Principles of Antimicrobial Therapy :lecture 13 sheet

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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Faculty of Medicine

The Hashemite University

Textbook reference: 355-367

Before We Discuss Chemotherapy…..

THINGS TO DO

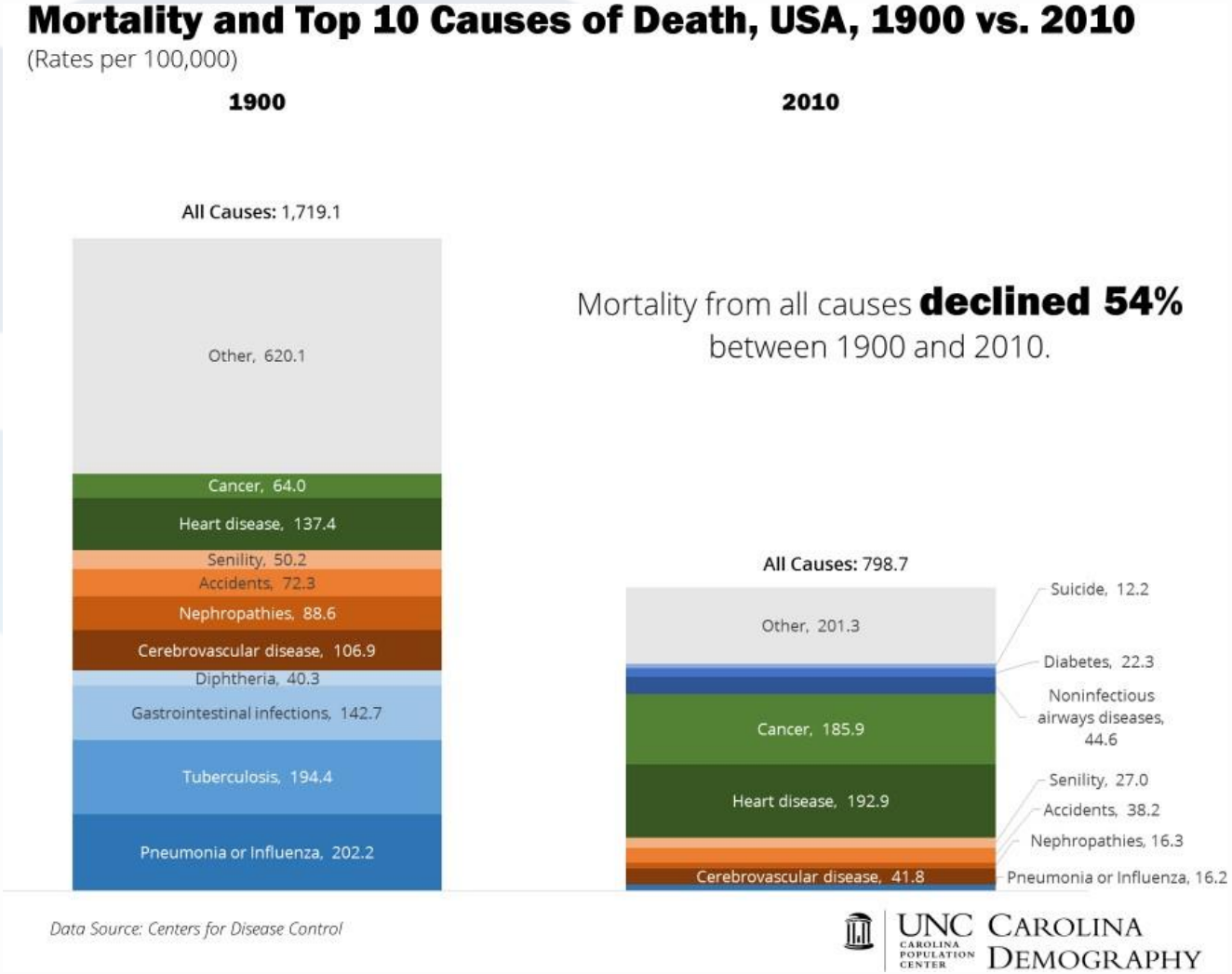
- Engage in discussion
- Ask a question, always raise your hand
- Use your phone to look for information
- Attend all classes
- Participate in quizzes

THINGS NOT TO DO

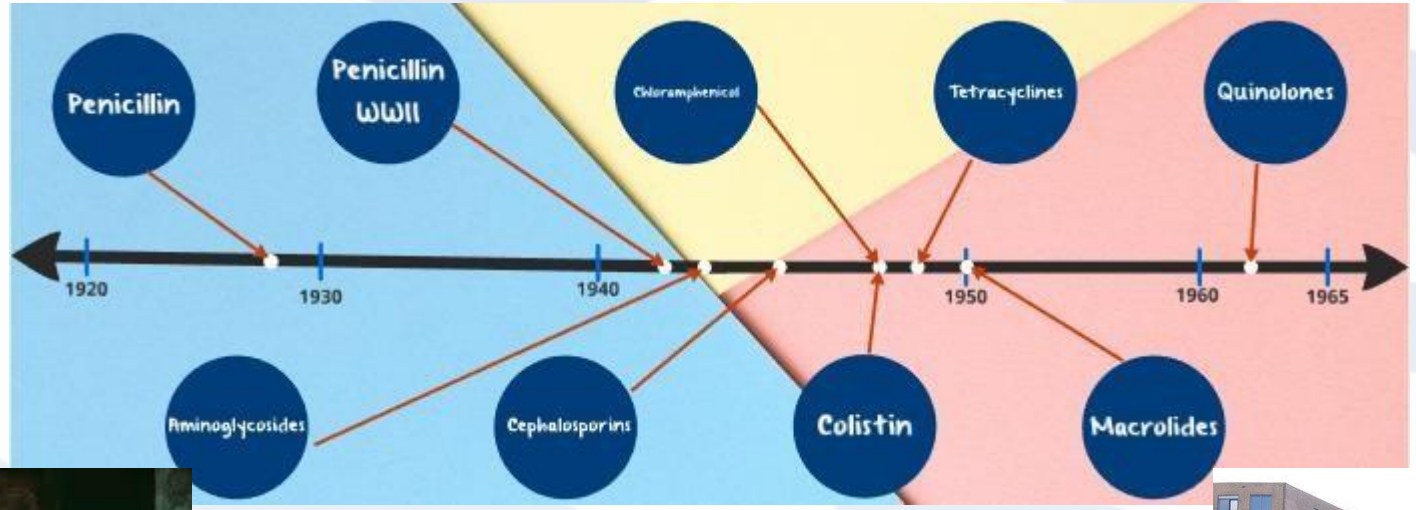
- Side talk
- Ask your friend on something
- Keep your phone on ringtone mode
- Come late to classroom (later than 10 minutes of beginning)
- Cheat

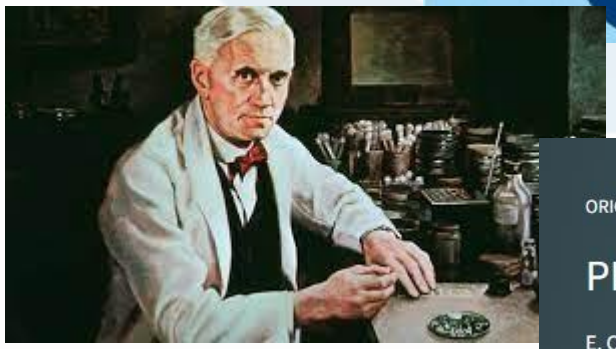
How Did Antibiotics Change The World?

- **Life expectancy**: 47 years to 78 years (Western countries)
- **Major cause of death**: communicable diseases to non-communicable diseases(heart disease first, then cancer and road traffic accidents)



The Story of Penicillin





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PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

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When we say chemotherapy, the 1st thing that comes into our mind is anti-cancer drugs, but actually if you break down the word, you'll find out that in pharma it is a general term that includes antibiotics too! So the word chemotherapy means a drug that kills microorganisms!

In the era of world war 1, there were lots of injuries and wounds and so wound infections were rising. Scientists were aiming to discover an antimicrobial substance and Alexander flemming was one of them!

The discovery of penicillin is what we call serendipity(good luck)!
Alexander flemming was conducting experiments on bacteria and he forgot to close one of the petri dishes. The bacterial colony was contaminated with fungi but he noticed that there were no bacteria around the fungi, this led to discovery of penicillin.
Flemming conducted an inaccurate experiment that led him to think penicillin will be ineffective in living organisms. However, 10 years later scientists conducted experiments on infected mice and found that it actually works!

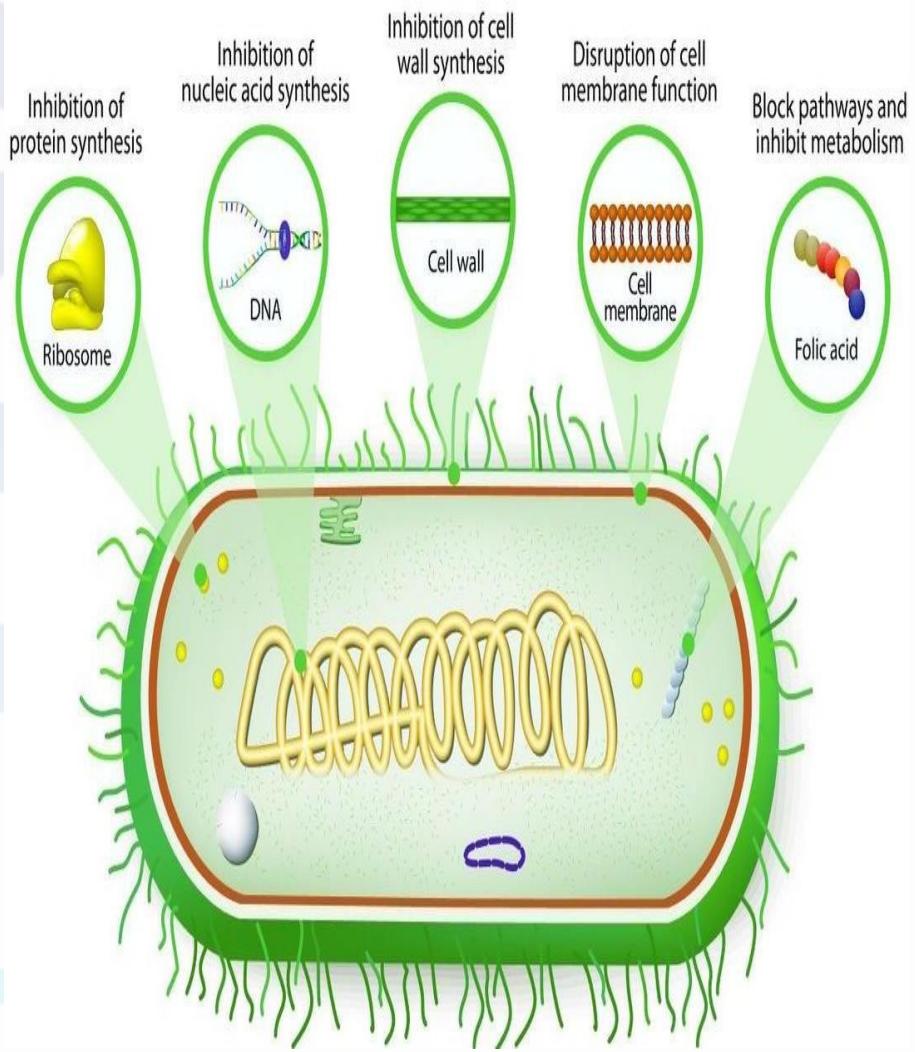
Overview

Selective Toxicity:

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

Microorganisms(especially prokaryotes usually have different processes than those of human cells

Are prokaryotic processes completely different from eukaryotic processes though? No, there are differences but they still share the basic principles.(evolutionary conserved as they call it)



On the other hand, there are structures and processes that are completely specific to microorganisms but not humans
(like the cell wall for example)

The selective toxicity of cancer chemotherapy is much much lower than antibacterial chemotherapy. Why?because cancer cells are human cells and so if you interfere with cancer cells processes you'll interfere with other normal human cells processes too!

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(doesn't cause toxicity) by the host

Selection of Antimicrobial Agent(according to FDA there are hundreds of antibiotics!)

What needs to be known?

- The organism's identity(whether gram(+),(-), aerobic, anaerobic etc..)

  Different microorganisms cause different infections.
- The organism's susceptibilityحساسية to a particular agent(because antibiotic resistance is emerging)
- The site of the infection(Central nervous system has blood brain barrier and this will affect pharmacokinetic passage of drugs)
- Patient factors
- The safety of the agent
- The cost of therapy

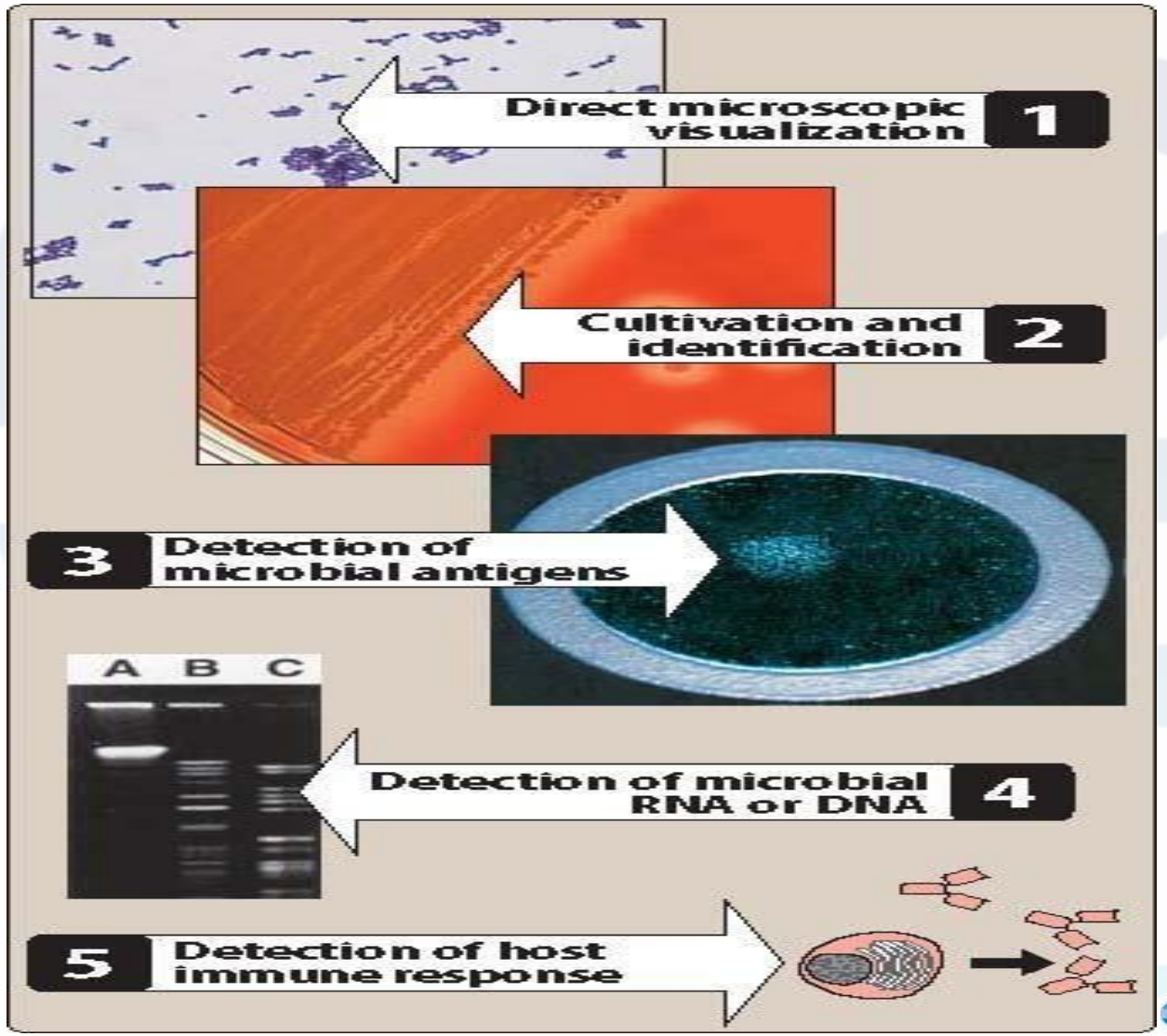
Identification of The Infecting Organism

- **Gram stain**:
  - presence of microorganisms in sterile body fluids(like the **cerebrospinal fluid, blood, urine ,synovial fluid, serosa,**the mere presence of bacteria indicates infection)
  - morphologic features**(gram+,-,coccus,bacilli etc…)**
  - **Drawback: Not very accurate in identifying the organism**
- **Culture(the gold standard in identifying the organism)**:
  - diagnosis
  - antibiotic susceptibility**(very important advantage! We try antibiotics on the cultured bacteria, if an antibiotic doesn't work, then bacteria is resistant so don't use it on the patient)**
  - **Drawbacks: 1-It is impossible to know whether negative culture is due to absence of infection or due to antibiotics the patient has taken before coming to you!**

2-takes time! Fastest growing bacteria takes 24-48 hours

So if a patient presents with a life-threatening infection, you have to take samples for gram stain and culture then immediately give empiric antibiotic therapy

- **Microbial antigens:**DNA, RNA,(via PCR) , antibodies, etc



Wolters Kluwer

Empiric Therapy prior to Identification of The Organism

- Greek *empeiria* = experience. We give antibiotics based on our knowledge of the most common causative organisms in the region and their local antibiotic sensitivity data(antibiograms)

❑**Timing**

- Immediate treatment: e.g., critically-ill, neutropenic, neonate meningitis.

❑**Selecting a drug**

- Site of infection
- Clinical picture+
- Broad-spectrum therapy(covers a wide range of organisms, used in empiric therapy and polymicrobial infections)

Example:

A 40-year-old patient with gram- positive cocci in the spinal fluid. These are most likely be *S. pneumoniae. S. pneumoniae* is frequently resistant to penicillin G. Empirically treat with a high-dose third-generation cephalosporin (such as ceftriaxone) or vancomycin.

If an adult patient comes with meningitis, then I know empirically that the organisms are most likely to be Neisseria meningitides(also called meningococcus) or more commonly strep pneumoniae(also called pneumococcus). But if the patient was a 24-hour neonate(مولود جديد), then the organism likely came from mother's birth canal during passage of the fetus(such as listeria or group B strep)

See how we gave different empirical treatments to the same disease based on different age groups! That's because different age groups have different causative organisms.

Important: Always remember to take samples for stain,culture, etc.. before giving the empirical therapy. If you take the samples after giving antibiotics, the samples might show false negative results

Determining Antimicrobial Susceptibility of Infective Organisms

- Predictable vs unpredictable susceptibility
- Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing
- The susceptibility of a microorganism to a drug can be experimentally determined

MIC

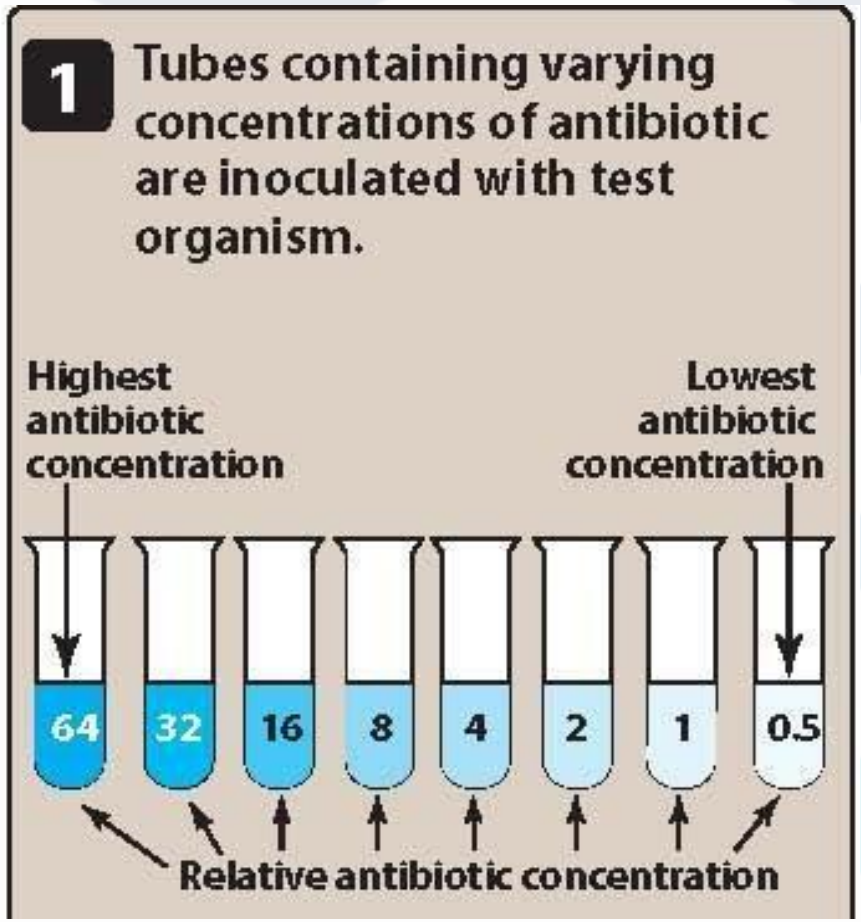
MBC

In order to determine bacterial susceptibility to antibiotics, you can't have guesses(ما بيزبط تحزر). You need a standard(معيار) and a mathematical value(numbers). So we have 2 parameters for antibiotic susceptibility, MIC(minimum inhibitory concentration) and MBC(minimum bacteriostatic concentration).

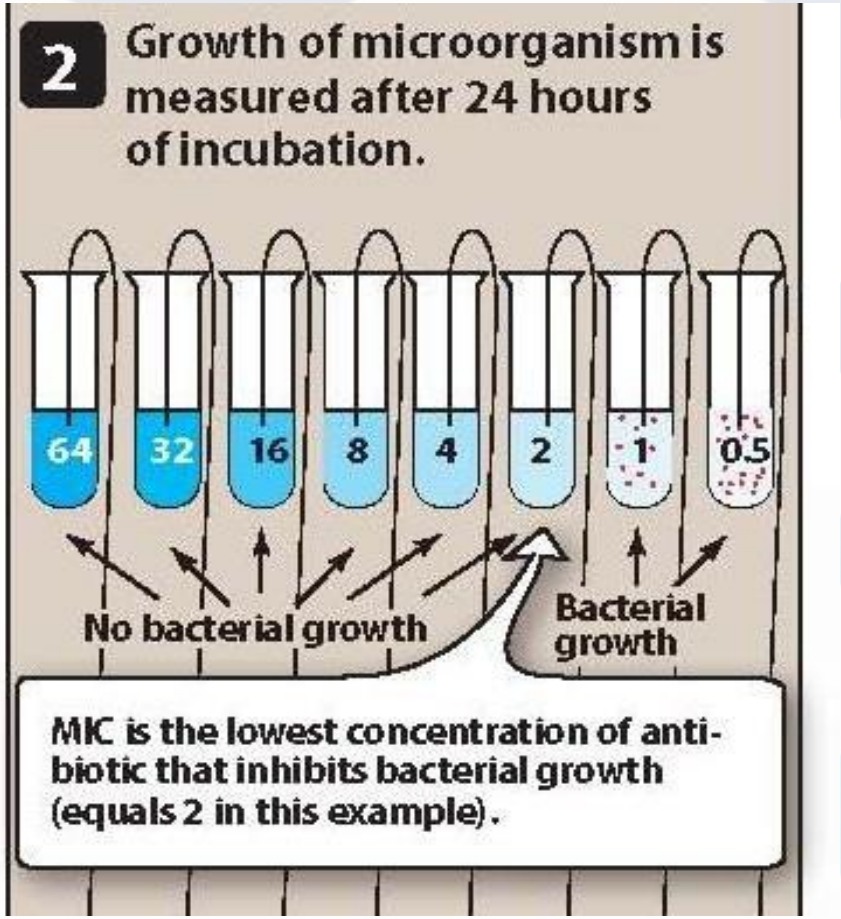
MIC(the definition is very important): lowest concentration of antibiotic that can inhibit **visible** bacterial growth in culture.

What do we mean by visible growth, we mean growth that can be seen by naked eye.

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



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



If there is no visible growth, then it is either that:-

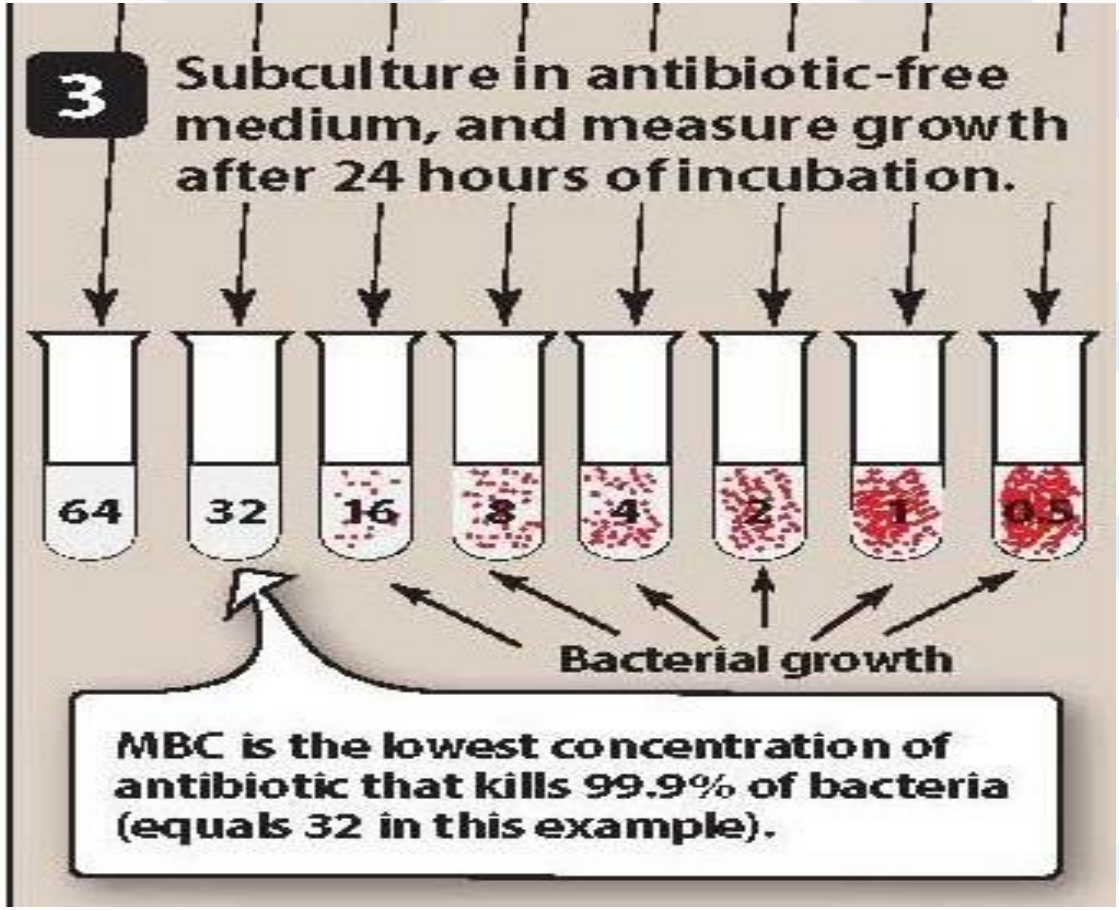
1. the antibiotic has completely eradicated the bacteria and no bacteria is left in the tube
2. The antibiotic did have action but hasn't completely eradicated the bacteria and so few bacteria are left.These bacteria still undergo replication and growth but not to the level to be seen by visible growth

To recap the previous 3 slides

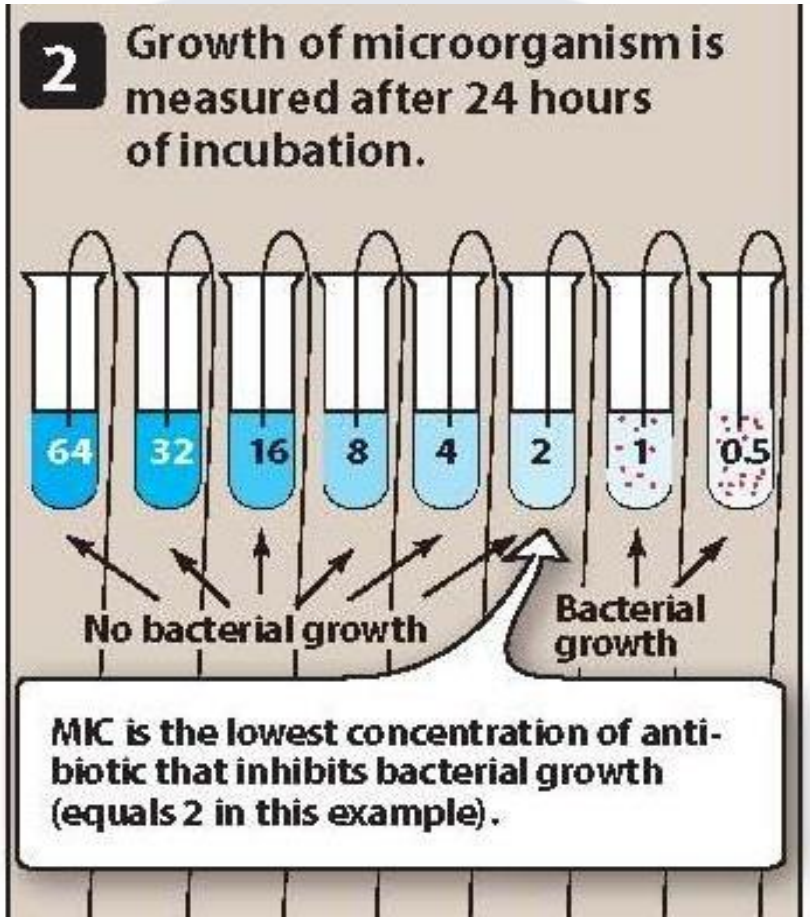
Let’s do the MIC experiment, say that a person comes with dysuria(painful urination) and it turned out that he has urinary tract infection and we want to determine antibiotic susceptibility for the causative organism. We take multiple samples of urine(equal amounts of course!) and we put each sample in a culture tube with each tube containing different concentration of the antibiotic. We leave the bacteria in the culture tube for a while and then we go back and asses visible growth with our eyes. The lowest concentration that has prevented the visible growth is the MIC.

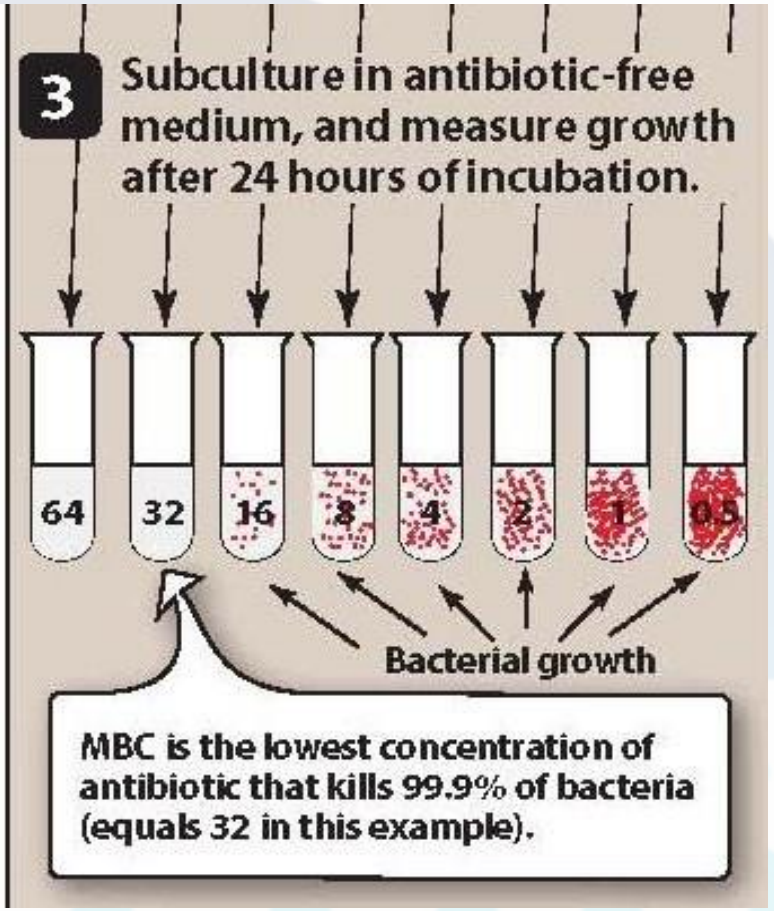
However, tubes with no visible growth might either be totally free from the bacteria(the antibiotic concentration has killed the bacteria) or still have few bacteria. Here comes the MBC which will help us know whether each antibiotic concentration result in total eradication of bacteria or not and so have another precise measurement for antibiotic effectiveness!

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



Slide is just for comparision.





Recap of the previous slide:MBC

After we are done with MIC,We take samples from each culture tube and we put each in a separate antibiotic free medium and leave for a day. The result is either:-

1. Visible growth, which means that the tube with no visible growth back in the MIC experiment did have few bacteria and so they produced visible growth in this antibiotic free medium.
2. If there is no visible growth, then the tube with no visible growth back in the MIC experiment didn't have any bacteria, all were eradicated!

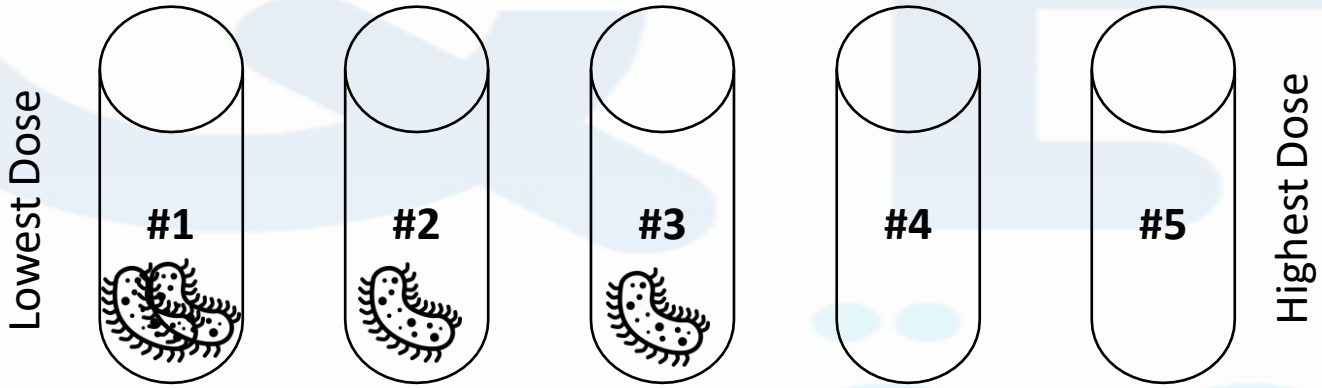
The lower the MBC(or MIC), the stronger is the antibiotic.
This is similar to Ed50, the lower it is the stronger the drug!

So If a question comes in the exam:-
Antibiotic a has an mic of 0.5 while antibiotic B has an mic of 0.7, then antibiotic a is the stronger and more potent.

MIC is more clinically used than MBC, why? Because it is faster! MBC requires 2 steps wheras MIC required 1 only.

Practice Question

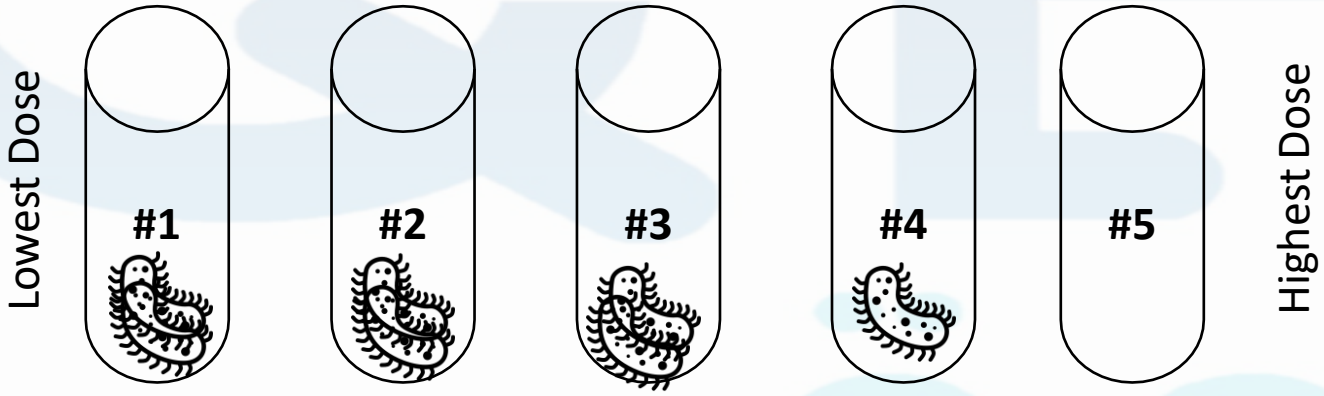
- You have 5 tubes and want to do 5 dilutions of antibiotic X on the growth of E.coli. Tubes 4-5 do not have growth, but tubes 1-3 have visible growth, the tube with the MIC would be?



Answer: test tube 4

Practice Question

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

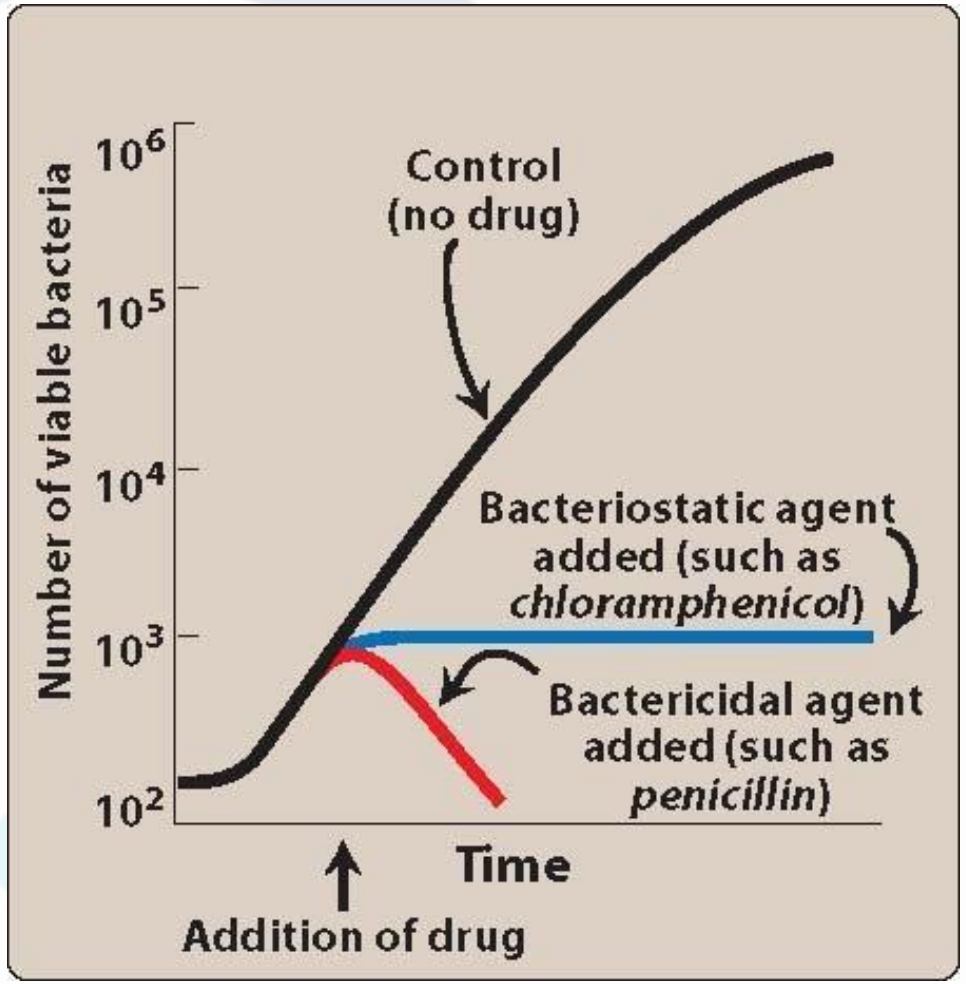


Test tube 5

Bacteriostatic vs Bactericidal

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

- **Bactericidal**: kills bacteria (kill ≥ 99.9% or 3-log reductions after 18-24 hours of incubation)



Bacteriostatic vs Bactericidal

But…

- Classification is too simplistic(a drug may be bacteriostatic or bactericidal depending on the dose)
- Microorganism-dependent
- Similar efficacy for clinical infections(In other words ,the classification isn't of much value clinically. Actually many of the strongest and most effective antibiotics are bacteriostatic. Other factors may be more important like the immune system, drug concentration at site of infection, and underlying severity of the illness.

So why do we give bacteriostatic antibiotics if it doesn't kill bacteria? To aid the immune system and ease things for it. Mild Self-limited infections don't need antibiotics because the immune system will clear the microorganisms after a few days. Taking antibiotics will just speed the recovery time but is not essential.so we actually prefer not to give in this case because it might increase bacterial resistance.

But what if the infection was severe like in pneumonia or meningitis? You have to give antibiotics to prevent severe long term complications(for example children with meningitis might develop hearing loss or seizures)

❖ **Effect of the site of infection on therapy:**

✓ **the blood-brain barrier :**

- **Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated.**
- **Capillaries with varying degrees of permeability carry drugs to the body tissues.**
- **Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta, the vitreous body of the eye, and the central nervous system (CNS).**
- **Of particular significance are 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, except those that are small and lipophilic.**

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

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. ……. 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.

Penicillin is a large, bulky, charged molecule that has difficulty in crossing BBB. So even if penicillin was effective against a certain bacterium. If this bacterium is causing a CNS infection(like meningitis) then penicillin will face difficulty in reaching this bacteria and acting on it! That's why they say the brain is one of the most difficult sites to treat!

Exam question!: Suppose that MIC was given for many antibiotics and you've found the most effective among them all but this most effective drug has difficulty in reaching site of infection due to its pharmacokinetics. Would it be your choice? Of course no!

In intestinal infections(gastroenteritis), we use antibiotics with poor absorption because we want the antibiotic to remain in intestines and not reach blood stream.

Patient Factors

1. Immune system:

It is the **immune system** that does the main killing of microbes, **antibiotics just help it**!! So the immune system is more important than antibiotics!!

host defense system must ultimately eliminate the invading organisms.

- factors influencing immunocompetence: alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, immunosuppressive drugs. In patients with immunosuppression. You have to give stronger/more potent antibiotics for prolonged periods of time. An immunosuppressed patient that has AIDS for example might have a different stronger antibiotic even if he gets infected with the same organisms normal people get!

2. Renal dysfunction(an antibiotic that causes renal toxicity must be avoided in people with renal dysfunction!)

Also, renal dysfunction may decreased excretion of antibiotic→antibiotic toxicity!!

Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.

However, direct monitoring of serum levels of some antibiotics (for example, vancomycin, aminoglycosides) is preferred to identify maximum and/or minimum values and prevent potential toxicities.

[Note: 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. So you might use lower dose in elderly]

2. **Hepatic dysfunction(same principle as above)**
3. **Poor perfusion(perfusion means blood supply, remember that it is the blood vessels that bring inflammation and immune cells!! So if there is poor perfusion few immune cells will come!So you have to give stronger antibiotics for prolonged periods and usually by IV)**

Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient(because diabetes increase atherosclerosis), reduces the amount of antibiotic that reaches that site of infection, making it more difficult to treat. That why diabetic ulcers are difficult to treat, both the immune cells and antibiotic can't reach!!

Decreased perfusion of the gastrointestinal tract may result in reduced absorption, making attainment of therapeutic concentrations more difficult with enteral routes.

Patient Factors

5. **Age**(for example, a neonate has an immature kidney and so drug excretion will not be as that in the adult!, this will affect your choice of antibiotics)
6. **Pregnancy**(a drug might cross the placenta and be teratogenic or be excreted in breast milk!)
7. **Risk factors for multidrug-resistant organisms:**

- prior antimicrobial therapy in the preceding 90 days
- hospitalization for greater than 2 days within the preceding 90 days
- current hospitalization exceeding 5 days(bacteria are constantly exposed to antibiotics in the hospitals and so hospitals contain multidrug resistant bacteria like MRSA and pseudomonas)
- high frequency of resistance in the community/geographical area or local hospital unit (assessed using hospital antibiograms) (e.g. in Sweden it is ok to treat respiratory infections with amoxicillin, in Jordan no way! 99% of circulating bacteria are resistant to it and so we use an improved version of amoxicillin,"the amoclan"
- immunosuppressive diseases and/or therapies

CATE-GORY	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-sulfa-methoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *genta-micin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

The 4th point, poor perfusion, usually occurs in patients having diabetic foot, diabetes is actually a vascular rather than a metabolic disease with lots of vascular structures being damaged , if this occurs in the already far-away-from-heart lower extremity vessels due to poor diabetes control, this will result in diabetic foot, a very difficult infection to treat!)
For you knowledge: severe infections are usually treated IV

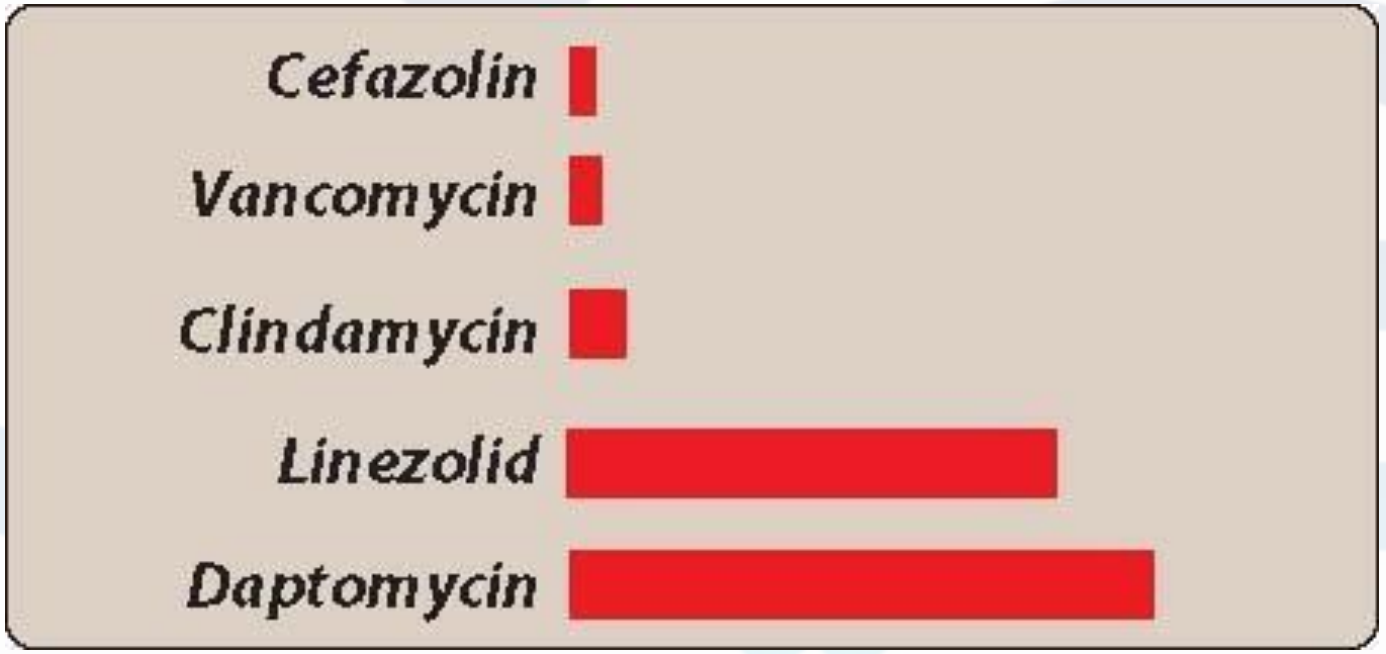
Safety of the agent(from the book)

Penicillins are among the least toxic of all antimicrobial drugs because they interfere with a site or function unique to the growth of microorganisms.

Other antimicrobial agents (for example, chloramphenicol) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient.

[Note: Safety is related not only to the inherent nature of the drug but also to the patient factors described above that can predispose to toxicity.]

Cost of Therapy: Is It Important?



Safety is much more important factor than cost!! Don't use a drug that is harmful to the patient just because it is cheaper!!

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

Unless the patient has contraindications to that drug, we use the cheapest drug possible بديهيا

Route of administration(from the book)

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 Gl tract and for treatment of patients with serious infections(emergencies) 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.

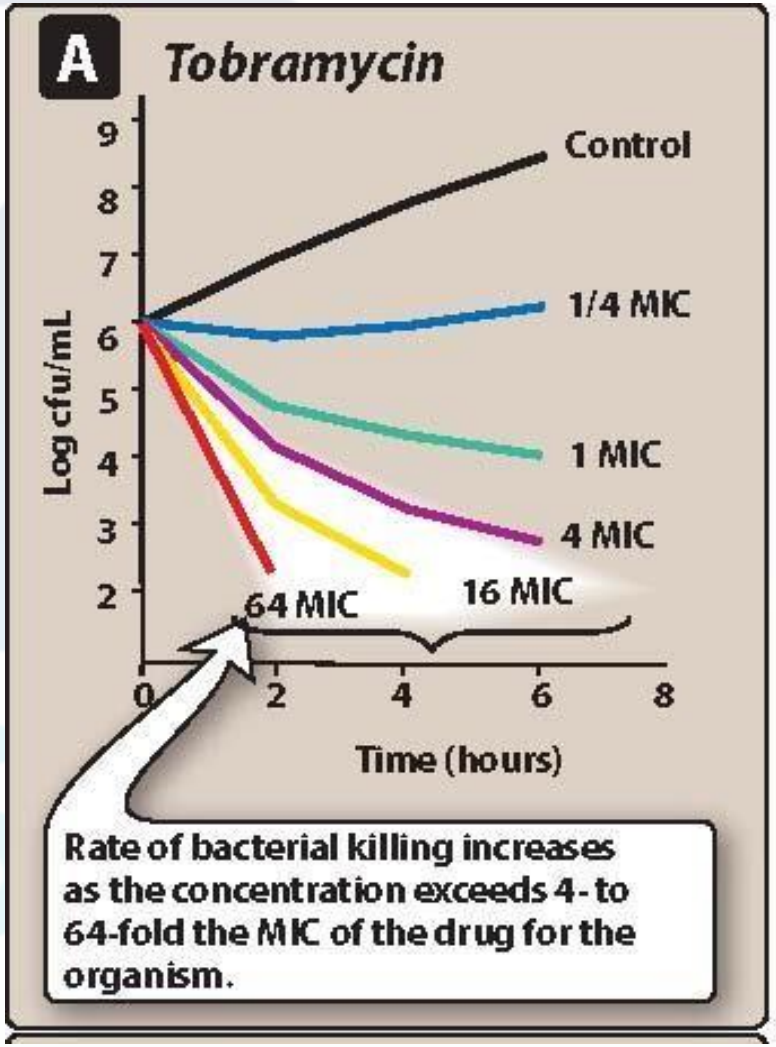
However, some antibiotics, such as vancomycin and aminoglycosides, are poorly absorbed from the gastrointestinal (GI} tract and do not achieve adequate serum levels via oral administration.

Determinants Of Rational Dosing

A. Concentration-dependent killing

Clinically, you have to give to single dose with highest concentration possible to get maximal benefit from concentration dependent antibiotics

We give concentration-dependent drugs by a **once-a-day bolus injection/bolus infusion** achieves **high peak levels**, favoring rapid killing of the infecting pathogen



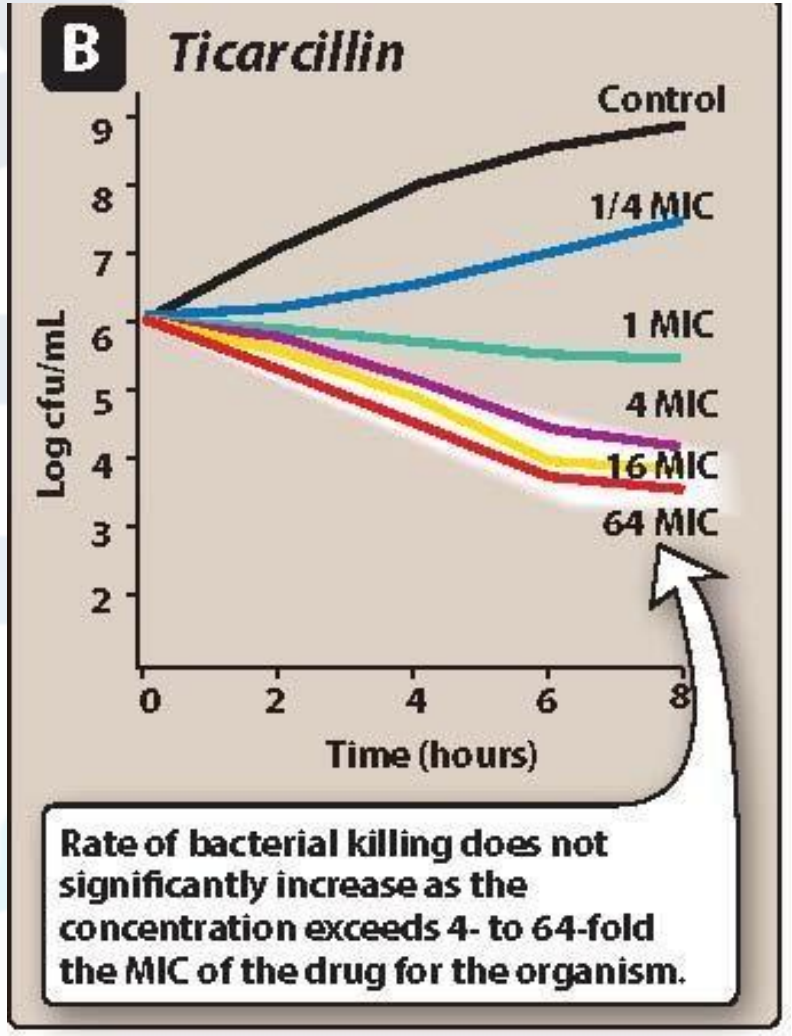
Determinants Of Rational Dosing

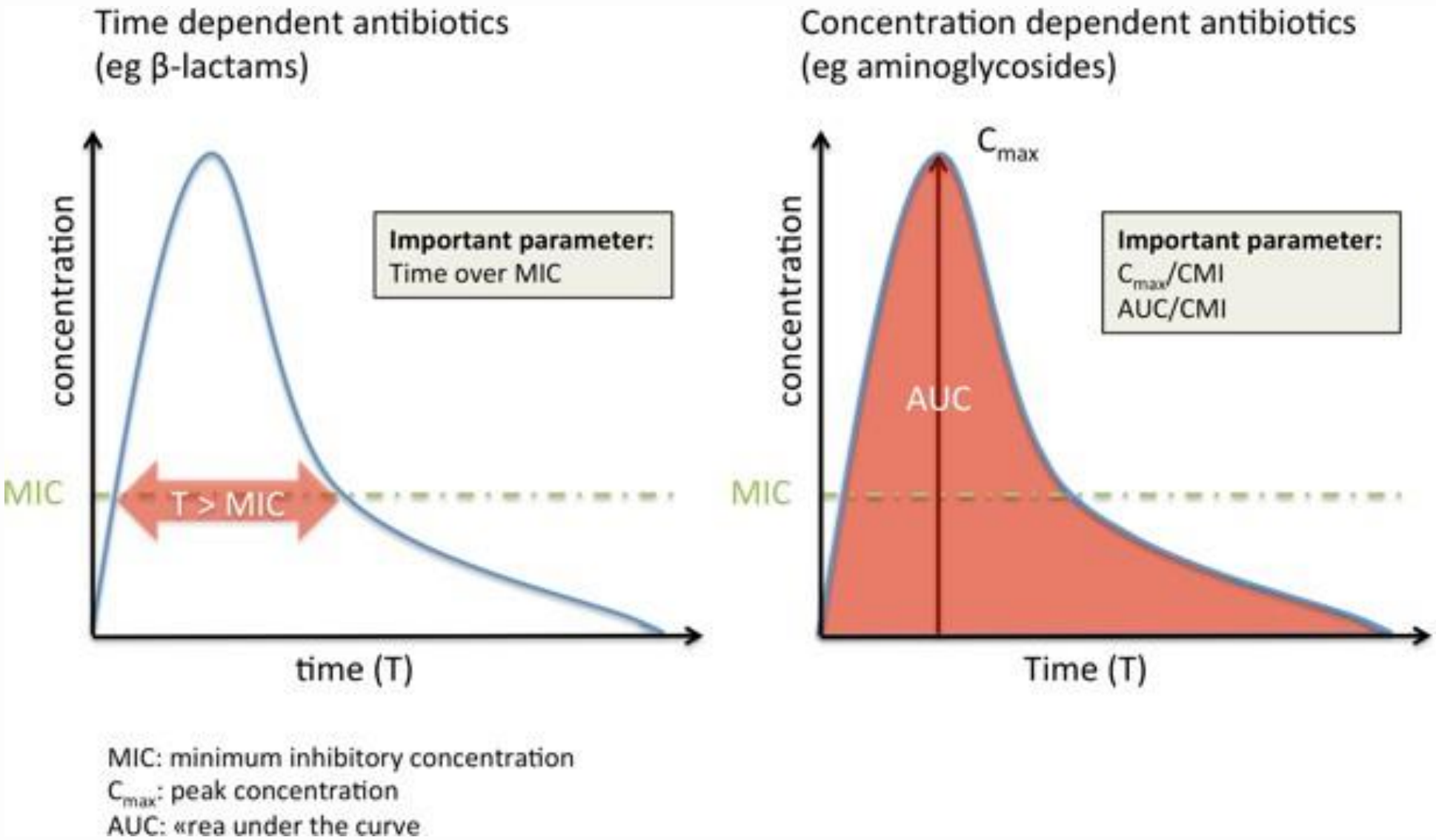
B. Time-dependent (concentration-independent) killing.

Important note: Time-dependent killing means that at a certain drug concentration, further increases won't significantly increase the rate of bacterial killing.

Clinically, you have to use more frequent dosing to get maximal benefit from the drug. Dose amount by itself is not very important

We usually use extended infusions(for 3-4 hours) and continuous infusions(24 hours) in time dependent





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

In time-dependent killing, we don't care about Cmax much.. So you have to use frequent dosing and whenever drug concentration falls below MIC you have to give another dose in order to keep plasma drug concentration above MIC for>60% of time.
So if you give treatment for about 8 hours, drug concentration should be above MIC for 5 hours!

e.g. if you give a dose at 12pm and the levels of drug fall below MIC at 6pm, you have to give another dose!

Are there drugs that work by a mix of time dependent and centration dependent killing? Yes

fluoroquinolones and vancomycin, work best by **optimizing** **the ratio of the 24-hour area under the concentration-time curve to MIC (AUC24/MIC}.** The AUC24 is the overall exposure of a drug during the dosing interval and takes into account the concentration as well as the time.

Clinical correlates: meningitis diagnosis

C. Diagnosis

1. CSF examination (LP)—Perform this if meningitis is a possible diagnosis unless there is evidence of a space-occupying lesion (see Table 10-2). Also note the opening pressure.
   a. Examine the CSF. Cloudy CSF is consistent with a pyogenic leukocytosis.
   b. CSF should be sent for the following: cell count, chemistry (e.g., protein, glucose), Gram stain, culture (including AFB), and cryptococcal antigen, or India ink.
   c. Bacterial meningitis—pyogenic inflammatory response in CSF
      - Elevated WBC count—PMNs predominate.
      - Low glucose.
      - High protein.
      - Gram stain—positive in 75% to 80% of patients with bacterial meningitis.
   d. Aseptic meningitis—nonpyogenic inflammatory response in CSF
      - There is an increase in mononuclear cells. Typically a lymphocytic pleocytosis is present.
      - Protein is normal or slightly elevated.
      - Glucose is usually normal.
      - CSF may be completely normal.
2. CT scan of the head is recommended before performing an LP if there are focal neurologic signs or if there is evidence of a space-occupying lesion with elevations in ICP.
3. Obtain blood cultures before antibiotics are given.

Clinical correlates: pneumonia diagnosis

b. After treatment, changes evident on CXR usually lag behind the clinical response (up to 6 weeks).
c. Changes include interstitial infiltrates, lobar consolidation, and/or cavitation.
d. False-negative chest radiographs occur with neutropenia, dehydration, infection with PCP (*Pneumocystis carinii* pneumonia), and early disease (<24 hours).

2. Pretreatment expectorated sputum for Gram stain and culture—low sensitivity and specificity, but still worthwhile tests because antimicrobial resistance is an increasing problem.
   a. Sputum Gram stain—try to obtain in all patients.
      - Commonly contaminated with oral secretions.
      - A good specimen has a sensitivity of 60% and specificity of 85% for identifying gram-positive cocci in chains (*S. pneumoniae*).
   b. Sputum culture—try to obtain in all patients requiring hospitalization.
      - Specificity is improved if the predominant organism growing on the culture media correlates with the Gram stain.
3. Special stains of the sputum in selected cases.
   a. Acid-fast stain (*Mycobacterium* spp.) if tuberculosis (TB) is suspected.
   b. Silver stain (fungi, *P. carinii*) for HIV/immunocompromised patients.
4. Urinary antigen assay for *Legionella* in selected patients.
   a. This test is very sensitive.
   b. The antigen persists in the urine for weeks (even after treatment has been started).
5. Consider two pretreatment blood cultures from different sites. Blood cultures positive in 5% to 15% of cases.

- Gram stain and culture of sputum
- Antibiotic therapy

Quick HIT

Radiographic changes and clinical findings do not help in identifying the causative pathogen in CAP.

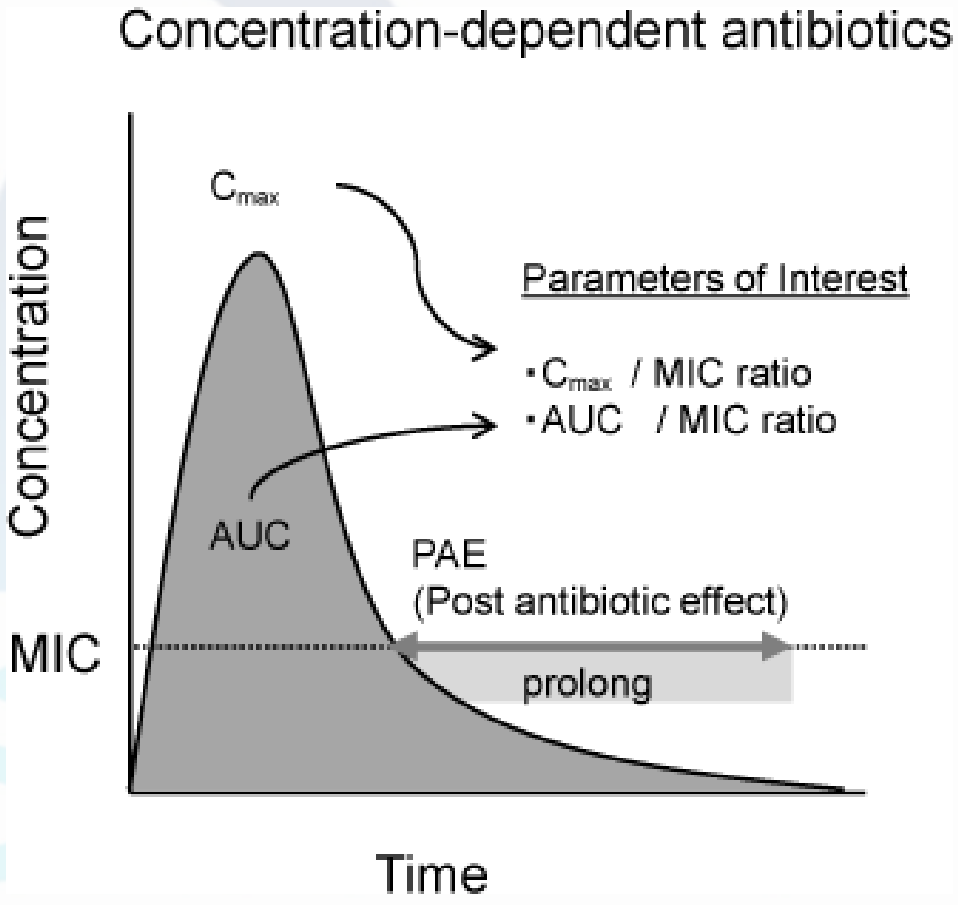
Quick HIT

Test for microbial diagnosis for outpatients is not required. Empiric treatment is often successful if CAP is suspected.

Quick HIT

Determinants Of Rational Dosing

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



Some antibiotics(but not all of them) exhibit post-antibiotic effect. **Concentration dependent drugs are very likely to have this effect.**

Mechanism of post antibiotic effect:-

1. The drug accumulates away from the plasma(falls below MIC) but into the bacteria and tissue at the site of infection and gets concentrated there.(like aminoglycosides/flouroquinolones)

- Post antibiotic effect, along with less frequent dosing regimen, is an advantage of concentration dependent drugs.(actually post antibiotic effect contributes to less frequent dosing). You give a single high dose

1. The drug binds irreversibly with its target in the bacteria

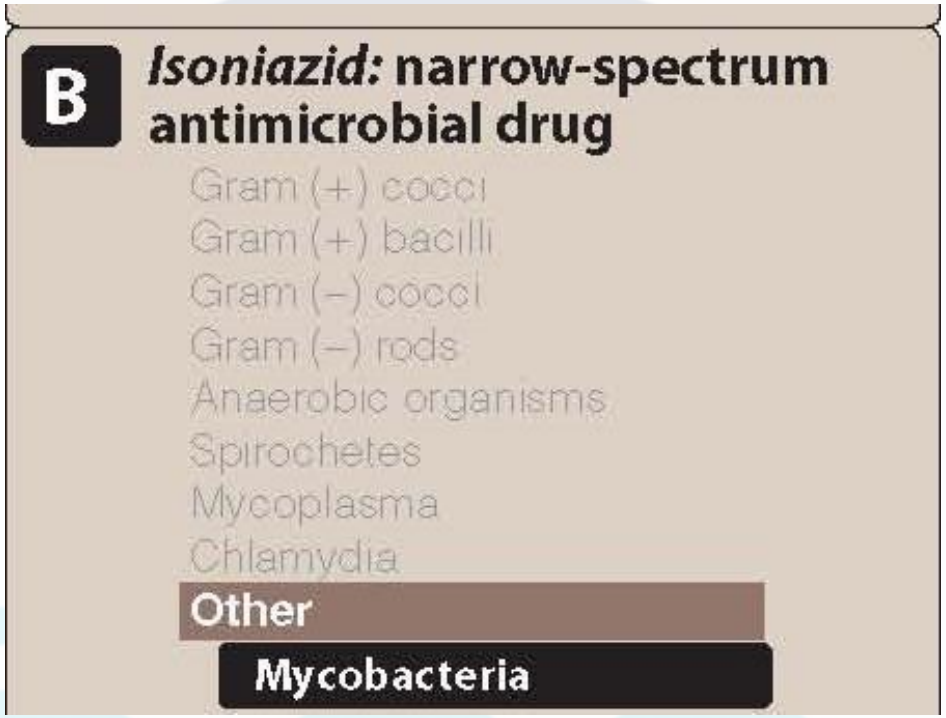
Chemotherapeutic Spectra

Chemotherapeutic Spectra

- **Narrow-spectrum antibiotics:**

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

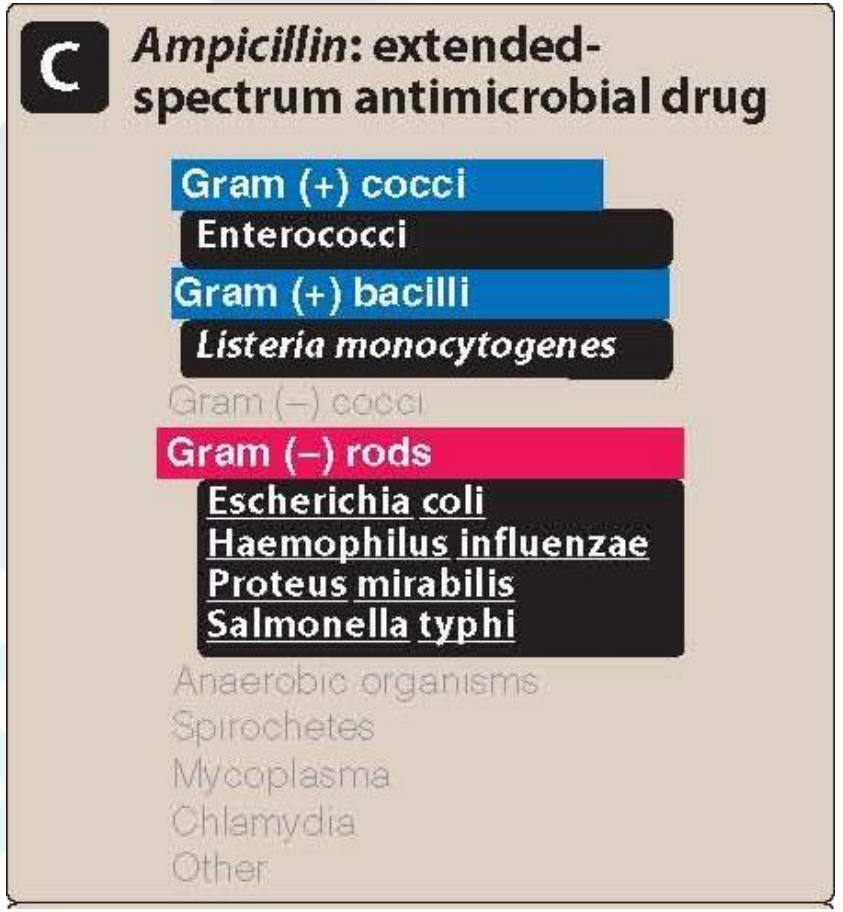
Advantage: Won't have any complications relating to killing of normal flora



Chemotherapeutic Spectra

- **Extended-spectrum antibiotics:**

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



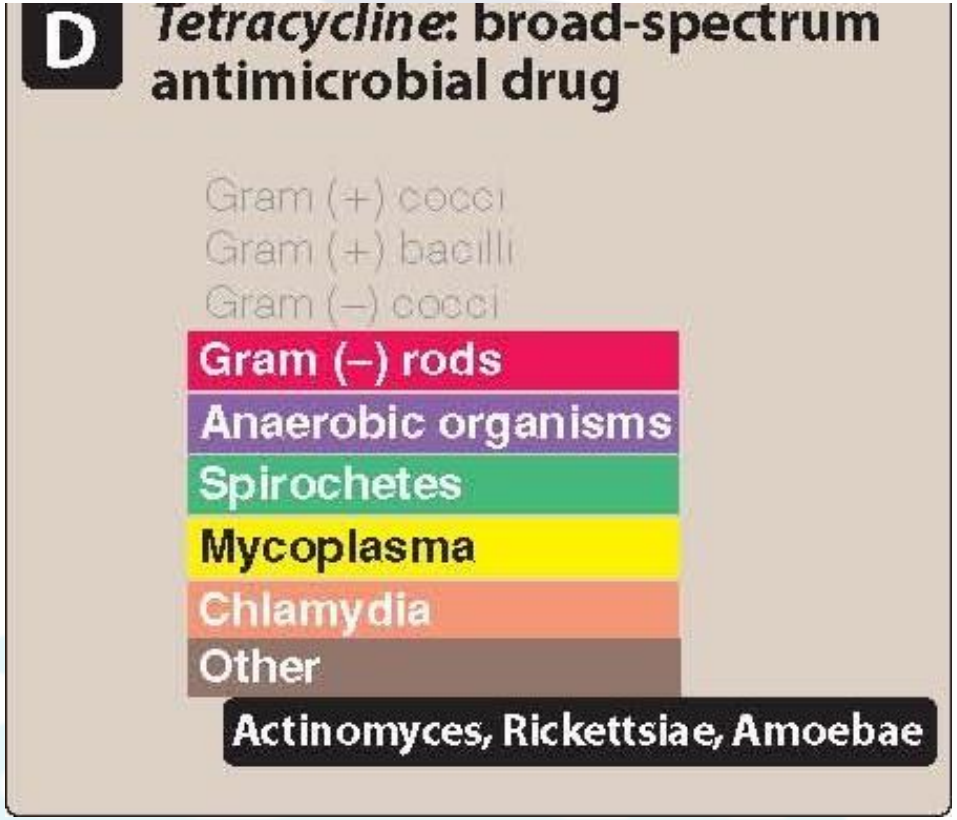
Our understanding of antimicrobial spectra is based in penicillin. Penicillin covers gram positive bacteria. So when we modiefied penicillin to cover additional few gram negatives we called it extended spectrum

Chemotherapeutic Spectra

- **Broad-spectrum antibiotics:**

antibiotic that acts on both gram-positive and gram-negative bacteria in addition to atypicals

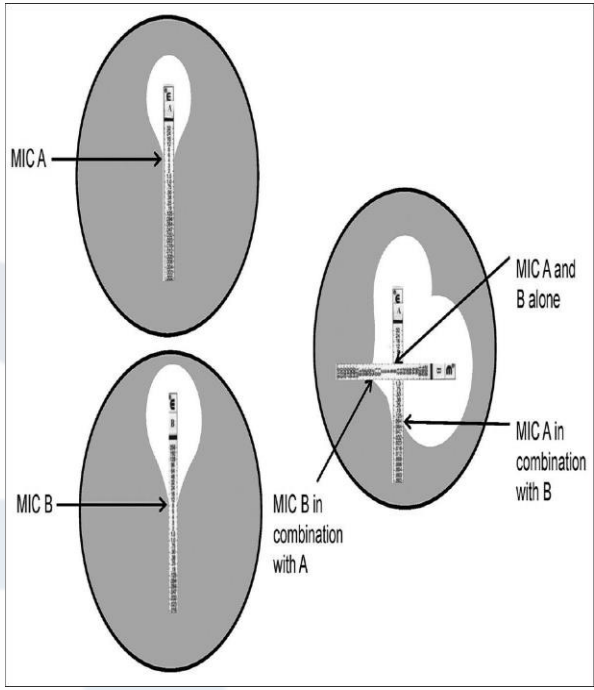
- Advantage: can be used in empiric therapy in life-threatening infections or in polymicrobial infections
- Disadvantages: risk of multi-drug resistance+ killing of microbial normal flora



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 sensitivityOrganisms that are already resistant: like TB, you can't use one antibiotic because it won't be effective



- A famous example of synergism is ampicillin+ gentamicin used to treat neonatal meningitis that is usually due to gram positives

B. Disadvantages of drug combinations:

- Interference in the mode of action: bacteriostatic + bactericidal (bacteriostatic inhibits growth but bactericidal needs fast growth)
- selection pressure/antimicrobial resistance

So we've seen the advantages and disadvantages of using combinations/broad-spectrum against one/narrow-spectrum. So the question remains, if you've done your tests and found antibiotic susceptibility of the bacteria and have chosen your drug, Should you go for one or combinations?

General rule is just one single best antibiotic, you've already made sure bacteria is susceptible to this antibiotic so this one antibiotic will be effective+ you are minimizing adverse reactions on the patient and preserving the flora+ minimizing future resistance to antibiotics.

However, there are scenarios where you need to use combination
Like in TB because the TB bacteria is multidrug resistant.

Prophylactic Use Of Antibiotics

"Prevention not treatment"

1

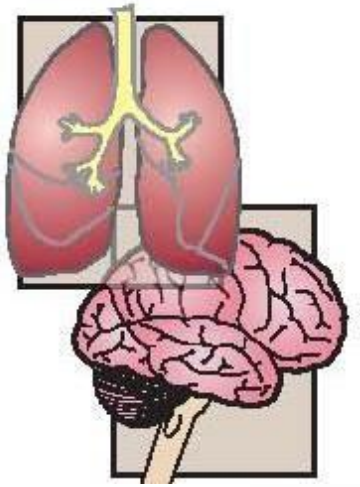
Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

2

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

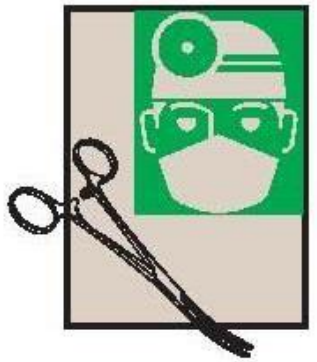
3

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



4

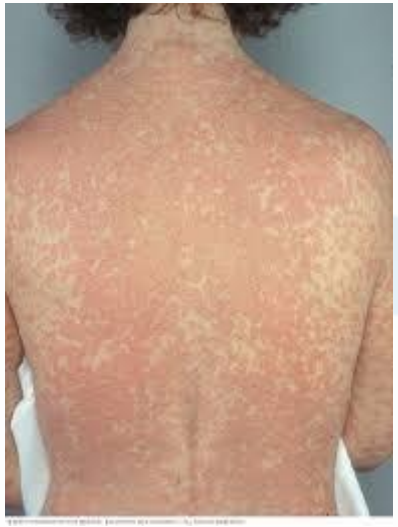
Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



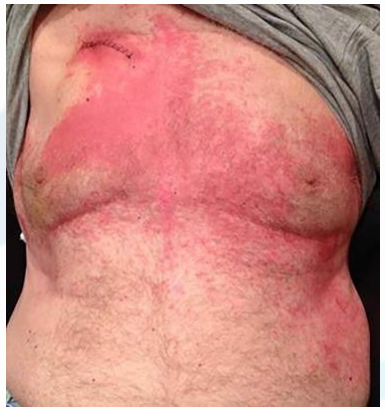
Complications Of Antibiotic Therapy

A. Hypersensitivity

-ranges from mild skin rash to life-threatening anaphylaxis



Urticaria
Drug: penicillin



Red man syndrome
Drug: vancomycin, it is related to rapid infusion of the drug

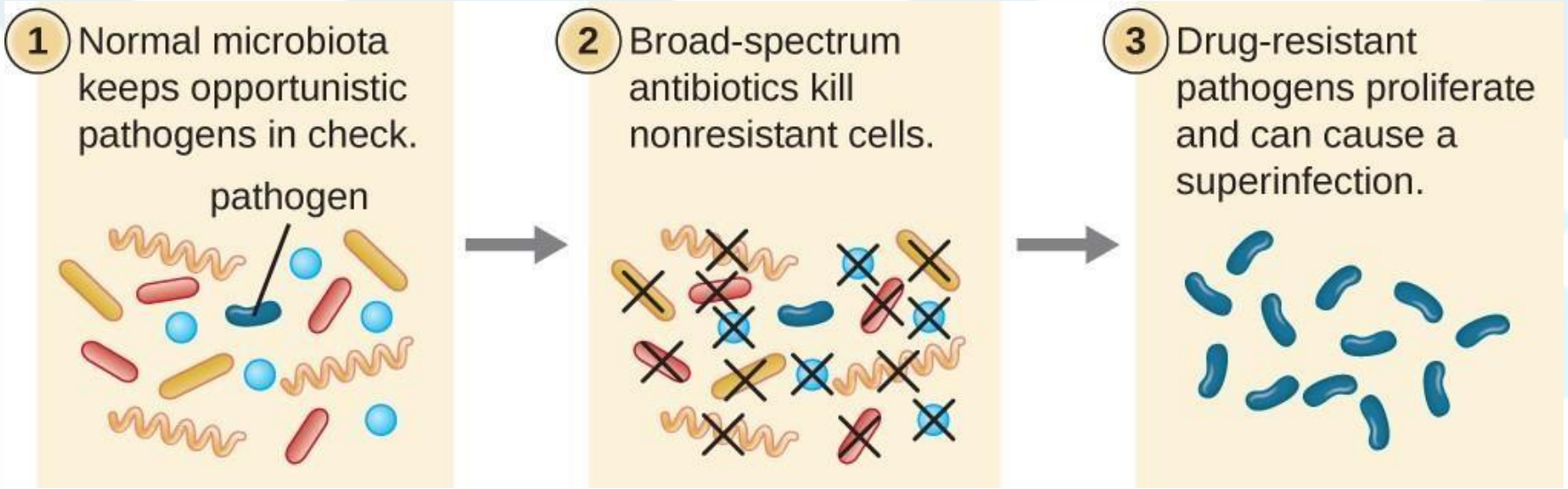
Steven-Johnson syndrome(toxic epidermal necrolysis)
Drug: penicillins, sulfa drugs. If a patient has history of steven johnson, don't even think about administrating the drug again/rechallenge

Complications Of Antibiotic Therapy

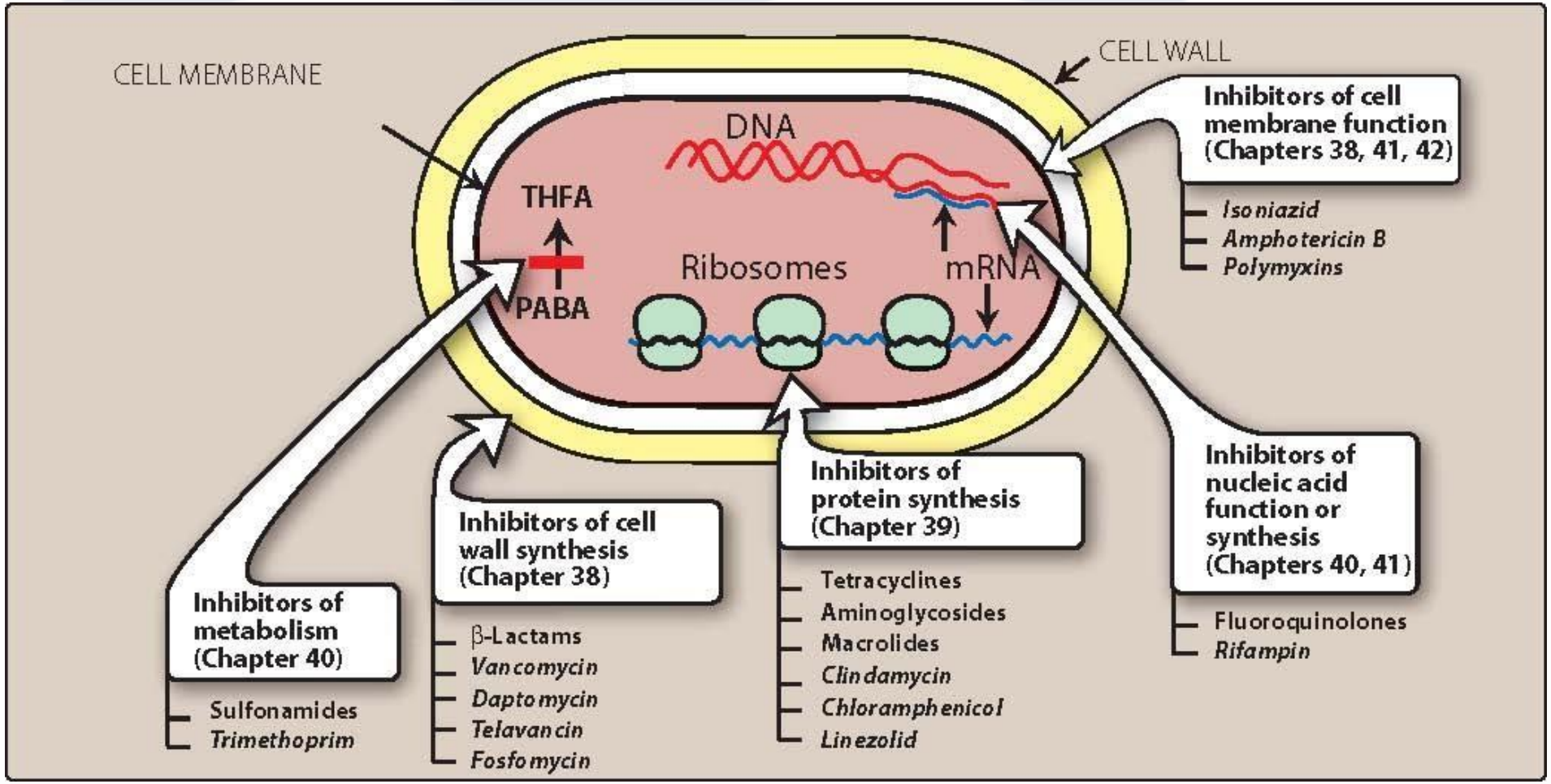
B. Direct Toxicity

C. Superinfections:

- mainly with broad-spectrum agents
- Overgrowth of opportunistic organisms(like clostridium difficile



Sites Of Antimicrobial Actions



Questions!

28.8 When evaluating drug therapy for meningitis, which of the following factors is expected to have the LEAST influence on the penetration and concentration of an antibacterial agent in the cerebrospinal fluid?

A. Lipid solubility of the drug
B. Minimum inhibitory concentration of the drug
C. Protein binding of the drug
D. Molecular weight of the drug

Correct answer = B. Although the minimum inhibitory concentration impacts the effectiveness of the drug against a given bacteria, it does not affect the ability of a drug to penetrate into the brain. Lipid solubility, protein binding, and molecular weight all determine the likelihood of a drug to penetrate the blood–brain barrier and concentrate in the brain.

28.9 A 72-year-old male presents with fever, cough, malaise, and shortness of breath. His chest x-ray shows bilateral infiltrates consistent with pneumonia. Bronchial wash cultures reveal Pseudomonas aeruginosa sensitive to cefepime. Which of the following is the best dosing scheme for cefepime based on the drug's time-dependent bactericidal activity?

A. 1 g every 6 hours given over 30 minutes
B. 2 g every 12 hours given over 3 hours
C. 4 g every 24 hours given over 30 minutes
D. 4 g given as continuous infusion over 24 hours

Correct answer = D. The clinical efficacy of cefepime is based on the percentage of time that the drug concentration remains above the MIC. A continuous infusion would allow for the greatest amount of time above the MIC compared to intermittent (30 minutes) and prolonged infusions (3 to 4 hours).

28.10 Which of the following adverse drug reactions precludes a patient from being rechallenged with that drug in the future?

A. Itching/rash from penicillin
B. Stevens-Johnson syndrome from sulfamethoxazole–trimethoprim
C. Gastrointestinal (GI) upset from clarithromycin
D. *Clostridium difficile* superinfection from moxifloxacin

Correct answer = B. Stevens-Johnson syndrome is a severe idiosyncratic reaction that can be life threatening, and these patients should never be rechallenged with the offending agent. Itching/rash is a commonly reported reaction in patients receiving penicillins but is not life threatening. A patient may be rechallenged if the benefits outweigh the risk (for example, pregnant patient with syphilis) or the patient could be exposed through a desensitization procedure. GI upset is a common side effect of clarithromycin but is not due to an allergic reaction. Moxifloxacin is a broad-spectrum antibiotic that can inhibit the normal flora of the GI tract, increasing the risk for the development of superinfections like *C. difficile*. This is not an allergic reaction, and the patient can be rechallenged; however, the patient might be at risk for developing *C. difficile* infection again.