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.

What you need to know and understand:

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

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

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

Antimicrobial agents target microbial molecules.

- **Drug targets:**

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

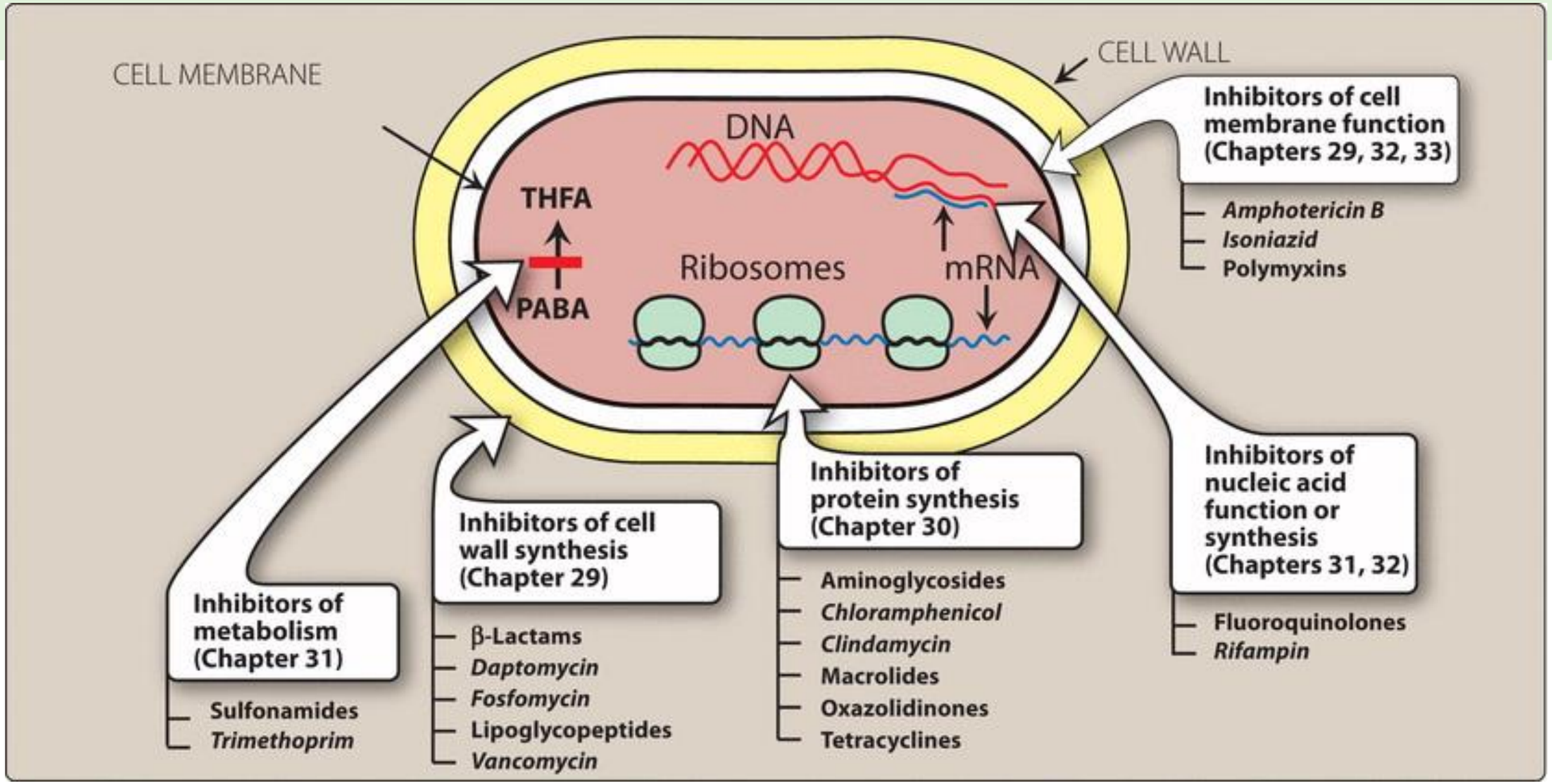
- **Effect:**

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.

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:

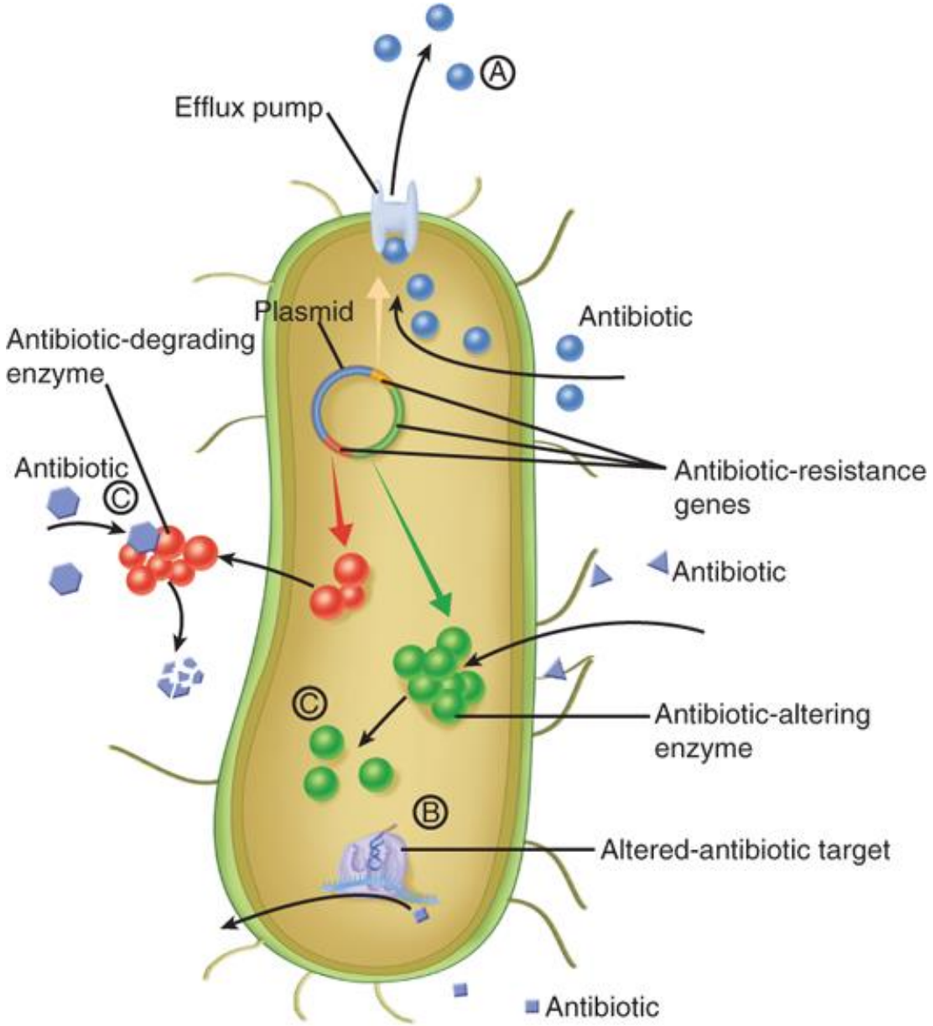
- *Use the most selective (active) drug*
- *that produces the fewest adverse effects.*

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.



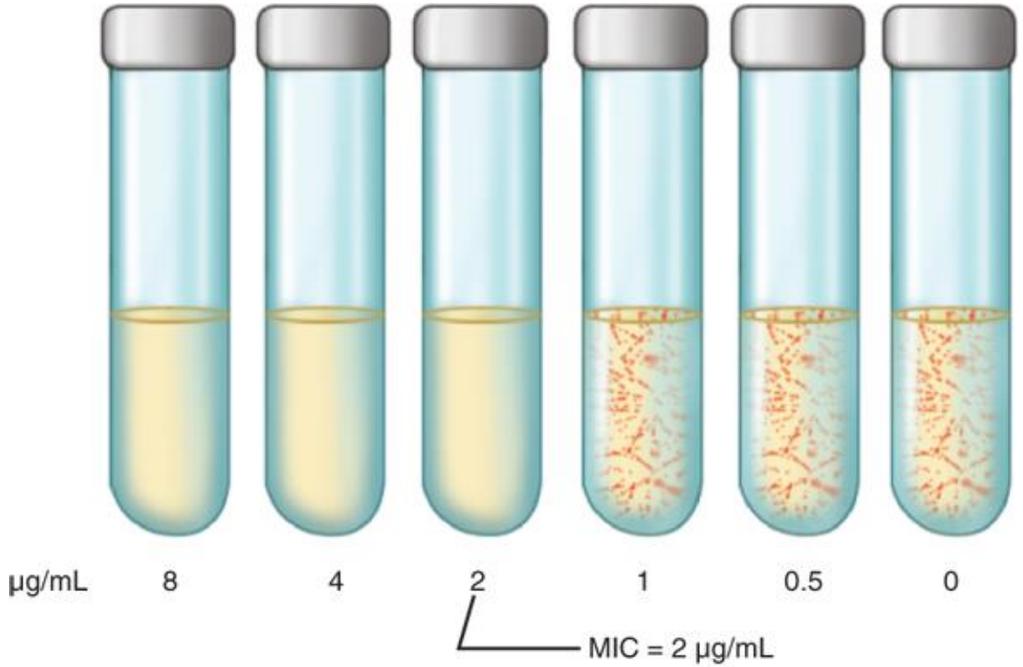
- The drugs target specific **essential components** of biochemical reactions in the microbes

↓

- The microbes develop mechanisms that protect these physiological pathways from the actions of the drugs

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.)



Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition
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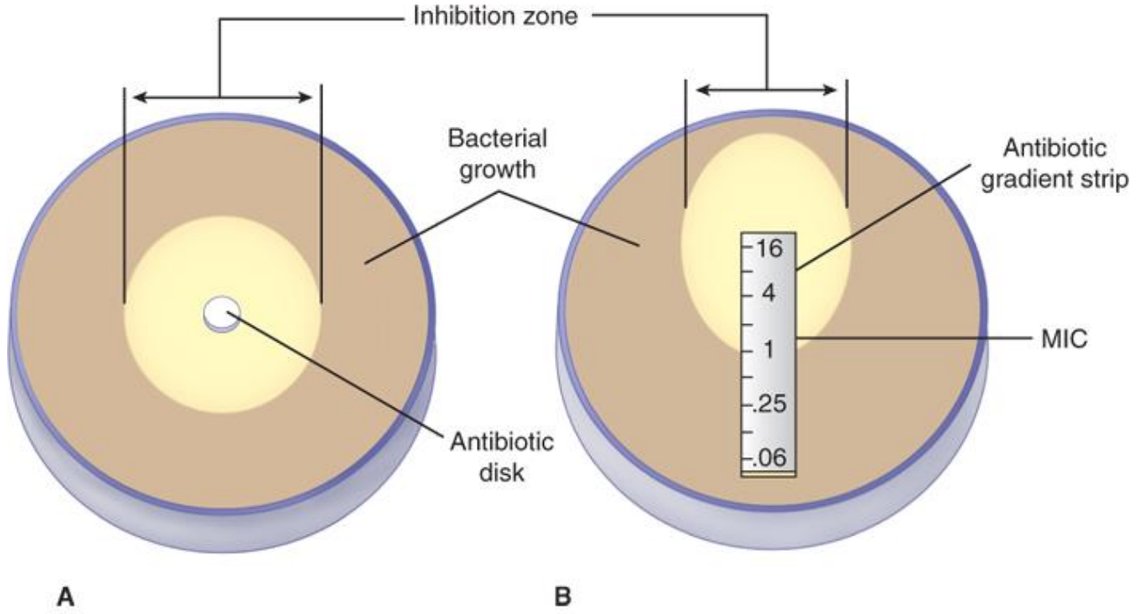
Broth dilution susceptibility test. The stippled tubes represent turbidity produced by bacterial growth. The MIC is 2 µg/mL.



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

A. 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.

B. 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.

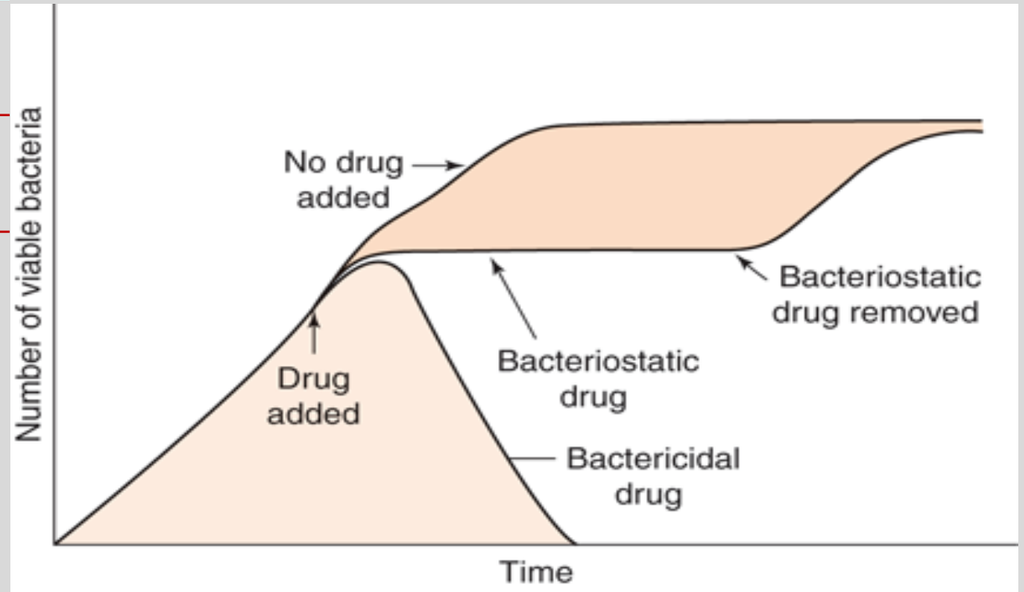
Citation: Chapter 23 Antibacterial Agents and Resistance, Ryan KJ. *Sherris Medical Microbiology, 7e;* 2017, Figure 23-5 and 23-6. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2268&sectionid=176085132 Accessed: September 23, 2021

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



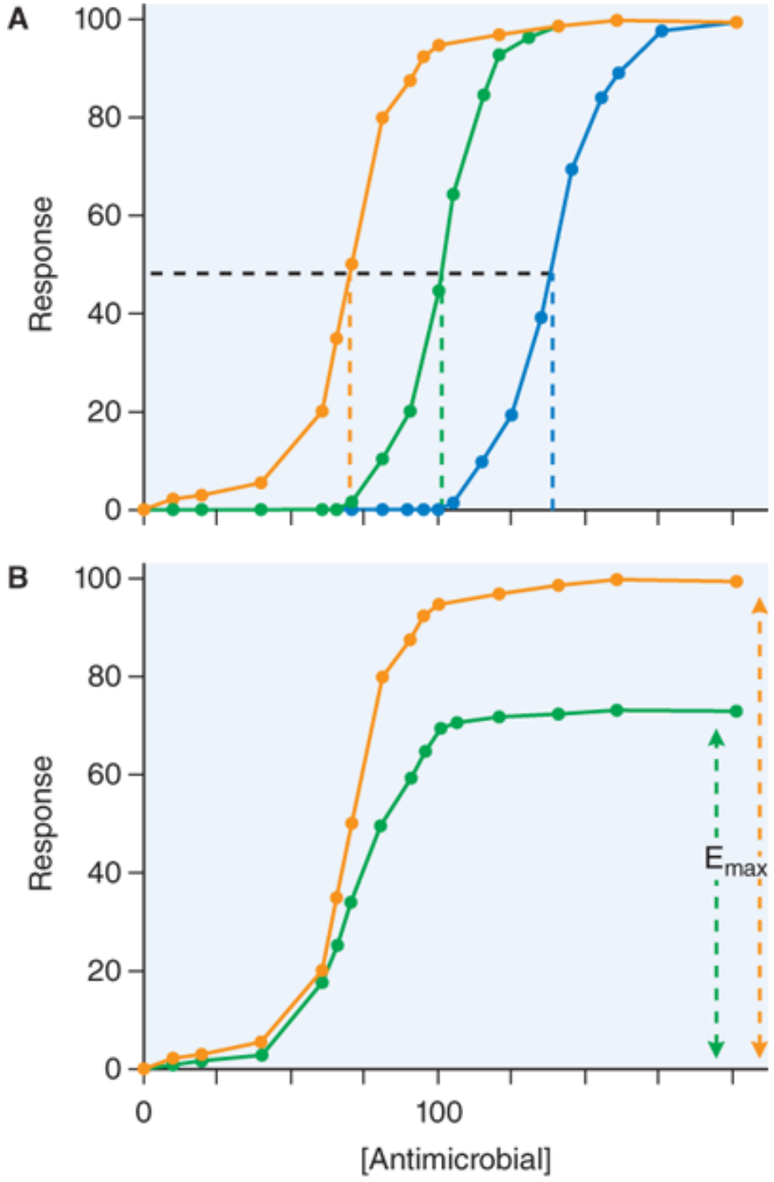
Source: Levinson W: *Review of Medical Microbiology & Immunology, 12th Edition*: www.accessmedicine.com

Microbistatic:

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

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

Figure: Access Medicine Review of Medical Microbiology and Immunology Figure 10-1



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 IC_{50} and E_{max}

IC_{50} half-maximal inhibitory concentration (IC_{50} is analgous to EC_{50}.)

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

- **Intermediate resistance:** → Increase IC_{50} (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 IC_{50} → 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 IC_{50}: In A, the IC_{50} 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).

Citation: Chapter 52 General Principles of Antimicrobial Therapy, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017, Figure 52-3. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172483986 Accessed: September 23, 2021

Slide adapted by LG

PK-PD Profiles: Predictors of Efficacy

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

- pharmacokinetics properties

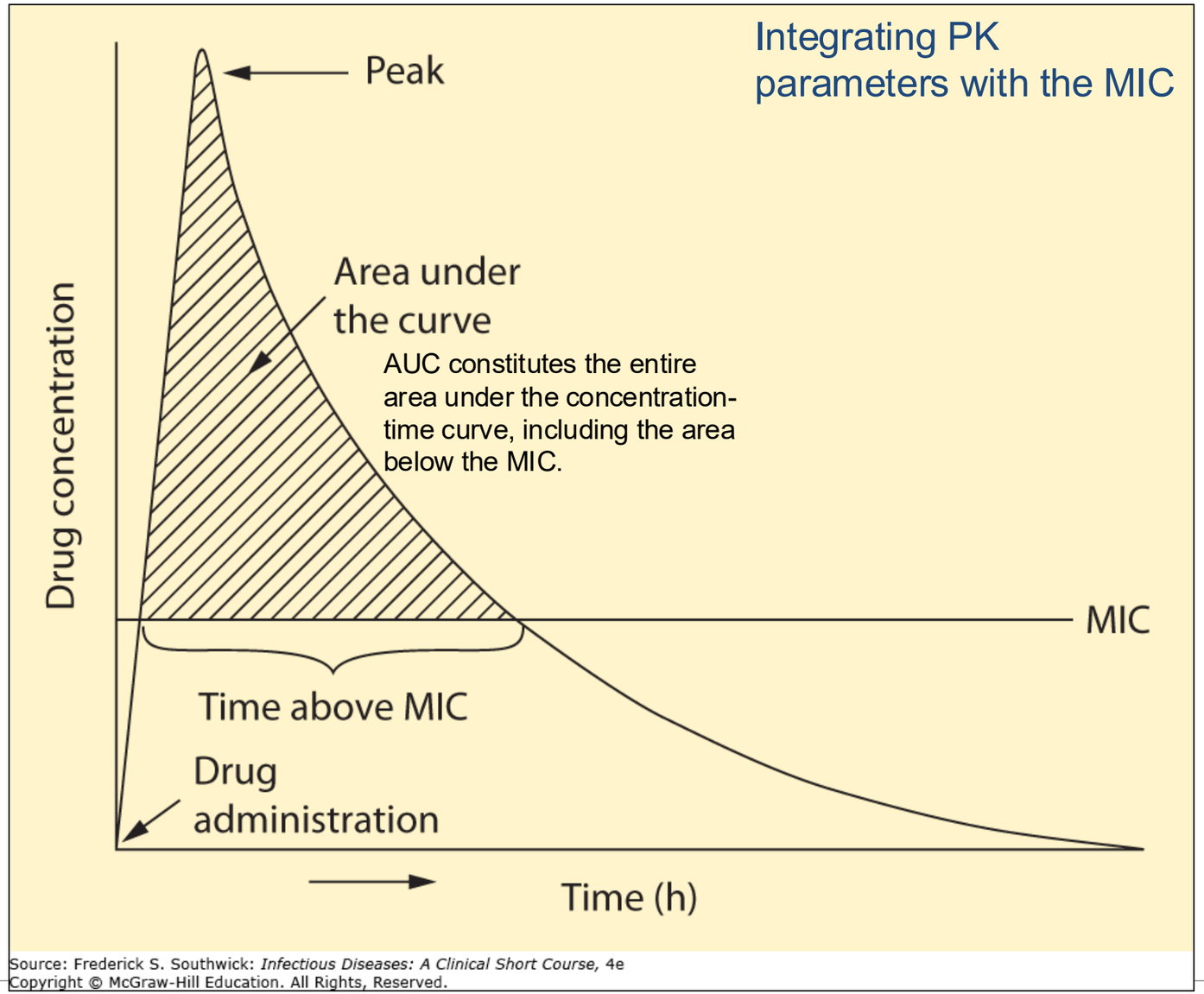
  (ADME → dose and plasma concentration)

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}.)



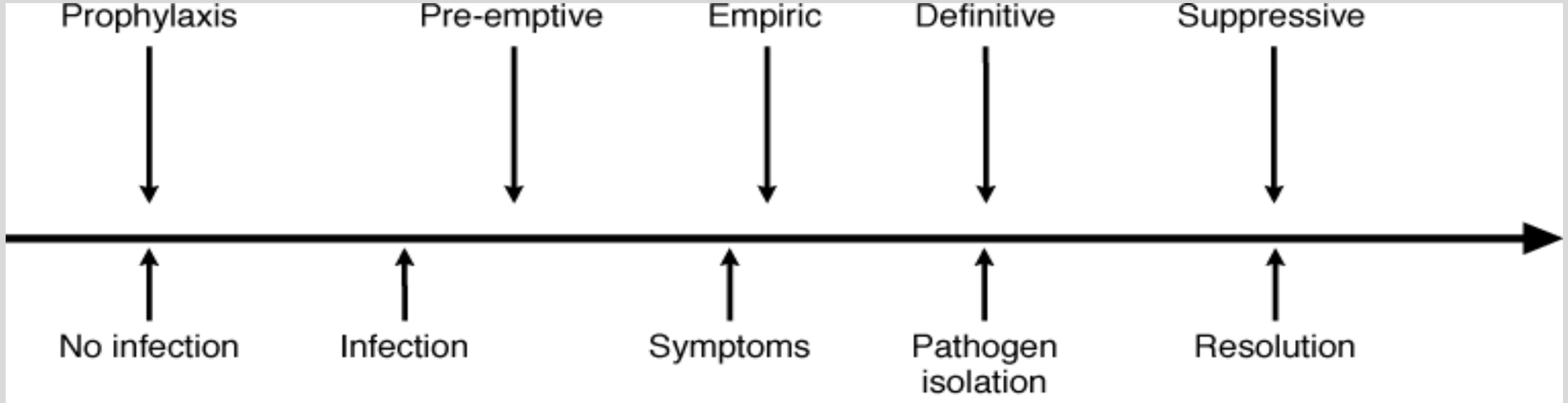
Source: Frederick S. Southwick: *Infectious Diseases: A Clinical Short Course*, 4e

PK-PD Profile and Dosing

Concentration-dependent killing	Time-dependent killing
· 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.	· 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 *in vitro* 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 → 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.	

Antimicrobial Agent Factors	Patient Factors
• Mechanisms of action • Pharmacodynamics • PK-PD Profile • Pharmacokinetics • Spectrum of activity • Microbial resistance • Safety: Inherent toxicity of the drug to the host	• 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*.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

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 asyptomatic 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.

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

Tamma PD, Cosgrove SE. Infect Dis Clin North Am. 2011 25:245; Ohl CA, Luther VP. J. Hosp. Med. 2011;6:S4

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

HANDLE ANTIBIOTICS WITH CARE

Antibiotics are given to patients, which can result in drug-resistant bacteria developing in the gut

Patient attends hospital or clinic

Drug-resistant bacteria spreads to other patients through poor hygiene and unclean facilities

Drug-resistant bacteria spreads to the general public

Drug-resistant bacteria reaches humans through food, the environment (water, soil, air) or by direct human-animal contact

Animals develop drug-resistant bacteria in their gut

Antibiotics are given to food producing animals and crops

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

www.who.int/drugresistance

#AntibioticResistance

World Health Organization