Chapter 13

Aerosolized Antiinfective Agents
Clinical Indications for Aerosolized Antiinfective Agents

- Indications for aerosolized pentamidine
  - Prevention of *Pneumocystis* pneumonia (PCP) in HIV-infected patients with history of one or more episodes of PCP or a peripheral CD4\(^+\) (T4 helper cell) lymphocyte count of 200/mm\(^3\) or less

- Indications for aerosolized ribavirin
  - *Treatment* of hospitalized infants with severe lower respiratory tract infection caused by respiratory syncytial virus (RSV)
Clinical Indications for Aerosolized Antiinfective Agents (cont’d)

- Indications for aerosolized tobramycin
  - Management of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis

- Indications for inhaled zanamivir
  - Influenza virus in adults and children age 5 years or over, who have been symptomatic for no more than 2 days
Aerosolized Pentamidine

Introduction of aerosolized pentamidine

- **Rationale for aerosol administration**
  - Local targeted lung delivery, with fewer or less severe side effects compared with systemic administration

- **Description of PCP**
  - Mammals usually infected at early age
  - Disease occurs when there is suppression of the immune system
  - a.k.a. *Pneumocystis jiroveci*
Dosage and Administration

- Dosage
  - 300 mg, given by inhalation once every 4 weeks
  - NebuPent
  - Dry powder (with 300 mg/vial)
  - Reconstituted with 6 ml of sterile water
  - Not saline (can cause precipitation)
Dosage and Administration (cont’d)

- Administration
  - Respirgard II nebulizer
  - Escaped particles may be filtered to limit exposure of healthcare workers

- Nebulizer performance
  - Mass median diameter (MMD) of 1 to 2 μm
Dosage and Administration (cont’d)

• Mode of action
  ➢ The exact mode of action not known
    • Blocks RNA and DNA synthesis, inhibits oxidative phosphorylation, and interferes with folate transformation
  ➢ 75% of the drug is excreted in urine and 25% in feces
Dosage and Administration (cont’d)

- Side effects (parenteral administration)
  - Pain, swelling, and abscess formation at the site of injection, with intramuscular administration
  - Thrombophlebitis and urticarial eruptions, with intravenous administration
  - Hypoglycemia (up to 62% of patients), with a cumulative cytotoxic effect on pancreatic beta cells
  - Impaired renal function and azotemia
  - Hypotension
  - Leukopenia
  - Hepatic dysfunction
Dosage and Administration (cont’d)

- Side effects (aerosol administration)
  - Cough and bronchial irritation in 36% of patients in one study
  - Shortness of breath
  - Bad taste (bitter or burning) of the aerosol impacting in the oropharynx
  - Bronchospasm and wheezing in 11% of patients
  - Spontaneous pneumothoraces
  - Conjunctivitis
  - Rash
  - Neutropenia
  - Pancreatitis
  - Renal insufficiency
  - Dysglycemia (hypoglycemia and diabetes)
  - Digital necrosis in both feet
  - Appearance of extrapulmonary *P. jiroveci* infection
Dosage and Administration (cont’d)

- Preventing airway effects
  - β-Adrenergic bronchodilator
  - Parasympatholytic
  - Small particle size
    - Reduces airway impaction and increases alveolar deposition
Dosage and Administration (cont’d)

- Environmental contamination by nebulized pentamidine
  - Exposure to the drug itself from the exhaust aerosol
  - Risk of infection with tuberculosis
  - Not known to be teratogenic
  - Not mutagenic
  - Carcinogenic potential is minimal
Dosage and Administration (cont’d)

- Environmental precautions
  - Use a nebulizer system with one-way valves and expiratory filter
  - Stop nebulization if the patient takes the mouthpiece out of the mouth (a thumb control on the power gas tubing gives more control)
  - Use nebulizers producing an MMD of 1 to 2 μm, to increase alveolar targeting and lessen large airway deposition and cough production
  - Always use a suitable expiratory filter and one-way valves with the nebulizer. Instruct patients to turn off the nebulizer when talking or when taking it out of the mouth
  - Screen patients for cough history and pretreat with a β agonist, with sufficient lead time for effect in reducing the bronchial reactivity
Dosage and Administration (cont’d)

- **Additional environmental precautions**
  - Administer aerosol in a negative-pressure room, with six air changes per hour, or consider using an isolation booth/hood assembly with an exhaust fan and air directed through a high-efficiency filter
  - Use barrier protection (gloves, mask, eyewear) for healthcare workers
  - Screen patients with HIV infection for TB, and treat where evidence of infection exists
  - Do not allow treatment patients to mix with others until coughing subsides
  - Healthcare workers should periodically screen themselves for TB
  - Pregnant women and nursing mothers should avoid exposure to the drug, and all practitioners should limit exposure to the extent possible
Dosage and Administration (cont’d)

- Aerosol therapy for prophylaxis of *Pneumocystis carinii* pneumonia: Clinical application
  
  ➢ 2004 CDC recommendations
    
    • *Oral trimethoprim–sulfamethoxazole (TMP–SMX)* was preferred for prophylaxis of PCP, as long as adverse side effects from TMP–SMX were absent or acceptable
    
    • *Aerosolized pentamidine was not recommended as therapy for prophylaxis of PCP*
Ribavirin

- Classified as an antiviral drug
  - Active against
    - RSV
    - Influenza viruses
    - Herpes simplex virus
- Nucleoside analog, resembles guanosine and inosine
- Virostatic, not virucidal
- Inhibits both DNA and RNA (retrovirus) viruses
Ribavirin (cont’d)

● Clinical use
  - In general, not recommended for RSV infection
  - Agency for Healthcare Research and Quality (AHRQ) has designated the drug as “possibly ineffective”
  - Risks environmental exposure to the drug by personnel
  - Conflicting results on whether use of ribavirin significantly reduces outcomes such as ventilator days, oxygen needs, intensive care unit days, hospital days, or mortality
Ribavirin (cont’d)

- **Nature of viral infection**
  - Adsorbs to the cell, penetrates the cell, uncoats itself, goes through a process of recoding cell DNA, assembles itself, and sheds from the cell
  - Diagnosis based on clinical signs
  - Definitive diagnosis
    - Requires isolating the virus or demonstrating an antibody titer increase
Ribavirin (cont’d)

- Complications in treating viral disease
  - Attacking the intracellular virus may harm the host cell
  - Viral replication is maximal before the appearance of symptoms
  - Viruses have the property of antigenic mutability; that is, they change their appearance to the immune system
Ribavirin (cont’d)

- **Respiratory syncytial virus infection**
  - Can cause bronchiolitis and pneumonia
  - Almost all children are exposed to the virus by their second year of life
    - In most the infection is mild and self-limiting
  - Outbreaks of RSV pneumonia are seasonal
  - Cause the formation of large, multinucleated cells, or a **syncytium**
**Ribavirin (cont’d)**

- **Dosage and administration**
  - **Dosage**
    - 20-mg/ml solution
    - SPAG-2
    - 12 to 18 hr/day
      - Minimum of 3 days
      - Not more than 7 days
    - Supplied as 6 g of powder in a 100-ml vial
    - Concentration of 6 g/300 ml
Ribavirin (cont’d)

- Administration
  - SPAG
  - Large volume, pneumatically powered nebulizer
  - Approximately 1.3 \( \mu \text{m} \), MMD
  - Solutions in the SPAG reservoir should be replaced after 24 hours
Ribavirin (cont’d)

- **Mode of action**
  - Not completely understood
  - Probably based on its structural resemblance to the nucleosides used to construct the DNA chain
Ribavirin (cont’d)

- Side effects
  - **Pulmonary**: Deterioration of pulmonary function and worsening of asthma or chronic obstructive disease; pneumothorax, apnea, and bacterial pneumonia
  - **Cardiovascular**: Cardiovascular instability, including hypotension, cardiac arrest, and digitalis toxicity
  - **Hematological**: Effects on blood cells have been reported with oral or parenteral administration but not with aerosol use. Reticulocytosis (excess of young erythrocytes in the circulation) has been reported, however, with aerosol use
Ribavirin (cont’d)

- **Additional side effects**
  - **Dermatological/topical:** Rash, eyelid erythema, and conjunctivitis have also been noted
  - **Equipment related:** Equipment-related adverse effects with ribavirin treatment include occlusion and impairment of expiratory valves and sensors with ventilator use and endotracheal tube blockage from drug precipitate
Ribavirin (cont’d)

- Environmental contamination with aerosolized ribavirin
  - Potential for mutagenic and carcinogenic effects
  - Effect on fertility is uncertain
    - Caused testicular lesions in rats
  - Effect on pregnancy is of particular concern
    - Teratogenic or embryocidal in animal species
Ribavirin (cont’d)

- Environmental contamination with aerosolized ribavirin (cont’d)
  - Acute effects
    - Conjunctivitis
    - Headache (51%)
    - Rhinitis
    - Nausea
    - Rash
    - Dizziness
    - Pharyngitis
    - Lacrimation (10 to 20%)
RespiratorySyncytialVirusInfection:
OtherAgents

- Respiratory syncytial virus immune globulin intravenous (human)-RespiGam

  - Indication for use
    - Prevention of serious lower respiratory tract infection with RSV in children younger than 24 months with bronchopulmonary dysplasia (BPD) or history of premature birth (less than 35 weeks of gestation)
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- *Respiratory syncytial virus immune globulin intravenous (human)-RespiGam* (cont’d)

  - Dosage and administration
    - Administered as a monthly intravenous infusion of 750 mg/kg
    - Maximal rate of 6 ml/kg/hr
    - Infuse children at risk (as indicated) each month during RSV season
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- *Respiratory syncytial virus immune globulin intravenous (human)*-RespiGam (cont’d)
  
  ➢ Mode of action
    
    • Places antibody to RSV in the bloodstream of the patient, and the patient achieves a level of immunity to RSV
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- *Respiratory syncytial virus immune globulin intravenous (human)-RespiGam (cont’d)*
  - Adverse reactions
    - Volume overload
    - Fever
    - Hypersensitivity
    - Dizziness
    - Flushing
    - Changes in blood pressure
    - Palpitations
    - Chest tightness
    - Dyspnea
    - Abdominal cramps
    - Pruritus
    - Myalgia
    - Arthralgia
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- *Respiratory syncytial virus immune globulin intravenous (human)-RespiGam (cont’d)*
  - Clinical efficacy
    - Monthly doses of 750 mg/kg of RSV-IGIV were effective in reducing RSV hospitalization in high-risk children with BPD or prematurity
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- **Palivizumab (Synagis)**
  - **Indication for use**
    - Prevention of serious lower respiratory tract disease caused by RSV in children and infants at high risk
  - **Dosage and administration**
    - 15 mg/kg, given IM monthly in RSV season
  - **Mode of action**
    - Provides neutralizing and fusion-inhibiting activity, preventing viral replication
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

Palivizumab (Synagis) (cont’d)

- Adverse reactions
  - Anaphylaxis
  - Fewer than 1 in 100,000 cases
  - Fever
  - Upper respiratory infection
  - Otitis media
  - Rhinitis
  - Rash
  - Pain
  - Hernia
  - Coughing
  - Wheezing
Respiratory Syncytial Virus Infection: Other Agents (cont’d)

- Palivizumab (Synagis) (cont’d)
  - Clinical efficacy
    - Reduced the rate of hospitalization resulting from RSV infection to 4.8%, compared with 10.6% in placebo recipients
Aerosolized Tobramycin

● Clinical use of inhaled tobramycin

  ➢ Pulmonary infections (CF)
    • Treat or prevent early colonization with *P. aeruginosa*
    • Maintain present lung function or reduce the rate of deterioration
Aerosolized Tobramycin (cont’d)

- Dosage and administration
  - 300 mg BID
  - 28 days consecutively/following 28 days off
  - 300 mg in a 5-ml ampoule
  - Administered with the PARI LC Plus
Aerosolized Tobramycin (cont’d)

- **Mode of action**
  - Binds irreversibly to the 30S subunit of bacterial ribosomes
    - Blocks protein synthesis in the bacteria and causes cellular death
Aerosolized Tobramycin (cont’d)

- **Side effects**
  - **Parenteral administration**
    - Ototoxicity
    - Nephrotoxicity
    - Neuromuscular blockade
    - Hypomagnesemia
    - Cross-allergenicity
    - Fetal harm
  - **Nebulized tobramycin**
    - Tinnitus
    - Voice alteration
Aerosolized Tobramycin (cont’d)

- Precautions in use of nebulized tobramycin
  - Renal, auditory, vestibular, or neuromuscular dysfunction
  - β-Lactam antibiotics (penicillins, cephalosporins) and aminoglycosides
  - Development of resistant organisms in the hospital
  - Fetal harm
  - *Local airway irritation*
  - *Allergic reaction*
Aerosolized Tobramycin (cont’d)

- Clinical efficacy
  - Improved pulmonary function
  - Decreased density of *P. aeruginosa* in expectorated sputum
  - Reduced need for intravenous antipseudomonal antibiotics and hospitalizations
  - No development of significant bacterial resistance
Aerosolized Tobramycin (cont’d)

- General considerations in aerosolizing antibiotics
  - May affect nebulizer performance
  - Environmental contamination
  - Incompatibility with other drugs
Inhaled Zanamivir

- Clinical use of inhaled zanamivir (Relenza)
  - Treatment of uncomplicated influenza illness in adults and children over 5 years of age, during the early onset (within the first 2 days) of infection
Inhaled Zanamivir (cont’d)

- Dosage and administration
  - DPI (Diskhaler)
    - 5 mg/blister
    - Adults and children 5 years or older
      - Two inhalations (two blisters, for a total of 10 mg) taken twice a day, approximately 12 hours apart, for 5 days
Inhaled Zanamivir (cont’d)

- Mode of action
  - Binding to the enzyme neuraminidase and thus blocking the enzyme’s action
  - Without neuraminidase viral particles would “stick” to each other and to the cell surface, preventing further infection
Inhaled Zanamivir (cont’d)

- Adverse effects
  - Bronchospasm and deterioration of lung function
  - Undertreatment of bacterial infection
  - Allergic reactions
  - Other adverse effects
    - Gastrointestinal
    - Respiratory
    - Dizziness/headache
Clinical efficacy and safety

- Treatment with 10 mg of zanamivir twice daily resulted in approximately 1 day of shortening of the median time to improvement in symptoms compared with placebo.
- Treatment with zanamivir 30 hours or less after onset of symptoms resulted in a shortening of 3 days in the median time to alleviation of symptoms.