Significance of antimicrobial drugs

Challenges
- Emerging resistance
- Fewer new drugs
- MRSA and other resistant pathogens are major problems

Definitions
- Antibiotic
- Selective Toxicity
- Antimicrobial spectrum

Antimicrobial resistance
- Innate
- Acquired
- Mutation
  - Gene transfer
  - Mechanisms
    - inactivation of drug
    - modification of target
    - prevention of access

Beta lactam antibiotics
- Penicillins, cephalosporins, beta lactamase inhibitors
- Structural analog of peptide portion of peptidoglycan
- Resistance
  - penicillinase, beta-lactamase
  - altered penicillin binding proteins
  - impermeability or efflux
- Low toxicity

MRSA: resistant to beta lactams by acquisition of new penicillin binding protein (which doesn’t bind penicillin!)
- Healthcare-associated, community acquired
- Vancomycin is best alternative to beta lactam, but susceptibility is decreasing

Macrolides
- Azithromycin
- Useful for respiratory tract infections
- Blocks protein synthesis by plugging up large ribosomal subunit
- Resistance
  - enzymatic modification of ribosome
  - efflux
Fluoroquinolones
  - Ciprofloxacin and other -floxacins
  - Useful for respiratory tract, intestinal, and urinary tract infections
  - Inhibits DNA replication
  - Resistance
    - mutations occur frequently
  - Toxicity- generally mild but some problems
  - Promote colonization with MRSA

Antimicrobial susceptibility determination in laboratory
  - MIC – minimum inhibitory concentration
  - Disk diffusion method

Ideal vs. empiric therapy

Antiviral, antifungal, and anti-parasitic antimicrobials
The greatest contribution of modern medicine to humanity has been the control of infectious diseases. This has been accomplished through:

- Sanitation
- Immunization
- Antimicrobial drugs

Current Challenges in the Effective Use of Antibiotics

- Increasing antibiotic resistance in bacterial pathogens
- 2,000,000 bacterial infections per year in U.S. hospitals
  - 90,000 of these have fatal outcomes
- 1,000,000 prescriptions/yr in U.S. by office based physicians
  - 500,000 of these are inappropriate
- Antibiotics are a reduced priority for pharmaceutical industry

Current Major Problems with Acquired Antibiotic Resistance

- **Staphylococcus aureus** (MRSA)
  - vancomycin resistance (VISA, VRSA)
- **Enterococcus faecium**
  - vancomycin resistance (VRE), multiple resistance
- **Mycobacterium tuberculosis**
  - multiple resistance
- **Pseudomonas aeruginosa, Acinetobacter baumanii**
  - rapid development of multiple resistance, carbapenemases
- Enteric bacteria: *Klebsiella, Enterobacter*
  - Extended spectrum beta-lactamases, carbapenemases

Antimicrobial Resistance

- **Innate Resistance**
  - Resistance to an antimicrobial is a characteristic property of a species
    - e.g. *Mycoplasma* species are innately resistant to antibiotics that target peptidoglycan synthesis
- **Acquired resistance**
  - Acquisition of resistance to an antimicrobial by members of a species that is normally sensitive
    - Mutation
    - Gene transfer
  - Mechanisms of acquired antimicrobial resistance
    - Inactivation of drug (usually enzymatic)
    - Modification of target (enzymatic or mutational)
    - Prevention of access to target
    - Blocking entry of the antibiotic to the cell
    - Active export of the antibiotic from the cell

Antimicrobial Drugs

- Definitions and Principles
  - **Antibiotic**
    - old definition: antimicrobial drugs of biologic origin
    - current usage: antibiotics are increasingly being defined as any substance that kills or inhibits the growth of bacteria
  - **Selective Toxicity**
    - Ratio of the toxic dose to the effective dose
  - **Antimicrobial spectrum**
    - Broad spectrum – effective against many species of microbes
    - Narrow spectrum – effective against one or a few species

Most Prescribed Antibiotic Classes

- **Beta lactam antibiotics**
- **Cell wall synthesis**
- **Macrolides**
- **Protein synthesis**
- **Fluoroquinolones**
- **DNA synthesis**
Beta lactam antibiotics

- Penicillins – penicillin, nafcillin, dicloxacillin, ampicillin, amoxicillin
- Cephalosporins - cephalexin, cefuroxime, ceftriaxone, cefepime
- Carbapenems – imipenem, meropenem
- Monobactams - aztreonam
- β-lactamase inhibitors – sulbactam, clavulanate

Mechanism of action
Act as structural analog of D-alanyl D-alanine. Prevent peptide crosslinking of peptidoglycan by binding critical enzymes

Mechanisms of resistance
- production of β-lactamase
- production of altered cross-linking enzymes (penicillin-binding proteins)
- impermeability and/or efflux

Toxicity: hypersensitivity
Very safe in non-sensitive individuals

Inhibitors of Protein Synthesis

Macrolides: erythromycin, clarithromycin, azithromycin (Zithromax)

- Achieves high levels in respiratory secretions, useful for pneumonia, sinusitis

Mechanism of action
Blocks polypeptide exit tunnel in 50S ribosomal subunit, inhibits translocation

Resistance
- methylation of ribosomal RNA efflux (seen in S. aureus)

Toxicity
- gastrointestinal irritation

Inhibitors of Nucleic Acid Synthesis

- Fluoroquinolones –
  - Broad spectrum, expanding range of drugs in this class
  - Ciprofloxacin, Levofloxacin, Moxifloxacin
  - Useful in treating enteric infections, urinary tract infections, pneumonia

Mechanism of action
- bind to DNA gyrase, topoisomerases, preventing DNA replication

Mechanism of resistance
- mutations in DNA gyrase, topoisomerases
- Efflux, target protection (plasmid mediated)

Toxicity
- tendon rupture in adults, especially those over 60 years of age
- mild gastrointestinal irritation
- reversible joint toxicity in children
- cardiac arrhythmias
- neuropathies
- Other adverse effect: promote colonization with MRSA

Antimicrobial Susceptibility

- MIC - minimum inhibitory concentration –
  - Lowest concentration which will inhibit the growth of a specific microorganism
- Laboratory methods of antimicrobial susceptibility determination
  - Broth tube dilution method of MIC determination
  - Disk diffusion method of MIC determination
  - Semiquantitative MIC determination based on diffusion of antibiotic through agar, and measurement of zone of inhibition of microbial growth
  - Automated methods, e.g. Vitek®
- Nucleic acid amplification techniques for identification of resistance determinants
  - Very useful for slow growing organisms, e.g. Mycobacterium tuberculosis
  - Predicts susceptibility based on gene sequences

It is important to remember that clinical efficacy cannot always be predicted by laboratory assays.

Clinical experience is an important factor in selecting antibiotics.
SOME PRINCIPLES OF ANTIBIOTIC THERAPY

The Ideal

Isolate pathogen, determine susceptibility prior to administration of antibiotics.
Select an antibiotic with a narrow spectrum of activity specific for the pathogen.
Avoid newer antibiotics if older antibiotics are effective.

The reality: empiric antibiotic therapy

Therapy based on history, physical examination, available laboratory results, and experience, initiated prior to isolation of the pathogen.
Culture material should be taken prior to administration of antibiotics in serious infections.
Antibiotics should be selected which will treat those most likely pathogens for which delay will result in bad outcome. (Resist urge to "leave no pathogen uncovered.")
Change to narrow-spectrum antibiotic when culture and susceptibility results become available.

Antiviral drugs

There is no specific antiviral therapy for most viral diseases

There are relatively few antiviral drugs, and each antiviral drug is very specific for a single virus or virus family.

• Examples
  • Acyclovir - specific for herpes viruses – converted to active form by viral enzyme, acts as a nucleotide analog and inhibits viral DNA synthesis
  • Oseltamivir (Tamiflu) – inhibits influenza virus enzyme (neuraminidase) required for detachment of mature progeny virus from infected cell
  • Reverse transcriptase inhibitors – nucleoside analogs and other inhibitors of reverse transcriptases of HIV and Hepatitis B viruses
  • Protease inhibitors – target HIV and hepatitis C virus proteases necessary for virion assembly
  • Integrase inhibitor – inhibits integration of HIV DNA into host cell genome

• Antifungal drugs
  • Amphotericin B – Binds ergosterol, forms pore in plasma membrane
  • Azoles, e.g. fluconazole, voraconazole – inhibits ergosterol synthesis
  • Echinocandins, e.g. caspofungin – inhibits β-1,3-glucan synthesis

• Antiprotozoan drugs – variety of drugs targeting specific enzymes, metabolic pathways, or causing oxidative damage. In several cases, mechanism of action unknown.

• Antihelmenthic drugs – most target neuromuscular function of helminths