Influenza Testing and Treatment

This update focuses on how to diagnose and treat influenza. It is in alignment with current CDC guidelines and AAP recommendations.1

1. How do I test for influenza?
Children’s Hospital Colorado Microbiology/Virology Laboratory will again have two laboratory tests for influenza virus, the influenza-only polymerase chain reaction (PCR) and a comprehensive Respiratory Pathogen PCR. Both PCR tests are significantly more sensitive and specific than the rapid influenza antigen detection tests (RIDTs), which are no longer offered here.

   - Influenza PCR detects influenza A and influenza B. It detects both hemagglutinin (HA) subtypes of influenza A that commonly affect humans, but does not report the subtype detected. The test is performed 24/7, with most results available in 2 hours or less once specimens arrive at the Anschutz Campus. Only nasopharyngeal (NP) aspirates or NP flocked swabs can be tested.

   - The comprehensive Respiratory Pathogen Panel (RPP) PCR detects influenza A and B, as well as other respiratory viruses and 3 bacteria. Unlike influenza PCR, RPP reports both influenza A HA subtypes (H3N2 or 2009 H1N1). RPP also provides results in about 3 hours. Many respiratory specimen types can be tested, including NP flocked swabs, NP aspirates, tracheal aspirates, bronchoalveolar lavage, and lung tissue.

2. Who should I 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.2 PCRs are very expensive, with the charge for Respiratory Pathogen PCR 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, risk status of the individual as well what viruses are circulating in the community. It is also important to recognize that numerous viruses can present in similar ways to influenza.

Have a higher consideration for influenza on your differential if:
- Patient presents with 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)
- Patient/family not vaccinated
- Patient not already on oseltamivir

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Our current recommendations for test ordering are depicted on the following chart:
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 and 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.¹

   ![](Individuals_at_High_Risk_for_Influenza_Complications.png)

   ¹Although 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?**
   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, observational studies suggest that antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when even if started 48 hours after illness onset.

5. **What is the current evidence in the literature to support the use of oseltamivir?**
   Clinical trials of oseltamivir demonstrate its effectiveness in decreasing the duration of symptoms from influenza, especially if given within 48 hours of illness onset.³ There are limited prospective data of the benefits of severe influenza in children, but several observational studies and meta-analyses demonstrate that timely oseltamivir treatment can reduce the duration of symptoms, and complications including hospitalization and death.⁴⁻⁹ A 2014 Cochrane meta-analysis of randomized, placebo controlled trials showed a modest benefit in decreased symptom duration, but since most studies were conducted in outpatient adults, it did not specifically address the question about decreasing the morbidity of severe influenza in children requiring hospitalization.¹⁰ The Children's Hospital...
Colorado ID group recommends that you start antiviral treatment for any inpatient with influenza or any child with severe influenza disease regardless of the day of illness.

<table>
<thead>
<tr>
<th>AGE</th>
<th>TREATMENT DOSE</th>
<th>PROPHYLAXIS DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks - 3 months&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 mg/kg/dose twice a day</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>&lt;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>

<sup>a</sup> Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants less 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.

<sup>b</sup> The American Academy of Pediatrics has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants aged 9-11 months for the 2013-14 season, on the basis of data which indicated that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the CASG 114 study (Kimberlin, 2013). It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

6. How do I 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 to them in vitro. They are classified as neuraminidase inhibitors (NAIs) because they inhibit the viral neuraminidase enzyme that helps new viruses 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. 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. Oseltamivir is now available in generic form. 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:

**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. The prophylaxis dose is 2 inhalations (10 mg) once daily for 5 yrs of age and older. It 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/Rimantadine:** These are not currently recommended for antiviral treatment of chemoprophylaxis, since most circulating influenza A strains have developed resistance to these drugs.

**Peramavir (Rapivab®)** is the third neuraminidase inhibitor approved to treat influenza infection and is the only agent in its class available in IV form. In September 2017, it was approved for the treatment of acute uncomplicated influenza in non-hospitalized children 2 years of age and older as a single dose (2-12 years of age- 12 mg/kg, 12 years and older- 600 mg)\textsuperscript{11}. Current RCT data do not demonstrate superior efficacy compared with oseltamivir for hospitalized patients.
**Investigational drugs:** Parenterally-administered zanamivir (another neuraminidase inhibitor) was used with variable success for treatment of severely-ill patients during the pH1N1 pandemic. Other novel agents remain in clinical trials, and there are limited outcomes data available at this time. Studies of IV formulations of oseltamivir in children are underway.

**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.**

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. Post exposure 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).

**Recommendations for the care of ED and Urgent Care patients**
We recommend influenza testing and treatment for children with a compatible illness who present with severe illness (requiring hospitalization, observation or oxygen), or who have risk factors as outlined in the above Table. Testing and treatment can be considered in children with a known influenza contact, or those who present within 48 hours of illness onset, and the reduction in illness duration is desired by the family.

**References:**
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