Clinical Diagnosis and Treatment of seasonal influenza in adults

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Clinical Keys to Diagnosis

- Transmission:
  - Speaking,
  - Sneezing or
  - Coughing
  - Fumets

- Incubation Period:
  - 1-4 days, with an average of 2 days.

Clinical Keys to Diagnosis

- Period of Infectivity:
  - Adults may be contagious from one day prior to the commencement of symptoms to up to 7 days after becoming sick.
  - Children, especially infants, may be contagious for longer periods
  - Viruses can live 2 hours or longer on surfaces like tables, desks, and doorknobs
  - 24 – 48 hr. non porous surfaces
  - 8 – 12 hr. on cloth, paper, tissue
  - 5 min. on hand
  - In water 22ºc → 4 days, 0ºc → 30 days
  - At 60ºc for 30 minutes
  - Inactivated by 70% alcohol and by Chlorine

Clinical Keys to Diagnosis

- Symptoms:
  - Sudden Onset of Disease with:
    - Fever
    - Myalgia
    - Headache
    - Cough
    - Runny Nose
    - Sore Throat
  - Other Symptoms:
    - Nausea
    - Vomiting
    - Diarrhea

Clinical Keys to Diagnosis

- Emergency Warning Signs in Adults:
  - Difficulty breathing or shortness of breath
  - Pain or pressure in the chest or abdomen
  - Sudden dizziness
  - Confusion
  - Severe or persistent vomiting

Clinical Keys to Diagnosis

- Emergency Warning Signs for Infants & Young Children:
  - Fast breathing or trouble breathing
  - Bluish skin color
  - Not drinking enough fluids
  - Not waking up or not interacting
  - Being so irritable that the child does not want to be held
  - Flu-like symptoms improve but then return with fever and worse cough
  - Fever with a rash

INTRODUCTION TO TREATMENT

- Three classes of antiviral drugs are available for the treatment of influenza:
  - The neuraminidase inhibitors, zanamivir, oseltamivir, and peramivir, which are active against both influenza A and B.
  - The selective inhibitor of influenza cap-dependent endonuclease, baloxavir, which is active against influenza A and B.
  - The adamantanes, which prevent viral replication by blocking the viral M2 protein ion channel, amantadine and rimantadine, which are only active against influenza A.

BENEFITS OF THERAPY

- When initiated promptly, antiviral therapy with a neuraminidase inhibitor or baloxavir can shorten the duration of influenza symptoms by approximately one half to three days
- Only 13 percent of patients called their clinician within 48 hours of the onset of influenza-like symptoms
- Some studies have suggested that antiviral therapy reduces the severity and incidence of complications of influenza, the length of stay in those hospitalized for influenza including older adults and influenza-associated mortality
- Empiric treatment of four high-risk outpatients with acute respiratory illness was needed to treat one patient with influenza infection

ANTIVIRAL THERAPY

- **Target populations for treatment**
- Individuals with severe disease (requiring hospitalization or evidence of lower respiratory tract infection) or at high risk for complications should receive antiviral therapy.
- Antiviral therapy, when indicated, should be initiated as promptly as possible.

Definition of high risk

Children <5 years, but especially <2 years*
Adults ≥65 years of age
Women who are pregnant or up to two weeks postpartum
Residents of nursing homes and long-term care facilities
Native Americans and Alaska Natives
People with medical conditions including: ■ Asthma ■ Neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, and peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, and spinal cord injury) ■ Chronic lung disease (eg, chronic obstructive pulmonary disease, cystic fibrosis) ■ Heart disease (eg, congenital heart disease, congestive heart failure, coronary artery disease) ■ Blood disorders (eg, sickle cell disease) ■ Endocrine disorders (eg, diabetes mellitus) ■ Kidney disorders ■ Liver disorders ■ Metabolic disorders (eg, inherited metabolic disorders and mitochondrial disorders) ■ Weakened immune system due to disease (eg, HIV, AIDS, cancer) or medication (eg, chronic glucocorticoids) ■ Children <19 years of age who are receiving long-term aspirin therapy ■ People with extreme obesity (body mass index [BMI] ≥40)

Indications for treatment

- IDSA's guidelines recommend prompt initiation of antiviral therapy for individuals with suspected or confirmed influenza infection and **any** of the following features, irrespective of influenza vaccination status:
  - Patients hospitalized with influenza, regardless of illness duration prior to hospitalization
  - Outpatients with severe or progressive illness, regardless of illness duration
  - Outpatients who are at high risk of influenza complications, as defined above and in the table

Indications for treatment

- The IDSA states that antiviral therapy can be considered for patients with suspected or confirmed influenza who are not at high risk for influenza complications, irrespective of influenza vaccination history, if they meet any of the following criteria:
  - Outpatients with illness onset ≤48 hours before presentation in order to reduce the duration of illness; those who present >48 hours after illness onset should **not** be treated with antivirals since they are unlikely to benefit
  - Symptomatic outpatients who are household contacts of persons at high risk for influenza complications, particularly those who are severely immunocompromised
  - Symptomatic health care providers who routinely care for patients at high risk for influenza complications, particularly those who are severely immunocompromised

Timing of antiviral initiation

- When indicated, treatment should be initiated as soon as possible since antiviral therapy is most likely to provide benefit when initiated within the first 48 hours of illness
- Treatment should **not** be delayed while awaiting the results of diagnostic testing, nor should it be withheld in patients with indications for therapy who present >48 hours after the onset of symptoms, particularly among patients requiring hospitalization.

Choice of antiviral drug

- Assess the risk of oseltamivir-resistant influenza before choosing therapy
- The recommended treatment is a neuraminidase inhibitor (oseltamivir, zanamivir, or peramivir) or baloxavir
- We favor an oral (oseltamivir, baloxavir) or inhaled (zanamivir) drug over intravenous (IV) peramivir
- Oseltamivir and peramivir should only be used if oseltamivir resistant Influenza is not suspected
- Oseltamivir is the preferred drug for severe influenza
- The adamantanes, amantadine and rimantadine, are active only against influenza A viruses, but high rates of resistance have developed among influenza A viruses, and these drugs are infrequently indicated.

Dosing

Recommended dosing of antiviral medications for the prophylaxis and/or treatment of seasonal influenza in adults

Antiviral agent	Dose
Oseltamivir	
Treatment, influenza A and B	75 mg orally twice daily for five days* ¶
Chemoprophylaxis, influenza A and B	75 mg orally once daily* Δ
Zanamivir ◊ §	
Treatment, influenza A and B	10 mg (two 5 mg inhalations) twice daily for five days
Chemoprophylaxis, influenza A and B	10 mg (two 5 mg inhalations) once daily Δ
Peramivir	
Treatment, influenza A and B	600 mg intravenously as a single dose*
Baloxavir	
Treatment, influenza A and B	40 kg to <80 kg: 40 mg orally as a single dose ≥80 kg: 80 mg orally as a single dose

Oseltamivir resistance

- Oseltamivir-resistant seasonal H1N1 influenza A viruses emerged in 2007 and were present at high rates worldwide during the 2008 to 2009 influenza season, prior to the onset of the 2009 H1N1 influenza A ("swine influenza") pandemic.
- The pandemic strain of H1N1 influenza A was generally susceptible to oseltamivir, except for sporadic cases of oseltamivir resistance.
- Since September 2009, 99 percent of influenza virus isolates tested in the United States have been susceptible to neuraminidase inhibitors

Duration

- The usual recommended duration of antiviral therapy with oseltamivir and zanamivir is five days
- Peramivir and baloxavir are typically given as a single dose

Pregnancy

- Aggressive treatment of influenza is important in pregnant women as they are at increased risk of complications of influenza.
- During the 2009 H1N1 influenza pandemic, pregnant women had a more severe clinical course and higher mortality compared with nonpregnant women.

Hematopoietic cell transplantation

- Prevalence is 1.3% in 120 days after HCT
- Untreated patients developed pneumonia in 20%
- HCT recipients should be treated for influenza according to the recommendations for patients at high risk for influenza complications

Adverse effects

- Adverse effects of neuraminidase inhibitors are typically mild, although more serious side effects have been described:
  - Zanamivir can cause bronchospasm and a decline in respiratory function in patients with asthma and other chronic respiratory disorders
  - There have been postmarketing reports of self-injury and delirium in patients (primarily children) receiving oseltamivir for treatment of influenza
  - Oseltamivir can also cause nausea and vomiting, but these side effects have not generally resulted in discontinuation of therapy
  - Diarrhea is a common adverse effect reported in patients receiving peramivir
  - Peramivir can cause serious skin or hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme
  - As with oseltamivir, there have been postmarketing reports from Japan of delirium and abnormal behavior leading to injury in patients with influenza who were receiving peramivir
- Baloxavir can cause diarrhea in 1.8%
- Adamantanes can cause largely attributable to central nervous system toxicity

Other agents

- Nitazoxanide is an antiparasitic agent that also has activity against influenza viruses; it blocks maturation of viral hemagglutinin at the post-translational level
- Ribavirin is a nucleoside analog that has in vitro activity against both influenza A and B viruses. However, clinical data regarding its efficacy have been inconclusive

Adjunctive therapies

- **Statins:** It has been hypothesized that the anti-inflammatory effects of statins could reduce the severity of illness
- **Glucocorticoids:** Given the suggestion of harm, glucocorticoids should not be used as adjunctive therapy in patients with influenza infection unless there is a separate clear indication for their use
- **Intravenous immunoglobulin**

SYMPTOM MANAGEMENT

- Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to treat fever, headache, and myalgia associated with influenza.
- Salicylates should be avoided, particularly in children and adolescents below 18 years of age because of the association between salicylate use and Reye syndrome in those with influenza
- Cough suppressants can be used
- Patients should be advised to maintain hydration
- Activity may need to be modified based on patient symptoms but can be resumed as tolerated