Athar Batch

Pharmacology

Lecture: 25

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Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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Textbook reference: 355-367

How Did Antibiotics Change The World?

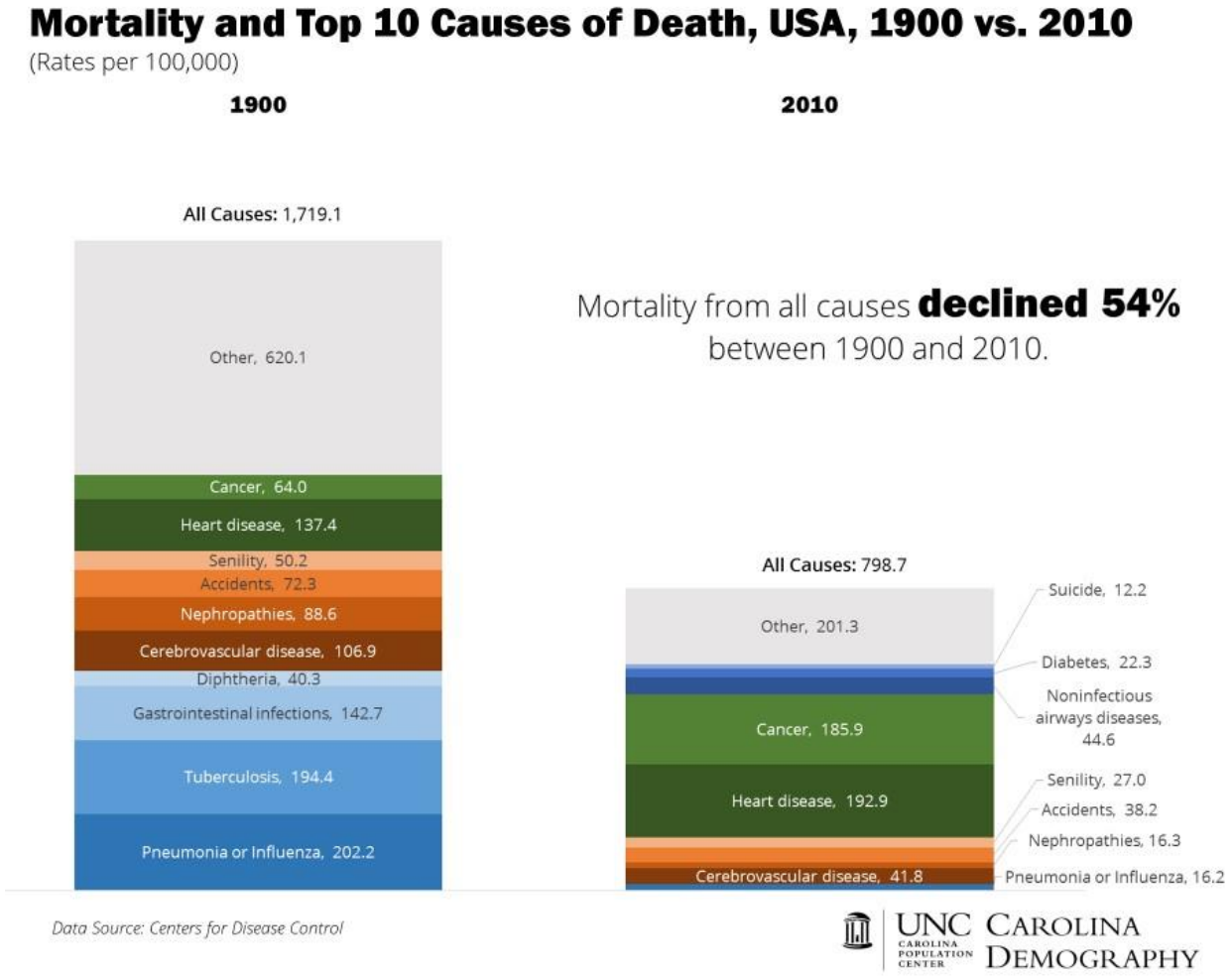
If we go back in time around 150 years ago:

Life expectancy: 47 years to 78 years (Western countries) the reason of that there was lot of disease that we did not have the treatment for e.g. : communicable diseases caused mainly by bacterial infections.

اذا المعدل العام الي كانو يعيشوه الناس كان ل 47 سنه .

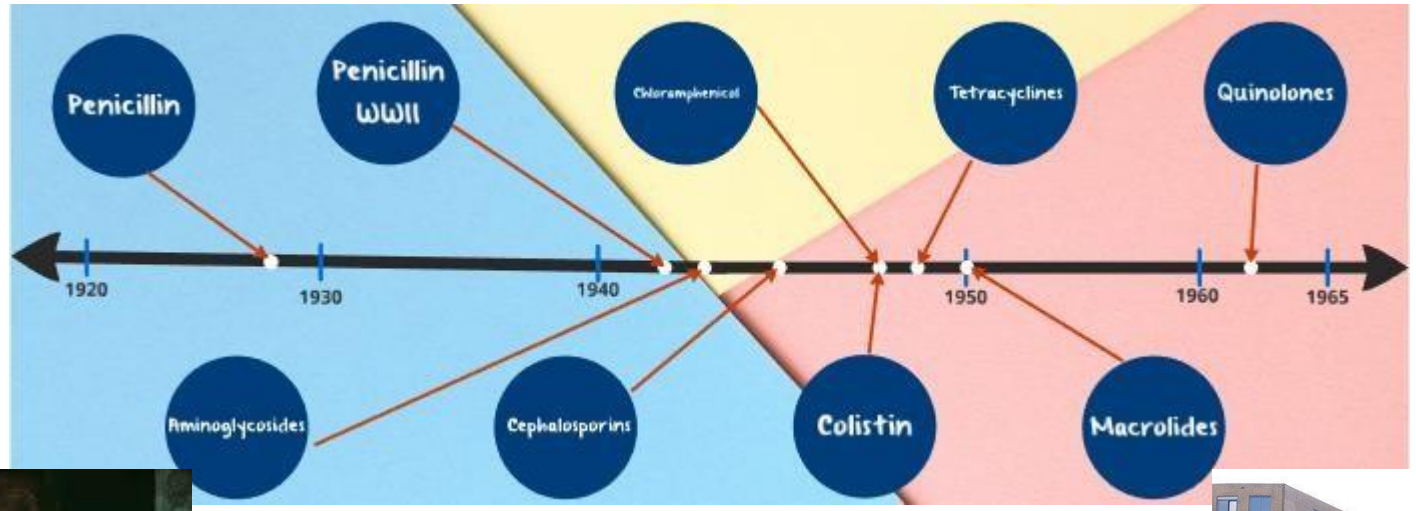
- **Major cause of death**: communicable diseases to non-communicable diseases

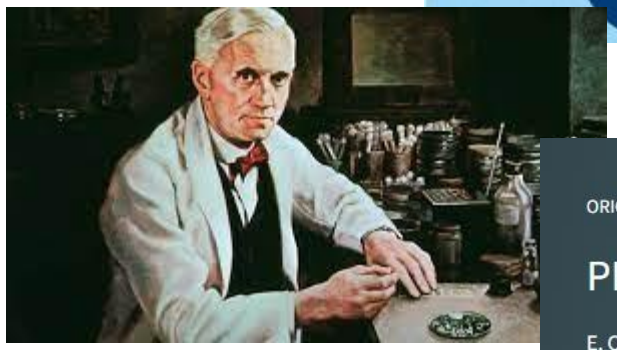
The discovery of antibiotics changed the world and humans life.



- The acquiring of the infection is very easy lot of people suffer and die from these infections.
- Infections was one of the main public health problems 100 years ago.
- Nowadays the main cause of disease has changed from communicable to non-communicable diseases.
- CVS Disease – cancer related disease
- So bacterial infections have dropped in the list from being the first cause of death of humans >>one of the causes is discovery of antimicrobial drugs which happened early in the 20th century → increases life expectancy.
- The first antibiotic is penicillin ... after penicillin there are a lot of classes of antibiotics.
- Antibiotics are most common drugs that is prescribed frequently as the bacterial infections are very common.

The story of penicillin





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PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

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

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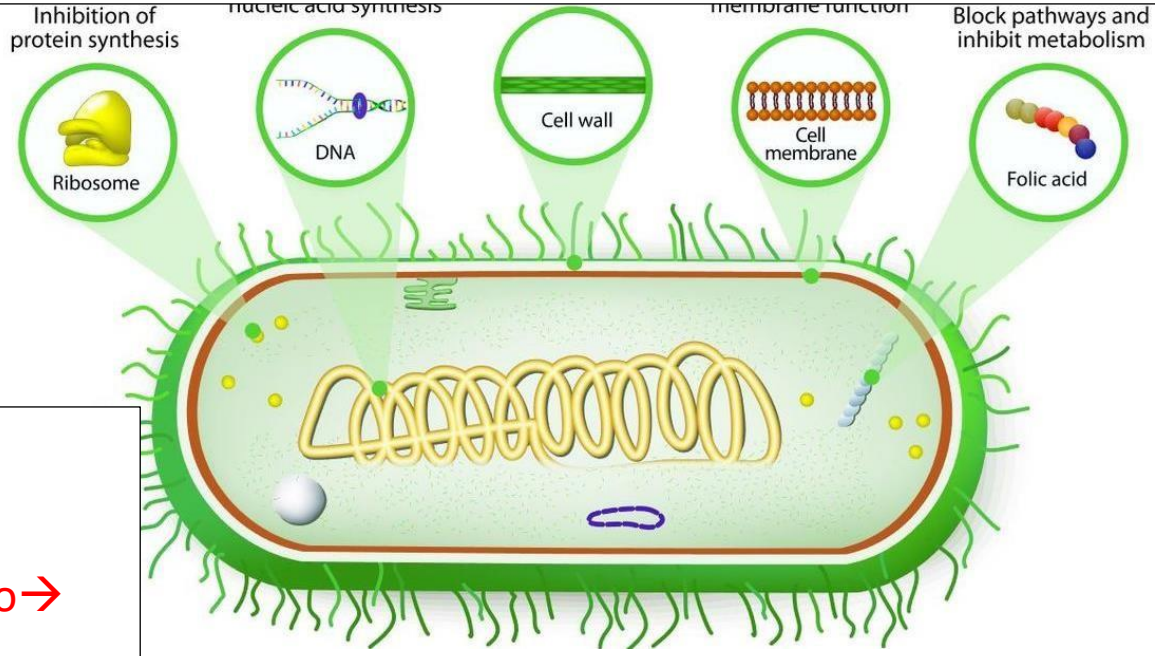
Overview

The main feature of using antimicrobial therapy is concept called selective toxicity

The antimicrobial and anticancer therapy are usually classified as chemotherapy

The word (chemotherapy) describes a class of drugs that have the ability to kill cells whether the cells are bacterial or human cells (cancer)

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



The main difference of these two types of chemotherapy is concept called selective toxicity.

Anticancer drugs targets cancer cells and the normal cells also→ no selective toxicity.

Selection of Antimicrobial Agent

What needs to be known?

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

Susceptibility is a term used when microbe such as bacteria and fungi are **unable to grow in the presence of one or more antimicrobial drugs**.

الصفحة هاي بتحكيلنا عن القواعد الي بدي انتبه عليها لم احدد العلاج لميكرواورغانيزم ..

بداية مهم اعرف شو هو الكائن الي بتعامل معاه سواء كان بكتيريا , فيروس, فطريات الخ..

بحال عرفت شو الكائن الي بتعامل معو بدي ابلش اشوف شو الدوا الي بدي استخدمو للتخلص من الكائن

فبدي اعمل عدة اختبارات بأستخدام ادوية واشوف الكائن لمين كان حساس اكثر شي وتوقف عن النمو وتخلصنا منو

معرفة المكان الي بصير فيه العدوى هون ايضا عامل مساعد.

The treatment of the lung different from the treatment of the UTIs, different from the treatment of meningitis

Pts factors:

Let's say

-Same infection (pneumonia) by the same organism (streptococcus pneumonia) in patient 70-year-old with multiple disease (kidney problems – heart disease – diabetes – hypertension etc....

This case is different when you treat a 10-year-old patient who have the same clinical condition despite the fact that the same organism cause the same disease.

- We said that antimicrobial drugs have selective toxicity >> ***but*** **this does not mean that antibiotics are completely safe**
- بالنهاية هاي المضادات الحيوية هي عبارة عن ادوية بنتعامل معها الها فوائدها والها نتائج سلبية نوعا ما تحت ظروف معينة
- For example, let's say that you want to treat patient for lung infection and at the same time the pt. have kidney disease >> you can not use antibiotic that might have nephrotoxicity.

بالنسبة للنقطة الاخيرة من العوامل لم بدنا نختار دواء للمريض ومثلا يكون عندي خيارين وهدول الخيارين متساويين من الناحية العلاجية والهم نفس التأثير ف بالتالي انا لم بدي اختار الدواء بدي اختارلو الدواء المناسب من الناحية العلاجية والناحية المادية ايضا للمريض ف بختارلو الدواء الرخيص او الي سعرو مناسب .

Identification of The Infecting Organism

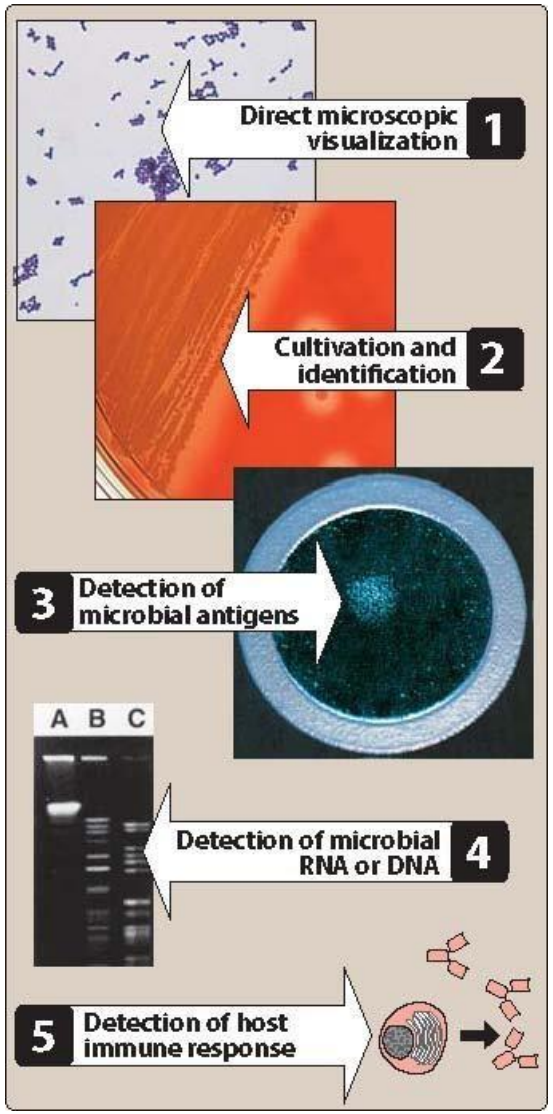
Gram stain:

- presence of microorganisms in sterile body fluids.
- morphologic features
- **Culture**: (not immediate tests) they take from 48 – 72 hours depending on microorganism
- diagnosis
- antibiotic susceptibility (the ability of that antibiotic to work on bacteria in culture)
- **Microbial antigens (GO HAND ON HAND WITH CELL CULTURE)**
- DNA, RNA, etc

Ex: PCR TEST

- **Host immune marker**

WHEN bacteria enter our body → immune cells will release antibodies against the bacteria ...



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

The simplest test and most straight forward test is gram staining → all what you have to do is taking a sample from the suspected site of infection and stain it with gram stain .

Keep in mind that many of body compartment should be free from bacteria (sterile) for example blood , urine , pericardium fluid , plural fluid and CSF ETC.

اذا كانت هاي الاماكن المذكورة فيها بكتيريا معناها اكيد المريض مصاب بعدوى ما

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

And we can determine the morphological features of the organism (cocci – bacilli – rods etc.)

If you want to exactly determent the organism to initiate proper antimicrobial therapy you must do cell culture

The bacterial culture is gold standard test to diagnose bacterial infections.

In the sever cases or critical cases first we take a swap from the pt. for culture and we start giving the pt. antibiotic before the result of the culture→ طبعا انا باخد العينة من المريض قبل ما ابلش العلاج يعني قبل ما اعطية اي مضاد حيوي لازم اكون قبل هيك اخذت العينه وبعدين مباشرة ببلش علاج المريض لانو الحالة حرجة وممكن تكون حياة المريض بخطر

Empiric Therapy prior to Identification of The Organism → empiric therapy is to start the treatment without knowing the actual cause of infection before you have the result of bacterial cell culture .

- Greek *empeiria* = experience.

❑Timing

-Immediate treatment: e.g., critically-ill, neutropenic, meningitis. الحالات الحرجة او الطارئة مثل المذكورة بتتطلب سرعة االبدء بالعلاج حتى لو نتائج الكلتشر ما طلعت او بدها وقت لتطلع

❑Selecting a drug

-Site of infection example in case of meningitis we know the site of infection is meninges.

-Clinical picture

-Broad-spectrum therapy

Pharyngitis is common infection in all ages and also is self-limited meaning thar it even do not require antibiotics >> but not all infections like this infection … pneumonia is life threatening infection or meningitis …these infections may associated with severe complications and may lead to death ..so in these cases we must to initiate antimicrobial therapy as soon as possible .

Even with out having the results of culture.

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.

Determining Antimicrobial Susceptibility of Infective Organisms

Predictable vs unpredictable susceptibility

THE susceptibility of a micro-organism to a drug can be experimentally determined

MIC

MBC

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

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

MIC: lowest concentration that can inhibit growth of bacteria within 24 hours of adding antibiotic to bacteria .

Steps:

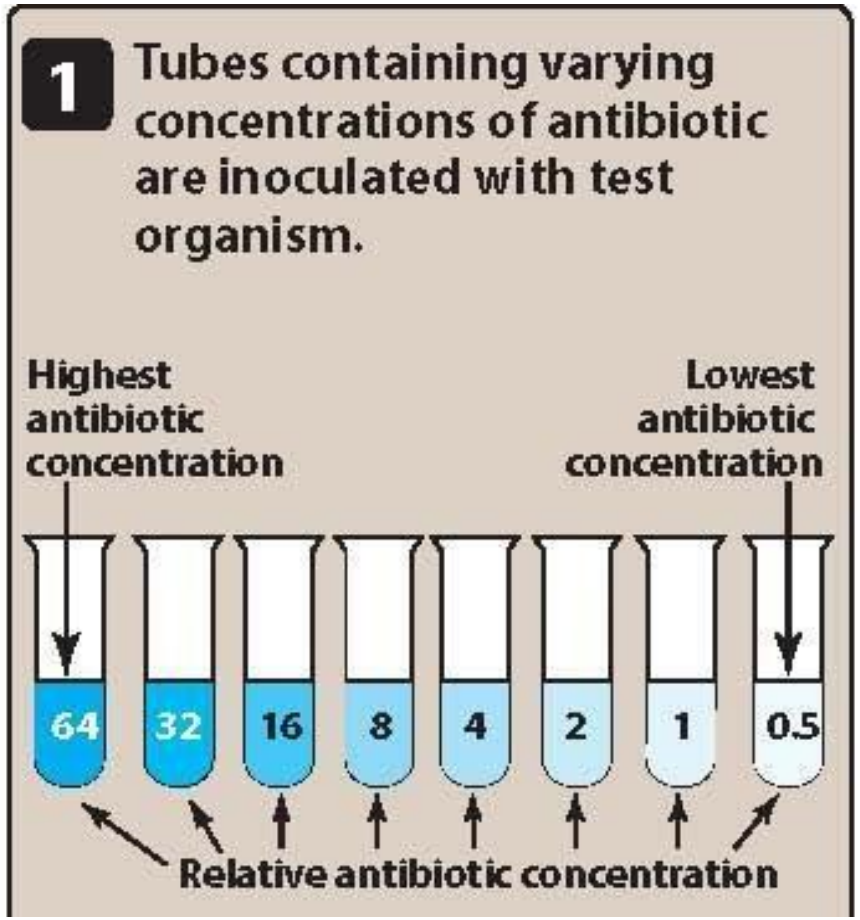
1- We take sample from the pt. whether blood or urine sample
2- Culture the sample in test tubes

In the tubes there is certain amounts of culture media to allow bacteria to grow

The we put the blood or urine sample in these tubes

At the same time solutions in the test tubes will have increase concentrations of antibiotic of choice

Then we will let the bacteria to grow for 24 hours



Determination of minimum inhibitory concentration (MIC) and

minimum bactericidal concentration (MBC) of an antibiotic.

The results after 24 hours:

There is a bacterial growth in 1 and 2 tubes

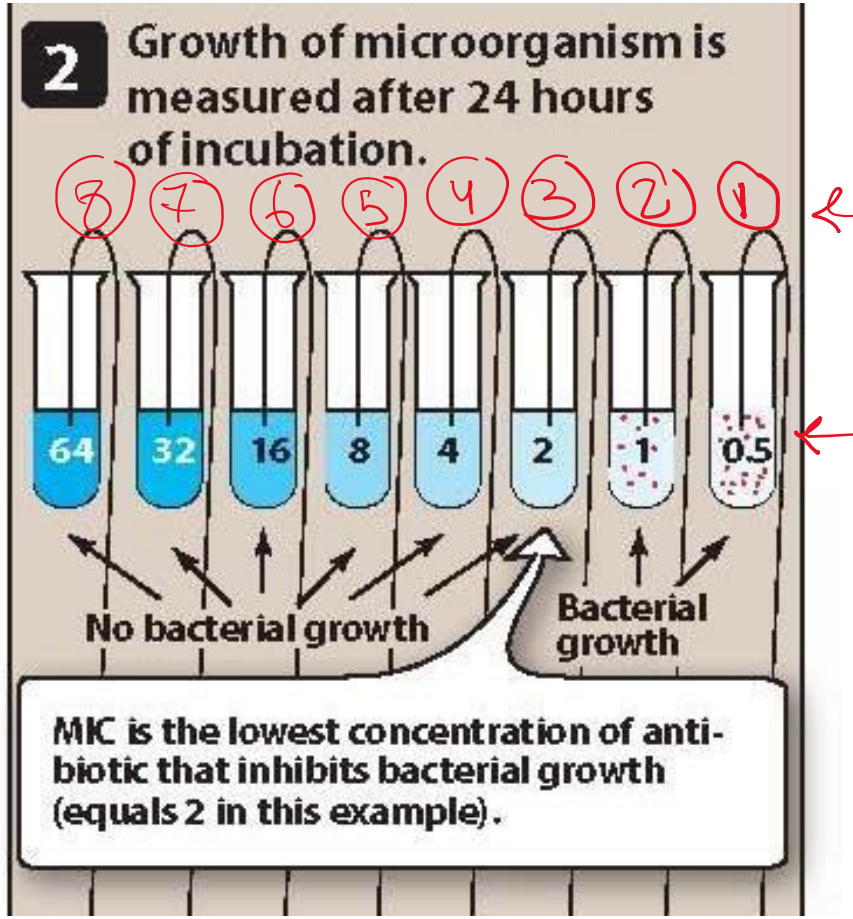
There is no bacterial growth in tube number 3 when the dose of antibiotic was double the dose in tube 1 and 2

So the doses from 2 to 64 were able to inhibit bacterial growth.

So what is the MIC or what is the lowest concentration of antibiotic that inhibit bacterial growth?

MIC = 2 DOSES OF ANTIBIOTIC

BUT THIS does not mean that this dose will ***kill*** the bacteria



Number of the Tube

concentrations of Antibiotic.

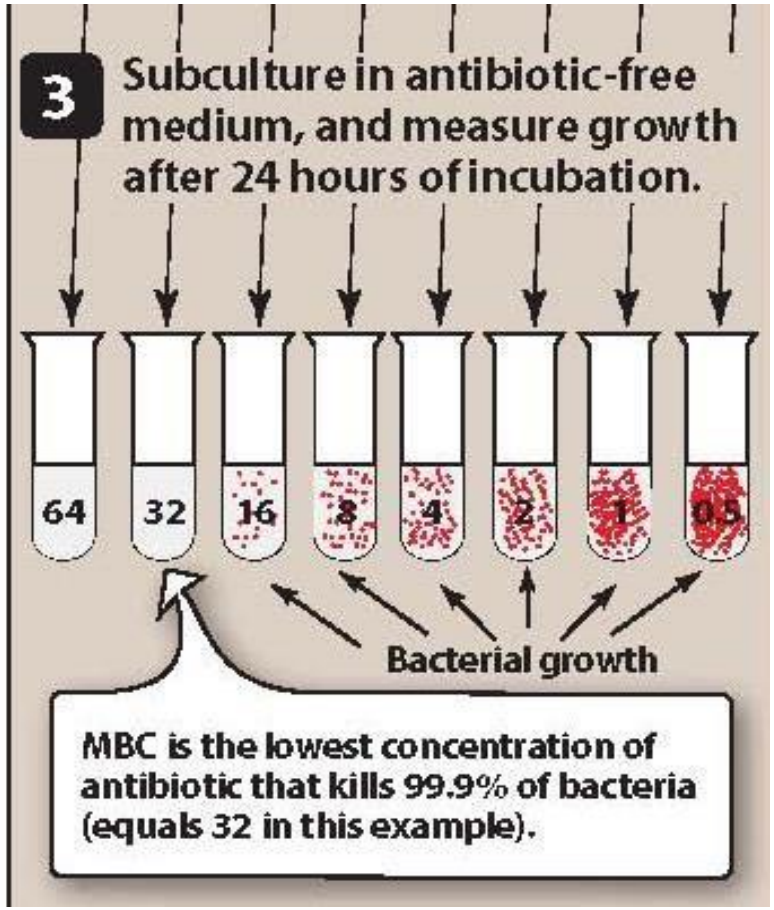
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

To determine the MBC → we will take subculture and allow it to grow in the absent of the antibiotic.

By this step we can determine which concentration kills the bacteria not only inhibit it growth.

The MIC WAS 2 in tube number three but when we do the subculture without the antibiotic, we can see that bacteria start to grow again that mean that MIC do not kill bacteria it only inhibits it growth

The MBC IS 32 in tube 7 >> no bacterial growth >> bacteria killed by this concentration of antibiotic.



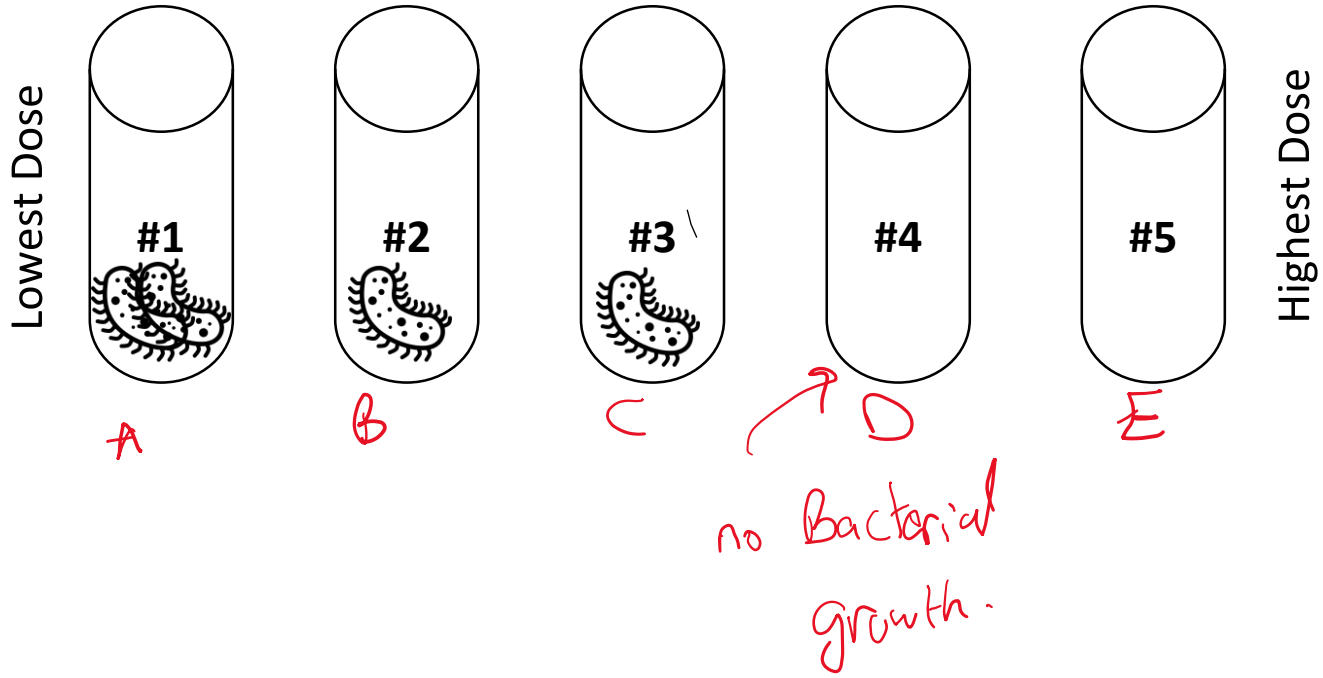
Usually, MBC > MIC

Means that we need high doses of antibiotic to kill bacteria than doses that inhibit the growth of bacteria.

- Drug that has low MBC means that we need small dose concentration to kill bacteria
- So drug with small MBC is more effective in killing bacteria than drug with high MBC

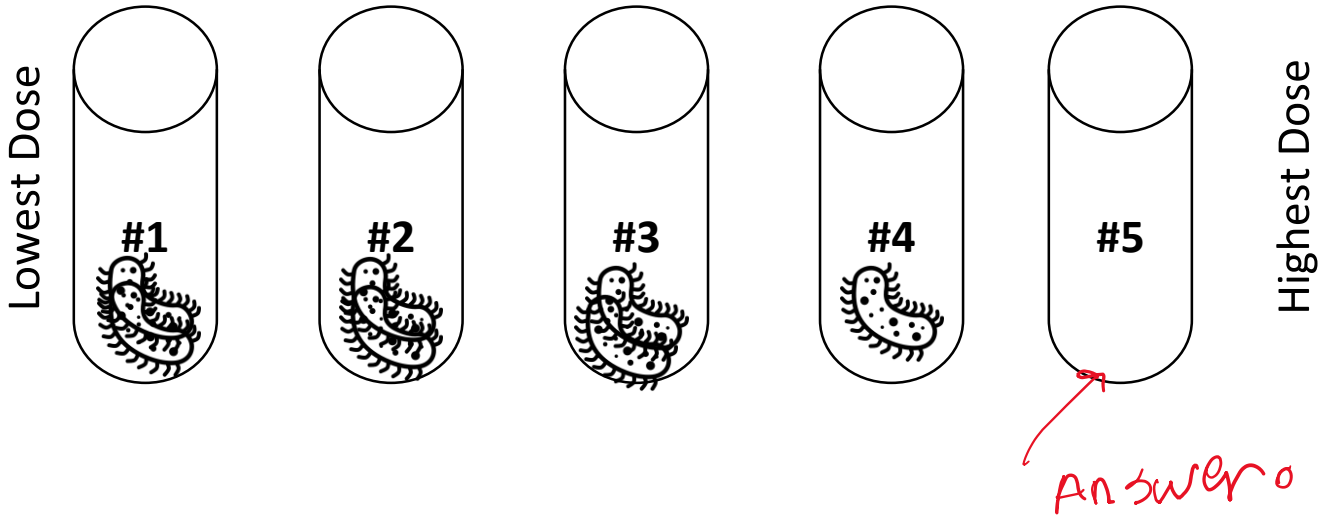
Practice Question

- 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= D



Practice Question

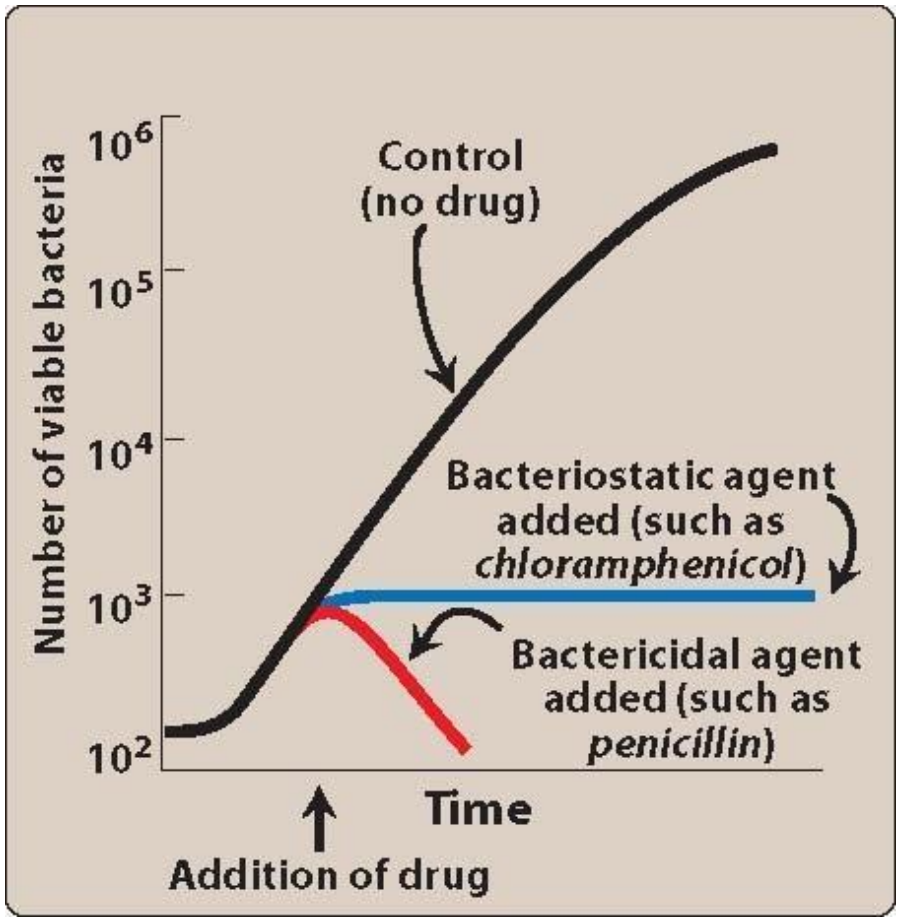
- Subcultures of the last 5 tubes gave the following results. Which tube has MBC?



Bacteriostatic vs Bactericidal

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

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



Bacteriostatic vs Bactericidal

Actually, most cell wall inhibitors → bactericidal effect

Protein synthesis inhibitors→ bacteriostatic effect

Keep in mind that this classification is important .. why??

1- For categorization of antibiotics (bacteriostatic or bactericidal)

But…

- ❑Classification is too simplistic (does not reflect what actually happens in the patient)
- ❑Microorganism-dependent it means that an antibiotic can be bacteriostatic on bacteria type a but can be bactericidal on bacteria type b →so I cannot say if the antibiotic is a bacteriostatic or bactericidal in general .
- ❑Similar efficacy for clinical infections

in the lab you can determine the antibiotic if its bactericidal or bacteriostatic but in the patient treating a bacterial infection with the help of immune system so if I use bacteriostatic antibiotic I'm helping the immune system and the same by using bactericidal .

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. …….

Patient Factors

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.

2. Renal dysfunction

3. Hepatic dysfunction

4. Poor perfusion

Patient Factors

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	

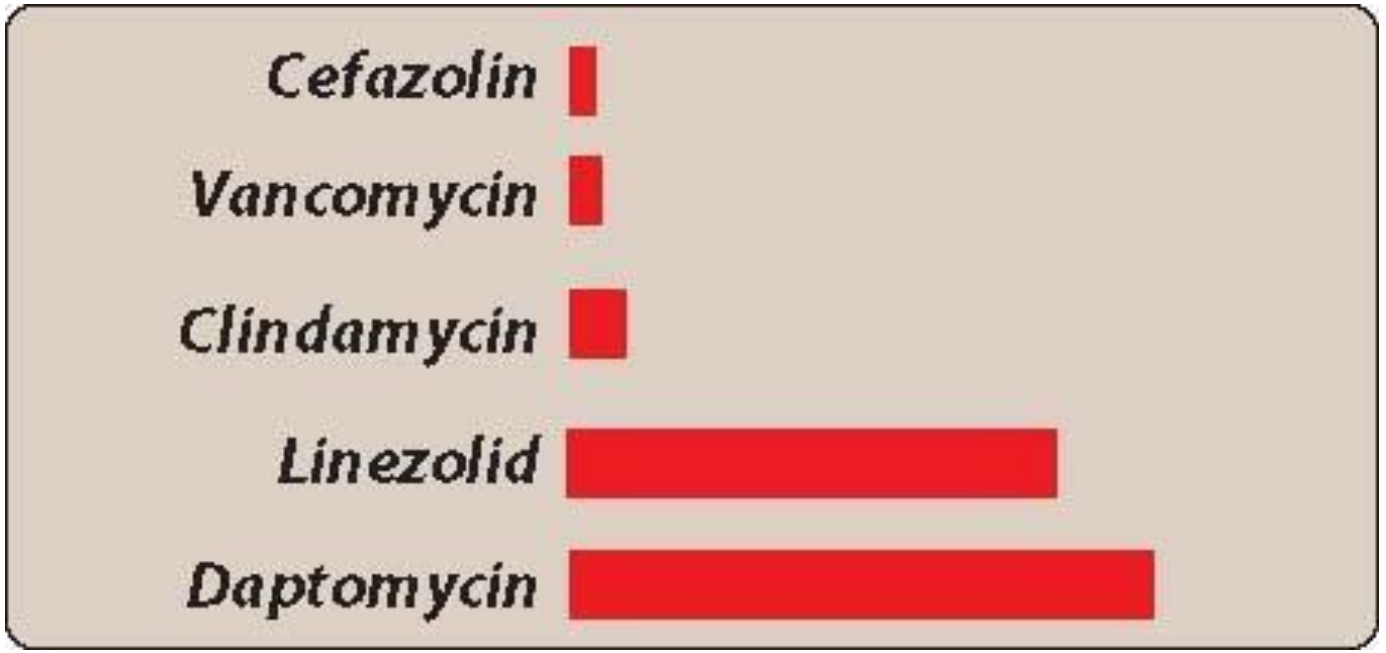
5. Age

6. Pregnancy

7. Risk factors for multidrug-resistant organisms:

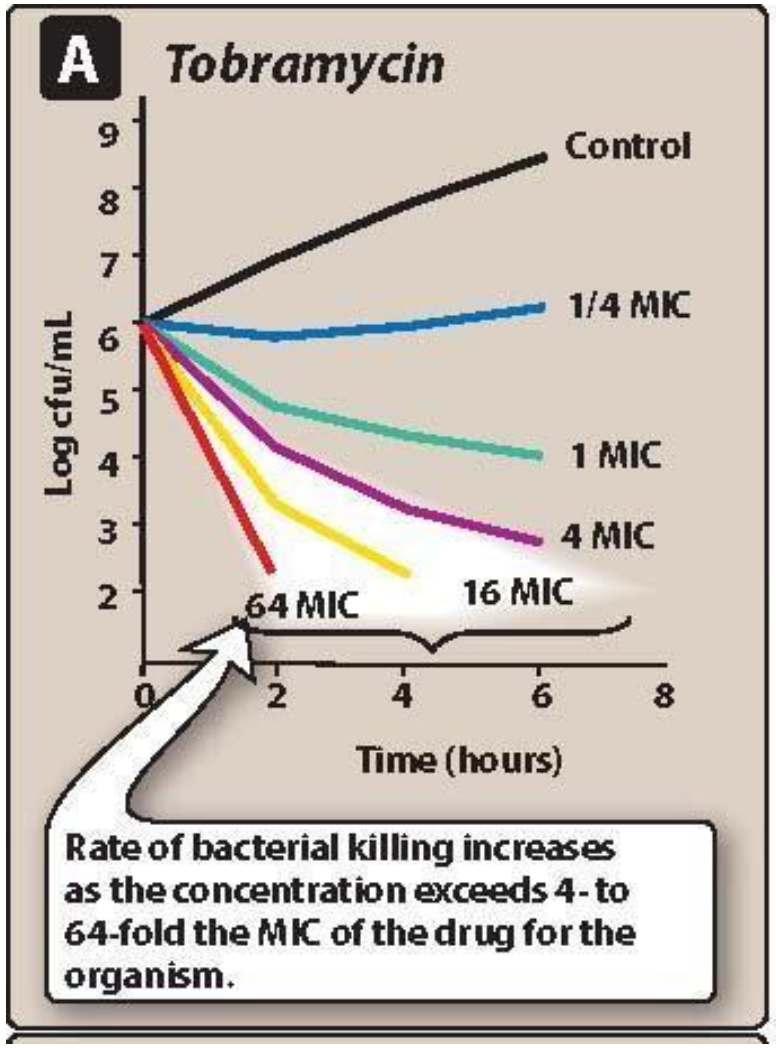
- prior antimicrobial therapy in the preceding 90 days
- hospitalization for greater than 2 days within the preceding 90 days
- current hospitalization exceeding 5 days
- high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms)
- immunosuppressive diseases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

Cost of Therapy: Is It Important?



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

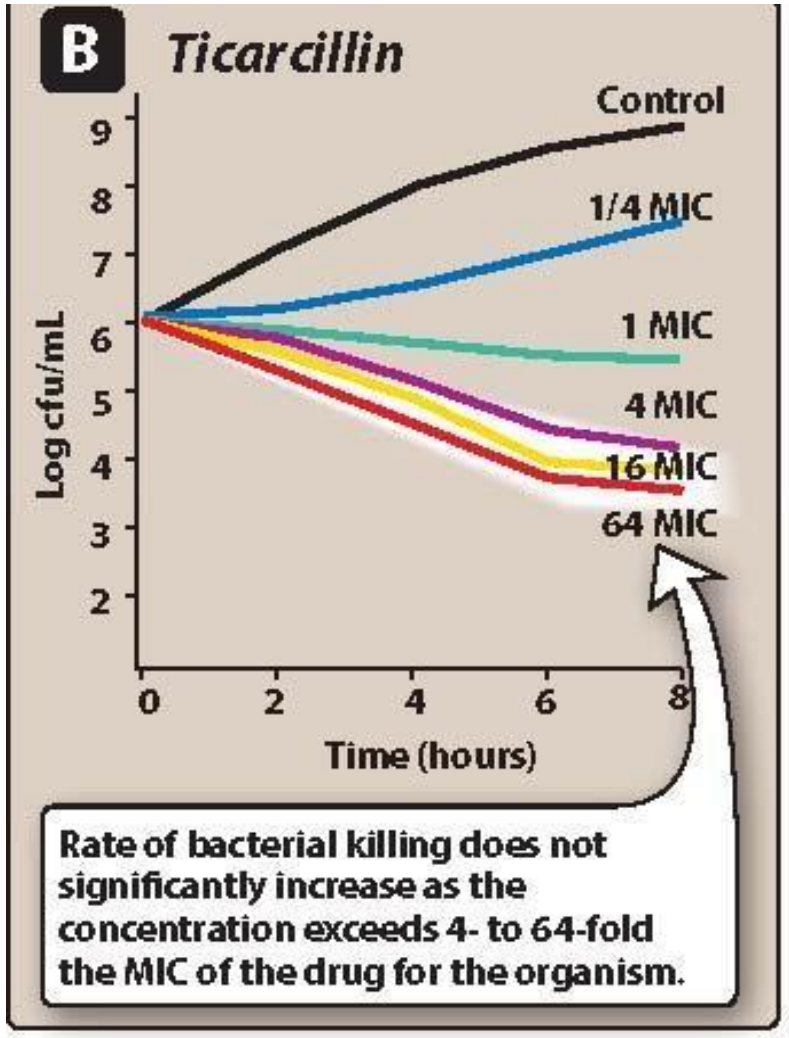
Determinants Of Rational Dosing



A. Concentration-dependent killing

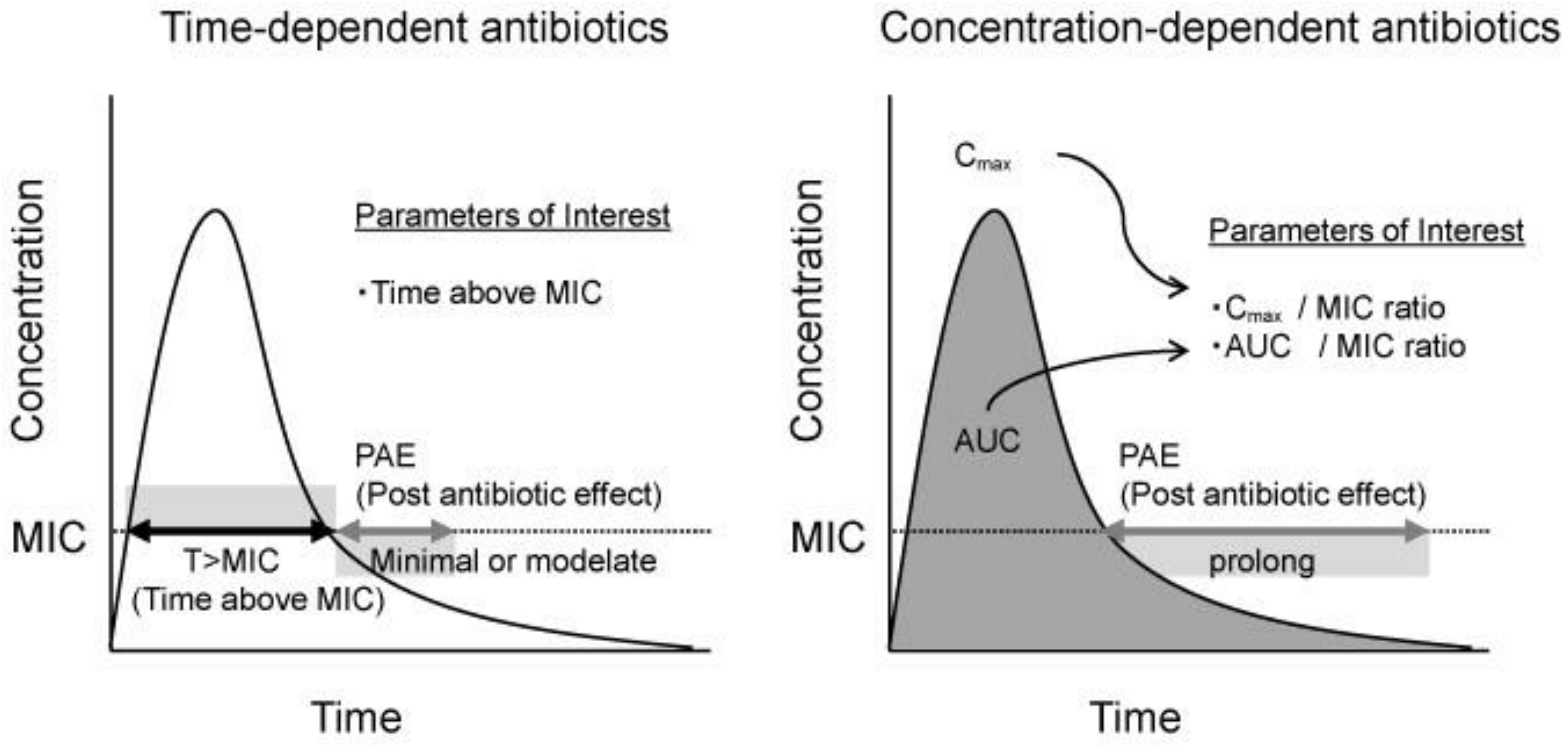
Determinants Of Rational Dosing

B. Time-dependent (concentrationindependent) killing



Determinants Of Rational Dosing

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

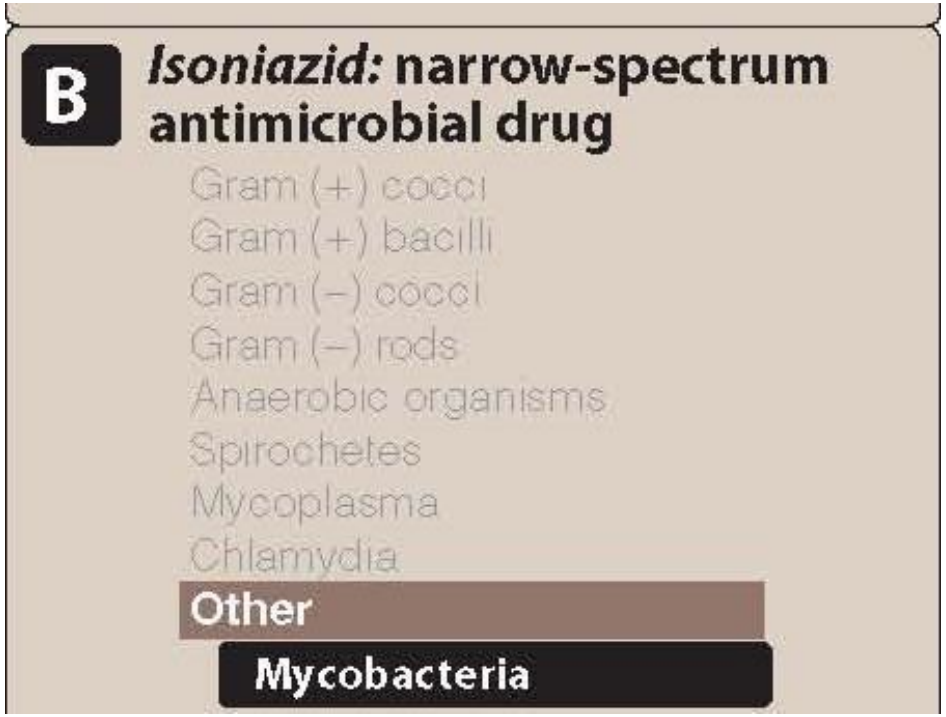


Chemotherapeutic Spectra

Chemotherapeutic Spectra

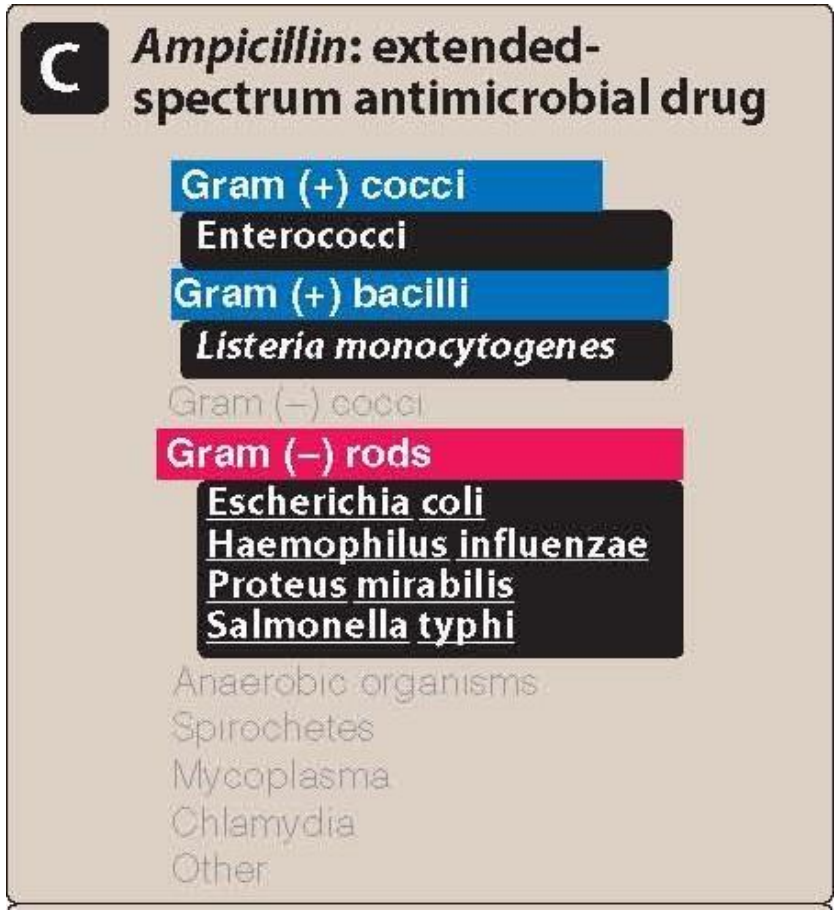
- **Narrow-spectrum antibiotics:**

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



Chemotherapeutic Spectra

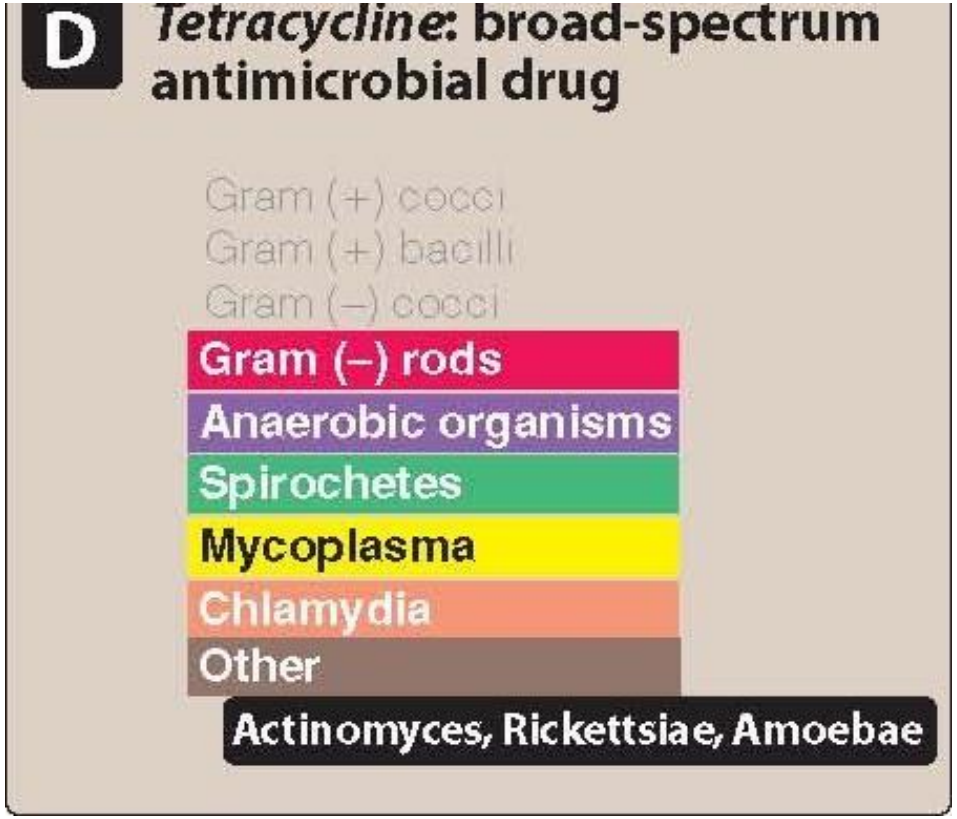
- **Extended-spectrum antibiotics:** antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria



Chemotherapeutic Spectra

- **Broad-spectrum antibiotics:**

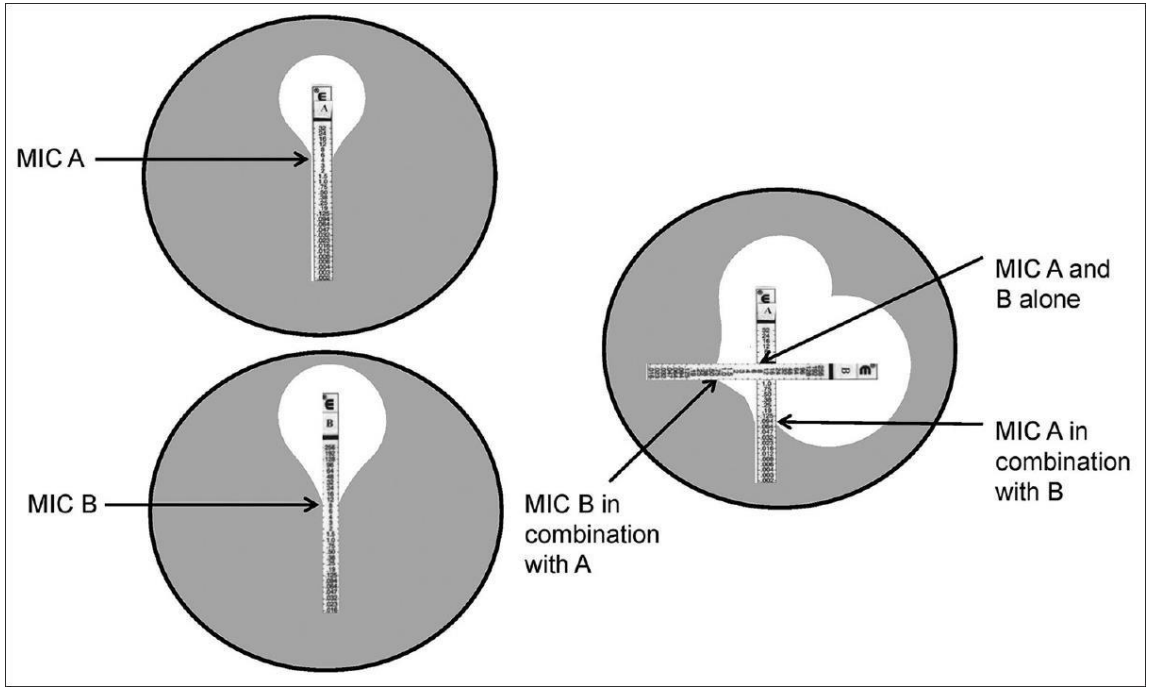
antibiotic that acts on both grampositive and gram-negative bacteria



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

Prophylactic Use Of Antibiotics

"Prevention not treatment"

1

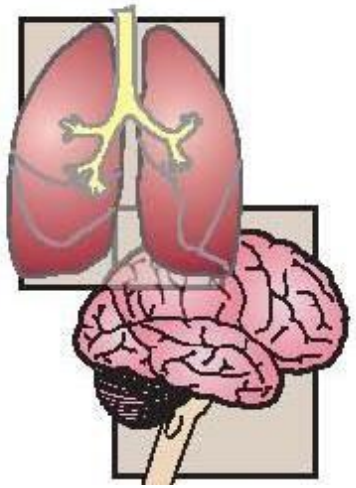
Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

2

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

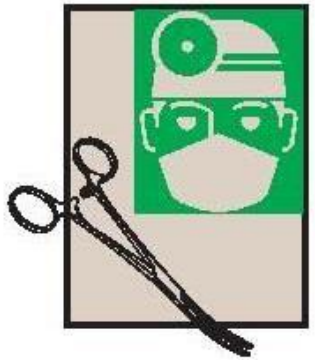
3

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



4

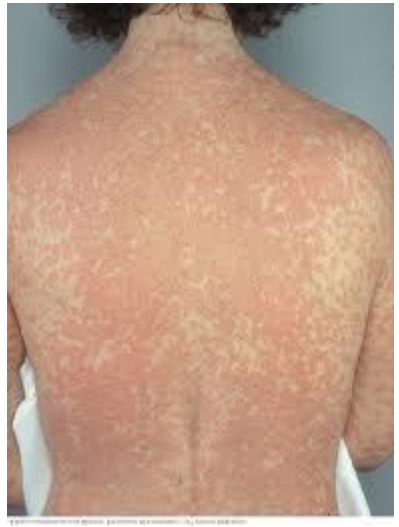
Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



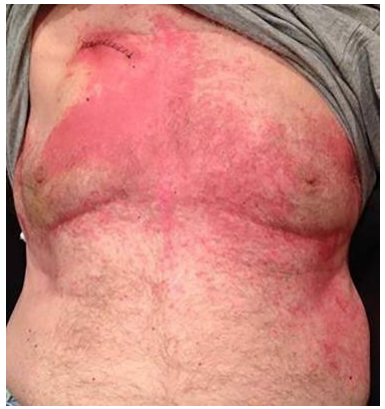
Complications Of Antibiotic Therapy

A. Hypersensitivity

-ranges from mild skin rash to life-threatening anaphylaxis



syndromeSteven-Johnson syndrome



Drug: vancomycin

Red man

Drug: penicillins, sulfa drugs

Urticaria

Drug: penicillin

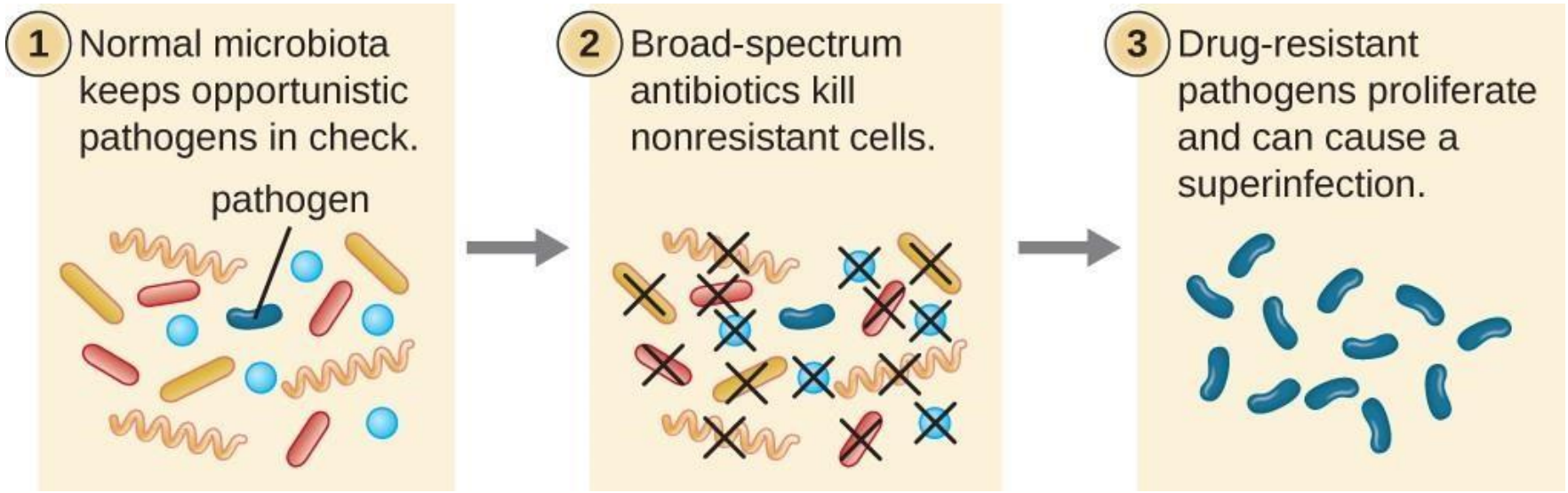
Complications Of Antibiotic Therapy

B. Direct Toxicity

C.

Superinfections:

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



Sites Of Antimicrobial Actions