Please refer to previous Contagious Comments release (VOL. XXVIII Number 5 October 2013) for information regarding influenza vaccination. The punch line is: “Give influenza vaccine to all children in your practice, yourself, your colleagues, and family members.” Vaccinate soon, as the first cases of influenza have already been detected in Colorado! This second edition focuses on how to diagnose and treat influenza. It is abstracted from, and is in agreement with, current CDC guidelines and AAP recommendations.1,2

1. HOW TO TEST FOR INFLUENZA?

This winter, Children’s Hospital Colorado will again have two laboratory tests for influenza virus, the influenza-only polymerase chain reaction (PCR) and a comprehensive respiratory virus PCR panel (RVP). PCRs are used because they are significantly more sensitive than rapid influenza antigen detection tests (>95% vs. 10-70%, respectively).

- Influenza PCR detects influenza A and influenza B and provides the influenza A 2009 H1N1 subtype. It is run 24/7 during flu season, with most results available in 6 hours once specimens arrive at the Anschutz Campus. Only nasopharyngeal (NP) aspirates or NP flocked swabs can be tested. The shortage of influenza PCR kits that occurred last winter is unlikely to recur.

- Comprehensive RVP detects influenza A and its two subtypes (H3N2 or 2009 H1N1) and influenza B, as well as other respiratory viruses. This winter, RVP will be performed only by Film Array, which provides results in 12 hours or less once specimens arrive at the Anschutz Campus. Many respiratory specimen types can be tested, including NP flocked swabs, NP aspirates, tracheal aspirates, bronchoalveolar lavage, and lung tissues.

2. WHO SHOULD WE TEST FOR INFLUENZA?

In general, influenza tests should be ordered only if positive or negative results will influence clinical management or influence the clinical practice for other patients. PCRs are very expensive, with the charge for RVP about four times higher than for influenza only-PCR, despite no significant difference in detection of influenza viruses between the two tests. Therefore, who to test and test choice depends on the clinical situation, as well what viruses are circulating in the community. It is important to recognize that numerous viruses can present similar to influenza and that an influenza test is more likely to be positive during the peak of influenza season (increased pretest probability).

Our current recommendations for test ordering are unchanged from last winter and are depicted on the following chart:
RESPIRATORY VIRUS TEST ALGORITHM

Child with respiratory or flu-like illness

Will results change clinical care of the patient or clinical practice for other patients?

YES
E.g. Start or stop antivirals, assess need for prophylaxis, limit antibiotics and/or ancillary testing, decrease hospitalization

NO
Do not test

If only influenza virus is relevant

INFLUENZA VIRUS PCR
Detects Influenza A/B only
Mean turnaround time 3 hrs
Cost $
Nasal wash or NP swab

If any respiratory virus (including influenza) is relevant

RESPIRATORY VIRUS PCR
Detects influenza A/B, RSV A/B, parainfluenza 1-4, HMPV, adenovirus, rhinovirus, CoVs OC43 229E,NL63, HKU1
Mean turnaround time 6 hrs
Cost $$$$ 
Nasal wash, NP swab, tracheal aspirates, BAL, lung

3. WHO SHOULD BE TREATED FOR PRESUMED OR PROVEN INFLUENZA?

a. Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of complications from influenza (e.g., otitis media in young children, pneumonia, respiratory failure) and death, and shorten the duration of hospitalization. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.

b. Treatment should not wait for laboratory confirmation of influenza but, when clinically indicated, should be started as soon as possible.

c. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who:
1) is hospitalized;
2) has severe, complicated, or progressive illness; or
3) is an outpatient who is at higher risk for influenza complications (see box) on the basis of their age or underlying medical conditions. Clinical judgment, based on 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 high-risk outpatients.

d. Antiviral treatment should be considered for any outpatient with confirmed or suspected influenza who is otherwise healthy for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her treating provider, if treatment can be initiated within 48 hours of illness onset.

<table>
<thead>
<tr>
<th>Individuals at High Risk for Influenza Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
</tr>
<tr>
<td>Severe, complicated, or progressive illness</td>
</tr>
<tr>
<td>Children aged &lt;2 years*</td>
</tr>
<tr>
<td>Individuals &lt;19 years receiving long-term aspirin therapy</td>
</tr>
<tr>
<td>Adults aged ≥65 years</td>
</tr>
<tr>
<td>Persons of all ages with:</td>
</tr>
<tr>
<td>- chronic pulmonary (including asthma), cardiovascular, renal, hepatic, metabolic (including diabetes) hematologic, neurologic (including seizure disorders) conditions, intellectual disability (mental retardation), moderate to severe developmental delay, and neurodevelopmental conditions</td>
</tr>
<tr>
<td>Persons with immunosuppression</td>
</tr>
<tr>
<td>Pregnant or recently post-partum women</td>
</tr>
<tr>
<td>American Indians/Alaska Natives</td>
</tr>
<tr>
<td>Persons who are morbidly obese (BMI ≥40)</td>
</tr>
</tbody>
</table>

*Although all children aged younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those aged younger than 2 years, with the highest hospitalization and death rates among infants aged younger than 6 months.

4. WHEN IS IT TOO LATE TO TREAT SOMEONE FOR INFLUENZA?

The CDC guidelines state that when indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when started after 48 hours of illness onset, as indicated by observational studies. The Children’s Colorado ID group would recommend that you strongly consider antiviral treatment for anyone with severe influenza disease regardless of the day of illness.

The CDC provides the following information and studies in support of the use of oseltamivir later in the course of influenza illness.

- **Antiviral treatment of pregnant women (of any trimester) with influenza A (2009 H1N1) virus infection has been shown to be most beneficial in preventing respiratory failure and death when started within less than 3 days of illness onset, but still provided benefit when started 3–4 days after onset compared to 5 or more days (Siston, et al JAMA 2009). A larger study reported similar findings and showed that starting oseltamivir treatment up to 4 days after illness onset provided benefit in reducing the risk of severe illness compared to later treatment of 2009 H1N1 (Yu, et al. Clinical Infectious Diseases 2011).**

- **Another study of critically ill patients and fatal cases with 2009 H1N1 virus infection reported that antiviral treatment with a neuraminidase inhibitor was associated with improved survival compared to untreated patients, and while early treatment conveyed the most benefit, patients who started antiviral treatment up to 5 days after illness onset had improved survival compared to untreated patients (Louie, et al. Clinical Infectious Diseases 2012).**

- **A meta-analysis of observational studies of oseltamivir for treatment of influenza concluded that treatment may reduce duration of symptoms, hospitalization, and mortality compared to no treatment (Hsu, et al. 2012). Another systematic review and meta-analysis of observational studies of neuraminidase inhibitor treatment of patients with 2009 H1N1 virus infection, primarily oseltamivir treatment, concluded that early initiation of treatment reduced the likelihood of severe outcomes compared to late or no treatment. This review found a 65% mortality reduction in early-treated versus untreated patients (Muthuri et al Clinical Infectious Diseases 2012).**
5. WHAT DO I USE TO TREAT INFLUENZA?

Neuraminidase Inhibitors Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are the antiviral medications still recommended for treatment and chemoprophylaxis of influenza A and influenza B virus infections, as virtually all US influenza viruses characterized from last winter were susceptible in vitro to them. They are classified as neuraminidase inhibitors (NAIs) because they inhibit the viral neuraminidase enzyme that helps progeny escape from infected cells. NAIs may also have efficacy against the novel influenza viruses.

Oseltamivir (Tamiflu®) is given orally for 5 days with dose adjustments required for renal impairment and weight of child.

Longer treatment courses (i.e. 10-14 days) can be considered for patients who remain severely ill after 5 days of treatment. The commercially manufactured liquid formulation of oseltamivir has a concentration of 6 mg/mL. The most common side effects of oseltamivir are nausea or vomiting. Transient neuropsychiatric events (self-injury or delirium) have been reported, mainly among Japanese adolescents and adults. Recommended dosing for treatment or prophylaxis for children by age and weight is summarized below:

<table>
<thead>
<tr>
<th>AGE</th>
<th>TREATMENT DOSE</th>
<th>PROPHYLAXIS DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 2 weeks old - 3 months</td>
<td>3 mg/kg/dose twice a day</td>
<td>Not recommended unless situation judged critical</td>
</tr>
<tr>
<td>Children 3-11 months</td>
<td>3 mg/kg/dose twice daily</td>
<td>3 mg/kg/dose once daily</td>
</tr>
<tr>
<td>Children 1-12 years old and weighing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 15 kg</td>
<td>30 mg/dose twice a day</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>&gt; 15-23 kg</td>
<td>45 mg/dose twice a day</td>
<td>45 mg once daily</td>
</tr>
<tr>
<td>&gt;23-40 kg</td>
<td>60 mg/dose twice a day</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>75 mg/dose twice a day</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Children &gt; 13 years of age and adults</td>
<td>75 mg/dose twice a day</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

Zanamivir (Relenza®) is a dry powder administered via oral inhalation. It is not FDA-cleared for treatment in children under 7 years of age. The dose is two breath-activated inhalations twice daily for 5 days. Prophylaxis dose is 2 inhalations once daily for ages 5 yrs and older.

Zanamivir is not recommended for patients with underlying airway disease including asthma or COPD because of a lack of safety and efficacy data in these individuals. Serious adverse events including bronchospasm and decline in lung function have been reported with zanamivir use, most commonly in patients with underlying airway disease. (If zanamivir is used in patients with underlying airway disease, they should be instructed to have a fast-acting bronchodilator available). Allergic reactions including rashes and oropharyngeal or facial edema are reported. Side effects can be diarrhea, nausea, sinusitis, runny or stuffy nose, bronchitis, cough, headache, dizziness, and ear, nose and throat complaints.

Amantadine: In recent years most circulating influenza A strains have developed resistance to amantadine and rimantadine, so these medications are not recommended for antiviral treatment or chemoprophylaxis. Recommendations may change if strains with different susceptibility patterns begin to circulate.
**Antiviral Resistance**  Antiviral resistance patterns can change over time, so clinicians should be aware of local antiviral resistance surveillance data. Antiviral resistance can emerge after treatment in certain patients, e.g. the immunosuppressed. See additional information about influenza virus resistance at [www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm](http://www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm).

**Investigational drugs**: Parenterally-administered zanamivir and peramivir (another neuraminidase inhibitor) were used with variable success for treatment of severely-ill patients during the pH1N1 pandemic. These medications remain in clinical trials. No outcomes data is available at this time.

**Bacterial Co-infections**: Patients with influenza are at high risk for secondary bacterial complications like bacterial pneumonia. Antibacterial therapy plus antiviral treatment are recommended for patients with community-acquired pneumonia when influenza also is suspected. Antibiotic treatment should be directed at likely bacterial pathogens most often associated with influenza such as *S. pneumoniae*, *S. pyogenes*, and *S. aureus*, including methicillin-resistant (MRSA), especially for hospitalized patients.

**Chemoprophylaxis**: Neuraminidase inhibitors are 70-90% effective in preventing influenza. Yet the CDC does not recommend widespread or routine use of chemoprophylaxis due to the possibility that resistant viruses could emerge, thus limiting the usefulness of these medications for high-risk or severely ill persons. **Annual vaccination is a better way to prevent influenza because vaccines can be given well before exposures occur and can provide safe and effective immunity throughout the influenza season if the vaccine and circulating strains are well-matched.**

Oseltamivir is cleared for chemoprophylaxis of influenza among infants aged <1 year when indicated although children less than 3 months of age should not receive prophylaxis unless the situation is judged critical, due to limited data in this age group.

Chemoprophylaxis is not usually recommended if more than 48 hours have elapsed since the last exposure to an infected person. Persons receiving chemoprophylaxis should be encouraged to seek medical attention as soon as they develop a febrile respiratory illness that might indicate influenza. For effective prophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza, and continued for 7 days after the last known exposure.

Postexposure prophylaxis should be considered for family members and close contacts of infected patients if they are at high risk of complications from influenza (see risk table above).

**REFERENCES**

1. Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests. [http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm#Figure1](http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm#Figure1).

The following algorithm is intended for use in the emergency departments and urgent cares within the Children’s Hospital Colorado system, and serves as an institutional complement to existing recommendations from the CDC and AAP. The contents were developed via a multidisciplinary collaboration between the Sections of Emergency Medicine and Infectious Diseases. These guidelines will go into effect at start and end of peak influenza season (determined by Epidemiology), as they are designed for periods of high pre-test probability of influenza in children with flu-like illness.

**Goals:**

1. **Optimize outcomes through use of antiviral medication as early as possible** when appropriate in accordance with CDC and AAP recommendations
2. **Minimize unnecessary testing and treatment,** and their associated side effects, costs, and impact on antiviral-resistance
3. **Minimize duplicate testing,** late or missed doses within our own system

**Indications that Influenza should be higher on differential:**

- Patient/family not vaccinated
- Patient not already on oseltamivir
- Classic flu symptoms (usually older patients): high fever, chills, sweats, myalgia, photophobia, headache, dry cough
- Exposure to someone with proven Influenza or with classic flu symptoms
- Patient with high fever without focus and symptoms not typical of other viral illnesses circulating at the time (e.g. bronchiolitis, URI, viral pneumonia)

**Recommendations for the care of ED patients in whom influenza is high on differential diagnosis**

**All Patients Requiring Hospitalization:**

**TREATMENT:** Initial one-time dose of oseltamivir given in the ED

**TESTING:** Admitted to an ICU, pulmonary, oncology: Respiratory PCR (RVP). Admitted to other services: Influenza PCR

**FOLLOW-UP:** Oseltamivir should be STOPPED if PCR is negative; full course must be ordered by inpatient team in order to continue; micro lab will call treatment team at the time of a positive result.

**PROPHYLAXIS:** At the time that a positive influenza result is reported, treating team should inquire whether there are any high risk household contacts recently exposed to the patient and ensure prescription of prophylactic antiviral in accordance with guidelines.

**Patients Being Discharged to Home**

**High Risk Patients (see chart above):**

**TREATMENT:** Prescribe oseltamivir treatment course.

**TESTING:** Influenza PCR only if there are high risk household contacts. DOCUMENT IN THE CHART that the specific contact who will require prophylaxis in the event of a positive result.

**PROPHYLAXIS:** Designated “culture call back provider” will call the family and ensure prescription of prophylactic antiviral in accordance with guidelines in any patients with positive PCR; call & instruct patient to stop oseltamivir in patients with negative flu PCR test.

**Patients Being Discharged to Home**

**Patients without Risk Factors:**

**TREATMENT:** Consider prescription of oseltamivir in any patient in whom a decrease in duration of symptoms would be beneficial if treatment begun within 48 hours of disease onset.

**TESTING:** Influenza PCR only if there are high risk household contacts. DOCUMENT IN THE CHART that the specific contact who will require prophylaxis in the event of a positive result

**PROPHYLAXIS:** Designated “culture call back provider” will call the family and ensure prescription of prophylactic antiviral in accordance with guidelines in any patients with positive PCR; call & instruct patient to stop oseltamivir in patients with negative flu PCR test.

**Bronchiolitis Patients Being Observed For Home Oxygen Use (Flu Season Only)**

**TESTING:** Order Influenza PCR at the outset of the observation period

**TREATMENT:** If influenza positive, institute oseltamivir treatment course while in ED, prior to discharge.

**PROPHYLAXIS:** At the time that a positive influenza result is reported, treating team should inquire whether there are any high risk household contacts recently exposed to the patient and ensure prescription of prophylactic antiviral in accordance with guidelines.
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