



Principles of Antimicrobial Therapy

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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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

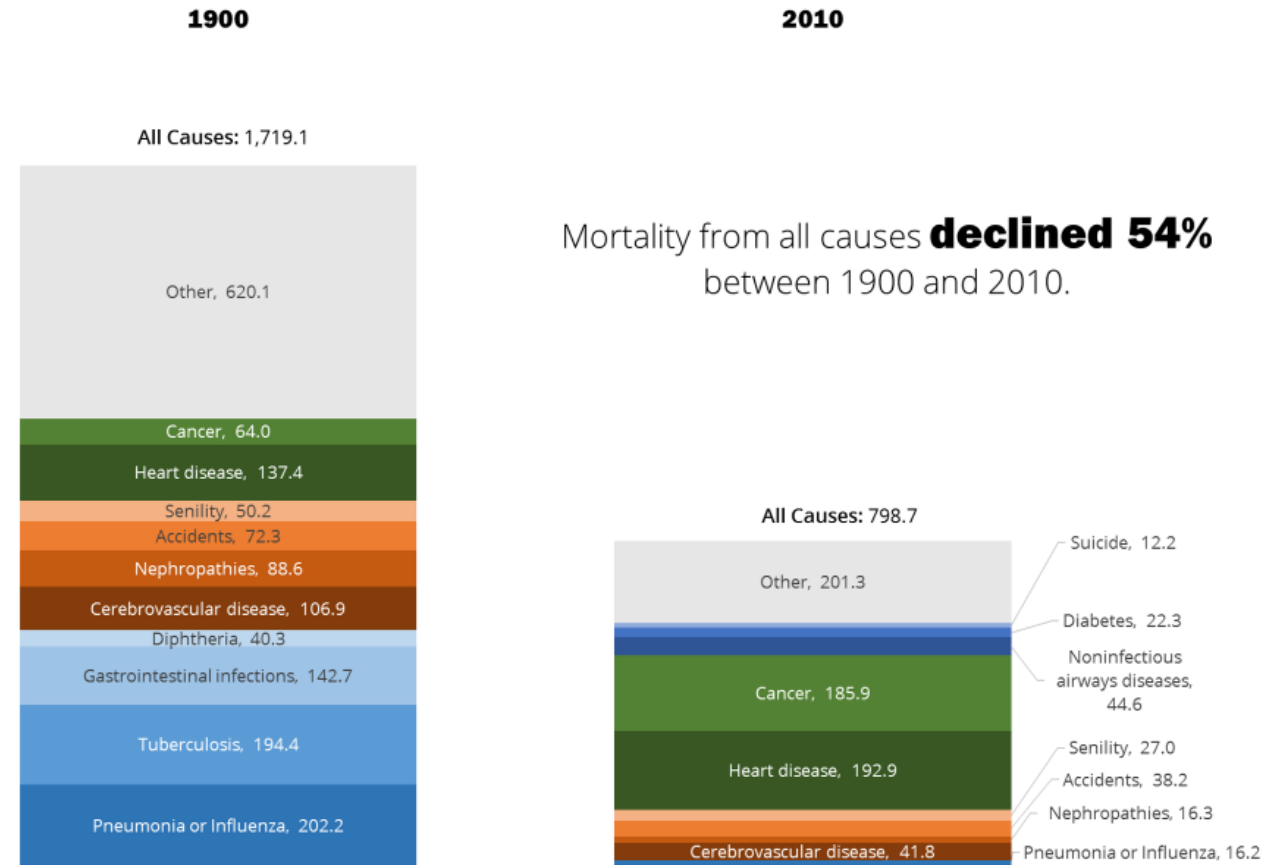


How Did Antibiotics Change The World?

- **Life expectancy:** 47 years to 78 years (Western countries)
- **Major cause of death:** communicable diseases to non-communicable diseases

Mortality and Top 10 Causes of Death, USA, 1900 vs. 2010

(Rates per 100,000)

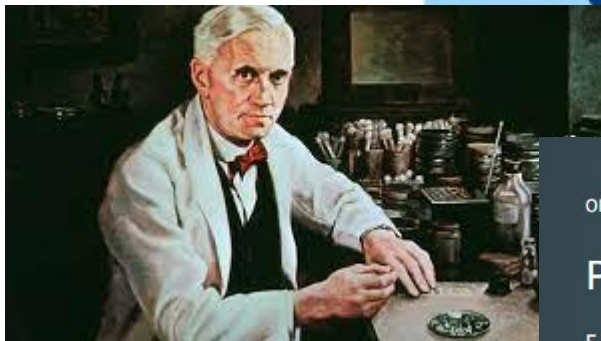
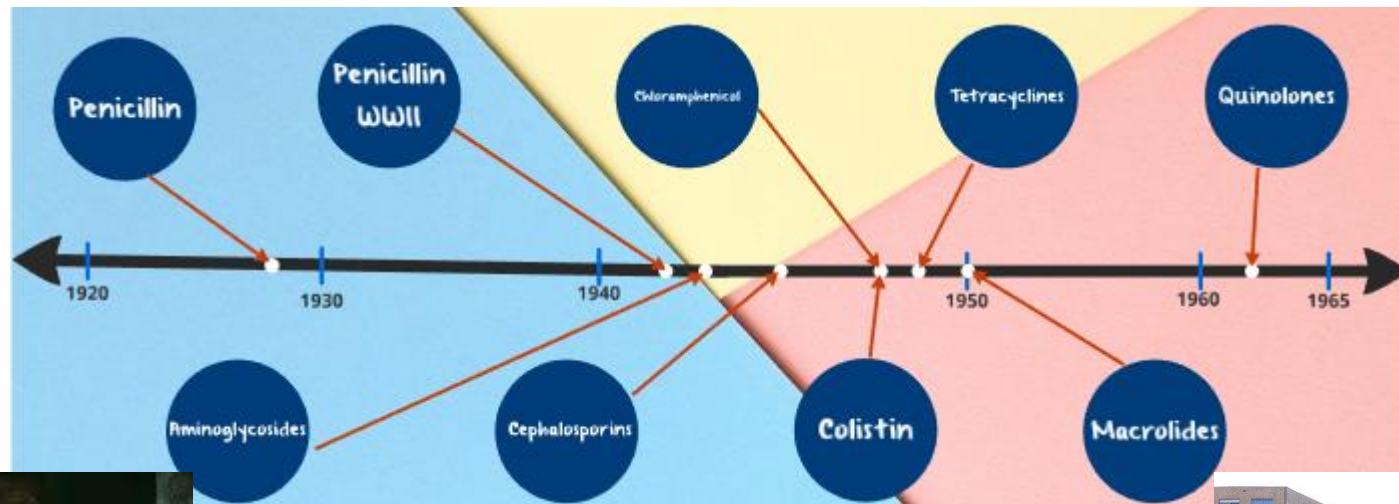


Mortality from all causes **declined 54%** between 1900 and 2010.

Data Source: Centers for Disease Control



The Story of Penicillin



ORIGINAL ARTICLES | VOLUME 236, ISSUE 6104, P226-228, AUGUST 24, 1940

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](#)

Published: August 24, 1940 • DOI: [https://doi.org/10.1016/S0140-6736\(01\)08728-1](https://doi.org/10.1016/S0140-6736(01)08728-1)



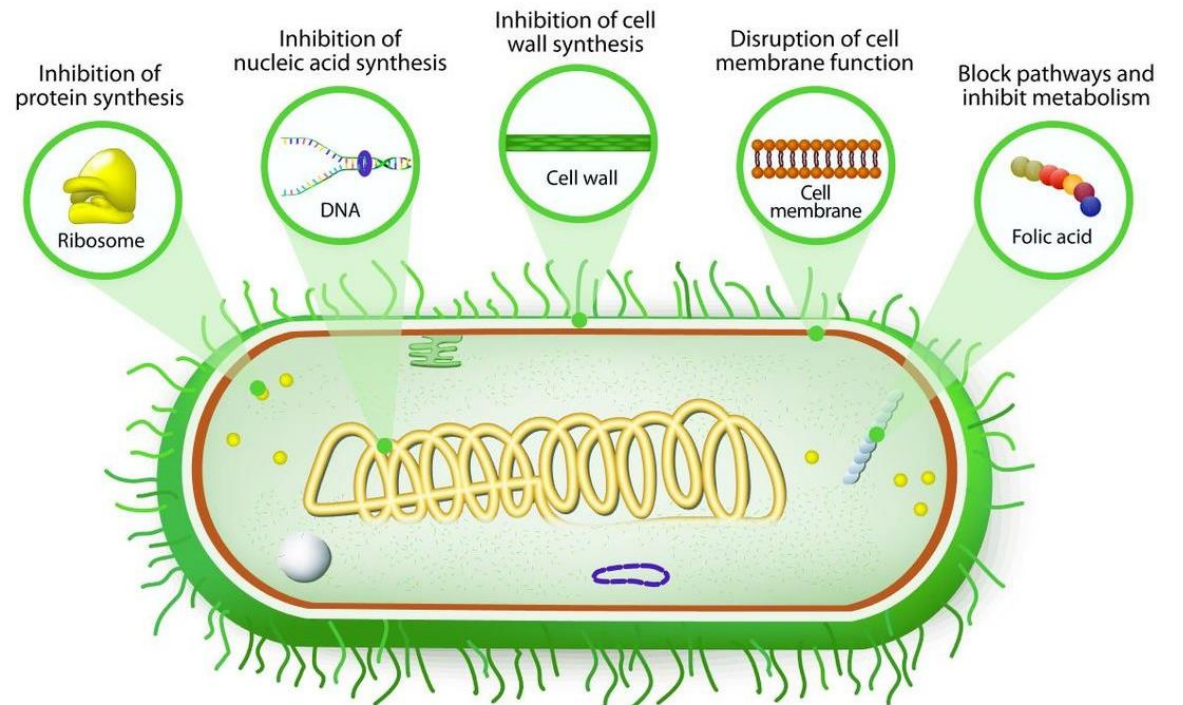


Overview

Selective Toxicity:

“The ability of an agent to injure or kill an invading microorganism without harming host cells”

Is it absolute?





Selection of Antimicrobial Agent

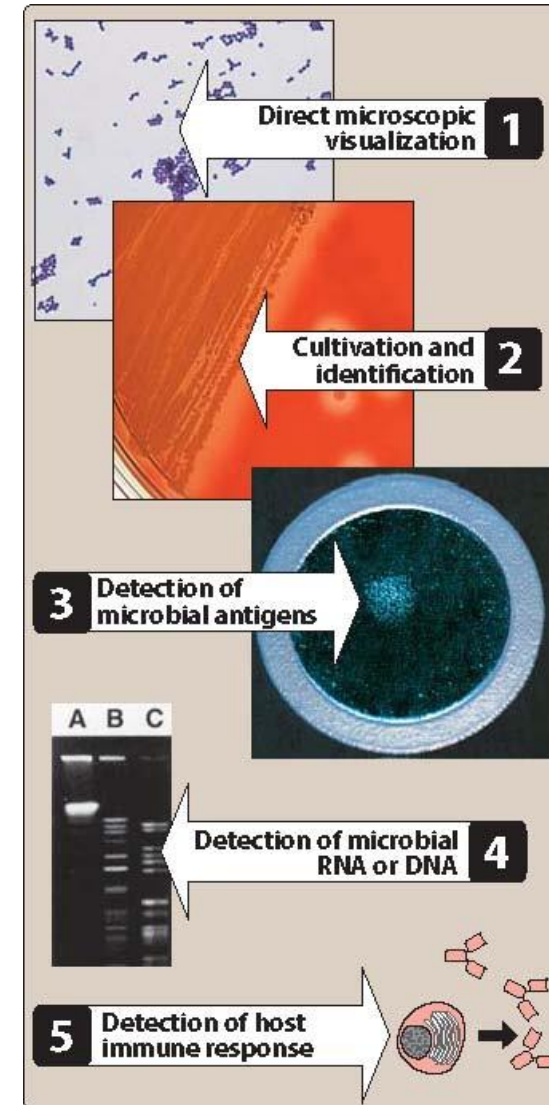
What needs to be known?

- 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



Identification of The Infecting Organism

- **Gram stain:**
 - presence of microorganisms in sterile body fluids.
 - morphologic features
- **Culture:**
 - diagnosis
 - antibiotic susceptibility
- **Microbial antigens**
 - DNA, RNA, etc
- **Host immune markers**





Empiric Therapy prior to Identification of The Organism

- Greek *empeiria* = experience.

□ Timing

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

□ Selecting a drug

- Site of infection
- Clinical picture
- Broad-spectrum therapy

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

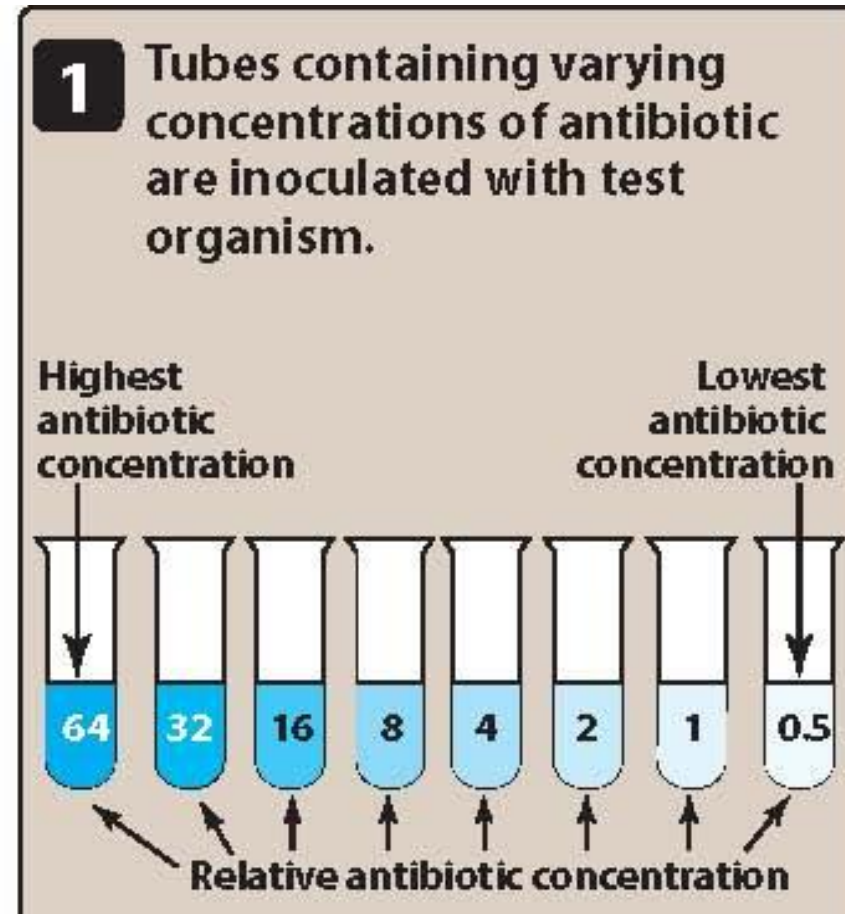
- Predictable vs unpredictable susceptibility
- The susceptibility of a microorganism to a drug can be experimentally determined

MIC

MBC

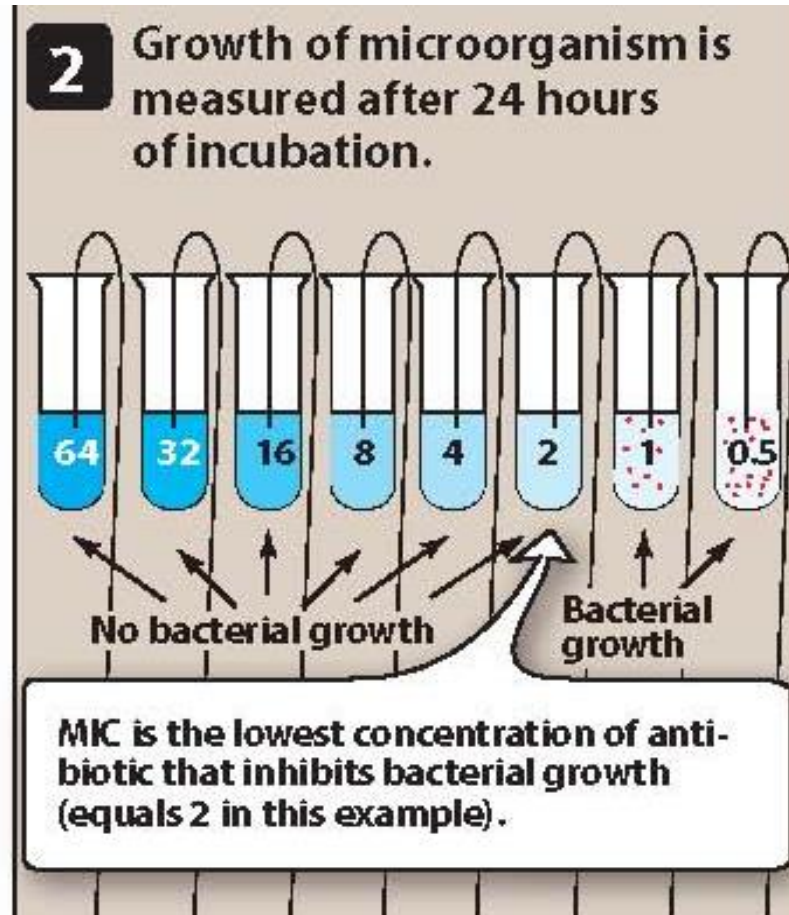


Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.



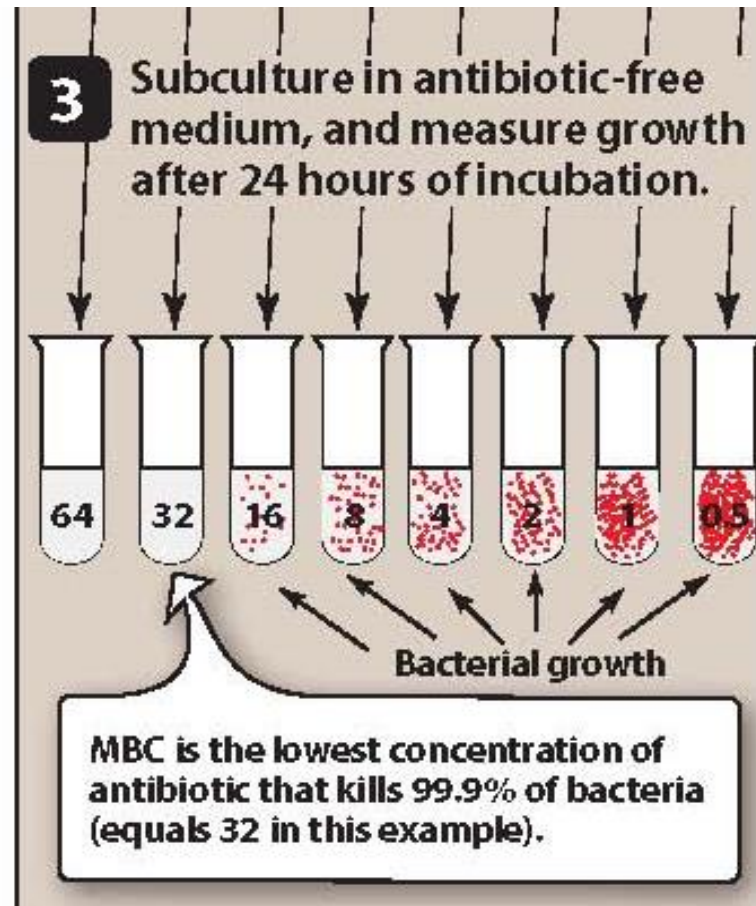


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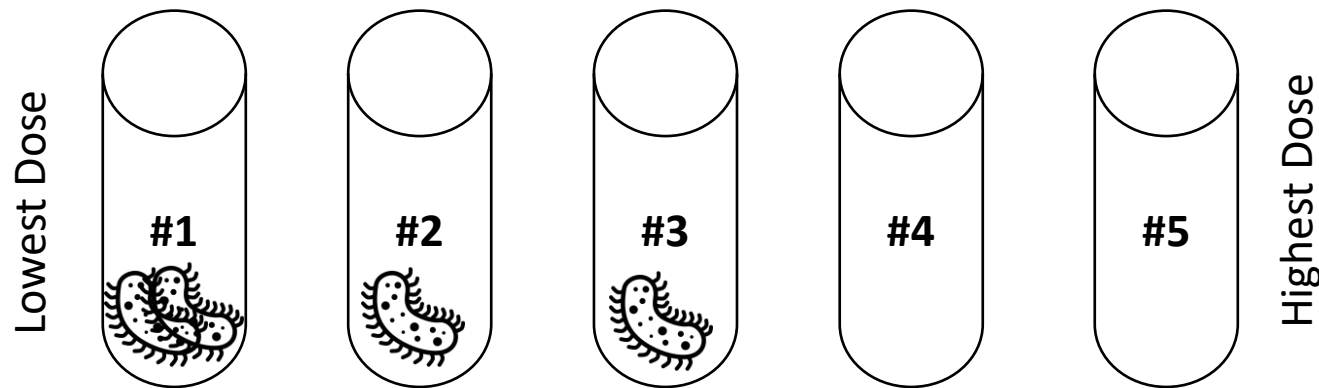
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Practice Question

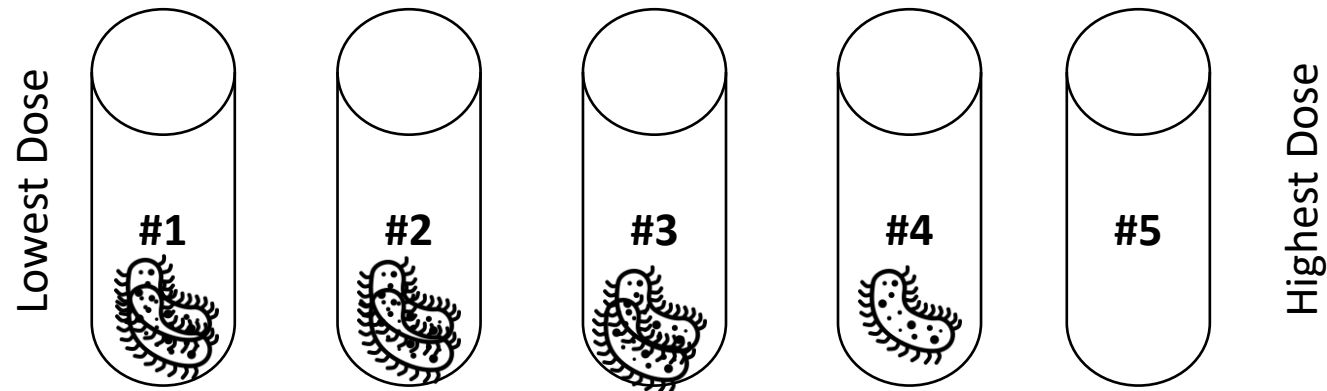
- You have 5 tubes and want to do 5 dilutions of antibiotic X on the growth of E.coli. Tubes 4-5 do not have growth, but tubes 1-3 have visible growth, the tube with the MIC would be?





Practice Question

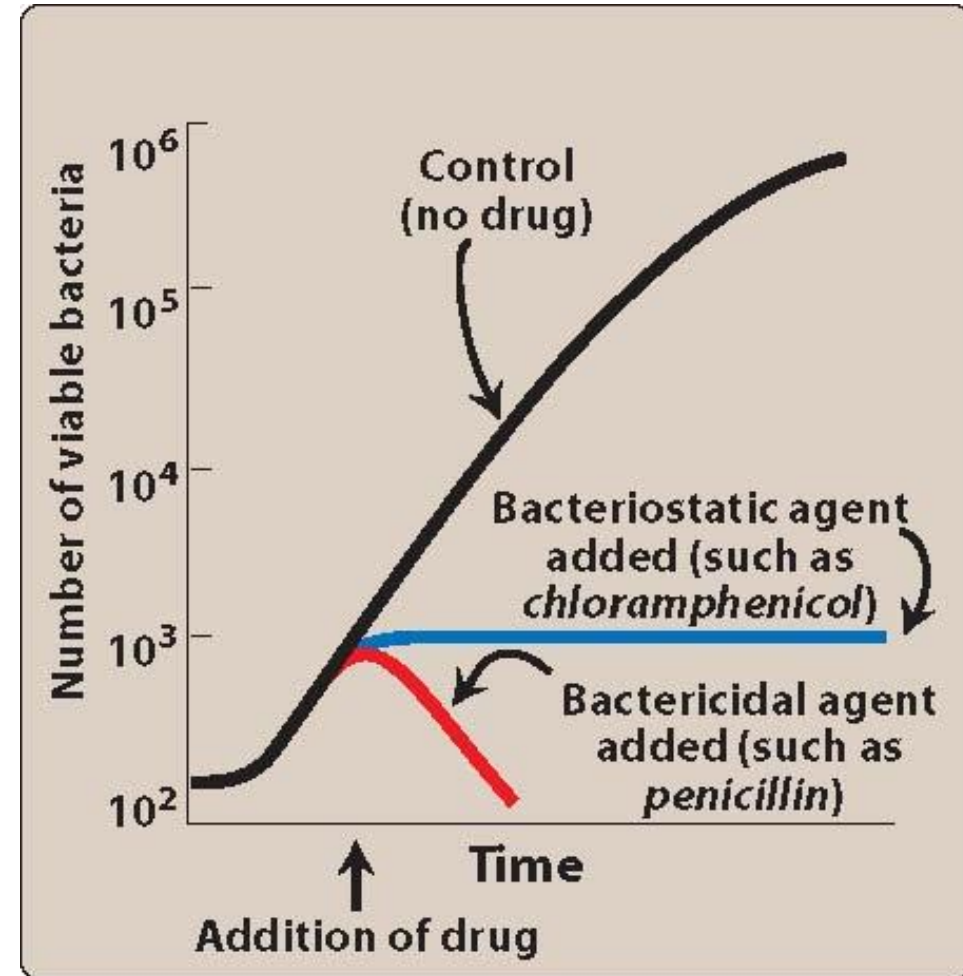
- Subcultures of the last 5 tubes gave the following results. Which tube has MBC?





Bacteriostatic vs Bactericidal

- ❑ **Bacteriostatic:** arrests the growth/replication of a microorganism
- ❑ **Bactericidal:** kills bacteria (kill $\geq 99.9\%$)





Bacteriostatic vs Bactericidal

But...

- Classification is too simplistic
- Microorganism-dependent
- Similar efficacy for clinical infections



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

5. Age

6. Pregnancy

7. Risk factors for multidrug-resistant organisms:

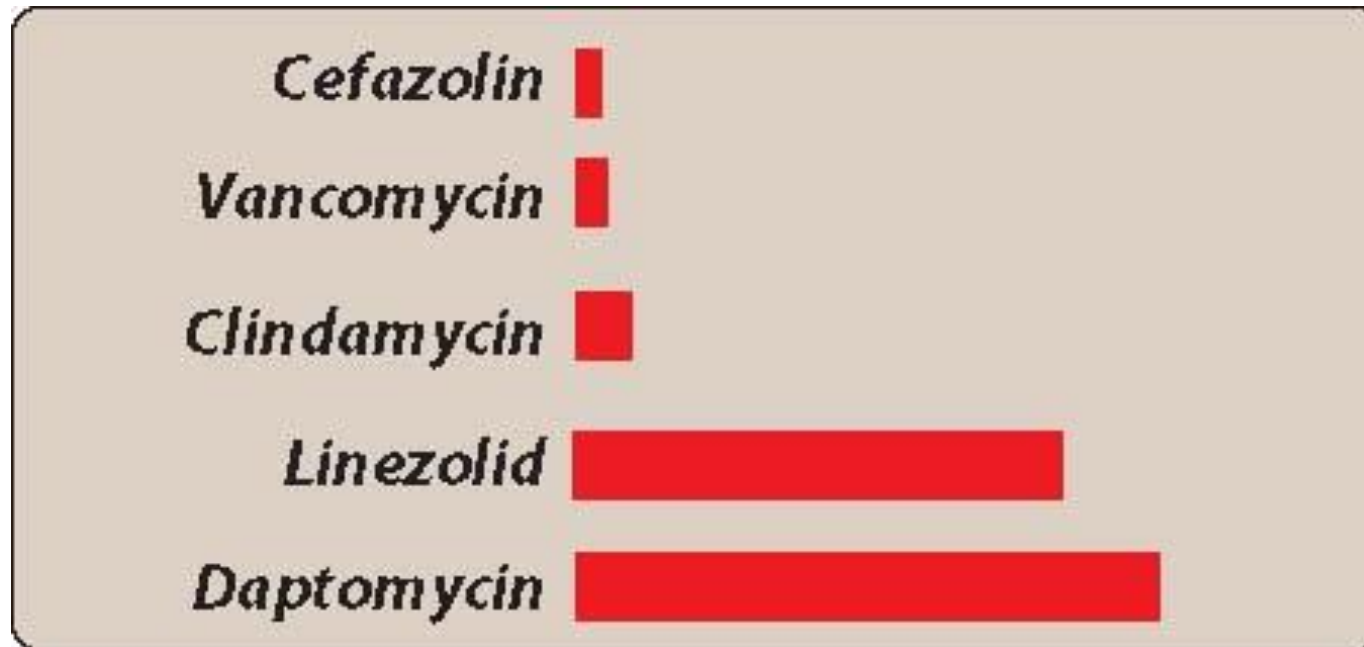
- prior antimicrobial therapy in the preceding 90 days
- hospitalization for greater than 2 days within the preceding 90 days
- current hospitalization exceeding 5 days
- high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms)
- immunosuppressive diseases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

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





Cost of Therapy: Is It Important?

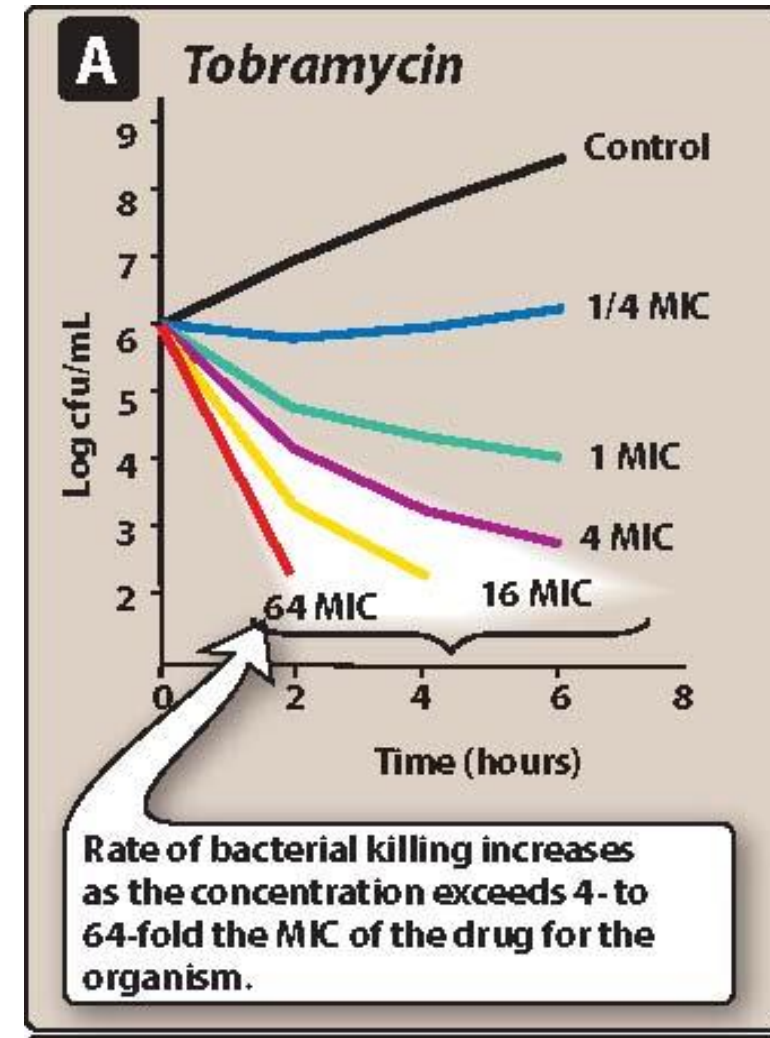


Relative cost of some drugs used for the treatment of *Staphylococcus aureus*.



Determinants Of Rational Dosing

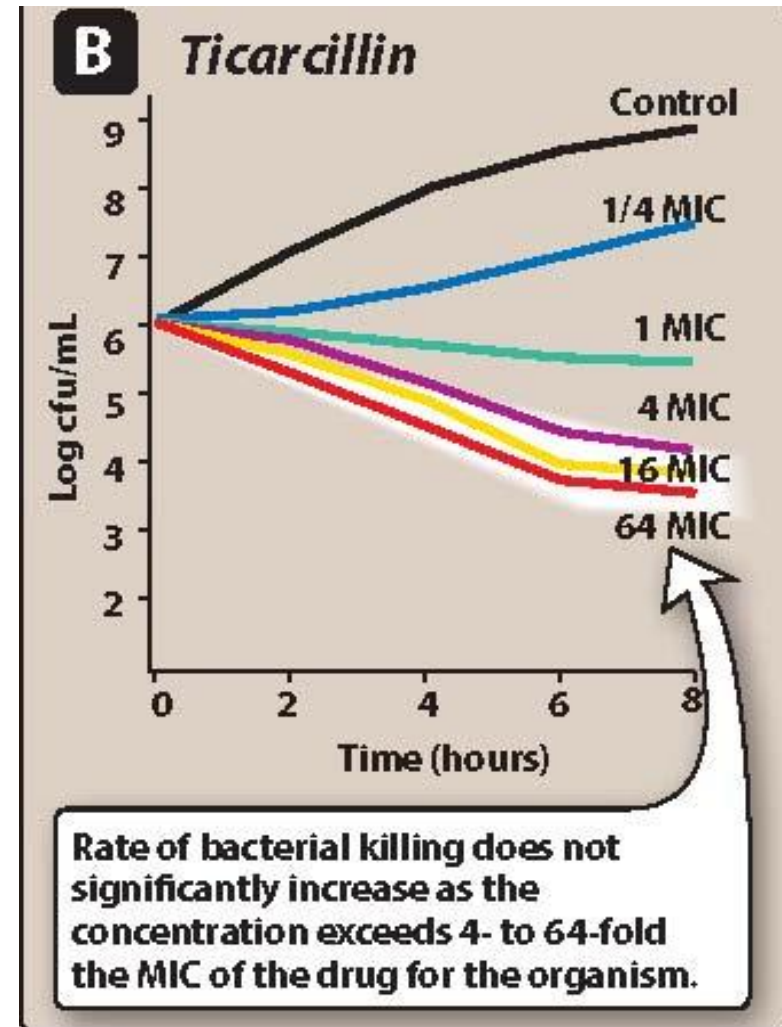
A. Concentration-dependent killing





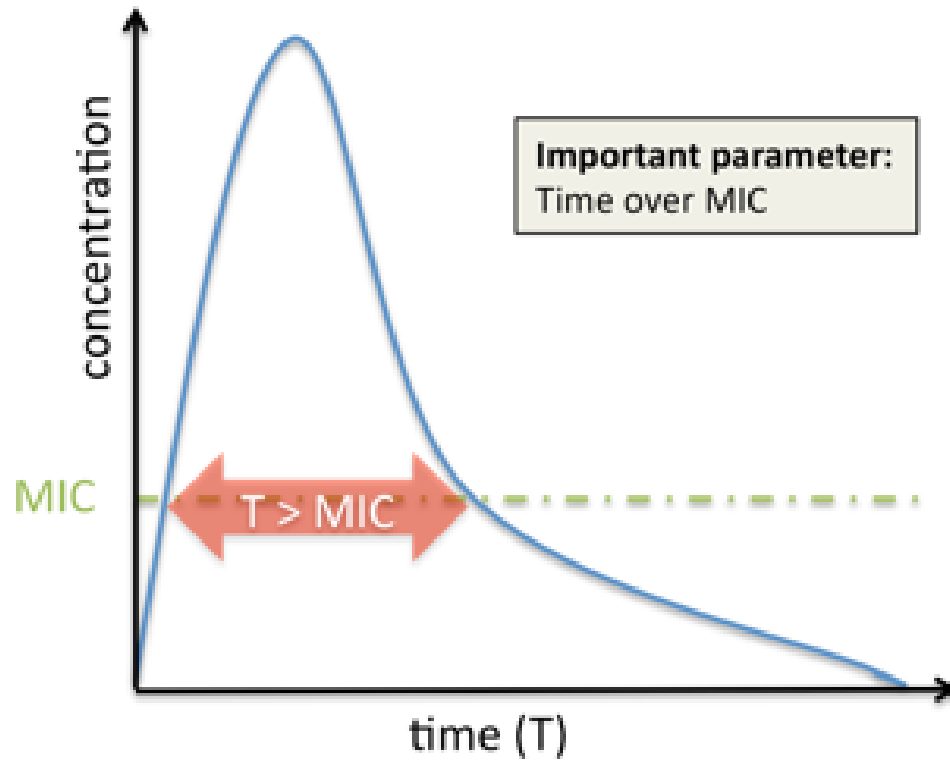
Determinants Of Rational Dosing

B. Time-dependent (concentration-independent) killing

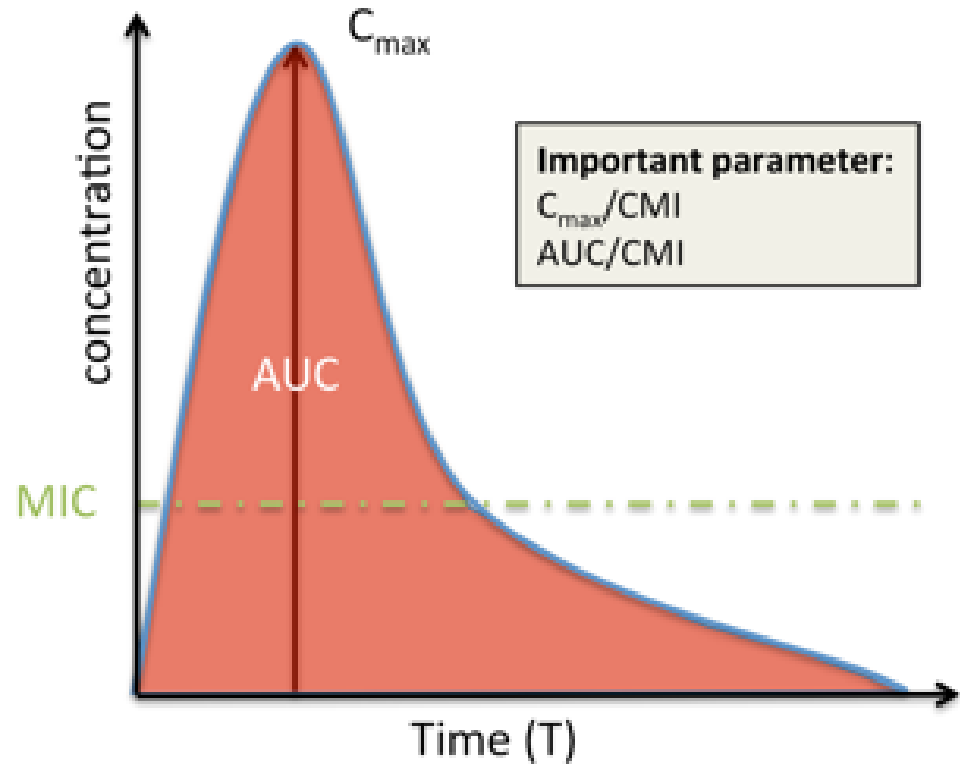




Time dependent antibiotics (eg β -lactams)



Concentration dependent antibiotics (eg aminoglycosides)



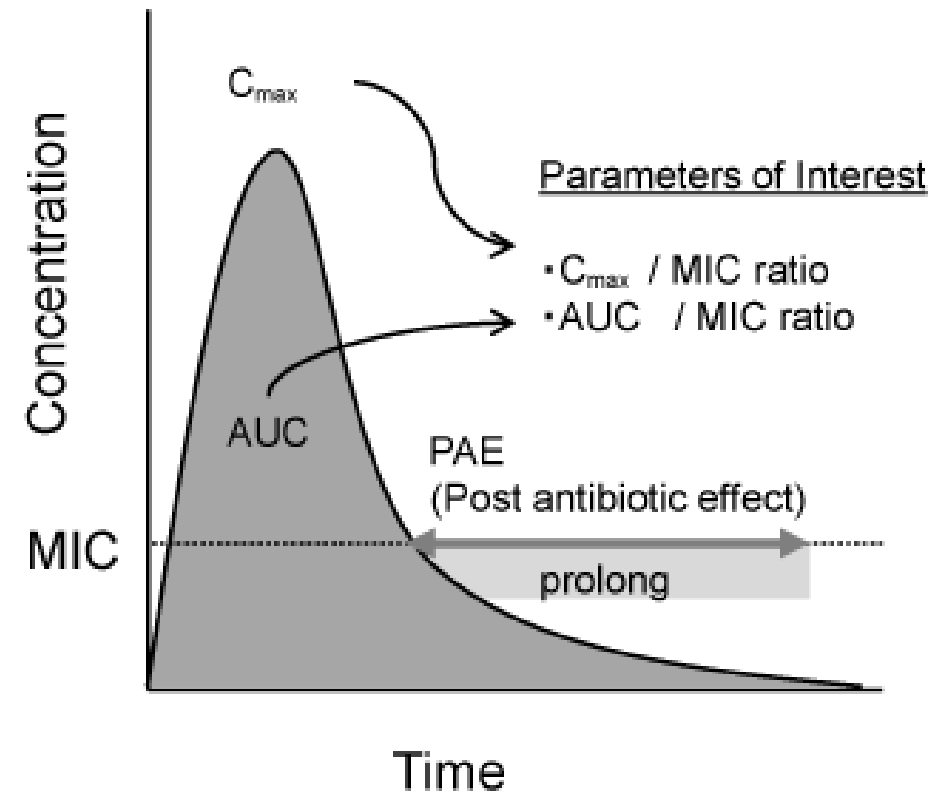
MIC: minimum inhibitory concentration
 C_{max} : peak concentration
AUC: «rea under the curve



Determinants Of Rational Dosing

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

Concentration-dependent antibiotics





Chemotherapeutic Spectra

A Medically important micro-organisms

Gram (+) cocci

Gram (+) bacilli

Gram (-) cocci

Gram (-) rods

Anaerobic organisms

Spirochetes

Mycoplasma

Chlamydia

Other



Chemotherapeutic Spectra

- **Narrow-spectrum antibiotics:**

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

B *Isoniazid*: narrow-spectrum antimicrobial drug

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

Other

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

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

- **Broad-spectrum antibiotics:**

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

D **Tetracycline: broad-spectrum antimicrobial drug**

Gram (+) cocci
Gram (+) bacilli
Gram (-) cocci

Gram (-) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other

Actinomyces, Rickettsiae, Amoebae



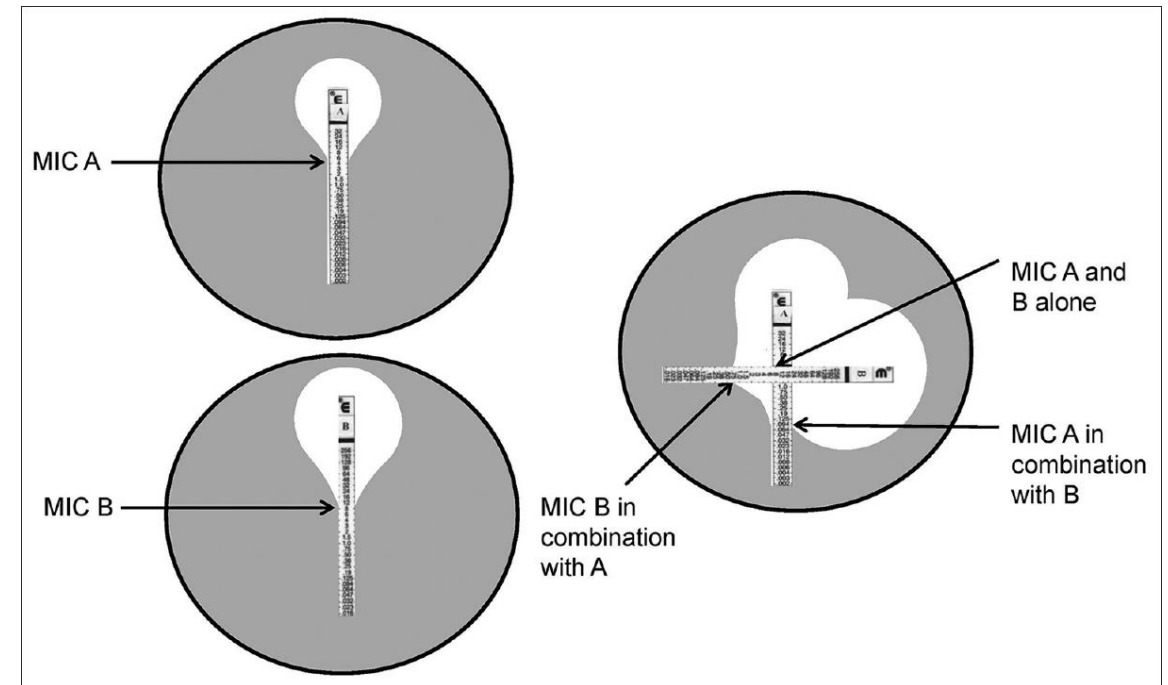
Combinations of Antimicrobial Agents

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.



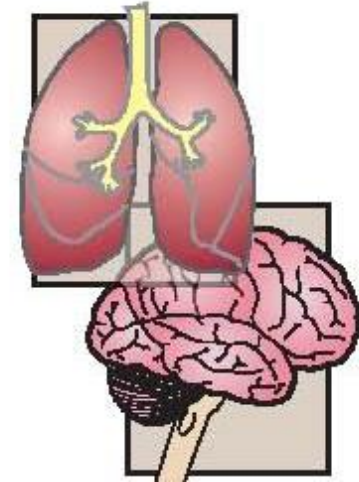
2

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



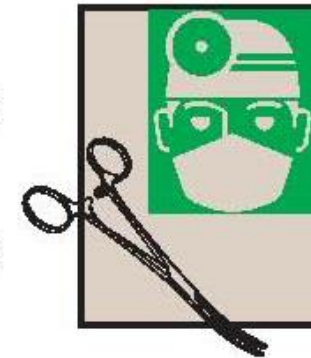
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Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



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



Steven-Johnson syndrome
Drug: penicillins, sulfa drugs

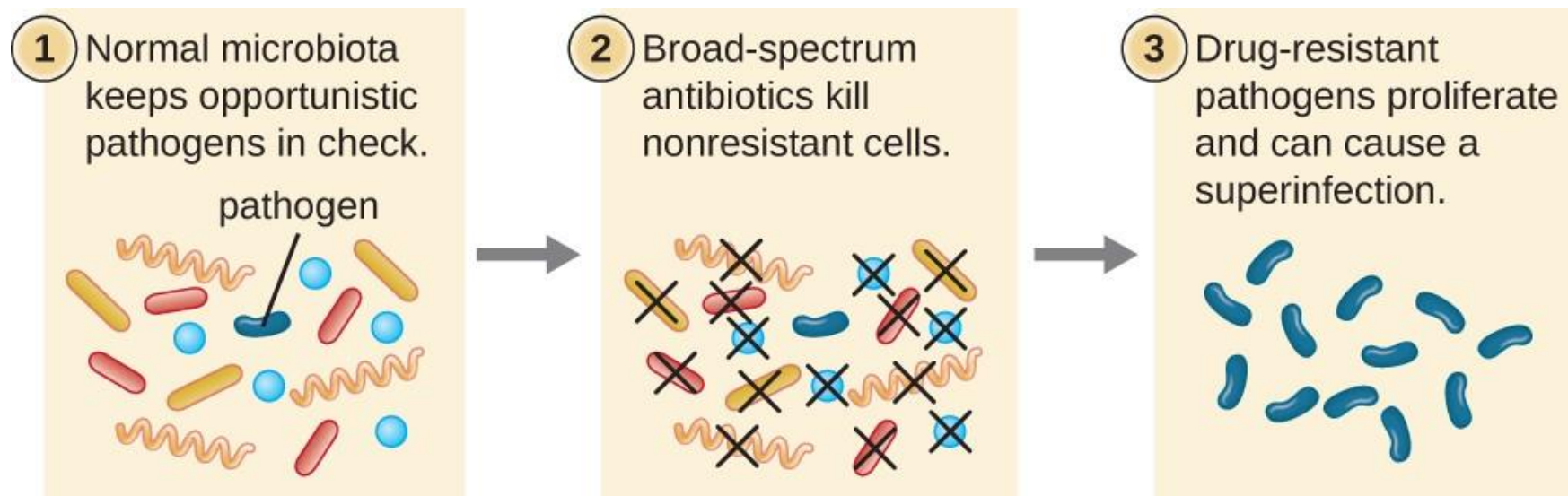


Complications Of Antibiotic Therapy

B. Direct Toxicity

C. Superinfections:

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





Sites Of Antimicrobial Actions

