PREVENTION AND TREATMENT OF INFLUENZA INFECTION

Russ Judd, PharmD
PGY2 Infectious Diseases Pharmacy Resident
UK HealthCare

Objectives

- Review the history and epidemiology of influenza
- Describe the structure and function of viral proteins, including targets for anti-influenza medications
- Discuss CDC recommendations for prevention and treatment of influenza
- Review the global impact of H5N1 infection and discuss treatment recommendations
History of Influenza

1918 "Spanish" pandemic
1957 "Asian" pandemic
1968 "Hong Kong" pandemic
1977 H1N1 virus reintroduced

Mandell, Bennett, and Dolin. Principles and Practices of Infectious Diseases, 6th ed.

Structure of Influenza Virus

Protein Targets:
1. Neuraminidase
2. M2 Protein

Above: Electron micrograph of influenza A/USSR/77 H1N1 (~189,000)

Mandell, Bennett, and Dolin. Principles and Practices of Infectious Diseases, 6th ed.
Naming the Influenza Virus

- **First** – Type of influenza virus (i.e., A or B)
- **Second** – Animal or Location where the virus was isolated
- **Third** – Isolate number (specific for each laboratory)
- **Fourth** – Year the virus was isolated
- **Last** – Subtype

**Example:** Influenza A/Brisbane/59/2007 (H1N1)

Epidemiology

- Estimated annual number of influenza-related hospitalizations in the US – 226,000 (1979 - 2001)
- Estimated annual number of influenza–related deaths in the US – 36,000 (1990 – 1999)

- Average rate of influenza-related pulmonary and circulatory deaths worldwide (per 100,000):
  - Aged 0-49: 0.4 – 0.6
  - Aged 50-64: 7.5
  - Aged ≥ 65: 98.3
(Interpandemic) Epidemic Curve

U-shaped epidemic curve:
- Attack rates higher among younger patients
- Mortality rates higher among older adults
- Underestimation of influenza-related mortality
- Highest mortality among influenza A (H3N2) isolates

Health & Economic Impact

- Average disability and lost productivity
  - 5-6 days of restricted activity
  - 3-4 days of bed disability
  - 3 days lost from work or school
  - Average number of medical visits: 1.1 – 3.6

- Decreased job performance
- Reduced levels of independent functioning

Epidemics, Pandemics, Shifts & Drifts

- Epidemics
  - Confined to one location (i.e., city, town or country)
  - Average overall attack rates – 10-20%
  - Occur almost exclusively during the winter months
    - October to April in the Northern hemisphere
    - May to September in the Southern hemisphere
  - Often associated with a single strain of influenza

Mandell, Bennett, and Dolin. Principles and Practices of Infectious Diseases, 6th ed.

Epidemics, Pandemics, Shifts & Drifts

- Pandemics
  - Extremely rapid transmission
  - Concurrent outbreaks throughout the world
  - Associated with the emergence of a new virus (e.g., H5N1)
  - Overall population possesses no immunity
  - Multiple waves of disease
  - Influenza A viruses ONLY

Epidemics, Pandemics, Shifts & Drifts

- Antigenic Drifts
  - Minor antigenic variations in HA and NA
  - Gradual accumulation of altered amino acid sequences
  - Immunologic selection

- Antigenic Shift
  - New viruses to which the population has no immunity
  - Cause of influenza pandemic
  - Little to no relationship between HA/NA antigens of the new and wild-type viruses

Pathogenesis

- Person-to-person transmission
  - Virus-containing respiratory secretions
  - Large-particle aerosols (sneezing, coughing & talking)

- Attachment and penetration of columnar epithelial cells

- Activation of host-defense mechanisms
  - Secretory IgA
  - Mucociliary apparatus

- Viral replication and cell death – Limited to the respiratory tract
  - Inhibition of host-cell protein synthesis
  - Apoptosis (induction of Fas ligand)
  - Systemic manifestations
Clinical Signs and Symptoms

- **Influenza A**
  - Abrupt onset after a 1-4 incubation period
  - Systemic symptoms: fever (100-104°F), chills, rigors, HAs, myalgias, malaise and anorexia
  - Respiratory symptoms: dry cough, pharyngeal pain, nasal obstruction & discharge
  - Elderly patients: fever, debility or confusion
  - Convalescent period: 1-2 weeks for full recovery


Clinical Signs and Symptoms

- **Influenza B**
  - Symptoms may resemble influenza A infection
  - Lower severity symptoms (compared to influenza A)

- **Influenza C**
  - Often afebrile
  - Similar to the common cold
  - Rarely associated with influenza syndrome

Mandell, Bennett, and Dolin. Principles and Practices of Infectious Diseases, 6th ed.
## Complications of Influenza

- **Primary influenza viral pneumonia**
  - History of CV disease (e.g., rheumatic fever) or chronic pulmonary disorders
  - Viral cultures yield high titers of influenza A
  - Gram stain negative
  - No response to antibiotics
  - High mortality rate

## Complications of Influenza

- **Risk factors for Bacterial Superinfection**
  - Mucociliary apparatus abnormalities
  - Increased bacterial adherence to virus-infected cells
  - Loss of epithelial cell barrier to infection
  - Upregulation of cell-surface receptors
  - Alterations in host immunity (e.g., PMNs)
Complications of Influenza

- Secondary Bacterial Pneumonia
  - Predominantly among older adults
  - Chronic pulmonary, cardiac or metabolic disorders
  - Cough, sputum production and consolidation on CXR
  - Gram stain and sputum culture positive
    - *Streptococcus pneumoniae*
    - *Haemophilus influenzae*
    - *Staphylococcus aureus*


Complications of Influenza

- Pulmonary Complications
  - Mixed viral/bacterial pneumonia
  - Localized viral pneumonia
  - COPD exacerbations

- Non-Pulmonary Complications
  - Myositis
  - Myocarditis/pericarditis
  - Toxic shock syndrome
  - CNS complications (e.g., Guillain-Barré syndrome)
  - Reye’s syndrome

Antiviral Agents for Influenza

- General Considerations
  - Early initiation of therapy is required (< 48 hours)
  - Optimal therapy within 24 hours of symptom onset
  - Duration of fever reduced by ~24 hours
  - Less viral shedding at 48 hours
  - Combination antiviral therapy PLUS vaccine

- **NOTE:** Due to high levels of resistance, M2 inhibitors (i.e., amantadine & rimantadine) should **NOT** be used for treatment or prophylaxis during the 2007-08 season


Antiviral Treatment Recommendations

- High-Priority Patients (NA inhibitors ONLY)
  - Hospitalized patients with laboratory-confirmed influenza
  - Patients with laboratory-confirmed influenza who are at higher risk for influenza-related complications
  - Patients with laboratory-confirmed influenza within 48 hours of symptom onset who want to decrease the duration or severity of their symptoms
Antiviral Prophylaxis Recommendations

- Patients at risk during the 2 wks post-vaccination
- High-risk patients unable to receive the vaccine
- Unvaccinated family members or health-care providers in close contact with high-risk patients
- High-risk patients and close contacts during seasons with unmatched vaccines
- Patients with immune deficiencies or those who might not respond to the vaccine

Antivirals for Influenza - M2 Inhibitors

- Amantadine (Symmetrel®)
  - Protein target: M2 protein
  - Susceptible strains of **influenza A ONLY**
  - Adverse effects: orthostatic hypotension; CNS effects (insomnia, dizziness, hallucinations); GI effects (N, D, anorexia); seizures; livedo reticularis*
  - PK considerations: Elderly patients and renal failure
  - Adult dose (influenza A)
    - Treatment: 100mg PO BID (w/in 24-48 hrs of symptoms)
    - Prophylaxis: 100mg PO BID

Lexi-Comp Online: Amantadine. Last updated 8/14/2008.
Antivirals for Influenza - M2 Inhibitors

- Rimantadine (Flumadine®)
  - Protein target: M2 protein
  - Susceptible strains of influenza A ONLY
  - Adverse effects: CNS effects (similar to placebo); GI effects (N, V, abdominal pain, anorexia)
  - PK considerations: Elderly, severe renal impairment
  - Adult dose (influenza A)
    - Treatment: 100mg PO BID
    - Prophylaxis: 100mg PO BID

Lexi-Comp Online: Rimantadine. Last updated 8/14/2008.

Antivirals for Influenza - NA Inhibitors

- Oseltamivir (Tamiflu®)
  - Protein target: Neuraminidase
  - Susceptible strains of influenza A and B
  - Adverse effects: GI effects (N, V, abdominal pain)
  - PK considerations: Dosage adjustment in renal failure
  - Adult dose (influenza A and B)
    - Treatment: 75mg PO BID x 5 days
    - Prophylaxis: 75mg PO once daily
      - Close contact: Initiate w/in 2 days of contact; Duration of 10 days
      - Community outbreaks: Duration of up to 6 weeks

Antivirals for Influenza - NA Inhibitors

- Zanamivir (Relenza®)
  - Protein target: Neuraminidase
  - Susceptible strains of influenza A and B
  - Adverse effects: CNS effects (HA, fever, chills, hallucinations, seizures); GI effects (N, V, D, throat/tonsil discomfort); Respiratory effects
  - PK considerations: Poor oral bioavailability
  - Dose (influenza A and B)
    - Treatment: 2 inhalations (10mg) BID x 5 days
    - Prophylaxis: 2 inhalations (10mg) once daily
      - Household contact: Initiate w/in 1.5 days of contact x 10 days
      - Community outbreak: Initiate w/in 5 days of outbreak x 28 days

Lexi-Comp Online: Zanamivir. Last updated 8/14/2008.

Types of Influenza Vaccine

- Trivalent Inactivated Vaccine (TIV)
  - All persons aged ≥ 6 months
  - Patients with high-risk medical conditions

- Live, Attenuated Influenza Vaccine (LAIV)
  - Healthy, non-pregnant persons aged 2-49 years
  - Safety and effectiveness not established in patients with high-risk medical conditions
  - Not indicated in children aged 2-4 years with RAD or children receiving aspirin or other salicylates
Influenza Vaccine Composition

- 2008-09 Influenza Vaccine
  - A/Brisbane/59/2007 (H1N1)
  - A/Brisbane/10/2007 (H3N2)
  - B/Florida/4/2006

- Viruses forecasted to be in circulation during the influenza season

- Favorable growth properties for mass production


Target Populations

- Children and Adolescents
  - 6 months–18 years
  - Two doses of influenza vaccine recommended for all children aged 6 months-8 years who have never received an influenza vaccine (separated by ≥ 4 wks)
  - Indications for TIV
    - Children aged 6-23 months
    - Children aged 2-4 years with reactive airway disease
    - Children with high-risk chronic medical conditions
  - Indications for LAIV
    - Healthy children aged 2-18 years
Target Populations

- **High-Risk Conditions**
  - All children aged 6 months-4 years (59 months)
  - All patients aged ≥ 50 years
  - Children receiving long-term aspirin therapy
  - Pregnancy during the influenza season
  - Chronic pulmonary, CV, renal, hepatic, hematological or metabolic disorders
  - Immunosuppression (iatrogenic or HIV)
  - Nursing home or LTCF residents

- **Household Contacts or Caregivers**
  - Health care providers
  - Household contacts of children aged ≤ 59 months and adults aged ≥ 50 years
  - Household contacts of other high-risk patients

- Any person who wants to reduce the likelihood of becoming infected with influenza
### Approved Vaccines for 2008-09

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Trade Name</th>
<th>Availability</th>
<th>Mercury Content (mcg Hg/0.5mL)</th>
<th>Age</th>
<th>Doses</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV</td>
<td>Fluzone®</td>
<td>0.25 mL pre-filled syringe</td>
<td>0</td>
<td>6-35 mo</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mL pre-filled syringe</td>
<td>0</td>
<td>≥36 mo</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mL vial</td>
<td>0</td>
<td>≥36 mo</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mL multi-dose vial</td>
<td>25</td>
<td>≥6 mo</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluvirin®</td>
<td>5 mL multi-dose vial</td>
<td>24.5</td>
<td>≥4 yrs</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mL pre-filled syringe</td>
<td>&lt;1</td>
<td>≥4 yrs</td>
<td>1 or 2</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluarix®</td>
<td>0.5 mL pre-filled syringe</td>
<td>&lt;1</td>
<td>≥18 yrs</td>
<td>1</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>FluLuval®</td>
<td>5 mL multi-dose vial</td>
<td>25</td>
<td>≥18 yrs</td>
<td>1</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Afluria®</td>
<td>0.5 mL pre-filled syringe</td>
<td>0</td>
<td>≥18 yrs</td>
<td>1</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mL multi-dose vial</td>
<td>25</td>
<td>≥18 yrs</td>
<td>1</td>
<td>IM</td>
</tr>
<tr>
<td>LAIV</td>
<td>FluMist®</td>
<td>0.2 mL sprayer</td>
<td>0</td>
<td>2-49 yrs</td>
<td>1 or 2</td>
<td>Nasal</td>
</tr>
</tbody>
</table>

*Adapted from CDC/ACIP Guidelines for Prevention and Control of Influenza

### Vaccine Considerations

- **History of egg allergy**
  - IgE-mediated reactions; anaphylaxis
  - Consider other options – antiviral medications

- **Co-administration of influenza vaccine and antiviral medications**
  - LAIV at least 48 hours after cessation of antivirals
  - Antivirals at least 2 weeks after receipt of LAIV
  - Re-vaccination if within time period
Avian Influenza (Bird Flu)

- Naturally occurring viruses among wild birds
- Shedding of influenza virus in saliva, nasal secretions and feces
- Virus transmitted from wild to domestic birds
- Two main forms of disease among domestic poultry
  - Low pathogenicity (mild symptoms)
  - High pathogenicity (high mortality rate)

Human Infection (H5N1)

- H5N1 infection in humans first reported in Hong Kong in 1997
- Two main influenza A subtypes currently circulating among humans (H1N1, H3N2)
- Influenza A (H5N1) occurs mainly in birds
- Direct or close contact with H5N1-infected poultry or contaminated surfaces
Human Infection (H5N1)

- Reported cases in Asia, Africa and Europe
- Highest incidence in Indonesia and Vietnam
- Epidemiologic trends in H5N1 infection
  - Overall mortality ~60%
  - Children and adults < 40 years of age
  - Highest mortality in cases 10-19 years of age
  - Significant risk factors include close contact with sick or dead poultry or exposure to live poultry markets
Management of H5N1 Infection

- Neuraminidase Inhibitors (e.g., oseltamivir)
  - Possible reduction in H5N1-associated mortality
  - Modified dosing regimens
  - Combination therapy??

- Adamantanes (e.g., amantadine, rimantadine)
  - May be considered in areas of low resistance
  - Monotherapy not recommended when neuraminidase inhibitors are available

World Health Organization - Clinical Management of Human Infection with H5N1 Virus
Management of H5N1 Infection

- Secondary Bacterial Pneumonia
  - Antibiotic prophylaxis is NOT recommended
  - Treatment of community-acquired pneumonia according to evidence-based guidelines

- Supportive Care
  - Oxygen therapy
  - Management of septic shock and ARDS

- Infection Control

World Health Organization - Clinical Management of Human Infection with H5N1 Virus

H5N1 Vaccine Development

- Early Antigenic Variation
  - Occurrence after initial vaccine development
  - Genetic variations in H5 HA genes

  - FDA Approves First US Vaccine for Humans Against the Avian Influenza Virus H5N1

World Health Organization - Epidemic and Pandemic Alert and Response