Anti-infective Drugs -- Pharmacology

Introduction
- Infectious diseases comprise of diseases that are caused by microorganisms or their products.
- Causative agents can be bacteria, fungi, viruses, and parasites.
- Clinical manifestations of an infection occur only when sufficient tissue injury has been inflicted directly by microbial products or indirectly by host response.
- An antibiotic was originally defined as a substance, produced by a microorganism, which inhibited the growth of other microorganisms.

General concepts
1. Selective toxicity
   - An antimicrobial agent is selectively toxic to the pathogen, not to the patient.
   - Selective toxicity is possible when there are differences in the cell structures or functions.
   - A selective toxic antimicrobial, however, does not imply that the agent is free of adverse effects to the patient.

2. Spectrum of Activity -- “Narrow” Versus “Broad”
   - Different microbial groups differ in their susceptibility to antimicrobial agents.
     - Variation even within the same species
   - A narrow-spectrum antimicrobial agent has activity against only a few species of pathogens
     - Suitable for treatment of infections caused by a known pathogen -- Definitive therapy
   - A broad-spectrum antimicrobial agent has activity against many different species of pathogens
     - Suitable for treatment of infections caused by more than one pathogen or when the identity of the pathogen is not known -- Empirical therapy

3. Antimicrobial Effects -- “Micribicial” Versus “Microbiostatic”
   - Agents that irreversibly destroy the ability of a microbe to replicate are microbicidal.
   - Agents that reversibly impair the microbe’s ability to replicate, with this function being restored when the drug concentrations fall below critical inhibitory levels, are microbiostatic.

4. Susceptibility Versus Resistance
   - In quantitative assays of *in vitro* antimicrobial activity, a microbe is said to be “susceptible” to an antimicrobial agent when *in vitro* microbicidal or microbiostatic concentrations of the agent are comparable to those that can be safely achieved in plasma during clinical use.
   - Disk diffusion (Kirby Bauer) test, E-test, and broth dilution test are the three commonly used susceptibility tests for aerobic bacteria.
I. Antibacterial Agents

- Bacteria are the common causes of infection in community-acquired infections, resulting in the patients seek medical attention.
- Most bacteria are prokaryotes that there are many differences in cell structures and functions with mammalian (eukaryotic) cells, allowing selective toxicity achieved in many antibacterial agents.

A. Agents inhibiting Bacterial cell wall synthesis

- Cell wall is present in most bacteria, but is absent in mammalian cells.
- Absolute selective toxicity for agents affecting bacterial cell wall.
- Bacterial cell wall
  - Peptidoglycan, a chemically distinct and complex macromolecule made up of a glycan backbone of two alternating amino sugars, cross-linked by short peptides
  - Synthesis can be divided into 3 stages, involving about 30 bacterial enzymes.
    - Stage I  Precursor formation
    - Stage II  Elongation of glycan (amino sugars) chain
    - Stage III Cross-linking of glycan chain by forming short peptide chains

1. Beta-lactam antibiotics

- Presence of a 4-membered β-lactam ring

Mechanisms of action

- Two possible actions
  - Inhibition of cross-linking at Stage III of cell wall synthesis
  - Activation of endogenous autolytic enzymes that break down the cell wall
- β-lactam antibiotics cause rapid cell lysis in susceptible bacteria.

a. Penicillins

- One of the most important groups of antibacterial agents
  - Safe and efficacious
  - Adverse effects
    - Frequent: Hypersensitivity reactions; GI disturbance
    - Occasional: Platelet dysfunction with high doses of Piperacillin and Ticarcillin; Pseudomembranous colitis
    - Rare: Anaphylactic reactions

i. Natural penicillins -- Benzylpenicillin (Penicillin G) and Phenoxyethylpenicillin (Penicillin V)

- Benzylpenicillin
  - Resistance developed among many bacterial species
  - Antibiotic of choice for a number of bacterial infections, such as *S. pyogenes* and other *Streptococcus* species, *T. pallidum*
  - Parenteral use for serious infections caused by susceptible bacteria
  - Benzathine penicillin G, a suspension for IM injection for a prolonged blood and tissue concentrations
- Phenoxyethylpenicillin
  - Oral use for less serious infections
    - Better oral bioavailability
ii. Anti-staphylococcal (Penicillinase-resistant) penicillins -- Cloxacillin
- Semi-synthetic penicillins to overcome the resistant problem due to expression of bacterial enzymes (β-lactamases) by *Staphylococcus* to break down the β-lactam ring
- Methicillin is the first one for clinical use
- Cloxacillin (both oral and parenteral use) for treating infections caused by Gram-positive bacteria that express β-lactamases, such as Methicillin-sensitive *Staphylococcus aureus* (MSSA).
  - Not active against Methicillin-resistant *Staphylococcus aureus* (MRSA) due to changes in penicillin-binding proteins

iii. Aminopenicillins -- Ampicillin and Amoxicillin
- Semi-synthetic penicillins that penetrate more readily the outer membrane of Gram-negative bacteria
- Both ampicillin and amoxicillin can be used orally or parenterally to treat infections caused by susceptible Gram-positive and some “easy-to-kill” Gram-negative bacteria (such as *Escherichia coli*, *Proteus mirabilis* and *Haemophilus influenzae*).
  - The spectrum of antibacterial activity of the two is basically the same, but the oral bioavailability of amoxicillin is better than that of ampicillin.
- Both are not resistant to the action of β-lactamases and, therefore, are not useful if the *E. coli* or *H. influenzae* expresses β-lactamases.
  - Combination with a beta-lactamase inhibitor (e.g., Amoxicillin with Clavulanic acid and Ampicillin with Sulbactam) may extend their antibacterial coverage.

iv. Anti-pseudomonal penicillins -- Ticarcillin and Piperacillin
- Semi-synthetic penicillins with improved coverage to include the “hard-to-kill” Gram-negative bacteria, such as *Proteus vulgaris*, and *Enterobacter* species, and *Pseudomonas aeruginosa*, but with less activity than Penicillin G against Gram-positive bacteria
- Piperacillin is, in general, the more active member in this group.
- Parenteral use only
- Penicillins in this group are also not resistant to the hydrolytic action of β-lactamases.
  - Combination with a β-lactamase inhibitor extends their spectrum of activity
  - Ticarcillin with Clavulanic acid and Piperacillin with Tazobactam

b. Cephalosporins
- A second group of β-lactam antibiotics that are more resistant to different β-lactamases
- Classification by “generation”
  - By their spectrum of activity against Gram-negative bacteria
  - All cephalosporins are active against most gram-positive cocci and many strains of gram-negative bacilli.
  - None of them are active against MRSA, *Enterococcus* species, *Listeria*, and *Clostridium difficile*
- Adverse effects
  - Frequent: Thrombophlebitis with IV administration
  - Occasional: Hypersensitivity reactions (Cross-hypersensitivity in patients who are allergic to penicillin possible); GI disturbance; Hypoprothrombinemia and hemorrhage with Cefamandole and Cefoperazone
  - Rare: Pseudomembranous colitis (as a group -- the most common class of antibiotic due to the large number of doses used)
i. First-generation cephalosporins
   • Good activity against Gram-positive and some “easy-to-kill” Gram-negative bacteria
   • Oral: Cephalexin, Cefadroxil, Cephradine
   • Parenteral: Cefazolin, Cephradine

ii. Second-generation cephalosporins
   • Improved Gram-negative activity with reduced Gram-positive activity
     • No activity against Ps. aeruginosa
   • Oral: Cefaclor, Cefuroxime axetil
   • Parenteral: Cefamandole (Improved activity against H. influenzae), Cefonicid (Long T1/2), Cefuroxime, Cefoxitin (anaerobic coverage for Bacteroides fragilis)

iii. Third-generation cephalosporins
   • Better Gram-negative activity and CNS penetration
   • Oral: Ceftibuten
   • Parenteral: Cefotaxime (good Gram-positive activity; excellent CNS penetration), Cefoperazone (antipseudomonal activity), Ceftazidime (antipseudomonal activity), Ceftriaxone (long T1/2; excellent CNS penetration)
   • Widely used in hospitalized patients for Gram-negative bacillary infections

iv. Fourth-generation cephalosporins
   • More resistant to β-lactamases than cephalosporins from the previous generations
   • Parenteral: Cefepime

c. Carbapenems
   • A new class of broad-spectrum β-lactam antibiotic with high resistant to most β-lactamases
     • Excellent activity against many Gram-positive, Gram-negative, and anaerobic bacteria
     • Antibiotics reserved for serious infections caused by bacteria resistant to other antibiotics or used empirically
     • Cross-hypersensitivity in patients who are allergic to penicillin possible

i. Imipenem
   • Active against many Gram-negative bacteria resistant to the third- and the fourth-generation cephalosporins, aztreonam, and aminoglycosides
     • Resistance by Ps. aeruginosa may develop during treatment
     • In combination with cilistatin (an enzyme inhibitor to reduce metabolism of imipenem by the body)
   • Adverse effects
     • Occasional: Phlebitis and pain at injection site; GI disturbance
     • Rare: Seizures (especially in meningitis); Pseudomembranous colitis

ii. Meropenem
   • Similar to Imipenem
   • Less potential for seizures (suitable for bacterial meningitis)
d. Monobactam
   - A single-ring molecular structure
   - Cross-hypersensitivity not expected in patients who are allergic to penicillin

i. Aztreonam
   - Parenteral use with Gram-negative activity, including *Ps. aeruginosa*
     - Narrow spectrum
   - Adverse effects
     - Occasional: Local reactions at injection site; Rash; GI disturbance; Increased aminotransferase activity

2. Glycopeptides
   - Antibiotics reserved for serious infections caused by Gram-positive bacteria resistant to other antibiotics
     - Concerns about emergence of vancomycin-resistant *Enterococcus* (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA)

i. Vancomycin
   - Mechanisms of action
     - Inhibition of peptidoglycan elongation and the subsequent cross-linking in the cell wall synthesis
     - Possible mechanisms other than inhibiting cell wall synthesis
   - Adverse effects
     - Frequent: Chill; Injection related: Red-man syndrome and thrombophlebitis with rapid IV infusion
     - Occasional: Hypersensitivity reactions; Nephrotoxicity and ototoxicity with high doses
   - Uses
     - Parenteral use for systemic infections caused by resistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multiple-resistant *Streptococcus pneumoniae*
     - Oral use for pseudomembranous (antibiotic-associated) colitis caused by *Clostridium difficile*

ii. Teicoplanin
   - An alternative to vancomycin with a long T½

B. Agents inhibiting Bacterial protein synthesis
   - The nucleotide sequence in the DNA (Gene) determines the amino acid sequence in a protein, expression of genetic information via the messenger RNA (mRNA).
   - Ribosome is the apparatus in the cell that translates the nucleotide sequence encoded in the mRNA.
   - Structurally different from mammalian ribosome, bacterial ribosome consists of two subunits, 30S and 50S subunits.
   - Proteins produced may serve as structural proteins or enzymes.
   - Inhibition of protein synthesis by antibacterial agents impairs many cell functions and activities and may result even in cell death.
1. Agents with an action site on the 30S ribosomal subunit

a. Aminoglycosides
   • Polar antibiotics for parenteral use for systemic infections
     • Poor oral absorption and CNS penetration
     • Highly effective for many aerobic Gram-negative bacteria, including *Ps. aeruginosa*
   
   i. Amikacin
      • Reserved for treatment of infections caused by bacteria resistant to Gentamicin and Tobramycin
   
   ii. Gentamicin:
      • Less expensive
   
   iii. Tobramycin:
      • Similar to Gentamicin, but more active in vitro against *Ps. aeruginosa* and less active against *Serratia*

   Mechanism of action
   • Irreversible binding to 30S subunit preventing initiation of protein synthesis, error in translation, and premature termination of protein synthesis
   • Rapid bactericidal effect

   Adverse effects (serious and characteristic)
   • Ototoxicity and nephrotoxicity, especially in renal impaired patients
     • Dose adjustment and drug monitoring are important

   Uses
   • Treatment of serious infections caused by aerobic “hard-to-kill” Gram-negative bacilli
   • In combination with an antipseudomonal β-lactam antibiotics for serious infections caused by *Ps. aeruginosa*
   • In combination with cell-wall inhibitors for the treatment of serious infections caused by *Staphylococcus* and *Enterococcus*

b. Tetracyclines
   • Antibiotics with a “wide” spectrum of activity, but resistance among common bacterial pathogens are prevalent.

   Mechanism of action
   • Reversible binding to 30S subunit that blocks the adding of new amino acid to the growing peptide chain

   i. Tetracycline
      • Less expensive
      • Adverse effects
        • Frequent: GI disturbance; Bone lesions; Staining and deformity of teeth in children up to 8 years old
        • Occasional: Increased azotemia in renal impairment; Esophageal ulceration
ii. Doxycycline
- A semi-synthetic tetracycline with a longer $T_{1/2}$ and less GI disturbance
- Preferred tetracycline for the renal impaired
- Use (for Doxycycline)
  - Prophylaxis of malaria and Treatment of amebiasis

iii. Minocycline
- A semi-synthetic tetracycline with a longer $T_{1/2}$
- Occasional: Vestibular toxicity; Cutaneous and mucosal hyperpigmentation and tooth discoloration in adults
- Uses (for minocycline)
  - Prophylaxis for close contacts of patients with meningococcal infection
  - Rheumatoid arthritis

Uses
- Treatment for a number of “less” common bacteria, such as *Rickettsia, Chlamydia, Mycoplasma*
- In moderate to severe inflammatory acne vulgaris

2. Agents with an action site on the 50S ribosomal subunit

a. Erythromycin and other semi-synthetic macrolides
- A group of antibiotics with a large lactone ring

Mechanism of Action
- Reversible binding to 50S of ribosomal subunit that inhibits translocation of t-RNA, leading to inhibition of protein synthesis

i. Erythromycin base and many salts or esters
- Active against many Gram-negative cocci and many “atypical” bacteria
- Adverse effects
  - Frequent: GI disturbance
- Drug interactions
  - Inhibitor of cytochrome P-450 enzyme system

ii. Azithromycin
- A long half-life for once daily dosing
- Take on an empty stomach for better oral bioavailability
- Drug interaction -- Uncommon
- Adverse effects
  - Occasional: GI disturbance; Headache, Dizziness

ii. Clarithromycin
- Take with food improves oral bioavailability
- Drug interaction -- Similar to erythromycin
- Adverse effects
  - Occasional: GI disturbance; Abnormal taste; Headache; Dizziness
- Uses
  - For eradication of *Helicobacter pylori* in one of the more popular combination therapies
iv. Roxithromycin
• Rapidly accumulated intracellularly in leukocytes, such as macrophages

Uses
• A useful and safe antibiotic for a number “less” common bacteria, such as *Chlamydia*, *Mycoplasma*, *Legionella*, *Bordetella pertussis*
• As an alternative to penicillins for some Gram-positive cocci

b. Lincosamides
• Chemically distinct from erythromycin but share similar mechanism of action

i. Lincomycin
• A natural antibiotic as the starting material for synthesis of clindamycin

ii. Clindamycin
• A more potent, chlorinated derivative of lincomycin
• Adverse effects
  • Frequent: Diarrhea; Allergic reactions
  • Occasional: Pseudomembranous colitis
• Uses
  • One of the alternatives for anaerobic infections (outside CNS)
  • An alternative for Gram-positive cocci in patients allergic to penicillin
  • Treatment for *Pneumocystis carinii* pneumonia (with Primaquine) and toxoplasmosis (with Pyrimethamine)

c. Chloramphenicol
• The only member in this class
• Well absorbed and penetrates well into many tissues, including CSF
• Mechanism of action
  • Reversible binding to 50S subunit that inhibits formation of peptide bond
  • Bacteriostatic
• Adverse effects
  • Occasional: Blood dyscrasias, Gray syndrome; GI disturbances
  • Rare: Aplastic anemia
• Uses
  • Systemic use only for those serious infections when less toxic antimicrobial agents are not useful or contraindicated
    • Typhoid fever, bacterial meningitis
    • Ophthalmic use
d. Streptogramins  
• A relatively new class of antibiotics unrelated to existing antibiotics  
  i. Quinuprisin and Dalfopristin (in 30:70 ratio)  
    • Mechanism of action  
      • Inhibition of formation of peptide bond and elongation of peptide chain  
    • Adverse effects  
      • Frequent: Local irritation and thrombophlebitis; Arthralgia; Myalgia  
      • Occasional: Nausea; Rash; Increased aminotransferase activity  
    • Uses  
      • Treatment for drug-resistant gram-positive cocci  

e. Oxazolidinone  
• A new class of synthetic antibacterial agent with a narrow spectrum of activity  
  i. Linezolid  
    • Oral and parenteral use  
    • Mechanism of action  
      • Inhibition of initiation of protein synthesis  
    • Adverse effects  
      • Frequent: GI disturbance; myelosuppression; increased aminotransferase activity  
    • Uses  
      • Treatment for drug-resistant gram-positive cocci  

C. Agents affecting Nucleic acid  

1. Fluoroquinolones  
• An important class of synthetic fluorinated analogues of nalidixic acid  
• Orally bioavailable, broad-spectrum of antibacterial activity (including *Ps. aeruginosa* and many gram-negative bacilli, good tissue penetration, long serum half-life, and generally safe  
• First generation: Nalidixic acid  
• Second generation: Norfloxacin, Ciprofloxacin, Ofloxacin, Levofloxacin  
  • Norfloxacin for UTI  
  • Ciprofloxacin (PO and IV): Most potent against *Ps. aeruginosa*, poor activity against *S. pneumoniae*  
• Third generation: Gatifloxacin, Grepafloxacin, Sparfloxacin and Fourth generation: Trovafl oxacin, Moxifloxacin  
  • Better antibacterial activity against gram-positive bacteria and some atypical organisms  
  • Anaerobic coverage for fourth generation agents  

Mechanism of action  
• Inhibition of a DNA gyrase, an enzyme essential for separation of double-helical DNA permitting DNA replication and transcription  

Adverse effects  
• Occasional: GI disturbances; CNS disturbances (such as dizziness, headache, restlessness)  
• Not for children
Uses
- Ciprofloxacin: Treatment for many infections caused by *S. aureus* (including MRSA), Gram-negative bacteria, including *H. influenzae, M. catarrhalis*, members in the *Enterobacteriaceae* family (including the hard-to-kill, e.g., *Enterobacter*), *P. aeruginosa*, and many atypical pathogens (e.g., *Legionella* species, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Rickettsia*)
- Levofloxacin, Gatifloxacin, Moxifloxacin: *S. pneumoniae* (including highly resistant to penicillin; NOT for meningitis)

2. Antifolates
- Folic acid coenzymes are required for the synthesis of precursors of nucleic acids (RNA and DNA) and other compounds essential for growth and replication
- Being impermeable to folic acid, many bacteria must synthesize their folate from para-aminobenzoic acid (PABA), pteridine, and glutamate.
  - Dihydropteroate synthase mediates the initial step.
  - Folate is then reduced by Dihydrofolate reductase to the biological active form.

a. Sulfonamides
- Synthetic structural analogs of PABA
- Mechanism of action
  - Competitive inhibitor of dihydropteroate synthase that inhibits folate synthesis

b. Trimethoprim
- An analog of dihydrofolic acid
- Mechanism of action
  - Inhibitor of dihydrofolate reductase that inhibits conversion of folate to biologically active reduced form
- Monotherapy for UTI

c. Co-trimoxazole -- Sulfamethoxazole and Trimethoprim (5:1 ratio)
- Sequential inhibition of folate metabolism
  - Synergistic effect against many gram-positive and gram-negative bacteria
- Adverse effects
  - Common: Rash, nausea and vomiting
  - Hemolysis (hemolytic anemia) in G-6-PD deficiency
  - Kernicterus in Newborn
- Uses
  - As an alternative for many Gram-positive and Gram-negative bacteria and atypical pathogens
  - Treatment and prophylaxis for *Pneumocystis carinii* pneumonia

3. Metronidazole
- A synthetic antiprotozoal agent with a striking antibacterial activity against most anaerobes, including *Bacteroides* and *Clostridia*
- Mechanism of action
  - Formation of reactive toxic intermediates under anaerobic condition that interfere nucleic acid synthesis, leading to cell death
- Adverse effects
• Frequent: Nausea; Headache; Anorexia; Metallic taste
• Disulfiram-like reaction with alcohol
• Uses
  • Treatment of infections involving anaerobes (e.g., *B. fragilis*)
  • Treatment for Pseudomembranous (antibiotic-associated) colitis caused by *Cl. difficile*
  • Treatment for a number of parasitic infections -- Trichomoniasis, Amebiasis, and Giardiasis

D. Antimycobacterial Agents
• *Mycobacterium tuberculosis* is an important human pathogen that continues to be a problem worldwide.
• It often causes intracellular infections, exhibits long periods of metabolic inactivity, and tends to develop resistance to any one drug when treated with monotherapy.
• The cell has a layer of peptidoglycan overlaying the innermost cell membrane. Atop of the peptidoglycan layer is a sugary coating (arabino-galactan) that bridges to a layer of mycolic acids. The outermost layer is tightly packed waxy molecules that render the cell nearly waterproof.
• First-line agents include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin.
  • DOTS (by WHO): Isoniazid and Rifampin for 6 months; along with Pyrazinamide and Ethambutol or Streptomycin for the first 2 months
• Second-line agents include capreomycin, amikacin, kanamycin, cycloserine, ethionamide, ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin, aminosalicylic acid

i. Isoniazid
• Mechanism of action
  • Inhibition of synthesis of mycolic acid
• Adverse effects
  • Occasional: Peripheral neuropathy (Pyridoxine supplement); Liver damage; GI disturbances; Allergic reactions; Fever

ii. Rifampin
• Mechanism of action
  • Inhibition of DNA-dependent RNA polymerase that suppresses RNA synthesis
• Adverse effects
  • Discoloration of body secretions
  • Occasional: Liver damage; GI disturbance; Allergic reactions
• Drug interaction
  • Cytochrome P-450 enzyme inhibitors
• Uses (other than TB)
  • Treatment of leprosy
  • Prophylaxis of meningococcal disease and *Haemophilus influenzae* meningitis

iii. Pyrazinamide
• Unknown mechanism of action
• Adverse effects
  • Frequent: Arthralgia; Hyperuricemia
  • Occasional: Liver damage; GI disturbance; Acute gout; Rash

iv. Ethambutol
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- Mechanism of action
  - Inhibition of synthesis of arabino-galactan, a component of mycobacterial cell wall
- Adverse effects
  - Occasional: Optic neuritis; Allergic reactions; GI disturbance; Mental confusion; Precipitation of acute gout

v. Streptomycin
- An aminoglycoside
  - Parenteral administration

II. Antifungal Agents
- Fungi are saprophytes that live off living or dead organic matter.
- Fungal cells are eukaryotic cells; selective toxicity of antifungal agents is much hard to achieve.
  - Ergosterol, the sterol in fungal cell membrane
  - A cell wall consisting of a polysaccharide matrix in which glucans appear to be important structurally
  - Fungal infections are customarily divided into systemic (subcutaneous and internal organs) and superficial infections.

A. Systemic agents for Systemic Fungal Infections
1. Polyene
   i. Amphotericin B
      - A wide-spectrum antifungal agent
      - Formulations for IV use
        - Amphotericin deoxycholate
        - Newer lipid formulations for better tolerance (less renal and neurologic toxicity)
      - Mechanism of action
        - Binding to ergosterol in cell membrane of susceptible fungi, leading to increased permeability to small molecules, such as K⁺ ions
      - Adverse effects
        - Acute: Thrombophlebitis, Headache; Fever and chills; Malaise, Muscle and joint pain; GI disturbance
        - Frequent: Renal damage; Hypokalemia

2. Azole antifungal agents
   - A group of relatively broad-spectrum synthetic antifungal agents
   - Mechanism of action
     - Inhibition of ergosterol synthesis by inhibiting conversion of lanosterol to ergosterol
   - Drug interactions
     - Cytochrome P-450 enzyme system inhibitors
   - Adverse effects
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- Ketoconazole -- Frequent: Nausea; Vomiting. Occasional: Decreased testosterone synthesis; Gynecomastia; Impotence in men; Hepatitis; Headache; Dizziness; Rash
- Fluconazole -- Occasional: GI disturbance; Headache; Increased aminotransferase activity; Rash
- Itraconazole -- Occasional: GI disturbance; Headache; Dizziness; Hepatic damage; Edema; Hypokalemia; Rash

Comparison among the four Azole antifungal agents for systemic use

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<th>Ketoconazole</th>
<th>Fluconazole</th>
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<td>Drug interaction</td>
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<td>Inhibition of mammalian sterol synthesis</td>
<td>Dose-dependent inhibition</td>
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3. Flucytosine
- A fluorinated pyrimidine that is well absorbed orally and penetrates into cerebrospinal fluid
- Mechanism of action
  - Conversion to fluorouracil (5-FU) in the cells of susceptible fungi
  - Fluorouracil is a cytotoxic agent that inhibits DNA and RNA synthesis
- Adverse effects
  - Frequent: Blood dyscrasias; GI disturbance; Rash; Hepatic dysfunction
  - Occasional: Confusion; Hallucination

4. Caspofungin
- The latest semi-synthetic antifungal approved for IV use
  - The only antifungal agent active against *Pneumocystis carinii*
- Mechanism of action
  - Inhibition of synthesis of fungal glucan (an essential polysaccharide in fungal wall)
- Adverse effects
  - Occasional: Fever; Rash; Increased aminotransferase activity; GI disturbance; Facial flushing

B. Systemic agents for Superficial fungal infections

a. Terbinafine
- A synthetic antifungal agent with a high keratophilic property
  - Rapid accumulation in stratum corneum and hair and diffusion into nail plate
- Mechanism of action
  - Inhibition of ergosterol synthesis by inhibiting epoxidation of squalene to lanosterol
- Adverse effects
  - Frequent: Headache; GI disturbance
  - Occasional: Skin reactions; Taste disturbance; Increased aminotransferase activity
- Uses
  - Oral treatment for extensive dermatophyte infections (tinea) of the skin and onychomycosis
b. Griseofulvin
• An antibiotic with a poor oral bioavailability
• Mechanism of action
  • Disruption of nuclear division
• Adverse effects
  • Occasional: GI disturbance; Allergic and photosensitivity reactions
• Use
  • Prolonged oral treatment of dermatophytoses of the skin, hair, and nails
  • Its use should be superseded by newer antifungal agents

C. Topical agents for Superficial fungal infections
a. Nystatin and Amphotericin B
  • For mucocutaneous candidiasis

b. Azole -- Clotrimazole, Econazole, Isoconazole, Miconazole, Tioconazole
  • For mucocutaneous candidiasis, dermatophytoses (tinea), and other superficial mycoses

c. Allylamines -- Naftifine and Terbinafine
  • For cutaneous candidiasis, dermatophytoses (Tinea), and other superficial mycoses

III. Antiviral Agents
• Viruses are obligate intracellular parasites that multiply at the expense of the host’s metabolic system because they cannot produce their own energy nor synthesize their own proteins.
• There are more than 300 distinct viruses that infect human and cause about 50 different syndromes.
• Because replication of viruses depends on the host’ cellular machinery, selectivity toxicity is hard to achieve.
• Targets for antiviral agents include blockade of attachment to the host cell membrane and entry into the cell, integration into the host genome, inhibition of the processes of transcription (synthesis of mRNA) and translation (synthesis of protein) of viral genome, and interference of viral assembly and release.
• All the potential sites of antiviral action involve an active process and, therefore, have no effect on a virus in the latent state.

A. Antiviral agents for Influenza
• Influenza viruses can be classified into 3 immunologic types: Types A, B, and C
  • Types A and B are more important in causing an epidemic.
• Type A and Type B viruses with surface antigens, hemagglutinin (HA) and neuraminidase (NA)
  • HA is involved in attachment -- Early in the infection cycle
  • NA is involved in the release of the newly formed virions -- Late in the infection cycle
  • M2 protein, an integral ion channel protein occurs only in Type A virus, involves in release of the viral genome once taken up by the host cell -- Early in the infection cycle
• For high-risk patients, annual flu vaccine is the best prophylactic measure.
  1. Amantadine
• The first antiviral agent approved for use
  • Mechanism of action
    • Inhibiting uncoating of virion by interfering M2 protein
  • Adverse effects
    • Frequent: Livedo reticularis and ankle edema, Insomnia, Dizziness, Lethargy
    • Occasional: Depression, psychosis, confusion, slurred speech, increased seizures in epilepsy; Congestive heart failure; Orthostatic hypotension; GI disturbance; Urinary retention
  • Uses
    • Treatment and prophylaxis of Influenza caused by Type A virus

2. Neuraminidase (NA) inhibitors
  • A computer-aid designer agent specifically for inhibition of neuraminidase
  • Inhibition of release of the newly formed virions from the infected host cells
  • For BOTH type A and type B influenza

i. Zanamivir
  • Use
    • A powder for inhalation for treatment of influenza
  • Adverse effects
    • Occasional: Nasal and throat discomfort, Headache, Cough, Bronchospasm in patients with asthma

ii. Oseltamivir
  • Use
    • An oral formulation for treatment and prophylaxis of influenza
  • Adverse effects
    • Occasional: Nausea, Vomiting, Headache

3. Ribavirin
  • A synthetic guanosine analog with a wide-spectrum antiviral activity
  • In vitro antiviral activity
    • RNA virus: Respiratory syncytial virus (RSV), many strains of influenza A and B viruses, measles virus, parainfluenza virus, mumps viruses, enterovirus 72, human rhinoviruses, human immunodeficiency virus (HIV), various hantaviruses, yellow fever virus, Lassa fever virus, etc.
    • DNA virus: Herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), human cytomegalovirus, vaccinia virus (smallpox), and human adenovirus

Mechanism of action
• Phosphorylated metabolites inhibit nucleic acid synthesis

Adverse effects
• Occasional: Anemia, Headache, Abdominal discomfort, Fatigue, Elevation of bilirubin. Aerosol use (conjunctivitis, bronchospasm)
• Teratogenic and embryolethal in animals and mutagenic in mammalian cells
• Contraindicated in pregnancy; use of an effective contraceptive during treatment and 6 month post-treatment for BOTH male and female patients recommended

Uses
Clinical Workshop on Anti-infective Drugs -- Pharmacology

- Aerosol treatment (with special equipment) of severe lower respiratory tract infections (e.g., bronchitis and pneumonia) caused by RSV in hospitalized infants and young children
- Treatment (IV) for Lassa fever and Hantavirus infections
- Treatment (IV or aerosol) for influenza A and B infections
- Treatment (oral) for chronic hepatitis C (in combination with parenteral interferon alfa)

B. Antitherpes Agents
- Herpesvirus family contains several important human pathogens.
  - Herpes simplex viruses (HSV) -- Type 1 and 2 that infect epithelial cells and establish latent infection in neurons.
  - Varicella-zoster virus (VZV) -- Chickenpox (varicella) on primary infection and establish latent infection in neurons. Upon reactivation, the virus causes zoster (shingles).
  - Cytomegalovirus (CMV) -- Important in immunosuppressed or immunocompromised patients
  - Epstein-Barr virus (EBV) -- Infectious mononucleosis and linked to nasopharyngeal carcinoma
- Mechanism of action
  - Most antitherpes agents are nucleoside analogs that are phosphorylated to active triphosphate compounds that inhibit viral DNA polymerase.
  - Some also cause termination of DNA chain elongation.

a. Acyclovir
  - A guanosine analog that preferentially inhibits HSV
  - Valaciclovir
    - An oral prodrug of Acyclovir for better oral bioavailability
  - Adverse effects
    - Frequent: Local irritation at infusion site
  - Uses
    - Treatment of HSV and VZV infections

b. Ganciclovir
  - A guanosine analog that preferentially inhibits CMV DNA polymerase
  - Valganciclovir
    - An oral prodrug of ganciclovir with plasma drug levels similar to that of IV ganciclovir
  - Adverse effects
    - Frequent: Neutropenia, Thrombocytopenia
    - Occasional: Anemia, Fever, Rash, Abnormal liver function, Neurological toxicity, Phlebitis
  - Uses
    - Treatment of CMV infections

c. Foscarnet
• Not a nucleoside analog for IV use
  • Inhibition of DNA polymerase of various herpesvirus
  • As an alternative to Ganciclovir to treat CMV infections

C. Antiviral agents for Viral hepatitis

• Hepatitis B virus
  • A double-stranded DNA virus
• Hepatitis C virus
  • A positive-stranded RNA virus

1. Interferon Alfa
• Interferon is a family of glycoproteins that has complex antiviral, antiproliferative, and immunomodulating activities
  • Endogenous interferons are produced and secreted in response to viral infections
  • The antiviral activity is postulated to be due to induction of cellular enzymes that interferes with the synthesis of viral proteins and by augmenting the cellular immune function.
• Commercial preparations are products of recombinant DNA technology
  • Interferon alfa 2a, Interferon alfa 2b, Interferon beta
  • Pegylated interferons (interferons covalently joined to PEG) for prolonged half-life
    • Treatment of chronic hepatitis C
• Adverse effects
  • Frequent: Flu-like syndrome; GI disturbance; Rash; Dry skin or pruritus; Weight loss; Change of taste; Bone marrow suppression; Increased aminotransferase activity; Depression; Anxiety; Insomnia
• Uses
  • IM or SC administration for infections caused by papillomaviruses, human herpesvirus 8 (Kaposi's sarcoma), hepatitis B virus, and hepatitis C virus.

2. Lamivudine
• A cytidine analog that metabolized to form lamivudine triphosphate that inhibits hepatitis B DNA polymerase and HIV reverse transcriptase
• Use
  • Monotherapy for chronic hepatitis B infection
  • In combination therapy (HAART) for HIV infection

3. Adefovir
• A newly approved agent for chronic hepatitis B infection
D. Antiretroviral agents for Human Immunodeficiency Virus (HIV) infections

- Human immunodeficiency virus (HIV), the causative agent of AIDS, is a retrovirus (an enveloped RNA virus). Mostly, HIV Type 1 (HIV-1) is involved.
  - Attachment to CD4 on host cell
  - Viral RNA-dependent DNA polymerase (reverse transcriptase) to convert single stranded viral RNA to double-stranded viral DNA that will integrate into the genome of the host cell (Early phase of the infectious cycle)
  - Synthesis of a polyprotein that a protease will break away from and starts to cleave the remaining polyprotein into individual functional proteins before assembly of infectious virions (Late phase of the infectious cycle)

- Disease load is heavy globally; the prevalence is still relatively low in Hong Kong.

- Clinical manifestations of AIDS
  - Opportunistic infections (e.g., *Pneumocystis carinii* pneumonia, chronic cryptosporidiosis, toxoplasmosis of the CNS, esophageal or LRT candidiasis, disseminated or CNS cryptococcosis, and cytomegalovirus infections, herpes simplex infections, and many more) and tumors (e.g., Kaposi sarcoma)

- Three classes currently available for clinical use.
  - Nucleoside Reverse transcriptase inhibitors
  - Non-nucleoside reverse transcriptase inhibitors
  - HIV protease inhibitors

- Highly active anti-retroviral therapy (HAART) consists of combination of 3 to 4 agents that becomes the standard of care in the HIV infection.
  - None of the treatment regimens currently available can eradicate HIV infection, but HAART can decreases viral replication, improve immunologic status of the patients, and prolong life.

1. Nucleoside reverse transcriptase inhibitors (nRTIs)

- The mainstay of antiretroviral therapy for the first 10 years of the AIDS epidemic.
  - Zidovudine (= Azidothymidine, AZT)
  - Didanosine (= Dideoxyinosine, ddI)
  - Lamivudine
  - Stavudine

- All nRTIs can cause a rare but potentially fatal syndrome of lactic acidosis with hepatic steatosis.
- Another adverse effect associated with this group is peripheral fat wasting.

Mechanism of action

- Nucleoside analogs (agents with molecular structures similar to a physiological nucleoside, i.e., a nitrogen base and a 5-C sugar) are phosphorylated to triphosphate compounds
  - Inhibition of reverse transcriptase
  - Being incorporated into viral DNA chain causing chain termination
  - Early phase of Infectious cycle
  - Slowing down or inhibition of integration in newly infected cells
2. Non-nucleoside reverse transcriptase inhibitors (nnRTIs)
   - A group of structurally diverse agents without first converted to triphosphate compounds
   - All nnRTIs can cause rash that can be serious.
   - All nnRTIs are metabolized by hepatic cytochrome P-450 enzyme system.
     - Drug interactions -- Common
     - Nevirapine and Efavirenz

   Mechanism of action
   - nnRTIs bind directly to reverse transcriptase
     - Inhibition of reverse transcriptase
     - Not being incorporated into viral DNA chain, thus not causing chain termination

3. HIV protease inhibitors
   - Peptidyl analogs
   - All HIV protease inhibitors can cause GI intolerance and increased aminotransferase activity.
   - Other class associated adverse effects include increased bleeding in hemophiliacs, hyperglycemia, new onset or worsening diabetes, insulin resistance, fat wasting, and hyperlipidemia.
   - All HIV protease inhibitors are metabolized by hepatic cytochrome P-450 enzyme system.
     - Drug interactions -- Common
     - Indinavir and Ritonavir

   Mechanism of action
   - Inhibition of HIV protease prevents maturation of virions capable of infecting other cells
   - Late phase of Infectious cycle
     - Inhibition of subsequent waves of infections
     - No effects on cells already harboring the integrated proviral DNA