Antimicrobial Agents

A. DEFINITIONS
B. HISTORY
C. IMPACT OF ANTIMICROBIALS ON HEALTH CARE
D. PRODUCTION, ISOLATION, AND PURIFICATION
E. NECESSARY INFORMATION

Mechanisms of Action of Antimicrobial Agents

I. INHIBITORS OF BACTERIAL CELL WALL BIOSYNTHESIS
II. INHIBITION OF PROTEIN BIOSYNTHESIS
III. INHIBITION OF NUCLEIC ACID BIOSYNTHESIS
IV. ALTERATION OF CELL MEMBRANE FUNCTION
V. INHIBITION OF CELL METABOLISM (ANTIMETABOLITES)

Mechanisms of Antibiotic Resistance

I. PROBLEM OF RESISTANCE
II. MOLECULAR GENETICS OF ANTIBIOTIC RESISTANCE
III. SPECIFIC MECHANISMS OF RESISTANCE
IV. CONTROL OF RESISTANCE

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Table 6. Top Notifiable Bacterial Diseases in U.S.
Table 7. Bacteria Associated with Human Disease
IDENTIFICATION AND CLASSIFICATION OF BACTERIA
GRAM POSITIVE BACTERIA
GRAM NEGATIVE BACTERIA

Host Factors in Antimicrobial Treatment

I. NON-SPECIFIC HOST DEFENCE MECHANISMS
II. NON-SPECIFIC IMMUNITY
III. ACQUIRED OR ADAPTIVE IMMUNITY
IV. HOST-IMMUNE RESPONSES
V. OTHER HOST FACTORS ASSOCIATED WITH TREATMENT

The Penicillins

I. CHEMISTRY AND MECHANISM OF ACTION
II. CLASSIFICATION OF THE PENICILLINS
III. MECHANISMS OF RESISTANCE
IV. SPECTRUM & USES
V. ABSORPTION, DISPOSITION, AND METABOLISM
V. ADVERSE EFFECTS
VI. DRUG INTERACTIONS
VII. PRODUCTS and DOSAGES

The Cephalosporins

I. CHEMISTRY AND MECHANISM OF ACTION
II. CLASSIFICATION OF THE CEPHALOSPORINS
III. MECHANISMS OF RESISTANCE
IV. SPECTRUM & USES
IV. ABSORPTION, DISPOSITION, AND METABOLISM
V. ADVERSE REACTIONS
VI. DRUG INTERACTIONS
VII. PRODUCTS and DOSING

Carbapenem and Monobactam Antibiotics

Imipenem-Cilastatin & Meropenem
Aztreonam

ACQUISITION COSTS OF PARENTERAL ANTIBIOTICS

Macrolides

I. HISTORY AND STRUCTURAL FEATURES
II. MECHANISM OF ACTION
III. SPECTRUM
IV. USES
V. RESISTANCE
VI. DISPOSITION, METABOLISM, AND EXCRETION
**Mycobacterial Infections**

**Triacetin**

**Haloprigin**

**Tolnaftate**

**Polyenes - Amphotericin B and Nystatin**

**III. Fosfomycin**

**Sulfonamides**

**VII. ADVERSE REACTIONS**

**The Quinolones**

**I. STRUCTURE AND MECHANISM OF ACTION**

**II. MECHANISMS OF RESISTANCE**

**III. SPECTRUM**

**IV. USES**

**V. RESISTANCE**

**VI. DISPOSITION, METABOLISM, AND EXCRETION**

**VII. ADVERSE REACTIONS**

**VIII. INTRAVENOUS PRODUCTS**

**IX. TOPICAL PRODUCTS**

**Tetracyclines**

**I. HISTORY AND MECHANISM OF ACTION**

**II. STRUCTURAL CHARACTERISTICS**

**III. SPECTRUM**

**IV. USES**

**V. RESISTANCE**

**VI. DISPOSITION, EXCRETION, AND METABOLISM**

**VII. ADVERSE EFFECTS**

**VIII. PRODUCTS**

**Chloramphenicol**

**Vancomycin**

**Quinupristin/Dalfopristin**

**Bacitracin and Polymyxins**

**Mupirocin**

**Clindamycin**

**Metronidazole**

Opportunistic Fungal Infections

**Systemic Antifungal Agents**

**Polyenes - Amphotericin B and Nystatin**

**Flucytosine (5-Fluorocytosine)**

**Imidazoles and Triazoles**

**Terbinafine**

**Griseofulvin**

**Topical Antifungal Agents**

**Polyenes**

**Imidazole Antifungals (Topical)**

**Tolnaftate**

**Undecylenic acid**

**Cicloprox olamine**

**Haloprigin**

**Nattifine and Terbinafine**

**Butenafine**

**Triacetin**

**Antimycobacterial Agents**

Mycobacterial Infections
Other Antimalarial Drugs

Mefloquine
Pentamidine Isethionate
Pyrantel Pamoate
Clofazamine
Isoniazid

Antiparasitic Agents
Mebendazole & Albendazole
Pyrantel Pamoate
Praziquantel
Niclosamide
Drugs for Pneumocystis carinii pneumonia
Atovaquone
Pentamidine Isethionate
Drugs for Toxoplasmosis
Pyrimethamine
Drugs for Cryptosporidium sp.
Antimalarial Drugs
Chloroquine
Mefloquine
Primaquine
Other Antimalarial Drugs
Antimicrobial Agents

**INTRODUCTION**

**A. DEFINITIONS**

1. Antimicrobial vs. Anti-infective vs. Antibacterial vs. Antibiotic

2. Bactericidal vs. Bacteriostatic

**B. HISTORY**

500 B.C. - China
1877 - Pasteur
1876-90 - Koch
1929 - Fleming
1930’s – Domagk (Bayer)
1939-41 - Florey & Chain

**C. IMPACT OF ANTIMICROBIALS ON HEALTH CARE**

1. Infectious disease - first drugs to actually result in a "cure"

2. Usage & Market share

3. Cost/Benefit ratio - complex issue

**D. PRODUCTION, ISOLATION, AND PURIFICATION**

1. Natural Antibiotics - produced by fermentation

2. Semi-Synthetic

3. Synthetic
E. NECESSARY INFORMATION

To fully understand antimicrobial therapy and provide the best pharmaceutical care to our patients, pharmacists and physicians need to be able to answer several questions to select the most appropriate drug for treatment of infection. Selection of the optimal antibiotic also requires a fundamental basis in medical microbiology in order to identify the most likely causative agent of infection.

Table 1. What Do we Need to Know about Antimicrobials?

<table>
<thead>
<tr>
<th>What is it ?</th>
<th>Chemical structure and class natural or synthetic product</th>
</tr>
</thead>
<tbody>
<tr>
<td>How does it work ?</td>
<td>Target site Mechanism of action</td>
</tr>
<tr>
<td>When is it used ?</td>
<td>Spectrum of activity and important clinical uses</td>
</tr>
<tr>
<td>What are the problems ?</td>
<td>Side Effects/Toxicity Microbial Resistance</td>
</tr>
<tr>
<td>Where does it go ?</td>
<td>Absorption, Distribution, Metabolism, &amp; Excretion</td>
</tr>
<tr>
<td>How do we get it there ?</td>
<td>Route of administration Product formulation</td>
</tr>
<tr>
<td>How much does it cost ?</td>
<td>Cost effectiveness</td>
</tr>
</tbody>
</table>

Adapted from Mims, Playfair, Roitt, Wakelin, & Williams, Medical Microbiology, Mosby Europe Ltd., London, 1993.

F. EMPIRIC VS. DEFINITIVE THERAPY

1. Empiric therapy - based on treatment of most likely organisms for a specific infection

2. Definitive therapy - after organism is identified. May or may not have information on susceptibility & resistance.
Mechanisms of Action of Antimicrobial Agents

Antimicrobial agents take advantage of the differences between animals cells and bacteria (prokaryotes), fungi, or protozoa. The goal is to have highly selective toxicity towards these microbes with minimal or no toxicity in humans. Table 2 shows the basic differences between eukaryotes and prokaryotes.

Table 2. Characteristics of Eukaryotes and Prokaryotes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eukaryotes</th>
<th>Prokaryotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Groups</td>
<td>Algae, Fungi, Protozoa, Plants, Animals</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Size (approximate)</td>
<td>5 µm</td>
<td>0.5 - 3.0 µm</td>
</tr>
<tr>
<td>Nuclear Structure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus</td>
<td>Classic nuclear membrane</td>
<td>No nuclear membrane</td>
</tr>
<tr>
<td>Chromosomes</td>
<td>Double Stranded DNA arranged in multiple chromosomes</td>
<td>Single, closed strand of genomic DNA. Additional DNA found in plasmids</td>
</tr>
<tr>
<td>Cytoplasmic Structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Golgi bodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Endoplasmic reticulum</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Ribosomes (sedimentation coefficient)</td>
<td>80S (60S and 40S subunits)</td>
<td>70S (50S and 30S subunits)</td>
</tr>
<tr>
<td>Cytoplasmic membrane</td>
<td>Contains sterols. In animals, membranes contain cholesterol. Egosterol present in fungal membranes.</td>
<td>No sterols present*</td>
</tr>
<tr>
<td>Cell Wall</td>
<td>Absent or composed of cellulose (plants) or chitin (insects, fungi)</td>
<td>Complex structure containing lipids, proteins, and peptidoglycan</td>
</tr>
<tr>
<td>Reproduction</td>
<td>Sexual and asexual</td>
<td>Binary fission (asexual)</td>
</tr>
<tr>
<td>Movement</td>
<td>Usually none. If present, flagella are complex</td>
<td>Simple flagella, if present</td>
</tr>
<tr>
<td>Respiration</td>
<td>via mitochondria</td>
<td>via cytoplasmic membrane</td>
</tr>
</tbody>
</table>

* except in *Mycoplasma sp.*


The most common targets for antimicrobial drug actions fall into 5 basic categories:

A. Inhibition of Cell Wall Synthesis
B. Inhibition of Protein Synthesis
C. Inhibition of Nucleic Acid Synthesis
D. Effects on cell membrane sterols (antifungal agents)
E. Inhibition of unique metabolic steps
Table 3. Specific Mechanism of Action of Antimicrobial Agents

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibition of Cell Wall Synthesis</strong></td>
<td></td>
</tr>
<tr>
<td>Inhibit cross-linking of peptidoglycan by inactivating transpeptidases (PBPs)</td>
<td>Penicillins, Cephalosporins, Aztreonam, Imipenem</td>
</tr>
<tr>
<td>Bind to terminal D-ala-D-ala &amp; prevent incorporation into growing peptidoglycan</td>
<td>Vancomycin, Teicoplanin</td>
</tr>
<tr>
<td>Inhibition of transglycosylation</td>
<td></td>
</tr>
<tr>
<td>Oritavancin, Teicoplanin, lipophilic vancomycin analogs, ramiplanin</td>
<td></td>
</tr>
<tr>
<td>Inhibit dephosphorylation of phospholipid carrier in peptidoglycan structure</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Prevents incorporation of D-alanine into peptidoglycan</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibition of Protein Synthesis</strong></td>
<td></td>
</tr>
<tr>
<td>Bind to 50S ribosomal subunit</td>
<td>Macrolides, Chloramphenicol, Clindamycin</td>
</tr>
<tr>
<td>Bind to 30S ribosomal subunit</td>
<td>Aminoglycosides, Tetracyclines</td>
</tr>
<tr>
<td><strong>Inhibition of Nucleic acid synthesis</strong></td>
<td></td>
</tr>
<tr>
<td>Inhibition of DNA gyrase &amp; topoisomerase</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Inhibition of nucleic acid biosynthesis</td>
<td>Flucytosine, Griseofulvin</td>
</tr>
<tr>
<td>Inhibition of mRNA synthesis</td>
<td>Rifampin, Rifabutin, Rifapentine</td>
</tr>
<tr>
<td><strong>Alteration of Cell Membrane Function</strong></td>
<td></td>
</tr>
<tr>
<td>Inhibition of ergosterol biosynthesis</td>
<td>Imidazole antifungals</td>
</tr>
<tr>
<td>Bind to membrane sterols</td>
<td>Polymyxins, Amphotericin B, Nystatin</td>
</tr>
<tr>
<td><strong>Alteration of Cell Metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Inhibition of tetrahydrofolic acid production (cofactor for nucleotide synthesis)</td>
<td>Sulfonamides, Trimethoprim, Trimetrexate Pyrimethamine</td>
</tr>
<tr>
<td>Inhibition of mycolic acid biosynthesis</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Interference with ubiquinone biosynthesis &amp; cell respiration</td>
<td>Atovaquone</td>
</tr>
<tr>
<td>Bind to macromolecules</td>
<td>Metronidazole, Nitrofurantoin</td>
</tr>
</tbody>
</table>
I. INHIBITORS OF BACTERIAL CELL WALL BIOSYNTHESIS
  e.g. Penicillins, Cephalosporins, Vancomycin, Bacitracin, Fosfomycin

A. CELL WALL BIOSYNTHESIS

1. Peptidoglycan layer - Basic Building Blocks of

   a. N-acetyl glucosamine (NAG) and N-acetyl muramic acid (NAM)

   ![Chemical structures of NAG and NAM]

   - Transglycosylation – attachment of sugars to pentapeptide and membrane. C55-phospholipid - (Lipid A intermediate) involved in anchorage of peptidoglycan to membrane by connection through NAG via a pyrophosphate bond.
   - Transpeptidation. Crosslinking of Amino-acid pentapeptide

   ![Peptidoglycan structure diagram]

   - Peptidoglycan of Staph. aureus

   i. Composition of amino acids may vary from one bacterium to another
   ii. Unusual D-amino acids are present. D-alanine and diaminopipelic acid are unique to bacteria.
Bacterial Cell Wall Biosynthesis and the Steps blocked by Antibiotics

**Cytoplasm**

**Synthesis of Cell Wall Precursors**

- **UDP-NAG** → **UDP-NAM**
  - **fosfomycin** inhibits formation of glycosidic bonds
- cycloserine prevents incorporation of D-ala
- D-ala → D-ala

**Cytoplasmic Membranes**

**Synthesis of new cell wall subunit attached to lipid carrier**

- UDP-NAG → NAM
  - **bacitracin** prevents dephosphorylation of lipid carrier
  - **vancomycin** binds to terminal D-ala-D-ala

**Cell Wall**

**attachment of new subunit to growing peptidoglycan**

- **β-lactams** inhibit crosslinking enzymes

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UDP-NAG
UDP-NAM
C55-lipid
NAG
NAM
NAG
NAM
NAG
NAM
NAG
NAM
β-lactams
II. INHIBITION OF PROTEIN BIOSYNTHESIS

A. Interaction with 30S ribosomal subunit - Aminoglycosides & Tetracyclines
B. Interaction with 50S ribosomal subunit - Chloramphenicol, Macrolides, Clindamycin

- Binding of fmet tRNA and formation of initiation complex on 70S ribosome
- Translocation of fmet tRNA from acceptor site (A) to donor site (P)
- Binding of new aminoacyl tRNA (1) to the acceptor site
- Formation of peptide bond catalyzed by peptidyl transferase
- Release of uncharge t-RNA
- Translocation of peptidyl tRNA (1)
- Binding of aminoacyl tRNA (2)
- Formation of peptide bond & peptide chain elongation
- Translocation of peptidyl tRNA(n) Exposes terminator codon
- Termination & release of peptide

Adapted from Mims, Playfair, Roitt, Wakelin, & Williams, Medical Microbiology, Mosby Europe Ltd, London, 1993.
III. INHIBITION OF NUCLEIC ACID BIOSYNTHESIS

A. **Quinolones** - inhibit DNA gyrase & topoisomerase

B. **Flucytosine** - converted to 5-Fluorouracil in fungi. 5-FU inhibits thymidylate synthetase. Incorporated into fungal RNA.

C. **Griseofulvin** - binds to RNA of actively growing fungi

D. **Rifampin & Rifabutin** - inhibition of DNA dependent RNA polymerase

IV. ALTERATION OF CELL MEMBRANE FUNCTION

A. **Amphotericin B, Nystatin, Polymyxin B** - bind avidly to membrane sterols. Higher affinity for ergosterol (present in fungal membranes) than for cholesterol (in mammalian membranes).

B. **Imidazole antifungals** e.g. ketoconazole, fluconazole - inhibit 14-demethylation of lanosterol to ergosterol (essential component of fungal membranes).

V. INHIBITION OF CELL METABOLISM (ANTIMETABOLITES)

A. **Sulfonamides** - p-aminobenzoic acid (PABA) analogs that competitively inhibit incorporation of tetrahydropteroic acid, an initial step in the synthesis of folic acid.

B. **Trimethoprim, Trimetrexate, Pyrimethamine** - inhibitors of dihydrofolate reductase in bacteria (trimethoprim) or protozoa (pyrimethamine, trimetrexate).

C. **Atovaquone** - inhibits ubiquinone biosynthesis & cell respiration in protozoa

D. **Isoniazid, Ethionamide** - inhibit mycolic acid biosynthesis in Mycobacterium sp.

E. **Metronidazole, Nitrofurantoin** - reduced to highly reactive metabolites. Bind to cell macromolecules.