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# CDC HEALTH UPDATE

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## CDC Health Update Regarding Treatment of Patients with Influenza with Antiviral Medications

*As a follow-up to HAN 00374 (http://emergency.cdc.gov/han/han00374.asp, Dec. 3, 2014), CDC is providing 1) a summary of influenza antiviral drug treatment recommendations, 2) an update about approved treatment drugs and supply this season, and 3) background information for patients regarding anti-influenza treatment.*

## Summary

Widespread influenza activity is being reported in most U.S. states, with influenza A (H3N2) viruses most common. H3N2-predominant flu seasons have been associated with more hospitalizations and deaths in older people and young children in the past. In addition, approximately two-thirds of H3N2 viruses that have been tested at CDC are antigenically or genetically different from the H3N2 vaccine virus. This difference suggests that vaccine effectiveness may be reduced this season. High hospitalization rates are being observed, similar to what was seen during the 2012-2013 influenza season. Hospitalization rates are especially high among people 65 years and older. In this context, the use of influenza antiviral drugs as an adjunct to vaccination becomes even more important than usual in protecting people from influenza. Antiviral medications are effective in treating influenza and reducing complications. Antivirals are available and recommended, but evidence from the current and previous influenza seasons suggests that they are severely underutilized.

**This CDC Health Update is being issued**

1) **to remind clinicians that influenza should be high on their list of possible diagnoses for ill patients, because influenza activity is elevated nationwide, and**
2) **to advise clinicians that all hospitalized patients and all high-risk patients (either hospitalized or outpatient) with suspected influenza should be treated as soon as possible with one of three available influenza antiviral medications. This should be done *without* waiting for confirmatory influenza testing. While antiviral drugs work best when given early, therapeutic benefit has been observed even when treatment is initiated later.**

## CDC Antiviral Recommendations for the 2014-2015 Season

CDC recommends antiviral medications for treatment of influenza as an important adjunct to annual influenza vaccination. Treatment with neuraminidase inhibitors has been shown to have clinical and public health benefit in reducing illness and severe outcomes of influenza, as evidenced from randomized controlled trials, meta-analyses of randomized controlled trials, and observational studies of oral oseltamivir, inhaled zanamivir, or parenteral peramivir treatment during past influenza seasons and during the 2009 H1N1 pandemic.

**All Hospitalized, Severely Ill, and High Risk Patients with Suspected Influenza Should Be Treated with Antivirals**

Any patient with suspected or confirmed influenza in the following categories should be treated with a neuraminidase inhibitor:

1) Is hospitalized – treatment is recommended for all hospitalized patients

2) Has severe, complicated, or progressive illness – this may include outpatients with severe or prolonged progressive symptoms or who develop complications such as pneumonia

3) Is at higher risk for influenza complications (hospitalized or outpatient) – patients in this group include:

- children younger than 2 years (although all children younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 years);
- adults aged 65 years and older;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged younger than 19 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40); and
- residents of nursing homes and other chronic-care facilities.

**Timing of Treatment and Implications for Patient Evaluation, Treatment and Testing**

Clinical benefit is greatest when antiviral treatment is administered early in the illness course. When indicated, antiviral treatment should be started as soon as possible after illness onset and **should not be delayed** even for a few hours to wait for the results of testing. Ideally, treatment should be initiated within 48 hours of symptom onset. **However, antiviral treatment initiated later than 48 hours after illness onset can still be beneficial for some patients.** Observational studies of hospitalized patients suggest that while the greatest benefit occurs when antiviral treatment is initiated within 48 hours of illness onset, treatment might still be beneficial when initiated up to 4 or 5 days after symptom onset. Also, a randomized placebo controlled study suggested clinical benefit when oseltamivir was initiated 72 hours after illness onset among febrile children with uncomplicated influenza. Clinical judgment, on the basis of

the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients.

Because of the importance of early treatment, **decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza**. Therefore, treatment should generally be initiated empirically. During influenza season especially, health care providers should advise high risk patients to call their provider promptly if they have symptoms of influenza. It may be useful for providers to implement phone triage lines to enable high risk patients to discuss symptoms over the phone. To facilitate early initiation of treatment, when feasible, an antiviral prescription can be provided without testing and before an office visit.

The results of rapid influenza diagnostic tests (RIDTs; immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens) may not be accurate; test sensitivities are approximately 50-70% when compared with viral culture or reverse transcription-polymerase chain reaction (RT-PCR). **Clinicians should realize that a negative RIDT result does not exclude a diagnosis of influenza in a patient with suspected influenza.** Other factors such as the quality of the specimen and timing of specimen collection may also affect test results. Rapid molecular assays are a new type of molecular influenza diagnostic test (http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm). Molecular testing is not needed for all patients with suspected influenza, but is most appropriate for hospitalized patients if a test result would lead to a change in clinical management.

**Antivirals in Non-High Risk Patients with Uncomplicated Influenza**

Neuraminidase inhibitors can benefit other individuals with influenza. While current guidance focuses treatment on those with severe illness or at high risk of complications from influenza, antiviral treatment may be prescribed on the basis of clinical judgment for any previously healthy (non-high risk) outpatient with suspected or confirmed influenza. Neuraminidase inhibitors reduce the duration of symptoms by ~1 day in healthy persons with uncomplicated influenza.

For previously healthy, symptomatic outpatients, if treatment is given, it is recommended that treatment be initiated within 48 hours of illness onset, although it is possible that treatment started after 48 hours may offer some benefit.

**Antiviral Medications**

Three prescription neuraminidase inhibitor antiviral medications are approved by the U.S. Food and Drug Administration (FDA) and are recommended for use in the United States during the 2014-2015 influenza season: oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®).

- Oral oseltamivir is FDA-approved for treatment of influenza in persons aged 2 weeks and older, and for chemoprophylaxis to prevent influenza in people 1 year of age and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for chemoprophylaxis in infants 3 months to 1 year of age, is recommended by the CDC and the American Academy of Pediatrics. Due to limited data, use of oseltamivir for chemoprophylaxis is not recommended in children younger than 3 months unless the situation is judged critical.

- Inhaled zanamivir is FDA-approved for treatment of persons 7 years and older and for prevention of influenza in persons 5 years and older.

- Intravenous peramivir was approved on December 19, 2014, for the treatment of acute uncomplicated influenza in persons 18 years and older. An FDA press release related to this announcement is available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427755.htm.

- Adamantanes (rimantadine and amantadine) are not currently recommended for treatment or prevention of influenza because of high levels of resistance among circulating influenza A viruses.

There are no current national shortages of neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir). However, local spot shortages have been reported for some formulations. Therefore, it may be necessary to contact more than one pharmacy to fill a prescription for an antiviral medication.

If there is difficulty locating commercial Tamiflu® for Oral Suspension, oral suspension can be compounded by a pharmacy from oseltamivir capsules. However, this compounded suspension should not be used for convenience or when the FDA-approved Tamiflu® for Oral Suspension is commercially available.

Please see information for health care professionals regarding compounding an oral suspension from oseltamivir 75 mg capsules at http://www.tamiflu.com/hcp/resources/hcp_resources_pharmacists.jsp.

**Additional Considerations for Clinicians**

Antibiotics are not effective against influenza infection, and early diagnosis of influenza can reduce the inappropriate use of antibiotics. However, because certain bacterial infections can produce symptoms similar to influenza and bacterial infections can occur as a complication of influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, because pneumococcal infections are a serious complication of influenza infection, new pneumococcal vaccine recommendations for adults 65 years of age or older, as well as adults and children at increased risk for invasive pneumococcal disease due to chronic underlying medical conditions should be followed (see http://www.cdc.gov/vaccines/vpd-vac/pneumo/vac-PCV13-adults.htm and http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm for further information).

The most common adverse events associated with oral oseltamivir include a slightly increased risk of nausea and vomiting over placebo, with nausea occurring in 10% of adults with influenza who received oseltamivir and 6% of people who received placebo in controlled clinical trials (3% and 4%, respectively, in children), and vomiting occurring in 9% of adults with influenza who received oseltamivir and 3% of people who received placebo in controlled clinical trials (15% and 9%, respectively, in children). These symptoms are generally transient and can be mitigated if oseltamivir is taken with food. Adverse events for inhaled zanamivir were not increased over placebo in clinical trials, but cases of bronchospasm have been reported during postmarketing; inhaled zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases). For people who received peramivir intravenously or intramuscularly in clinical trials, the most common adverse event was diarrhea, occurring in 8% versus 7% in people who received placebo.

## Resources for Patient Education

Results from unpublished CDC qualitative research shows that most people interviewed were not aware that drugs to treat influenza illness are available. Patients being provided a prescription for an influenza antiviral drug may have questions. A fact sheet for patients is available at http://www.cdc.gov/flu/antivirals/whatyoushould.htm.

Note the following important background information for patients:

- If you get the flu, antiviral drugs are a treatment option.
- It is very important that antiviral drugs are used early to treat hospitalized patients, people with severe flu illness, and people who are at high risk for flu complications because of their age, severity of illness, or underlying medical conditions.
- If you have severe illness or are at high risk of serious flu complications, you may be treated with flu antiviral drugs if you get the flu.
- For people with a high-risk condition, treatment with an antiviral drug can mean the difference between having milder illness instead of very serious illness that could result in a hospital stay.
- Other people also may be treated with antiviral drugs by their doctor this season. Most otherwise-healthy people who get the flu, however, do not need to be treated with antiviral drugs.
- Studies show that flu antiviral drugs work best for treatment when they are started within 2 days of getting sick. However, starting antivirals later can still be helpful for some people.
- If your health care provider thinks you have the flu, your health care provider may prescribe antiviral drugs. A test for flu is not necessary.
- Antibiotics are not effective against the flu. Using antibiotics inappropriately can lead to antibiotic resistance and may expose patients to unwanted side effects of the drug.
- Other practices that may help decrease the spread of influenza include respiratory hygiene, cough etiquette, social distancing (e.g., staying home from work and school when ill, staying away from people who are sick) and hand washing.

## For More Information

- Summary of Influenza Antiviral Treatment Recommendations for Clinicians: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
- Clinical Description and Lab Diagnosis of Influenza: http://www.cdc.gov/flu/professionals/diagnosis/index.htm

- Guidance for Clinicians on the Use of RT-PCR and Other Molecular Assays for Diagnosis of Influenza Virus Infection:
  http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

- Interim Guidance for Influenza Outbreak Management in Long-Term Care Facilities:
  http://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm

- FDA Influenza (Flu) Antiviral Drugs and Related Information (including package inserts):
  http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm