Chapter 51

Clinical Use of Antimicrobial Agents
## History of antimicrobial therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 17th century</td>
<td><em>Cinchona bark</em> was used as an important historical remedy against malaria.</td>
</tr>
<tr>
<td>1909</td>
<td><strong>Paul Ehrlich</strong> sought a “<em>magic bullet</em>” that would kill only bacteria while leaving human cells undamaged. He discovered a medicinally useful drug, the synthetic antibacterial <em>Salvarsan</em> for the treatment of syphilis.</td>
</tr>
<tr>
<td>1929</td>
<td><strong>Penicillin</strong> was discovered by <strong>Alexander Fleming</strong>.</td>
</tr>
<tr>
<td>1935</td>
<td><strong>Sulfa drugs</strong> were discovered.</td>
</tr>
<tr>
<td>1940</td>
<td><strong>Florey and Chain mass</strong> produce <strong>penicillin</strong> for war time use, becomes available to the public.</td>
</tr>
<tr>
<td>1943</td>
<td><strong>Streptomycin</strong> was discovered.</td>
</tr>
</tbody>
</table>
Misuse of Antibiotics:

Overuse and inappropriate use of antibiotics has fueled a major increase in prevalence of multidrug-resistant pathogens leading to speculate that we are nearing the end of antibiotic era. Development of novel drugs has slowed unfortunately. It seems likely that over the next decade we will have to rely on currently available families of drugs. So, it is extremely important that we prescribe antibiotics rationally in appropriate dosage and in appropriate routes.
Bacterial Resistance

Bacterial resistance to an antimicrobial agent is attributable to three general mechanisms

1- The drug does not reach its target (deactivation of transport mechanisms or activation of efflux mechanisms).

2- The drug is not active (inactivation of the drug or failure to activate prodrug).

3- The target is altered.
<table>
<thead>
<tr>
<th>Drugs showing resistance due to altered targets</th>
<th>Drugs showing resistance due to decreased accumulation</th>
<th>Drugs showing resistance due to enzymatic inactivation of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Permeability</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Efflux</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Lactams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td></td>
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<tr>
<td>Rifampin</td>
<td></td>
<td></td>
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<tr>
<td>Sulfonamides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoroquinolones.

β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalosporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.

Tetracycline was effective against gynecologic infection due to bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.

β-Lactamases destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.
Clinical uses of antimicrobial agents

Antimicrobials have three general uses

1- Empirical therapy or initial therapy: the antimicrobial should cover all the likely pathogens because the infecting organism(s) has not yet been defined.

2- Definitive therapy or pathogen-directed therapy: once the infecting microorganism is identified, definitive antimicrobial therapy should be instituted with a narrow-spectrum, low-toxicity agent to complete the course of treatment.

3- Prophylactic or preventive therapy.
EMPIRIC THERAPY

• The use of antimicrobial agents before the pathogen responsible for particular illness or the susceptibility to a particular antimicrobial agent is known.

• Should be approached rationally
  – Syndrome
  – Likely pathogens
  – Known resistance patterns
  – Host factors
Approach to empirical therapy I

A. Formulate a **clinical diagnosis** of microbial infection.
   Clinician should conclude that there is anatomic evidence of infection (e.g. pneumonia)

B. Obtain specimens for laboratory examination, empirical therapy begins.

C. Formulate a microbiologic diagnosis.
   A microbiologic diagnosis should be formulated with the history, physical examination, and immediately available laboratory results (e.g. Gram’s strain)
Approach to empirical therapy II

D. Determine the necessity for empirical therapy.

E. Institute treatment. Treatment should be instituted taking into account the most likely pathogens responsible for the patient’s illness.
Selection of antimicrobial agents depends on host factors and pharmacological factors.

Host factors:

1. Concomitant disease states
2. Prior adverse drug effect
3. Hepatic or renal function
4. Age
5. Pregnancy status
• **Age**
  - Gastric acidity low in young children and elderly
  - Renal, hepatic function vary with age
    - Dose adjustment for creatinine clearance and hepatic dysfunction is critical to avoid toxicities
  - Developing bone and teeth
    - Tetracyclines stain teeth
    - Quinolones may impair bone and cartilage growth

• **Pregnancy**
  - tetracyclines and chloramphenicol have well-described fetal or neonatal adverse effects and should be avoided
Pharmacological factors:

1. Kinetics of absorption, distribution, and elimination;
2. The ability of the drug to be delivered to the site of infections; Bacteriostatic vs bactericidal activity;
3. The potential toxicity of an agent;
4. Pharmacokinetic or pharmacodynamic interaction with other drugs.
• **Site of infection**
  – Adequate concentrations of antimicrobials must be delivered to the site of infection
  – Local concentrations greater than MIC
  – Subinhibitory concentrations may still alter bacterial adherence, morphology, aid in phagocytosis and killing
  – Serum concentration easy to determine, tissue concentrations more difficult to assess
  – Protein binding of drugs

• **Excretion**
  – Urine: Aminoglycosides, fluoroquinolones (Urinary tract infections)
  – Bile: Ceftriaxone

• **Penetration into various sites**
  – Central nervous system
  – Lung
  – Bone
  – Foreign bodies
ANTIMICROBIAL THERAPY OF INFECTIONS WITH KNOWN ETIOLOGY
Interpretation of culture results

Properly obtained and processed specimens for culture yield reliable information about the cause of infection frequently.

In the case of following conditions microbial confirmation may not be obtained:

- Sample error, eg, contamination of specimens sent for culture
- Noncultivable or slow-growing organisms (Histoplasma capsulatum, Bartonella or Brucella species)
- Requesting bacterial cultures when infection is due to other organisms
- Not recognizing the need for special media or isolation techniques (eg, charcoal yeast extract agar for isolation of legionella species)

The present culture technique may be inadequate to identify all cases of the disease.
Guiding antimicrobial therapy of established infections

- **Susceptibility testing**
- Specialized assay methods
  a. beta-lactamase assay
  b. synergy studies
Antimicrobial Susceptibility Testing

Minimal inhibitory concentration (MIC)
- MIC is the lowest concentration of antimicrobial agents that prevents visible growth in 18-24 hours incubation.

Minimum bactericidal concentration (MBC)
- The minimum concentration needs for kill 99.9% of testing microorganisms over 24 hours.
  
  If $\text{MBC} \geq 32 \times \text{MIC}$, it indicates that the microorganism has resistance to the drug.

- Multiple techniques
  - Disk: semi-quantitative
  - Broth Dilution: quantitative
In the lab, susceptibility is most often measured using a disk diffusion test.
1. Tubes containing varying concentrations of antibiotic are inoculated with test organism.

<table>
<thead>
<tr>
<th>Highest antibiotic concentration</th>
<th>Lowest antibiotic concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>32</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Relative antibiotic concentration

2. Growth of microorganism is measured after 24 hours of incubation.

<table>
<thead>
<tr>
<th>64</th>
<th>32</th>
<th>16</th>
<th>8</th>
<th>4</th>
<th>2</th>
<th>1</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bacterial growth</td>
<td>Bacterial growth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Minimal inhibitory concentration (MIC) is the lowest concentration of antibiotic that inhibits bacterial growth (equals 2 in this example).

3. Subculture in antibiotic-free medium, and measure growth after 24 hours of incubation.

<table>
<thead>
<tr>
<th>64</th>
<th>32</th>
<th>16</th>
<th>8</th>
<th>4</th>
<th>2</th>
<th>1</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial growth</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Minimal bactericidal concentration (MBC) is the lowest concentration of antibiotic that kills 99.9 percent of bacteria (equals 32 in this example).

Figure 30.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.
Monitoring therapeutic response - duration of therapy

- 2 methods
  - microbiology - cultures/specimens should become sterile
  - clinically - symptoms, inflammatory markers, radiology
Duration of therapy

- Duration depends on pathogen, site of infection, host factor
- Generally determined empirically
- Duration varies from a single dose to many months depending on the infection
- Serious infection: 7-10 days after pt is afebrile
- Recurrent infections: longer
- For certain infections a minimum duration is recommended
# Recommended minimum durations of therapy

<table>
<thead>
<tr>
<th>Infection</th>
<th>Minimum duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>4 - 6 months</td>
</tr>
<tr>
<td>Empyema/lung abscess</td>
<td>4 - 6 weeks</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Atypical pneumonia</td>
<td>2 - 3 weeks</td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td>7 days</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>5 days</td>
</tr>
</tbody>
</table>
Clinical failures

- check culture
- check host
- check antibiotics
**Antimicrobial pharmacodynamics**

Pharmacodynamic factors include

- Pathogen susceptibility testing
- Drug bactericidal versus bacteriostatic activity
- Drug synergism, antagonism
- Postantibiotic effects
Bactericidal versus bacteriostatic activity

Bacteriostatic drugs
- Bacteriostatic drugs agents arrest the growth or replication of the microorganism, but cannot kill them.

Bactericidal drugs
- The agents which can kill the microorganisms are called bactericidal drugs, but also can destroy them.
- It should be noted that a drug may be bacteriostatic for one organism but bactericidal for another.
- Bactericidal agents can be divided into two groups: agents that exhibit concentration-dependent killing (eg, aminoglycosides and quinolones) and agents that exhibit time-dependent killing (eg, beta-lactams and vancomycin).
Bactericidal vs bacteriostatic
Table. Bacteriostatic and bactericidal antibacterial agents.

<table>
<thead>
<tr>
<th>Bacteriostatic</th>
<th>Bactericidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol, Clindamycin, Ethambutol</td>
<td>Aminoglycosides, Bacitracin, Beta-lactam antibiotics</td>
</tr>
<tr>
<td>Macrolides, Nitrofurantoin, Oxazolidinones,</td>
<td>Isoniazid, Metronidazole, Polymyxins, Pyrazinamide</td>
</tr>
<tr>
<td>Sulfonamides, Tetracyclines, Trimethoprim</td>
<td>Quinolones, Rifampin, Vancomycin</td>
</tr>
</tbody>
</table>
Postantibiotic effect

- Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent is known as the postantibiotic effect (PAE).

- Most antimicrobials possess significant in vitro postantibiotic effects ($\geq 1.5 \text{ h}$) against susceptible Gram-positive cocci.

- In vivo PAE’s are usually longer than in vitro PAE’s due to postantibiotic leukocyte enhancement.

- Drug concentrations of the agents that lack postantibiotic effect should be maintained above the minimal inhibiting concentration for the entire dosage interval.
Table 51-4 Antibacterial Agents with In Vitro Postantibiotic Effects ≥1.5 Hours.

<table>
<thead>
<tr>
<th>Against gram-positive cocci</th>
<th>Against gram-negative bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Carbapenems</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Ketolides</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
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<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td></td>
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<tr>
<td>Tetracyclines</td>
<td></td>
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<tr>
<td>Tigecycline</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
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</tbody>
</table>
Pharmacokinetic considerations

A. Route of Administration
B. Conditions That Alter Antimicrobial
C. Drug Concentrations in Body Fluids
D. Monitoring Serum Concentrations of Antimicrobial Agents
A. Route of administration

- many drugs have similar pharmacokinetic properties po vs iv

tetracycline
trimethoprim-sulfamethoxazole
quinolones
chloramphenicol
metronidazole
clindamycin
rifampicin
fluconazole
Choice of regimen

- Oral vs parenteral
- Traditional view
  - “serious = parenteral”
  - previous lack of broad spectrum oral antibiotics with reliable bioavailability
- Improved oral agents
  - higher and more persistent serum and tissue levels
  - for certain infections as good as parenteral
Advantages of oral treatment

- Eliminates risks of complications associated with intravascular lines
- Shorter duration of hospital stay
- Savings in nursing time
- Savings in overall costs
- IV are for:
  • critically ill pt
  • bacterial meningitis/endocarditis
  • cannot swallow
  • abx that are poorly absorbed orally
B. Conditions That Alter Antimicrobial Pharmacokinetics

- Impairment of renal or hepatic function—drug dose requirements may be increased in patients with burns, cystic fibrosis, or trauma. Patients with these conditions may have increased dosage requirements for selected agents.

- Pharmacokinetics are also altered in the elderly, in neonates, and in pregnancy.
C. Drug Concentrations in Body Fluids

• Most antimicrobial agents are well distributed to most body tissues and fluids except for cerebrospinal fluid.
• In the presence of meningitis, however, the cerebrospinal fluid concentrations of many antimicrobials increase.
D. Monitoring Serum Concentrations of Antimicrobial Agents

To justify routine serum concentration monitoring, it should be established (1) that a direct relationship exists between drug concentrations and efficacy or toxicity; (2) that substantial interpatient variability exists in serum concentrations on standard doses; (3) that a small difference exists between therapeutic and toxic serum concentrations; (4) that the clinical efficacy or toxicity of the drug is delayed or difficult to measure; and (5) that an accurate assay is available.
MANAGEMENT OF ANTIMICROBIAL DRUG TOXICITY

- usually able to switch
- some no alternatives - eg neurosyphilis has anaphylaxis to penicillin - needs desensitisation
- penicillin + cephalosporin <10%

- penicillin + imipenem cross reaction - >50%
ANTIMICROBIAL DRUG COMBINATIONS

• Combinations of antimicrobial drugs should be used only for:
  1. To provide broad-spectrum empirical therapy in seriously ill patients.
  2. To treat polymicrobial infections.
  3. To decrease the emergence of resistant strains (e.g., TB).
  4. To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.
  5. To obtain enhanced inhibition or killing.
Effects of combinations of drugs

• Sometimes the chemotherapeutic effects of two drugs given simultaneously is greater than the effect of either given alone.

• This is called synergism. For example, penicillin and streptomycin in the treatment of bacterial endocarditis. Damage to bacterial cell walls by penicillin makes it easier for streptomycin to enter.
• Other combinations of drugs can be antagonistic.

• For example, the simultaneous use of penicillin and tetracycline is often less effective than when either drug is used alone. By stopping the growth of the bacteria, the bacteriostatic drug tetracycline interferes with the action of penicillin, which requires bacterial growth.
Mechanism of synergistic action:

1. Blockade of sequential steps in a metabolic sequence (TMP+SMZ)
2. Inhibition of enzymatic inactivation (beta-lactamases)
3. Enhancement of antimicrobial agent uptake (penicilins+aminoglycosides)
Mechanism of antagonistic action

1. Inhibition of –cidal activity by –static agents: cell wall agents need dividing cells to act upon - if stopping cell division = cannot work; eg: tetracycline + chloramphenicol inhibit cell wall agents

2. Induction of enzymatic inactivation-(enterobacter, pseudomonas, serratia, citrobacter) if given imipenem, cefoxitin, ampicillin - can induce beta-lactamase secretion --> hence beta-lactams will lose activity
ANTIMICROBIAL PROPHYLAXIS

Nonsurgical prophylaxis, e.g.,

1) Tuberculosis
2) Malaria
3) HIV infection
4) Meningococcal infection
5) Rheumatic fever
6) Urinary tract infections (UTI)
# Surgical prophylaxis

<table>
<thead>
<tr>
<th>National research council wound classification criteria</th>
<th>expected infection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean</td>
<td>≤ 2%</td>
</tr>
<tr>
<td>Clean contaminated</td>
<td>≤ 10%</td>
</tr>
<tr>
<td>Contaminated</td>
<td>about 20%</td>
</tr>
<tr>
<td>Dirty</td>
<td>about 40%</td>
</tr>
</tbody>
</table>
Surgical prophylaxis, e.g.,
1) Cardiac operation
2) Noncardiac, thoracic operation
3) Vascular (abdominal and lower extremity) operation
4) Head and neck operation
5) Gastroduodenal or biliary operation
6) Orthopedic operation (with hardware insertion)
7) Penetrating trauma
8) Burn wound
9) Colorectal operation
10) Appendectomy