

Applying Pharmacodynamics and Pharmacokinetics Principles To Antimicrobial Therapy

Leslie Goldstein, Pharm. D.
Associate Professor
Department of Clinical Specialties
Division of Pharmacology
lgolds01@nyit.edu



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I am available to groups and individuals for pharmacology help and discussions by appointment.

lgolds01@nyit.edu

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After completing preparation materials, students should be able to:

1. Identify the general principals of antimicrobial therapy in terms of the drugs' microbial targets, effects, spectrums of activity, and selective toxicity.
2. Discuss the general mechanisms of action and mechanisms of resistance.
3. Apply the principles of microbicidal and microbistatic effects, drug concentration and inhibitory effect, and the pharmacodynamics of antimicrobial effectiveness and resistance.
4. Draw graphs correlating the pharmacokinetics-pharmacodynamics (PK-PD) profiles and their relationship to effectiveness of the drugs.
5. Apply the AUC/MIC ratio to the dosing of antimicrobial drugs.
6. Explain the factors to consider in the clinical selection of antimicrobial agents, including:
 - specific antimicrobial and patient aspects
 - pharmacokinetics properties
 - PK-PD profiles
 - goals of antimicrobial therapy
 - components of antimicrobial stewardship practices.

Preparation Materials (links are in the CPG and on the next slide)

Required

- ScholarRx Bricks | Practice Questions and Clinical Vignettes

Optional resources

- Dr. Goldstein's Word handout | Video Lecture | Guided reading questions

SUGGESTIONS:

- ***Use the resources that work best for you.***
- ***You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)***
- ***Work through the GUIDED READING QUESTIONS with pen/pencil and paper.***

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- ***Practice questions (not graded): Simple Recall and Case Vignettes***

Links

Scholar Rx Bricks: (required) General Microbiology > Infectious Agents

Gram-Positive Bacteria: Foundations and Frameworks

<https://exchange.scholarrx.com/brick/gram-positive-bacteria-foundations-and-frameworks>

Gram-Negative Bacteria: Foundations and Framework

<https://exchange.scholarrx.com/brick/gram-negative-bacteria-foundations-and-frameworks>

Antimicrobial Agents > Principles of Antibacterial Therapy:

Antibacterial Drugs: Foundations and Frameworks <https://exchange.scholarrx.com/brick/antibacterial-drugs-foundations-and-frameworks>

Antibacterial Drug Resistance <https://exchange.scholarrx.com/brick/antibacterial-drug-resistance>

Suggested supplemental resources:

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 51: Clinical Use of Antimicrobial Agents

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382§ionid=281755786#1204144587>

Access Medicine Katzung's Pharmacology: Examination & Board Review, 14e, 2024; Chapter 51: Clinical Use of Antimicrobial Agents

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461§ionid=285599491>

LWW Health Library, Medical Education: Lippincott's Illustrated Reviews: Pharmacology, 8e, 2023; Chapter 28: Principles of Antimicrobial Therapy

<https://meded-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253328408&bookid=3222>

To understand the actions and uses of antimicrobials, students will need to know and understand basic microbiology concepts of medically important bacterial and fungal microorganisms.

- Medical Microbiology textbooks are available on NYITCOM Library website

What you need to know and understand:

For your convenience, definitions and concepts can be found on Dr. Goldstein's Notes handout.

Antimicrobial targets	Mechanisms of resistance	Post-antibiotic effects
Antimicrobial mechanisms	Antimicrobial effects	Susceptibility testing
Spectrum of activity	Microbicidal effects	Drug penetration
Selective toxicity	Microbistatic effects	General PK properties
Microbial resistance	Minimum inhibitory concentration	Goals of therapy
Impact of resistance	PD IC ₅₀ / E _{max} models	Empiric therapy
Emergence of resistance	PD of resistance	Definitive therapy
Selection pressure	PK-PD profiles	Prophylactic therapy
Intrinsic resistance	AUC/MIC ratio	Pre-emptive therapy
Acquired resistance	T>MIC	Suppressive therapy

Antibiotic Stewardship: Need, Programs and Practices

Mechanisms of Antimicrobial Action

Antimicrobial agents target microbial molecules.

- **Drug targets:**

Microbial molecules that are **essential components** of biochemical reactions in the microbes

- **Effect:**

Interference with these physiological pathways kills the microorganisms or slows their growth allowing host immune mechanisms to eradicate them

- **Selective toxicity:**

The extent to which an antimicrobial agent harms microbial cells, but does not damage host cells, at therapeutic concentrations determines its relative safety.

Mechanisms of Antimicrobial Action: Inhibition of Biological Targets

The
takeaways

🔑 Actively and rapidly growing organisms are more susceptible to drug action than those in the resting phase.

Bacteria / Fungi

1. Cell wall synthesis
2. Cell membrane function
3. Protein synthesis
4. Folate synthesis
5. Nucleic acid metabolism
6. RNA polymerase
7. Topoisomerases

Viruses

1. Polymerases
2. Proteases
3. Integrases
4. Envelope fusion
5. Uncoating
6. Budding

Protozoa

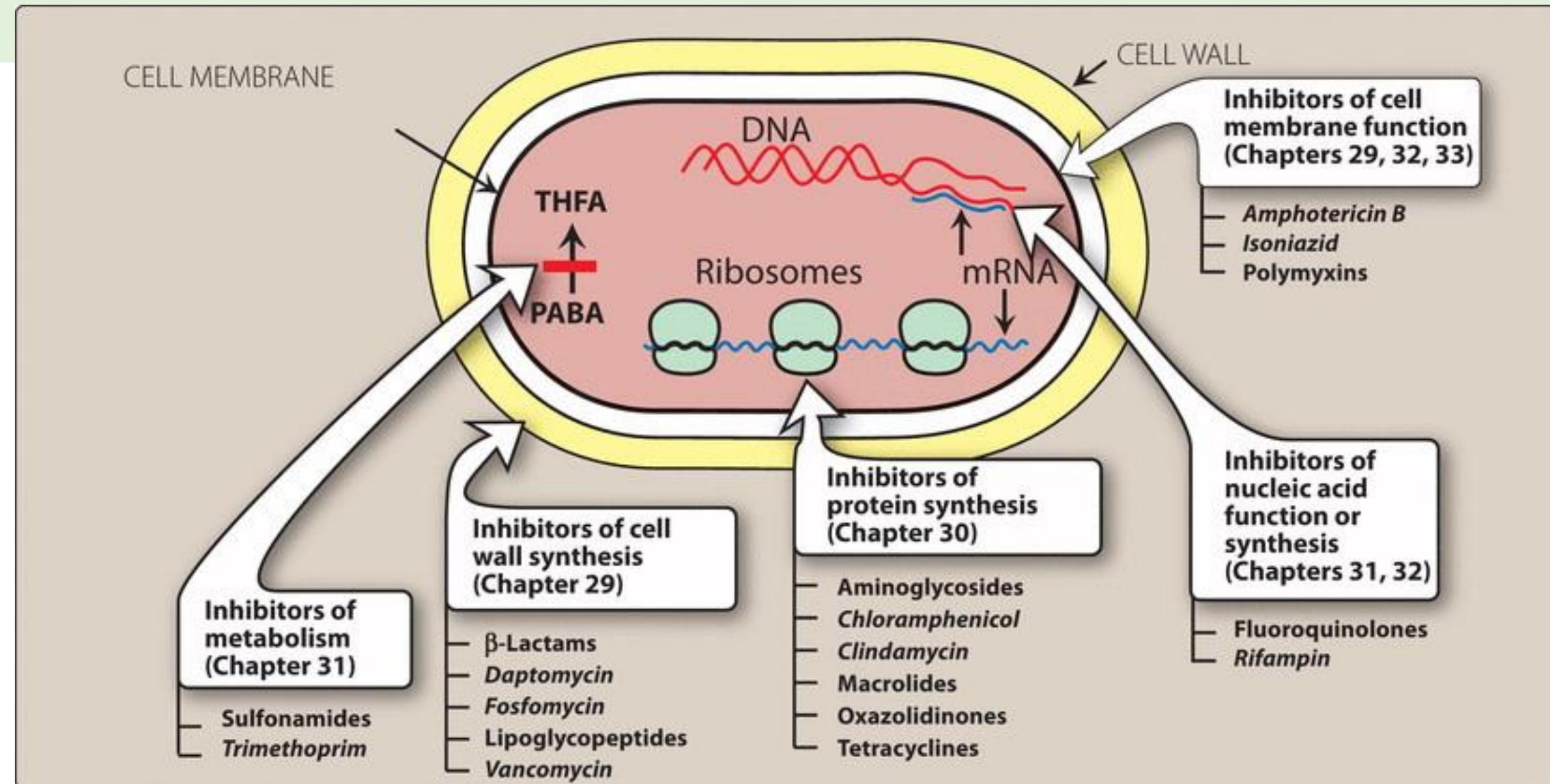
1. Chemical
2. Detoxification processes
3. Folate synthesis

Helminths

1. Various
2. physiological and
3. biochemical
4. pathways

From: 28 Principles of Antimicrobial Therapy, Figure 28.10

Lippincott® Illustrated Reviews: Pharmacology, 8e, 2022



Classification of some antimicrobial agents by their sites of action.

Spectrum of Activity / Selectivity

- **Narrow-spectrum antimicrobials:**

Drugs effective against a limited group of microorganisms

- **Broad-spectrum antimicrobials:**

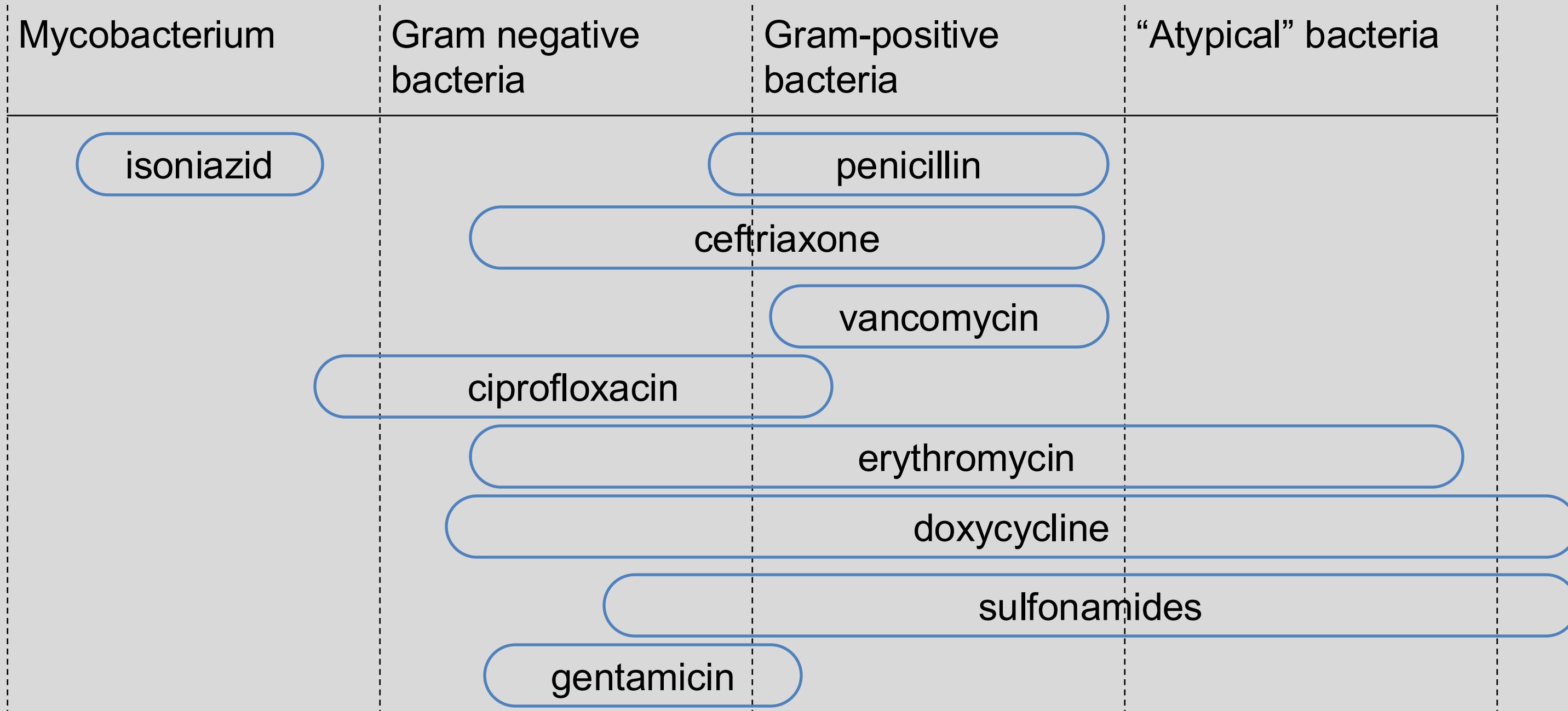
Drugs effective against a wide variety of microbial species

Clinical correlate:

- *Use the most selective (active) drug*
- *that produces the fewest adverse effects.*

Spectrums of activity using examples of antibacterial agents

The range of microorganisms an antimicrobial can kill or inhibit



Antimicrobial Resistance

Contributors to the Emergence of Resistance

Evolution

Random events → alteration of microbial genetic information.

Natural Selection

When the drug is present, these mutations confer a survival advantage to the microorganism.

Selection pressure

The mutations are not caused by exposure to the drug *per se*. However, increased exposure to the drug increases selection pressure.

- **Clinical practices**
 - Inappropriate prescribing practices
 - **Environmental practices**
 - Use of antibiotics in animal feed
-  ***Frequent or long-term use of a particular drug increases the risk of microbial mutations that produce resistance to the drug.***

Mechanisms of Antimicrobial Resistance

Intrinsic resistance

Microorganism has features that make it inherently resistant

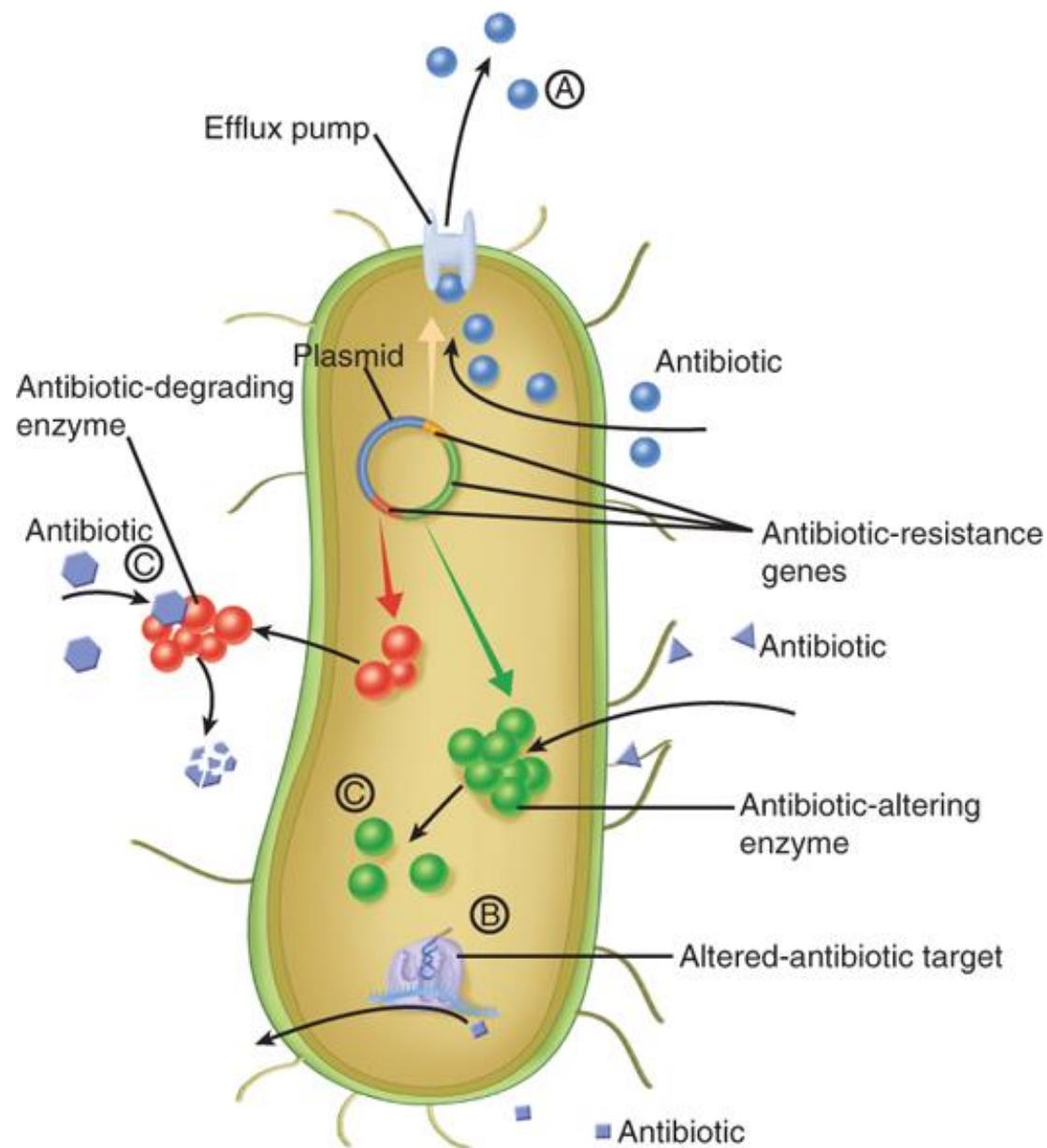
Acquired resistance

Normally responsive organism acquires:

- spontaneous, random chromosomal mutations, or
- transfer of resistance genes from other bacteria

1. Drug does not reach target
 - Efflux pumps
 - Altered porins (gram-negative bacteria)
2. Drug inactivation
3. Target alteration
4. Organism expresses alternative metabolic pathways

Porin: Protein channel that allows passage of ions and small molecules. It is located in the outer membrane of gram-negative bacteria.



- The drugs target specific **essential components** of biochemical reactions in the microbes
- ↓
- The microbes develop mechanisms that protect these physiological pathways from the actions of the drugs

Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition
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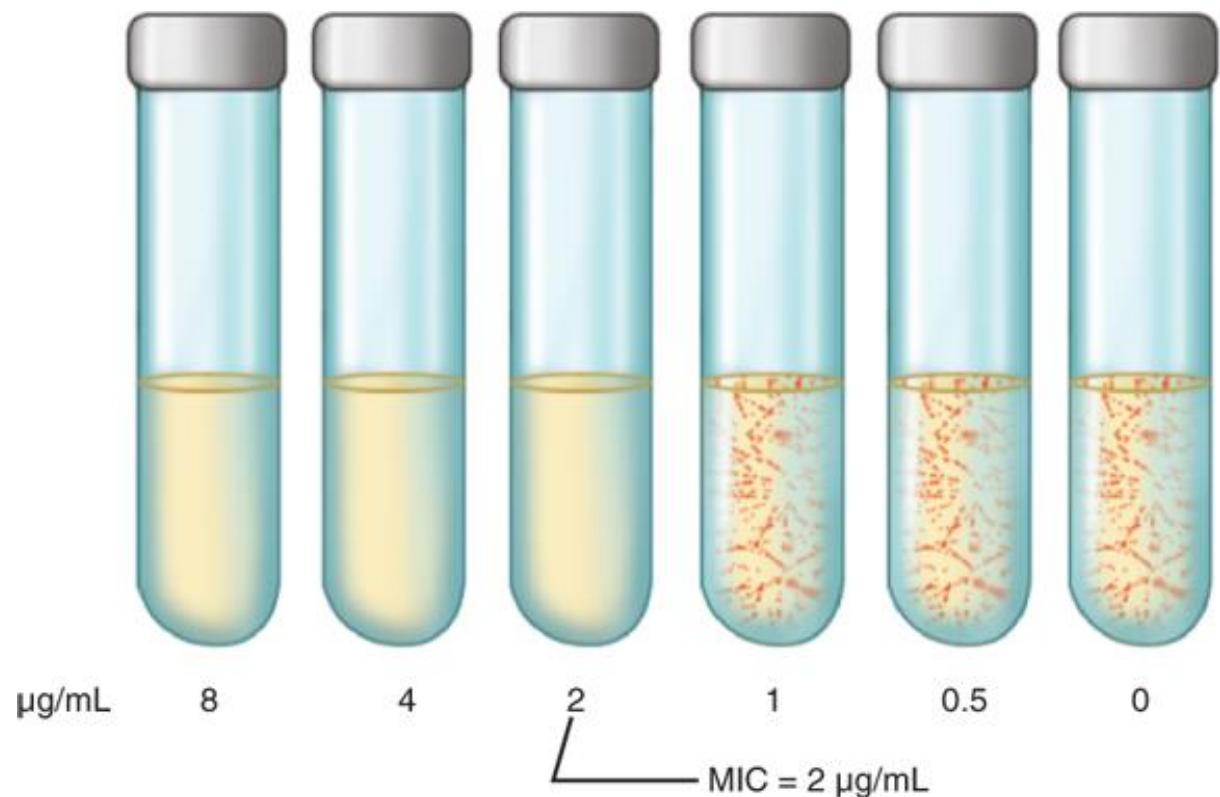
Antimicrobial resistance mechanisms. A. Exclusion barrier. B. Altered target. C. Enzymatic inactivation.

(Reproduced with permission from Willey JM: Prescott, Harley, & Klein's Microbiology, 7th edition. McGraw-Hill, 2008.)

Susceptibility testing: Laboratory test to determine the possible antimicrobials that would be effective in eradicating the infection

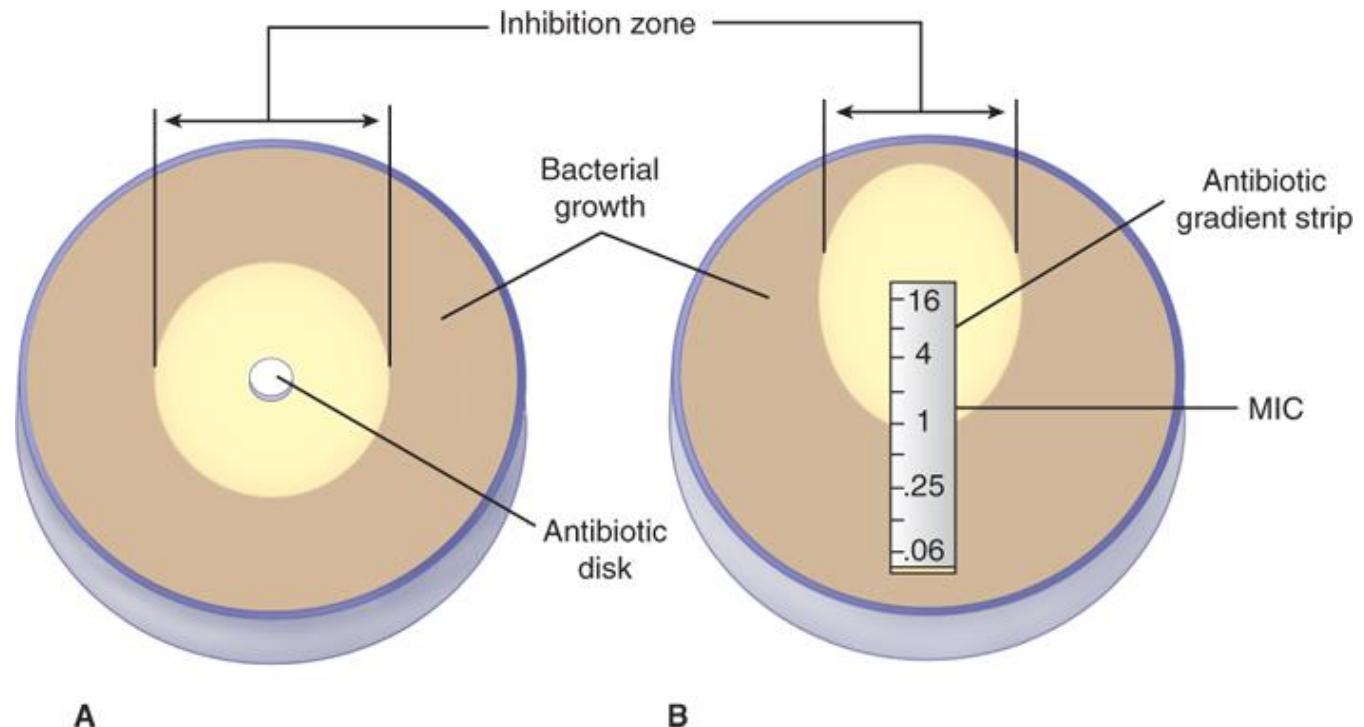
- **Minimum inhibitory concentration (MIC):**
 - The lowest concentration of an antibacterial agent that inhibits visible growth
- **Minimum bactericidal concentration (MBC):**
 - The lowest concentration of an antibacterial agent that either totally prevents growth or results in a greater than 99.9% decrease in the initial inoculum

Susceptibility testing is most commonly used to determine the likelihood that a particular antibiotic or antifungal agent will be effective in stopping the growth of the bacteria or fungi causing the infection.



Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition
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Broth dilution susceptibility test. The stippled tubes represent turbidity produced by bacterial growth. The MIC is 2 $\mu\text{g/mL}$.



Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition
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Diffusion tests.

- Disk diffusion.** The diameter of the zone of growth inhibition around a disk of fixed antimicrobial content is inversely proportional to the minimum inhibitory concentration (MIC) for that antimicrobial, that is, the larger the zone, the lower the MIC.
- The E test.** A strip containing a gradient of antimicrobial content creates an elliptical zone of inhibition. The conditions are empirically adjusted so that the MIC endpoint is where the growth intersects the strip.

Pharmacodynamics and Pharmacokinetics of Antimicrobial Therapy

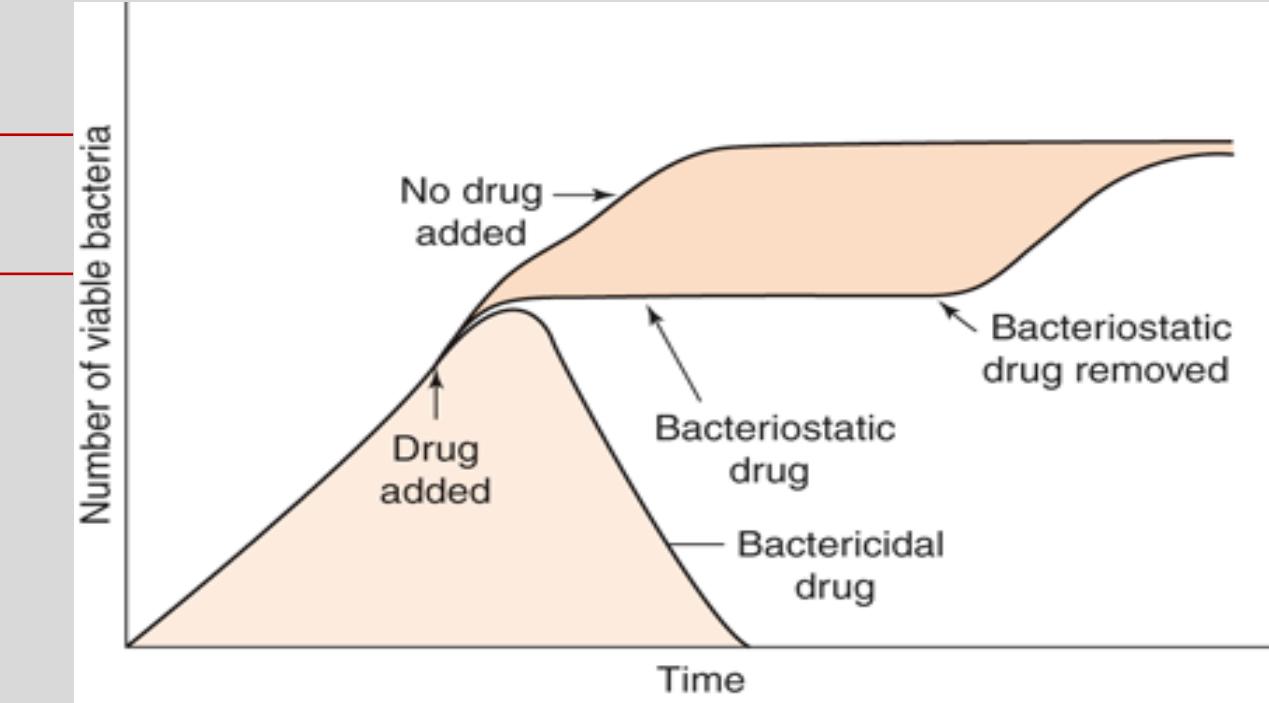
Inhibitory effects of antimicrobial agents

Microbicidal:

Kills infective organism

Bactericidal agents should be used when host defenses are impaired:

- immunocompromised patients
- infections in anatomical sites where the immune function is reduced
- meningitis, endocarditis, osteomyelitis



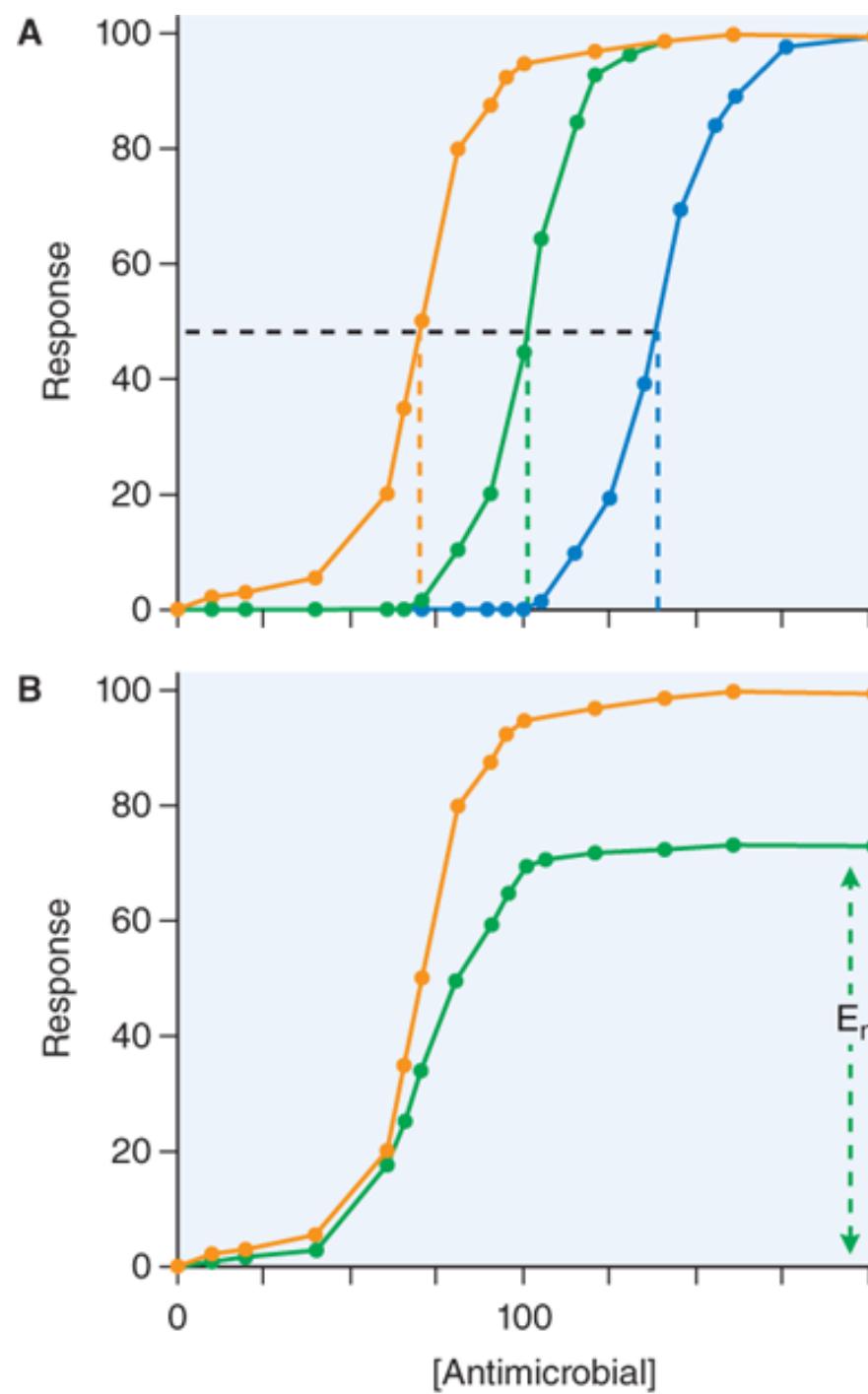
Source: Levinson W: *Review of Medical Microbiology & Immunology*, 12th Edition:
www.accessmedicine.com

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Microbistatic:

Inhibits microbial growth and replication, but does not kill the microbe

Intact immune system is required to remove the microorganisms from the body



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Effect of resistance on IC₅₀ and E_{max}

IC₅₀ half-maximal inhibitory concentration (IC₅₀ is analogous to EC₅₀.)

E_{max}: maximal effect as measured by microbial burden

- **Intermediate resistance:** → Increase IC₅₀ (shift to the right) → much **higher concentrations** needed to achieve a particular effect (↓microbial burden)
- **Resistance:** The microbe cannot be eradicated at achievable drug concentrations.
 - 1) Large increase in IC₅₀ → A very high dose would be required to kill the microbes, but the toxicity would be **intolerable to the patient**.
 - 2) Decrease in E_{max} → **increasing the dose would not increase the effect** beyond a certain point

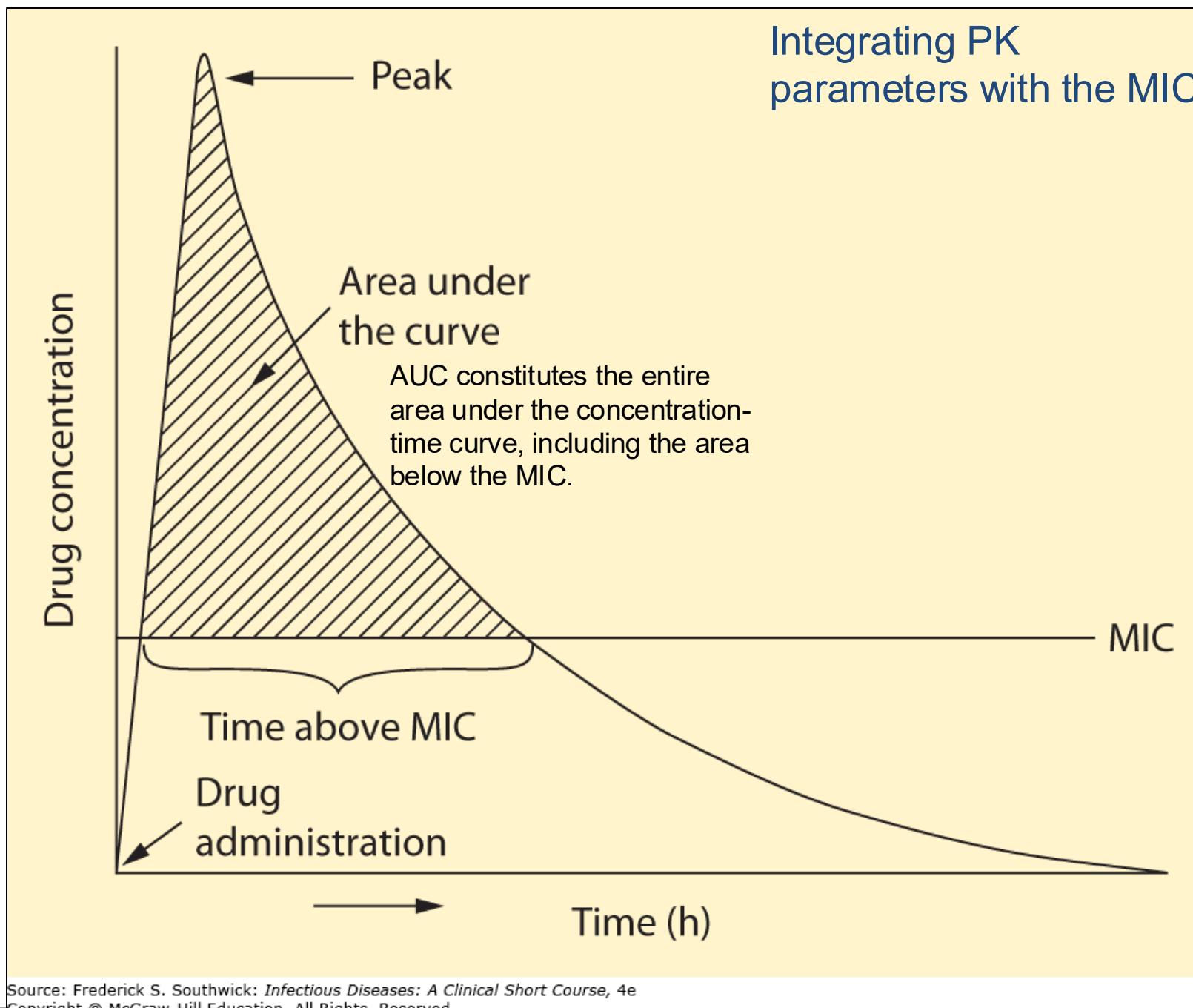
Changes in sigmoid E_{max} model with increases in drug resistance. An increase in resistance may show changes in IC₅₀: In A, the IC₅₀ increases from 70 (orange line) to 100 (green line) to 140 (blue line). An increase in resistance may also show a decrease in E_{max}: In B, efficacy decreases from full response (orange line) to 70% (green line).

PK-PD Profiles: Predictors of Efficacy

Rational dosing of antimicrobial therapy depends on the relationship between the:

- pharmacokinetics properties
(ADME → dose and plasma concentration)
- and
- pharmacodynamics properties
(drug concentration at the site of action and effect).

Pharmacokinetics of a typical antibiotic. Dashed area shows the area under the curve above the MIC. (Peak is also called C_{max} .)



PK-PD Profile and Dosing

Concentration-dependent killing	Time-dependent killing
<ul style="list-style-type: none">The rate and extent of bactericidal activity (killing) increase with increasing drug concentrations.High peak levels are more effective than low peak levels for curing infection.	<ul style="list-style-type: none">Bactericidal activity continues as long as drug concentrations are greater than the MIC.High peak levels (>8 times MIC) are of no benefit for curing infection.
Dosing recommendations to maximize success: High peak concentrations AUC_{24}/MIC	Dosing recommendations to maximize success: $T > MIC$ correlates with cure. Maintaining serum levels above the MIC for >50% of the time. AUC_{24}/MIC
➤ The greater the concentration above the MIC, the longer the PAE for concentration-dependent drugs.	➤ Most antimicrobials have <i>in vitro</i> PAE ≥ 1.5 hours against susceptible gram-positive cocci but minimal PAE against gram-negative bacilli.
AUC/MIC ratio: Clinical efficacy correlates with AUC/MIC ratio: maximizing the total amount in the body over time (a 24 hour period $\rightarrow AUC_{24}/MIC$) AUC-dependent dosing recommendations and post-antibiotic effect are provided in the drug monographs for both concentration-dependent and time-dependent antimicrobials.	

Pharmacokinetics of Antimicrobial Agents

General Concepts

Antimicrobial agent must **penetrate** into the infected compartment in **sufficient concentration** to prevent or inhibit the growth of the organism.

Physicochemical properties:
lipophilic; hydrophilic; polar

Tissue penetration:
anatomic and vascular barriers, such as
the blood-brain barrier

Active efflux (physiologic):
P-glycoprotein and other efflux pumps

Intracellular penetration:
some organisms hide in host cells

Endocardial vegetation:
deposition of platelets, fibrin, microbes,
inflammatory cells on endocardial tissue

Biofilm:
colonies of slow-growing microbes that
adhere to prosthetic devices

PK Parameter	Comment
Administration (oral, IM, IV, topical)	<p>Route of administration is determined by:</p> <ul style="list-style-type: none">• location and severity of infection• functional state of patient• the drug's stability in acid ⇒ drug absorption from GI tract
Distribution	<ul style="list-style-type: none">• widely distributed to most fluids and tissues• protein binding variable (relevant when $\geq 95\%$)• generally poor penetration into CNS (enhanced if meninges are inflamed)• Also, low concentrations in vitreous fluid; prostate; host cells
Elimination (metabolism and excretion)	<ul style="list-style-type: none">• renal excretion of unchanged drug and metabolites via glomerular filtration and proximal tubule transport• some antimicrobials are metabolized in the liver

Considerations in the selection of antimicrobial agents

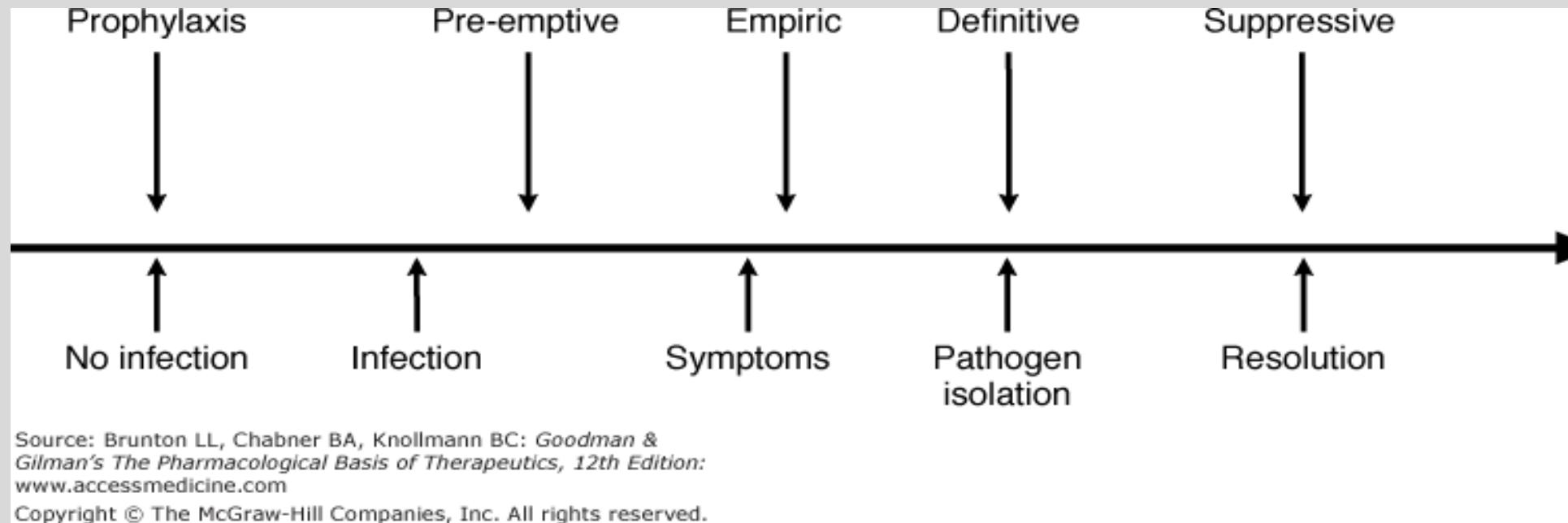
Antimicrobial Agent Factors

- Mechanisms of action
- Pharmacodynamics
- PK-PD Profile
- Pharmacokinetics
- Spectrum of activity
- Microbial resistance
- Safety: Inherent toxicity of the drug to the host

Patient Factors

- Perfusion of anatomic areas
- Immune system function
- Renal / hepatic function
- Age
- Comorbidities
- Pregnancy, Lactation
- Allergies
- Drug interactions
- Cost of therapy

🔑 The concentration of antibiotic must be adequate to kill or prevent growth of the infective microorganism *while being tolerable to the host.*



GOALS OF ANTIMICROBIAL THERAPY

Prophylactic therapy	Select circumstances
Preemptive therapy	Dangerous if infection arises
Empiric therapy	ABX needed urgently
Definitive therapy	When organism is known
Suppressive therapy	Immunosuppressed pts
Combination therapy	Synergism Broaden spectrum if needed

Know these terms and when these therapies are employed.

When are the antimicrobial approaches used?

Prophylactic	To prevent infection in patients at high-risk: Example: surgery, immunosuppression, endocarditis
Preemptive	To prevent development of a potentially dangerous disease in an asymptomatic patient who already has evidence of infection Example: cytomegalovirus (CMV) after hematopoietic stem cell transplantation and solid organ transplantation
Empiric	Immediate broad spectrum antimicrobial therapy when a delay in initiating antibiotic therapy could cause significant morbidity or fatality
Definitive	Specific, narrow-spectrum antimicrobial agent when the microorganism and its susceptibility to specific antibiotics are identified
Suppressive	For immunosuppressed individuals when the original infection is not completely eradicated by the initial therapy
Combination	To broaden the antibiotic spectrum or for synergistic or additive effect

Antibiotic Stewardship

- We are all responsible for the appropriate use of antimicrobials to improve patient outcomes, reduce microbial resistance, and decrease the spread of infections caused by multidrug-resistant organisms.

Antimicrobial stewardship is a coordinated program that:

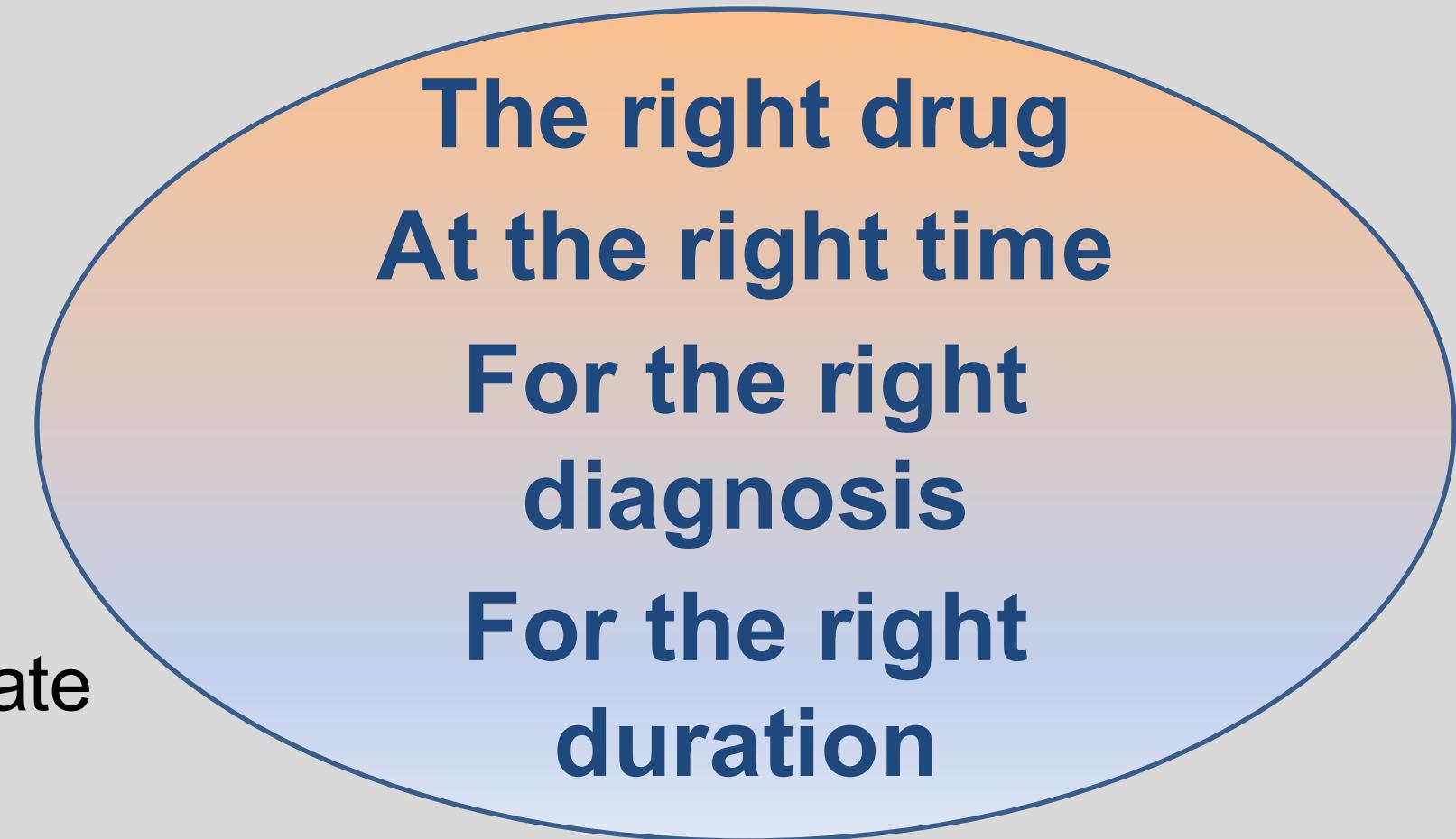
1. Promotes the appropriate use of antibiotics and other antimicrobials
2. Improves patient outcomes
3. Reduces microbial resistance, and
4. Decreases the spread of infections caused by multidrug-resistant organisms.

Six Goals of Antibiotic Stewardship Programs

1. Reduce antibiotic consumption and inappropriate use
2. Reduce *Clostridioides difficile* infections
3. Improve patient outcomes
4. Increase adherence/utilization of treatment guidelines
5. Reduce adverse drug events
6. Decrease or limit antibiotic resistance
 - Hardest to show
 - Best data for health-care associated gram-negative organisms

The 5Ds of Antibiotic Stewardship

1. Diagnosis
2. Drug
3. Dosing
4. Duration and
5. De-escalation when appropriate



Summary

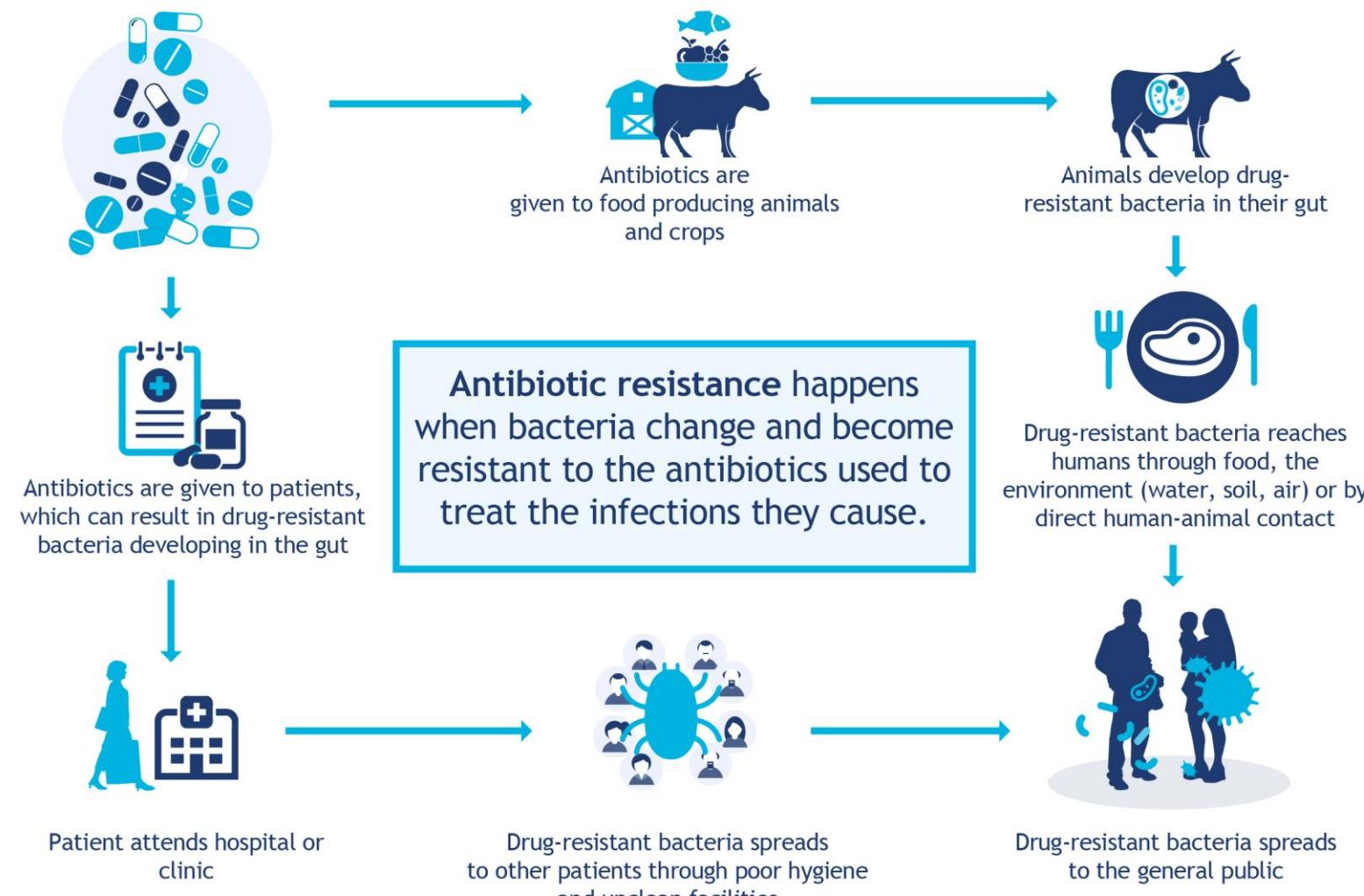
General actions and effects of antimicrobial agents.

- Antimicrobial agents work by targeting specific elements in biochemical pathways of pathogens.
- Important determinants of success of antimicrobial therapy include:
 - proper selection of antimicrobial therapy based on their selective toxicity to the microorganism and spectrums of activity,
 - laboratory identification and susceptibility testing,
 - dosing that achieves the proper concentration at the site of action,
 - knowledge of drug penetration into the infected compartment, and
 - a dosing schedule that maximizes antimicrobial effect.
- The proper dose and dosing schedule are chosen by integrating microbial pharmacokinetics and pharmacodynamics (PK-PD) information: expected pharmacokinetics variability and the minimum inhibitory concentration (MIC) of the pathogen.

- The goals of therapy should be clear.
- Prophylaxis, pre-emptive therapy, empirical therapy, definitive, and suppressive therapy should have treatment goals and duration of therapy clearly spelled out in the beginning, based on proper evidence.
- The general rule is monotherapy, except in select situations where combination therapy has been shown to be superior.
- Poor dosing strategies lead to catastrophic outcomes such as drug-resistant pathogens and untoward toxicity to the patients.
- Antimicrobial stewardship practices promote the proper use of antimicrobials, improve patient outcomes, and reduce the development of resistance.

ANTIBIOTIC RESISTANCE

HOW IT SPREADS



References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e, 2022; Chapter 56. General Principles of Antimicrobial Therapy
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024: Chapter 51: Clinical Use of Antimicrobial Agents

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