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Children's Hospital Colorado

CONTAGIOUS COMMENTS

Department of Epidemiology

Influenza Testing and Treatment

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

1. **What are the current testing options 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 used at Children's Hospital Colorado because they are unreliable.

   - 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. Currently, the Microbiology Laboratory prefers to test nasopharyngeal (NP) swabs but aspirates can also be sent.
   - Note our current rapid test is NOT the same as the older rapid influenza or RSV detection test (RIDT). Rapid PCR is highly specific and sensitive; rapid antigen-based detection tests should not be relied upon due to its poorer sensitivity and specificity. For this reason, RIDTs are no longer used at any Children's Hospital Colorado site.
   - 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. **Which test should I use for influenza?**
   In general, the influenza only PCR test is the preferred test. PCRs are very expensive, with the charge for RPP PCR about four times higher than for influenza only-PCR, despite no significant difference in detection rate of influenza viruses between the two tests. The RPP PCR is usually reserved for use in children who are immunocompromised, critically ill, as part of a fever work up, if influenza A subtyping is relevant. or if a lower airway specimen is to be tested.

3. **Can I diagnose influenza based on signs and symptoms?**
   Influenza can be difficult to diagnose based on clinical signs and symptoms alone because they can be similar to those caused by other infectious agents. The signs and symptoms of influenza can vary by age, immune status, and presence of underlying medication conditions. Uncomplicated influenza can include any or all of the following: fever, muscle aches, headache, lack of energy, dry cough, sore throat, nasal congestion, and possibly runny nose. Fever is not always present in influenza patients, but is more common in children. The fever and body aches can last 3-5 days and the cough and lack of energy may last for 2 or more weeks.

4. **Who should I test for influenza?**

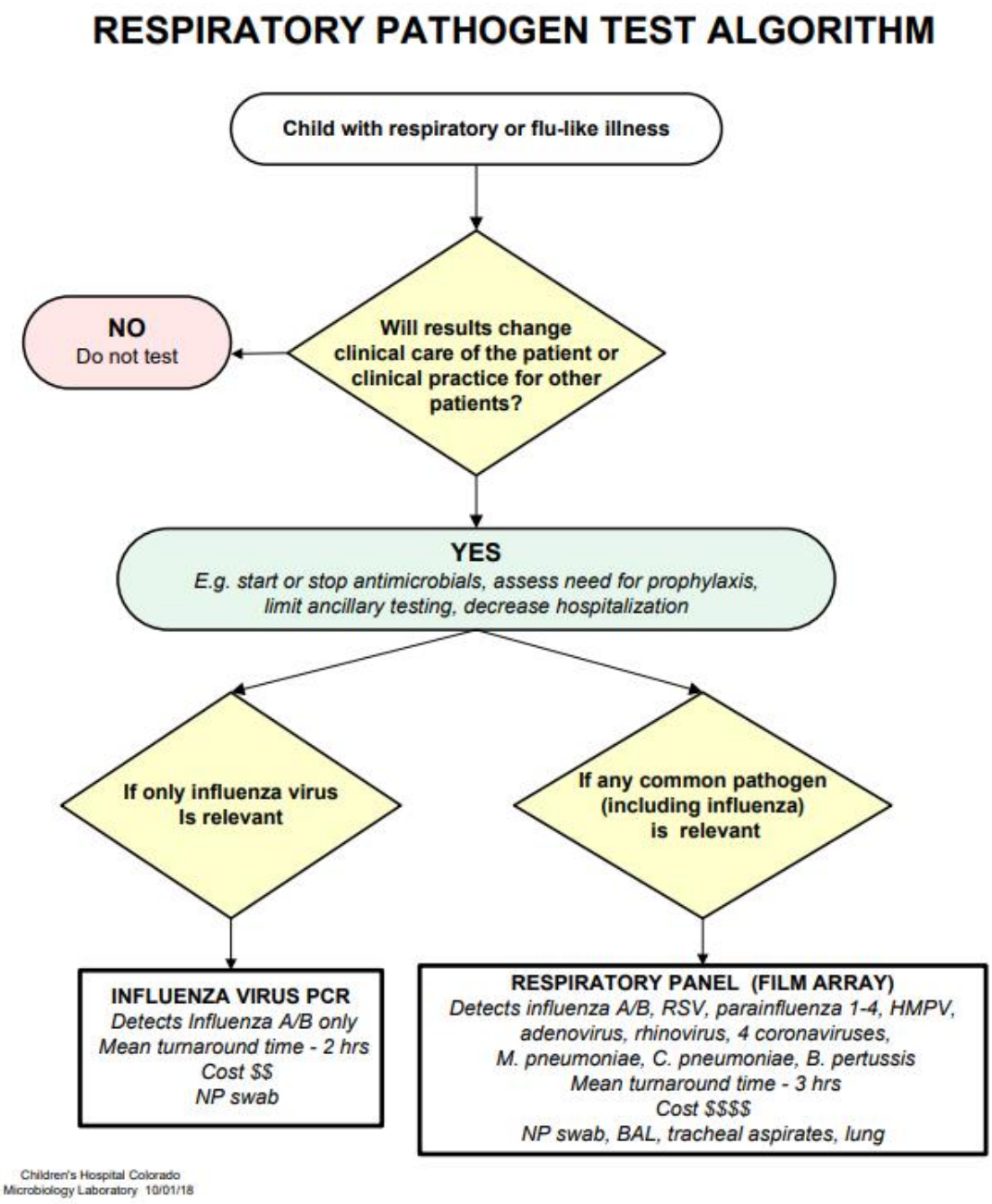
In general, **influenza tests should be ordered only if positive or negative results will influence clinical management or influence the clinical practice for other patients**[2]**.** Therefore, who to test and test choice depends on the clinical situation, risk status of the individual as well what 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, myalgias, photophobia, headache, dry cough
- Sudden onset of symptoms

- 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)

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



5. 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. 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.

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

d. Antiviral treatment may 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

Hospitalized
Severe, complicated, or progressive illness
Children aged <2 years*
Individuals <19 years receiving long-term aspirin therapy
Adults aged ≥65 years
Persons of all ages with:
chronic pulmonary (including asthma), cardiovascular, renal, hepatic, metabolic (including diabetes) hematologic, neurologic (including seizure disorders) conditions, intellectual disability, developmental delay, and neurodevelopmental conditions
Persons with immunosuppression
Pregnant or recently post-partum women
Native Americans/Alaska Natives
Persons who are morbidly obese (BMI ≥40)
Residents of nursing homes or chronic care facilities

*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.

6. 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.

7. What is the current evidence 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 patient hospitalized due to influenza or any child with severe influenza disease regardless of the day of illness.

Table 2. Oseltamivir treatment and prophylaxis dosing

AGE	TREATMENT DOSE	PROPHYLAXIS DOSE
2 weeks - 3 months[a]	3 mg/kg/dose **twice** a day	Not recommended unless situation judged critical
Children 3-11 months[b]	3 mg/kg/dose **twice** a day	3 mg/kg/dose once daily
Children 1-12 years old and weighing:		
≤ 15 kg	30 mg/dose **twice** a day	30 mg once daily
> 15-23 kg	45 mg/dose **twice** a day	45 mg once daily
>23-40 kg	60 mg/dose **twice** a day	60 mg once daily
>40 kg	75 mg/dose **twice** a day	75 mg once daily
Children ≥ 13 years of age and adults	75 mg/dose **twice** a day	75 mg once daily

[a] 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.

[b] 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.

8. What are the current antivirals available 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 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. Note that neuraminidase inhibitors should not be used in combination with agents in the same class, due to the potential for antagonism.

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 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.

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)[11]. Current RCT data do not demonstrate superior efficacy compared with oseltamivir for hospitalized patients.

Baloxavir marboxil is a new antiviral with a different mechanism of action than the neuraminidase inhibitors (small molecule inhibitor of cap-dependent endonuclease). It can be provided as a single dose oral treatment for the treatment of influenza. It is currently FDA approved for children 12 years of age and older, and has similar efficacy to oseltamivir. Dosing is weight-based (40mg as a single dose for those who weigh 40- <80kg, 80 mg once daily for those who weigh ≥ 80 kg. Children's Hospital Colorado does not have this antiviral available on our medication formulary.

Amantadine/Rimantadine: These are not currently recommended for antiviral treatment of chemoprophylaxis, since most circulating influenza A strains have developed resistance to these drugs.

Bacterial co-infections: Patients with influenza are at high risk for secondary bacterial complications like bacterial pneumonia. Antibacterial therapy plus antiviral treatment is 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. **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 can be considered for patients who are considered high risk for developing complications for influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (such as children who are severely immunocompromised)[11]. 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, whereby the reduction in illness duration is desired by the family. Please refer to separate guidelines for the evaluation and management of children with suspected influenza at Children's Hospital Colorado ED and Urgent care locations.

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