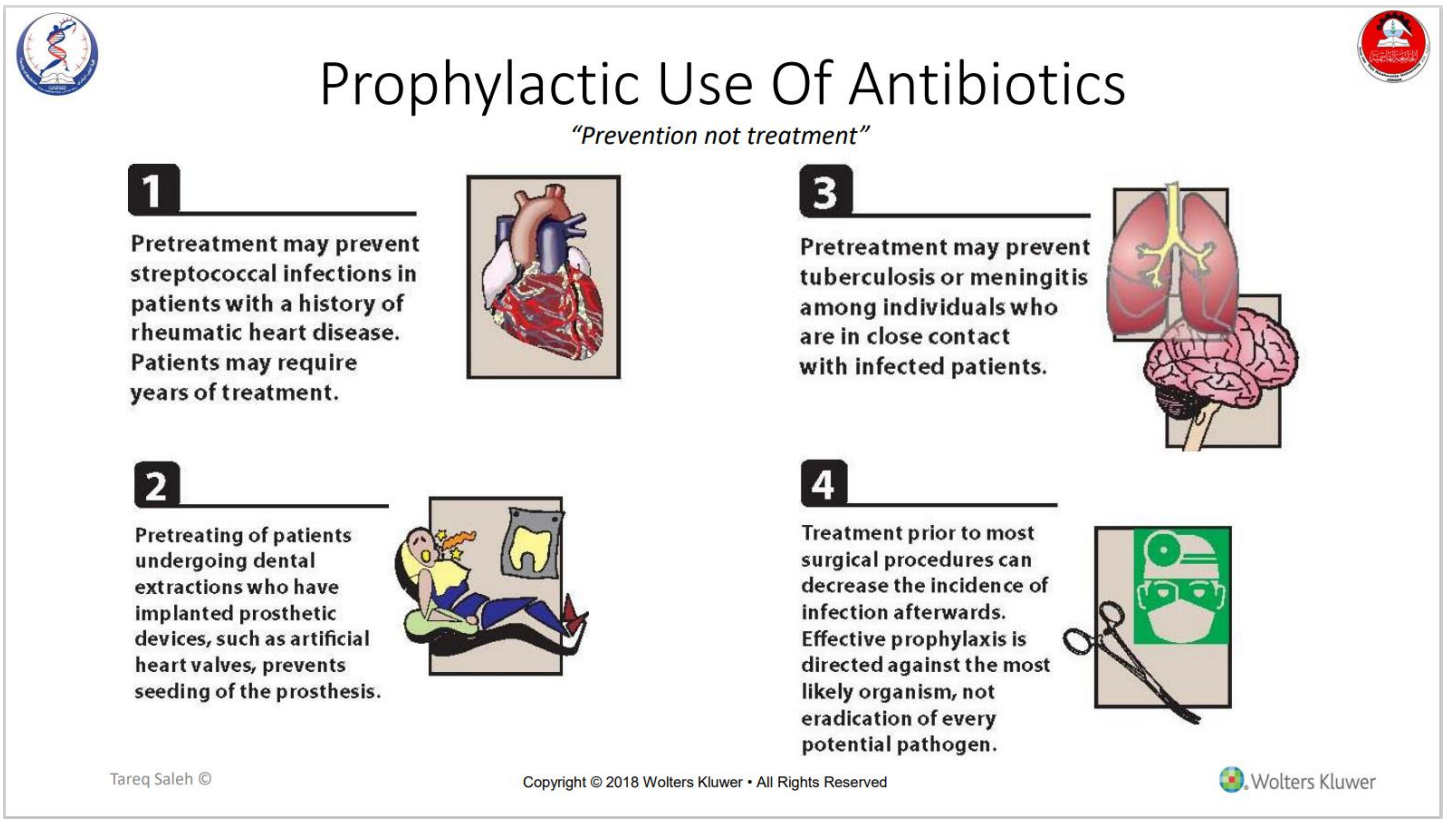


Tareq Saleh ©

Wolters Kluwer

- What is the difference between synergetic and additive drugs?
- Synergetic: the two drugs when combined with each other, the effect will be more than the addition of these two drugs. (1+1= 3 or more)
- Additive: (1+1= 2)
- The figure above explains the synergetic effect of the drug…
- Drug A: at certain concentration, kills the bacteria and forms a clean surface around the antibiotic
- Drug B: at certain concentration, kills the bacteria and forms a wider clean surface around the antibiotic
- Combination between drug A and B: the clean surface around the antibiotic is much wider (1+1 = more than 2)
- We can use combination therapy in empirical therapy or in case of unknown origin of bacterial infection.
- Another use of combination therapy is to treat microorganisms with variable sensitivity (bacteria that probably is resistant to single drug)
- The ideal way of treatment of bacterial infection is to use a single effective drug, but in certain situations (as we mentioned previously) we need to use combination therapy.
- Why do we avoid using combination therapy??
- Risk of resistance
- Risk of adverse effects of the two drugs used
- Disadvantages of using combination therapy:
    1) Interference with antimicrobial efficacy of the drugs (e.g: the combination of bacteriostatic and bactericidal antibiotics).

- The bacteriostatic (as cell wall inhibitors) antibiotics require rapidly proliferating dividing bacteria to be effective. If a bacteriostatic drug is given before the bactericidal, the bactericidal antibody will not function properly.
    2) Exposure of bacteria to selection pressure
- Selection pressure: when you expose certain species of microorganisms to difficult conditions, a fraction of this microorganism will survive and develop resistance.

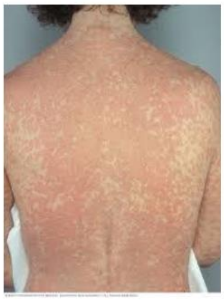


- Prophylactic therapy: using the drug to prevent the disease not to treat the disease
- When do we use antibiotics for prophylactic therapy??
    1) Prevention of streptococcal infections in patients with a history of rheumatic heart disease.
    2) Pretreating off patients undergoing dental extractions.
    3) Prevention of tuberculosis or meningitis: when we travel to an area of high incidence of certain bacterial infection (زي لما نروح للحج نتلقى مطعوم للوقاية من التهاب السحايا مثلا)
    4) Prior to surgical procedures: most patient who will undergo a surgery are exposed to acquire a bacterial infection since there will be a major wound.

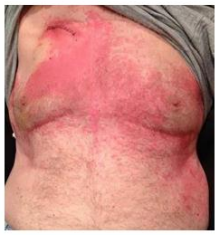
Complications Of Antibiotic Therapy

A. Hypersensitivity

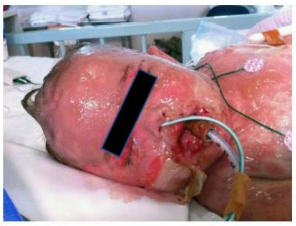
-ranges from mild skin rash to life-threatening anaphylaxis



Urticaria
Drug: penicillin



Red man syndrome
Drug: vancomycin



Steven-Johnson syndrome
Drug: penicillins, sulfa drugs

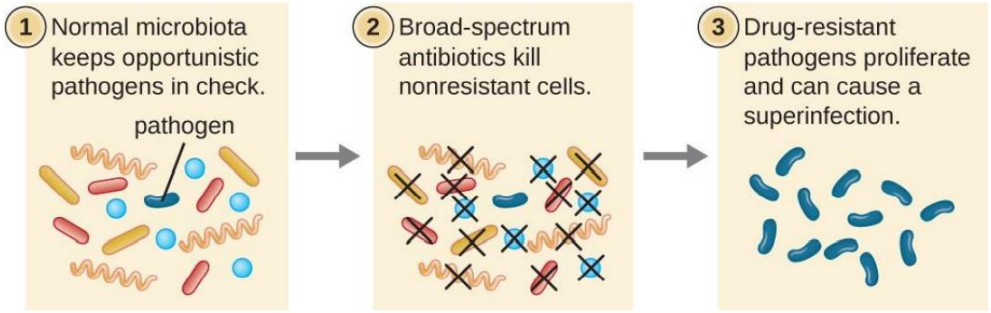
- Hypersensitivity: developing an allergic reaction from a certain antibiotic
- Hypersensitivity reactions may range from mild allergy (for example limited to the skin) to sever reactions.
- Steven-Johnson syndrome = toxic epidermal necrolysis: sever damage to the skin, usually in children. Loosing skin barrier means the loosing of fluids… may cause death

Complications Of Antibiotic Therapy

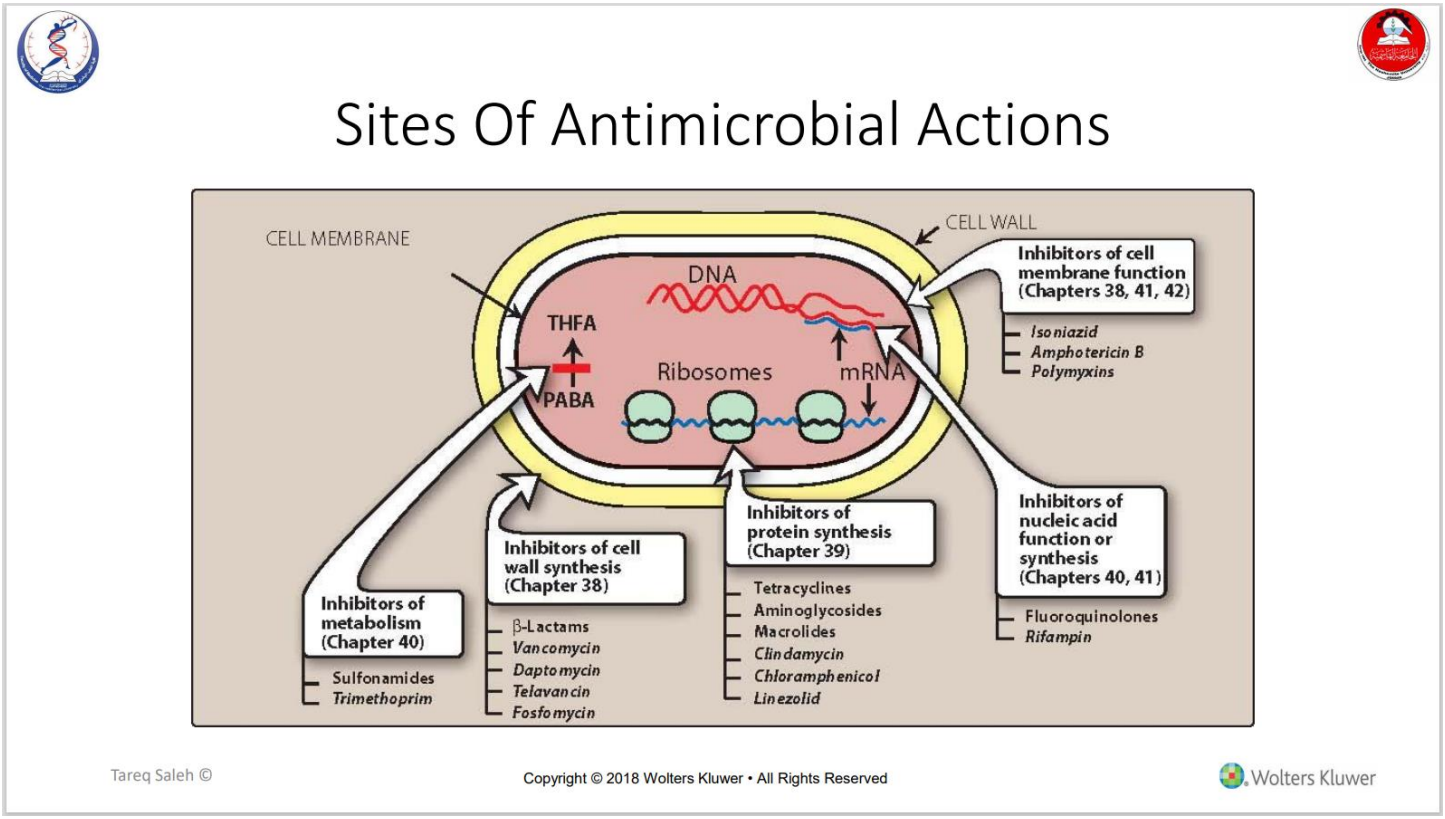
B. Direct Toxicity

C. Superinfections:

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



- Direct toxicity ~ (in other words, the adverse effects of the drug)
- All antibiotics have toxic profile
- Superinfections: occur with using of broad-spectrum antibiotics
- Broad-spectrum antibiotics do not differentiate between pathogenic and normal flora, so that these drugs kill the normal flora
- Normal flora protect the body from pathogenic microorganisms
- When normal flora is killed, opportunistic infections may develop.
- An example is the gastrointestinal infection in response to using clindamycin (used in treatment of MERSA)



- اجابات اسئلة الكويز مع التفسير:

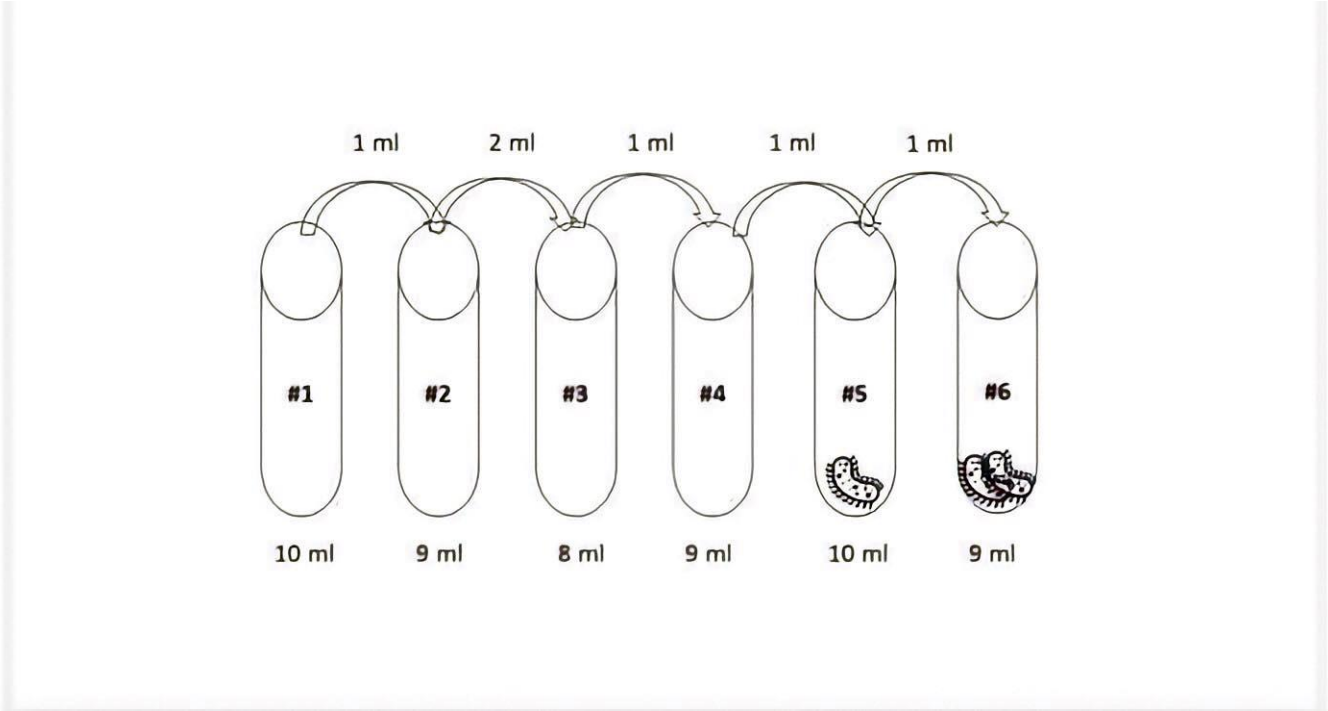
1) Which of the following adverse drug reactions precludes a patient from being rechallenged with that drug in the future:
   a) Skin rash-penicillin
   b) Pseudomembranous colitis-clindamycin
   c) Kidney injury-gentamicin
   d) Toxic epidermal necrolysis-sulfamethoxazole/trimethoprim

   ANSWER: D

   المفروض انه نختار ال REACTION اللي يكون عبارة عن Hypersensitivityلأنه اذا المريض تناول الدوا و صارت عنده حساسية منه و اعطيته اياه مرة ثانية رح يكون التفاعل اقوى لهيك في خيارين متاحين لحد الآن و اللي هم A & D طيب ليش اخترنا D مش A... لأنه البنسلين حتى لو صارت حساسية منه ممكن احتاج اني

اعطي المريض منه بالرغم من اني لازم اتجنبه و احاول اشوف بديل و اساسا تفاعل الحساسية الناتج منه يعتبر MILD REACTION بينما D عبارة عن SEVERE REACTION و ممنوع اعطي Sulfamethoxazole او Trimethoprim للمريض مرة ثانية اذا صار هاد التفاعل (منعا باتا)

2) The picture shows an MIC experiment testing the potency of the antibiotic penicillin V. Penicillin V was added to tube 1 at a concentration of 5 mM (final concentration in tube 1) and then serial dilutions were performed as shown by the arrows (each arrow represents the volume that is added to the next tube. Total volume of each tube before serial dilution is shown below. The tubes were injected with E. coli and incubated overnight. After incubation, visible bacterial growth was only observed in tubes 5 and 6. Which of the following represents the MIC of penicillin V in this experiment



a) 0.1 mM
b) 0.01 mM
c) 0.5 mM
d) 0.05 mM
e) 0.001 Mm

ANSWER: B

التوضيح:

الانبوب الأول :-

← التركيز = 5mM / 1mL

أخذنا 1mL من الانبوب الأول واضفناهم للانبوب الثاني :-

← الحجم قبل الاضافة = 9mL

← الحجم بعد الاضافة = 10mL

← التركيز للبنسلين في الانبوب (٢) نحسبه كالتالي :-

$V = \frac{A}{C} \Rightarrow \frac{10}{} = \frac{5}{C} \Rightarrow 10C = 5 \Rightarrow C = 0.5\,mM/mL$

10 ← الحجم في الانبوب (٢) بعد الاضافة

5 ← كمية الـ drug اللي أضفناها ونحسبها من خلال العلاقة :- $V = \frac{A}{C}$

1 = A ← الـ 1mL اللي أخذناها من (Tube1) واضفناها لـ (Tube2)

A = 5 ← تركيز البنسلين في الـ 1mL اللي أضفناهم

أخذنا 2mL من Tube2 واضفناهم لـ Tube3 :-

الحجم قبل الاضافة = 8 mL

الحجم بعد الاضافة = 10mL

التركيز بعد الاضافة يتم حسابه بنفس الطريقة اللي استخدمتها فوق

الكمية راح تكون = 2 X 0.5 mM = 1mM

$V = \frac{A}{C} \Rightarrow 10 = \frac{1}{C} \Rightarrow C = 0.1\,mM/1mL$

أخذنا 1mL من Tube3 وأضفناهم لـ Tube4 :-

الحجم قبل الاضافة = 9mL

الحجم بعد الاضافة = 10mL

التركيز بعد الاضافة لو حسبناه بنفس الطريقة السابقة راح يطلع = 0.01 mM

* وطبعًا حسب ما أخذنا ... الـ MIC راح تكون بـ Tube4 لهيك الجواب الصح هو (0.01)

طبعا الحل ممكن يكون ابسط و اقصر بس انا شرحت بالتفصيل