Chapter 14

Antimicrobial Agents
Principles of Antimicrobial Therapy

- Identification of the pathogen
  - Gram stain
  - Acid-fast stain
  - Enzyme-linked immunosorbent assay (ELISA)
Principles of Antimicrobial Therapy (cont’d)

- Susceptibility testing and resistance
  - Kirby-Bauer disk diffusion
  - E-test
    - Minimal inhibitory concentration (MIC)
  - Minimal bactericidal concentration (MBC)
Principles of Antimicrobial Therapy (cont’d)

- Host factors
  - Impaired immune function
  - Age
    - Liver and kidney function
    - Stomach pH
  - Pregnancy
    - Could drug harm fetus?
Principles of Antimicrobial Therapy (cont’d)

- Pharmacodynamics
  - Measured *in vitro* by time-kill studies
    - Concentration-dependent effect
    - Time-dependent effect (concentration independent)
    - Postantibiotic effect
Principles of Antimicrobial Therapy (cont’d)

- Antimicrobial combinations
  - May need to cover broad spectrum of organisms initially
  - Regimen may be narrowed once organism identified
  - Are drugs synergistic or antagonistic?
Principles of Antimicrobial Therapy (cont’d)

- Monitoring response to therapy
  - Fever?
  - WBC?
  - Cultures still positive?
  - Symptoms resolved?
  - Drug toxicity?
Antibiotics

- Penicillins
  - Mechanism of action
    - Inhibit cell wall synthesis
    - Activate endogenous autolytic system in bacteria
Antibiotics (cont’d)

- Clinical uses
  - Natural penicillins
  - Penicillinase-resistant penicillins
  - Aminopenicillins
  - Carboxypenicillins
  - Ureidopenicillins
  - β-lactam and β-lactamase inhibitor combinations
Antibiotics (cont’d)

- Adverse reactions and precautions for the penicillins
  - Hypersensitivity (most common)
  - Hematological reactions
  - Gastrointestinal disturbances
  - CNS toxicity
Antibiotics (cont’d)

- Cephalosporins
  - Mechanism of action
    - Inhibit bacterial cell wall synthesis
Antibiotics (cont’d)

- Clinical uses
  - First-generation cephalosporins
    • Wide variety of gram-positive organisms
  - Second-generation cephalosporins
    • Gram-positive and some gram-negative organisms
  - Third-generation cephalosporins
    • Active against most gram-negative organisms
  - Fourth-generation cephalosporins
    • Extended gram-positive and gram-negative coverage
Antibiotics (cont’d)

- Adverse reactions and precautions for cephalosporins
  - Hypersensitivity (1 to 3%)
  - Minor gastrointestinal complaints
  - Hypoprothrombinemia
    - Flushing
    - Nausea
    - Thirst
    - Palpitations
    - Chest pain
    - Vertigo
    - Death (in some cases)
Antibiotics (cont’d)

- Carbapenems
  - Mechanisms of action
    - Similar to other β-lactams
    - Inhibit cell wall synthesis
    - Bactericidal
Antibiotics (cont’d)

- Clinical uses
  - *Pseudomonas aeruginosa* (except ertapenem), gram-negative bacilli, most anaerobes, gram-positive organisms

- Adverse reactions and precautions
  - Low incidence of adverse reactions
  - Seizures in patients with decreased renal function
Antibiotics (cont’d)

- Monobactams (aztreonam)
  - Mechanism of action
    - Similar to other β-lactams
  - Clinical uses
    - Gram-negative aerobic bacilli
  - Adverse reactions and precautions
    - Well tolerated
    - Rare: Rash, anaphylaxis
Antibiotics (cont’d)

● Aminoglycosides
  ➢ Mechanism of action
    • Inhibit RNA translation
    • Destabilize cell wall
  ➢ Clinical uses
    • Nosocomial gram-negative infections
  ➢ Adverse reactions and precautions
    • Nephrotoxicity
    • Ototoxicity
    • Rare: Neuromuscular blockade with rapid high-dose use
Antibiotics (cont’d)

● Tetracyclines
  ➢ Mechanism of action
    • Inhibit attachment of RNA to acceptor site
    • Bacteriostatic
  ➢ Clinical uses
    • Gram-positive and gram-negative microorganisms
    • Rickettsiae
    • Chlamydiae
    • Mycoplasmas
    • Spirochetes
    • Protozoa
    • Protozoa
  ➢ Adverse reactions and precautions
    • Gastrointestinal: Nausea, vomiting, diarrhea
    • Inhibit bone growth and Ca, Mg, and Al, Fe absorption
Antibiotics (cont’d)

• Tigecycline
  ➢ Mechanism of action
    • Inhibits protein synthesis (even against most tetracycline-resistant organisms)
  ➢ Clinical uses
    • Complicated skin and intraabdominal infections
  ➢ Adverse reactions and precautions
    • Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain
Macrolides

- **Mechanism of action**
  - Induce dissociation of transfer RNA from ribosome during elongation phase
  - Bacteriostatic

- **Clinical uses**
  - Atypical and community-acquired pneumonia
  - Chlamydial infections in pregnant women

- **Adverse reactions and precautions**
  - Gastrointestinal complaints
  - May increase concentration of other drugs
    - Theophylline
    - Warfarin
    - Triazolam
Antibiotics (cont’d)

● Telithromycin
  ➢ Mechanism of action
    • Inhibits bacterial protein synthesis
  ➢ Clinical uses
    • Sinusitis and community-acquired pneumonia
  ➢ Adverse reactions and precautions
    • Gastrointestinal: Nausea and diarrhea
    • Visual disturbances
    • Prolonged Q-T interval
Antibiotics (cont’d)

- **Quinolones (Fluoroquinolones)**
  - **Mechanism of action**
    - Inhibit DNA synthesis
  - **Clinical uses**
    - Upper/lower respiratory infections
    - Gastrointestinal infections
    - Skin infections
  - **Adverse reactions and precautions**
    - One of safest antimicrobial classes
    - Gastrointestinal: Nausea, vomiting, diarrhea
    - Prolonged Q-T interval
Other Antibiotics

- **Chloramphenicol**
  - **Mechanism of action**
    - Inhibits protein synthesis
  - **Clinical uses**
    - Gastroenteritis/sepsis
    - Salmonella
    - Rickettsial diseases
  - **Adverse reactions and precautions**
    - Bone marrow suppression
    - Optic neuritis (blindness)
Other Antibiotics (cont’d)

- Colistin (colistimethate)
  - **Mechanism of action**
    - Surface active: Incorporates into cell membranes and causes disruption
  - **Clinical uses**
    - Systemic infections by gram-negative bacteria
    - Nebulized against multidrug-resistant *P. aeruginosa*
  - **Adverse reactions and precautions**
    - Reversible nephrotoxicity
    - Dose-dependent neuromuscular blockade
Other Antibiotics (cont’d)

- Daptomycin
  - Mechanism of action
    - Possibly disrupts cytoplasmic membrane
  - Clinical uses
    - Complicated skin infections by gram-positive bacteria
    - *Staphylococcus aureus* bacteremia
  - Adverse reactions and precautions
    - Creatine phosphokinase (CPK) elevation
    - Rhabdomyolysis
Other Antibiotics (cont’d)

- **Trimethoprim-sulfamethoxazole**
  - **Mechanism of action**
    - Blocks enzymes needed for bacteria to produce folic acid
    - Bacteriostatic
  - **Clinical uses**
    - *Pneumocystis carinii* pneumonia (PCP) prophylaxis
    - Acute bronchitis, otitis media, shigellosis
  - **Adverse reactions and precautions**
    - Relatively well tolerated
    - Nausea, vomiting, diarrhea, hypersensitivity
    - Neutropenia, thrombocytopenia, hemolytic anemia, jaundice, hepatic necrosis, drug-induced lupus (all due to sulfamethoxazole)
Other Antibiotics (cont’d)

- **Clindamycin**
  - **Mechanism of action**
    - Inhibits protein synthesis
    - Bacteriostatic
  - **Clinical uses**
    - Active against gram-positive and anaerobic bacteria
  - **Adverse reactions and precautions**
    - Nausea, vomiting, diarrhea
Other Antibiotics (cont’d)

- **Metronidazole**
  - **Mechanism of action**
    - Unknown
  - **Clinical uses**
    - Anaerobic infections
    - *Trichomonas, Clostridium difficile*
  - **Adverse reactions and precautions**
    - Metallic taste, nausea, vomiting
Other Antibiotics (cont'd)

- Nitrofurantoin
  - Mechanism of action
    - Not certain
      - Inhibits bacterial enzymes and protein synthesis?
      - Damages bacterial DNA?
  - Clinical uses
    - Urinary tract infections (UTIs)
  - Adverse reactions and precautions
    - Nausea, vomiting, hypersensitivity
    - Pneumonitis
Other Antibiotics (cont’d)

• Vancomycin
  ➢ Mechanism of action
    • Prevents formation of rigid cell wall
  ➢ Clinical uses
    • Methicillin-resistant *S. aureus* (MRSA)
    • Streptococcal endocarditis
  ➢ Adverse reactions and precautions
    • Red man syndrome
    • Ototoxicity
    • Nephrotoxicity
Other Antibiotics (cont’d)

- **Quinupristin and dalfopristin**
  - **Mechanism of action**
    - Inhibit protein synthesis
  - **Clinical uses**
    - MRSA
    - Vancomycin-resistant *Enterococcus faecium* (VREF)
  - **Adverse reactions and precautions**
    - Thrombophlebitis
    - Arthralgia
    - Myalgia
Other Antibiotics (cont’d)

- **Linezolid**
  - **Mechanism of action**
    - Prevents RNA translation
  - **Clinical uses**
    - VREF
  - **Adverse reactions and precautions**
    - Diarrhea, nausea, headaches
Antimycobacterials

- Used against *Mycobacterium tuberculosis*
- Isoniazid

  - **Mechanism of action**
    - Inhibits cell wall synthesis

  - **Adverse reactions and precautions**
    - Hepatotoxicity
    - Neurotoxicity
Antimycobacterials (cont’d)

- Rifampin and rifabutin
  - Mechanism of action
    - Inhibit RNA polymerase
  - Adverse reactions and precautions
    - Hepatotoxicity
Antimycobacterials (cont’d)

● Pyrazinamide
  ➢ Mechanism of action
    • Unknown
  ➢ Adverse reactions and precautions
    • Nausea and vomiting
    • Hepatotoxicity
Antimycobacterials (cont’d)

- **Ethambutol**
  
  - **Mechanism of action**
    - Decreases synthesis of cell wall polysaccharides
    - Bacteriostatic
  
  - **Adverse reactions and precautions**
    - Optic neuropathy
Antimycobacterials (cont’d)

- **Streptomycin**
  - **Mechanism of action**
    - Similar to other aminoglycosides
  - **Adverse reactions and precautions**
    - Nephrotoxicity
    - Ototoxicity
Antifungals

- Polyenes (amphotericin B and nystatin)
  - Mechanism of action
    - Increases permeability of cell membrane
  - Clinical uses
    - Aspergillosis, blastomycosis, histoplasmosis…
  - Adverse reactions and precautions
    -flushing, fever, chills (infusion related)
    - Renal impairment
Antifungals (cont’d)

- Azoles
  - Mechanism of action
    - Reduce ergosterol production
  - Clinical uses
    - Candidiasis (fluconazole)
  - Adverse reactions and precautions
    - Anorexia
    - Nausea
    - Vomiting
Antifungals (cont’d)

● Echinocandins
  ➢ Mechanism of action
    • Inhibit fungal cell wall synthesis
  ➢ Clinical uses
    • *Candida* and *Aspergillus*
  ➢ Adverse reactions and precautions
    • Fever, rash, flushing, thrombophlebitis
Antifungals (cont’d)

- **Flucytosine**
  - Mechanism of action
    - Inhibits fungal RNA formation (fungistatic)
  - Clinical use
    - *Candida, Cryptococcus, Aspergillus*
  - Adverse reactions and precautions
    - Bone marrow suppression
Antifungals (cont’d)

- Griseofulvin and terbinafine
  - Mechanism of action
    - Interferes with microtubule formation (griseofulvin) and reduces ergosterol production (terbinafine)
  - Clinical uses
    - Fungal infections of skin, hair, and nails
  - Adverse reactions and precautions
    - Gastrointestinal: Heartburn, flatulence
    - Headache
Antiviral Agents

- Acyclovir and valacyclovir
  - Mechanism of action
    - Terminate viral replication
  - Clinical uses
    - Herpesvirus family
    - Epstein-Barr virus (EBV)
    - Cytomegalovirus (CMV)
    - Varicella-zoster virus (VZV)
  - Adverse reactions and precautions
    - Neuropathy
    - Burning and irritation if used topically
Antiviral Agents (cont’d)

- Penciclovir and famciclovir
  - **Mechanism of action**
    - Interfere with viral DNA synthesis and replication
  - **Clinical uses**
    - Genital herpes simplex virus (HSV) and VZV
  - **Adverse reactions and precautions**
    - Considered well tolerated
    - Occasional nausea, vomiting, diarrhea, headache
    - Rare neutropenia
Antiviral Agents (cont’d)

- Ganciclovir and valganciclovir
  - Mechanism of action
    - Terminates viral DNA synthesis and replication
  - Clinical uses
    - HSV, VZV, CMV
  - Adverse reactions and precautions
    - Bone marrow suppression
Antiviral Agents (cont’d)

- Cidifovir
  - Mechanism of action
    - Inhibits viral replication
  - Clinical uses
    - Herpesvirus, EBV, CMV
  - Adverse reactions and precautions
    - Dose-dependent nephrotoxicity
    - Neutropenia, fever, headache, emesis, rash, diarrhea
Antiviral Agents (cont’d)

- **Foscarnet**
  - **Mechanism of action**
    - Blocks viral polymerase phosphorylation (inhibits viral replication)
  - **Clinical uses**
    - Herpesvirus, VZV, EBV, influenza A and B
  - **Adverse reactions and precautions**
    - Nephrotoxicity (25%)
    - Fever, nausea, vomiting, headache, diarrhea, electrolyte imbalance
Antiviral Agents (cont’d)

● Fomivirsen
  ➢ Mechanism of action
    • Terminates viral transcription by binding to complementary sequences within viral nucleic acid
  ➢ Clinical uses
    • CMV retinitis in patients with AIDS
  ➢ Adverse reactions and precautions
    • Transient increased intraocular pressures
Antiviral Agents (cont’d)

- Amantadine and rimantadine
  - Mechanism of action
    - Inhibit viral replication and assembly
    - May inhibit uncoating of influenza virus
  - Clinical uses
    - Active against influenza A virus
  - Adverse reactions
    - Well tolerated
    - CNS: Tremor, insomnia, lightheadedness, seizure, cardiac arrhythmias, agitation
Antiviral Agents (cont’d)

- Oseltamivir
  - Mechanism of action
    - Inhibits influenza A and B neuraminidase
    - Prevents virus from leaving host cells
  - Clinical uses
    - Treatment of influenza A and B infection
  - Adverse reactions and precautions
    - Nausea and vomiting in first 2 days of therapy