Applying Pharmacodynamics and Pharmacokinetics Principles To Antimicrobial Therapy

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Make.
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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.

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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

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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&sectionid=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&sectionid=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.

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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.

Mechanisms of Antimicrobial Action: Inhibition of Biological Targets

The takeaways

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

Bacteria / Fungi	Viruses	Protozoa
1. Cell wall synthesis	1. Polymerases	1. Chemical
2. Cell membrane function	2. Proteases	2. Detoxification processes
3. Protein synthesis	3. Integrases	3. Folate synthesis
4. Folate synthesis	4. Envelope fusion	**Helminths**
5. Nucleic acid metabolism	5. Uncoating	1. Various
6. RNA polymerase	6. Budding	2. physiological and
7. Topoisomerases		3. biochemical
		4. pathways

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.*

Contributors to the Emergence of Resistance

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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.

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

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- **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.

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	**Intracellular penetration:** some organisms hide in host cells
Tissue penetration: anatomic and vascular barriers, such as the blood-brain barrier	**Endocardial vegetation:** deposition of platelets, fibrin, microbes, inflammatory cells on endocardial tissue
Active efflux (physiologic): P-glycoprotein and other efflux pumps	**Biofilm:** colonies of slow-growing microbes that adhere to prosthetic devices

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*.

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.