2011 Update: Clinical Management of Influenza with Antiviral Agents

Online Patient Visits

PROJECT GOAL

The goal of this program is to improve outcomes of patients with influenza virus infection through greater physician awareness of recent clinical guidance, and better facility in their practical application. This program will address knowledge, performance, and competence gaps and will educate physicians on current management strategies for high-risk patients infected with influenza A or B virus.

PROBLEM STATEMENT

Influenza virus infection, one of the most common infectious diseases, occurs primarily in annual epidemics during late fall through early spring seasons. The majority of persons infected with influenza virus exhibit acute onset of fever, usually accompanied by respiratory signs and symptoms. Most infections are self-limited, but severe disease and complications, including hospitalization and death, can occur in high-risk populations.

However, in 2009 approximately 40% of children and 20% of adults hospitalized with influenza-associated complications did not have recognizable risk factors.[1] On average, the incidence of influenza-associated hospitalizations is more than 200,000 cases and 36,000 influenza-attributed deaths each year.[2]

Typically, the incidence of influenza virus infection is highest among children, while the incidence of serious illness and death is highest among individuals over 65 years of age and, to a lesser extent, children under 2 years. However, the epidemiology of severe influenza disease changed during the 2009 H1N1 pandemic, shifting from the very young and the elderly, to children and young adults.[3]

The most effective method for preventing seasonal influenza virus infection is annual vaccination, recommended for all individuals 6 months old or older. The level of immunity stimulated by influenza virus vaccination can provide between 80% and 100% protection against influenza infection.[4] However, influenza vaccine effectiveness can vary by patient age, host immune status, and the match between vaccine and circulating virus strains.[5] More importantly, compliance with annual vaccinations in our society is less than optimal,[6] even among healthcare personnel.[7]

To reduce the severity and duration of disease when influenza virus infections occur, there are two classes of antiviral treatment: adamantine inhibitors amantadine and rimantadine, and neuraminidase inhibitors oseltamivir and zanamivir. The adamantine agents inhibit the propagation of influenza A virus strains, but significant resistance against these agents has developed, and since the fall of 2005 they have not been recommended by the Centers for Disease Control and Prevention (CDC) for treatment or prevention of influenza A virus infections. Neuraminidase inhibitors block the propagation of influenza A and B virus strains; sporadic resistance to both neuraminidase inhibitors has been reported.

Surveillance of resistance by influenza virus strains to antiviral drugs is monitored and reported weekly by the CDC during the influenza season. In the 2009-2010 season, there were reports of 2009 H1N1 resistance to oseltamivir, but the most recent Advisory Committee on Immunization Practices (ACIP) 2011 update reports susceptibility of all circulating influenza virus strains to both oseltamivir and zanamivir, and recommend the use of either neuraminidase inhibitor where indicated.[3]

Because these antiviral agents work by blocking the propagation of the influenza virus, the earlier treatment is initiated, the more effective it is. For most patients not at high-risk for severe disease, maximum clinical benefit is derived when treatment is initiated within 48 hours of onset of symptoms.

However, a significant number of patients not recognizably at high-risk can still progress to severe disease, and would conceivably benefit from antiviral therapy initiated outside this treatment window.[1] There is no rapid test for influenza virus infection that is readily available and highly reliable. As a consequence, most pharmaceutical management of influenza virus infections must be based on clinical judgment of empirical findings.

Until recently, there was no standard guidance for the management of all patient populations infected with common influenza virus strains. In the past two years, clinical practice guidelines for the management of seasonal influenza[3,5] and H1N1 disease[3] have been published.

Gap: Day-to-day questions about the practical application of these recently released recommendations are not uncommon.[1] Physicians who manage patients infected with an influenza virus would benefit from a review of recently published guidelines and their clinical applications, especially in the management of high-risk patients. This program is designed to provide physicians with an overview of recent changes in the management of influenza disease and reinforce their learning through practical applications of this guidance.

STATEMENT OF NEEDS

Physicians need to acquire and utilize expertise in the evaluation of high-risk patients with possible influenza disease.

Timely initiation of antiviral treatment for influenza disease is critical to obtain maximum clinical benefit. However, identification of candidates for antiviral therapy is largely empiric, based on clinical findings during evaluation. Efficacy of antiviral treatments is derived from their ability to block the propagation of susceptible influenza virus strains. For this reason, the period when an antiviral treatment can reduce the severity and duration of influenza virus infection is during active viral replication, which is often prolonged in high-risk patients.[3] It is essential that physicians are able to accurately and quickly reach the diagnosis of probable influenza virus infection, and determine the appropriate course of treatment to minimize the risk of complications and severe influenza disease.

Physicians need to learn and implement recent evidence-based guidance to optimize and individualize treatment strategies for high-risk patients with probable influenza disease.

Physicians may not be aware of all the underlying conditions that place a patient at high-risk for severe influenza disease, or how general practices in antiviral treatment should be altered for these high-risk patient populations.[1]

Evidence-weighted influenza treatment guidelines and recommendations have been gathered from the CDC, the American Academy of Pediatrics, the American College of Physicians, the American Academy of Family Physicians, the Pediatric Infectious Diseases Society, the Society for Healthcare Epidemiology, the Infectious Diseases Society of America, and practicing physicians. These practice guidelines[5] and recommendations[3] have been recently published to assist practitioners in making appropriate decisions in the management of influenza disease with specific clinical circumstances.

TARGET AUDIENCE

- Primary care physicians
- Pediatricians
- Emergency medicine physicians
- Geriatricians
- Obstetricians

LEARNING OBJECTIVES

At the conclusion of this educational program, participants should be able to:

1. Conduct a comprehensive patient evaluation that leads to proper identification of high-risk patients with possible influenza virus.
2. Optimize and individualize treatment strategies for high-risk patients with probable influenza disease.

GAP ANALYSIS

Gap	Type of Gap	Need That Will Address Gap	Learning Objective(s) That Will Address Gap and Need	Results That Will be Measured	Method That Will be Used
Physicians have day-to-day questions about the practical application of recently released recommen-dations[1]	Knowledge, Performance, Competence	Physicians need to acquire and utilize expertise in the evaluation of high-risk patients with possible influenza disease	Conduct a comprehensive patient evaluation that leads to proper management of high-risk patients with possible influenza virus	1) Responses to vignette questions regarding evaluation of high-risk patients with possible influenza disease 2) Plans to change patient evaluations in their clinical practice	1) Posttest to be completed at end of program 2) Commitment to change assessment to be completed 3 months post-program
		Physicians need to learn and implement recent evidence-based guidance to optimize and individualize treatment strategies for high-risk patients with probable influenza disease	Develop treatment strategies that are optimized and individualized for high-risk patients with probable influenza disease	1) Responses to vignette questions regarding optimized treatment strategies for high-risk patients with probable influenza disease 2) Plans to change treatment strategies in their clinical practice	1) Posttest to be completed at end of program 2) Commitment to change assessment to be completed 3 months post-program

PROPOSED OUTLINE

- Primary changes in CDC's ACIP 2011 updated recommendations[3]
  - Who is at high-risk
  - When treatment can be effective relative to onset of symptoms
  - Recommended antiviral medications for 2010-2011 season
  - Chemoprophylaxis in infants <1 year
  - Monitoring local antiviral resistance surveillance data

- Overview of currently recommended influenza A and B antiviral treatments, zanamivir and oseltamivir[3,8-10]
  - Indications
  - Susceptible influenza virus strains
  - Contraindications
  - Dosage (treatment and chemoprophylaxis) and mode of administration
  - Systemic bioavailability
  - Safety profile

Case 1: Outpatient, second trimester pregnancy

- Chart review
  - Acute onset of high fever, cough, respiratory signs and symptoms
  - Unremarkable pregnancy to date
- Introductory remarks by Activity Leader
- Participant pretest
  - Learner receives their overall pre-test score, along with the average score of other learners who have participated in the activity
- Issue prioritization by Activity Leader
  - Rule out other respiratory virus infections (know local surveillance data)
  - Once influenza-like illness (ILI) confirmed, antiviral treatment should be initiated as soon as possible
  - Follow-up confirmation with diagnostic tests should be conducted
  - Reduce the fever with acetaminophen
  - Presence of secondary bacterial pneumonia should be considered
  - Need for hospitalization and mechanical ventilation should be evaluated
  - Fluid and electrolyte balance should be monitored
- Information gathering by learners, who select and prioritize work-up options
  - Serum and respiratory specimens should be collected within 5 days of onset of symptoms for confirmation of diagnosis[5]

    - Complete blood count (CBC) assay should be conducted for presence of typical leukopenia, relative lymphopenia, possible thrombocytopenia
    - Chest radiography should be ordered
- Work-up summary by Activity Leader
    - Learners are given feedback on their selections relative to those of the Activity Leader
- Consultant commentaries by additional faculty members on work-up
- Visit optimization question
    - What is the optimal management plan for this visit?
- Panel of Activity Leader and faculty discuss management issues and evidence-based recommendations relevant to this particular patient visit
    - Risk of influenza-associated complications, hospitalization and death are significantly elevated among pregnancy[11-13]
    - Symptoms of ILI such as shortness of breath may be falsely attributed to pregnancy[11]
    - Antiviral treatment within 48 hours of symptom onset reduced ICU admission or death four-fold[11]; but antiviral drugs should not be withheld from a severely ill patient who presents more than 48 hours after onset of symptoms[14]
    - Oseltamivir favored over zanamivir because of greater systemic exposure[15] and more data on its safety in pregnancy[16]
    - The recommended antiviral dosage is the same as for nonpregnant women[3]
    - Influenza vaccination during pregnancy can evoke a robust immune response without safety concerns[11]
- Closing commentary by Activity Leader
- Chart note
    - Learner enters management notes and follow-up visit schedule in the patient's virtual chart to be added to the Chart Review section of follow-up visits
- Participant posttest and evaluation

Case 2: Inpatient, 65-year old >48 hours since symptom onset

- Chart review
    - Acute onset and prolongation of mild fever and signs and symptoms of severe respiratory disease
    - Chronic heart disease
- Introductory remarks by Activity Leader
- Participant pretest
    - Learner receives their overall pre-test score, along with the average score of other learners who have participated in the activity

- Issue prioritization by Activity Leader
    - Rule out other respiratory virus infections (know local surveillance data)
    - Once ILI confirmed, antiviral treatment should be initiated as soon as possible
    - Follow-up confirmation with diagnostic tests should be conducted
    - Monitor fluid and electrolyte balance
    - Monitor for development of secondary bacterial pneumonia and need for mechanical ventilation
- Information gathering by learners, who select and prioritize work-up options
    - Serum and respiratory specimens should be collected within 5 days of onset of symptoms for confirmation of diagnosis[5]
    - CBC assay should be conducted for presence of typical leukopenia, relative lymphopenia, possible thrombocytopenia
    - Evaluate chest radiography for signs of consolidation
- Work-up summary by Activity Leader
    - Learners are given feedback on their selections relative to those of the Activity Leader
- Consultant commentaries by additional faculty members on work-up
- Visit optimization question
    - What is the optimal management plan for this visit?
- Panel of Activity Leader and faculty discuss management issues and evidence-based recommendations relevant to this particular patient visit
    - Antiviral drugs should not be withheld from a severely ill patient who presents more than 48 hours after onset of symptoms[14]
    - Initiation of antiviral treatment more than 48 hours after onset of symptoms proven to reduce length of hospital stay and mortality[17-19]
    - Improved survival was observed in elderly patients hospitalized for severe seasonal influenza when antiviral treatment was started within 4 days of symptom onset[20]
    - Oseltamivir significantly reduced the high rate of mortality associated with H5N1 infection when treatment was initiated within 6-8 days after symptom onset[15]
    - No reduction in dosage of neuraminidase inhibitors is required for the elderly due to age[3]
    - Differences in influenza symptoms in patients over 60-65 years old[3]
    - Highest risk for influenza-associated mortality is this age group[5]
    - Criteria for a second course of antiviral therapy[3]
- Closing commentary by Activity Leader
- Chart note

    - Learner enters management notes and follow-up visit schedule in the patient's virtual chart to be added to the Chart Review section of follow-up visits
- Participant posttest and evaluation

Case 3: Outpatient, pediatric asthma

- Chart review
    - Patient is 4.5 years old
    - Intermittent asthma controlled with short-acting bronchodilator
    - Acute onset of ILI: fever, respiratory symptoms, cough, diarrhea, dehydration
    - Presentation to emergency department within 48 hours of onset of symptoms
- Introductory remarks by Activity Leader
- Participant pretest
    - Learner receives their overall pre-test score, along with the average score of other learners who have participated in the activity
- Issue prioritization by Activity Leader
    - Rule out other respiratory virus infections (know local surveillance data), and bacterial pneumonia
    - Once ILI confirmed, antiviral treatment should be initiated as soon as possible
    - Follow-up confirmation with diagnostic tests should be conducted
    - Potential for pneumonia, bacterial co-infection should be considered
    - Fluid and electrolyte balance should be monitored
    - Evaluate need for chemoprophylaxis of family members
- Information gathering by learners, who select and prioritize work-up options
    - Serum and respiratory specimens should be collected within 5 days of onset of symptoms for confirmation of diagnosis[5]
    - CBC assay should be conducted for presence of typical leukopenia, relative lymphopenia, possible thrombocytopenia
    - Order chest radiography
- Work-up summary by Activity Leader
    - Learners are given feedback on their selections relative to those of the Activity Leader
- Consultant commentaries by additional faculty members on work-up
- Visit optimization question
    - What is the optimal management plan for this visit?
- Panel of Activity Leader and faculty discuss management issues and evidence-based recommendations relevant to this particular patient visit

    - Patients <5 years of age at greater risk for influenza-associated complications[3]
    - Presenting symptoms may be atypical in children <5 years old[21]
    - Unlike older patients, young children may shed virus for up to 10 days[5]
    - Oseltamivir the only neuraminidase inhibitor indicated for treatment of children <7 years old[3]
    - Inhaled zanamivir has the potential for provoking bronchospasm and thus should not be prescribed for patients prone to bronchospasm[5]
    - Oseltamivir treatment in children significantly reduced symptom duration, severity of illness, incidence of otitis media, and antibiotic prescriptions[4]
    - Oseltamivir in children with asthma significantly improved forced expiratory volume and reduced asthma exacerbations[4]
    - Recommended oseltamivir dosage varies by a child's weight[3]
- Closing commentary by Activity Leader
- Chart note
    - Learner enters management notes and follow-up visit schedule in the patient's virtual chart to be added to the Chart Review section of follow-up visits
- Participant posttest and evaluation

Case 4: Outpatient, pediatric diabetes

- Chart review
    - 15-year old American Indian
    - Recently diagnosed with type 2 diabetes
    - Body mass index = 28 kg/m^2
    - Acute onset high fever, respiratory signs and symptoms, myalgia
    - Presented at emergency department within 48 hours of onset of symptoms
- Introductory remarks by Activity Leader
- Participant pretest
    - Learner receives their overall pre-test score, along with the average score of other learners who have participated in the activity
- Issue prioritization by Activity Leader
    - Rule out other respiratory virus infections (know local surveillance data)
    - Once ILI confirmed, antiviral treatment should be initiated as soon as possible
    - Follow-up confirmation with diagnostic tests should be conducted
    - Potential for pneumonia, bacterial co-infection should be considered

    - Fluid and electrolyte balance should be monitored
    - Evaluate need for chemoprophylaxis of family members
- Information gathering by learners, who select and prioritize work-up options
    - Serum and respiratory specimens should be collected within 5 days of onset of symptoms for confirmation of diagnosis[5]
    - CBC assay should be conducted for presence of typical leukopenia, relative lymphopenia, possible thrombocytopenia
    - Order chest radiography
- Work-up summary by Activity Leader
    - Learners are given feedback on their selections relative to those of the Activity Leader
- Consultant commentaries by additional faculty members on work-up
- Visit optimization question
    - What is the optimal management plan for this visit?
- Panel of Activity Leader and faculty discuss management issues and evidence-based recommendations relevant to this particular patient visit
    - Diabetes and American Indian heritage are two patient characteristics that each increase the risk for influenza-associated complications and hospitalization[3]
    - Early antiviral treatment significantly reduced the risk of influenza-related complications or hospitalization in patients over 18 years of age with diabetes[22]
    - Live, attenuated influenza vaccination is contraindicated in patients with diabetes[23]
- Closing commentary by Activity Leader
- Chart note
    - Learner enters management notes and follow-up visit schedule in the patient's virtual chart to be added to the Chart Review section of follow-up visits
- Participant posttest and evaluation

Listed below are the names of potential faculty with expertise in influenza.

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