Treatment and Prevention of Influenza with Antiviral Medications – Adult/Pediatric – Inpatient Clinical Practice Guideline

Table of Contents

SCOPE.......................................................................................................................... 3
DEFINITIONS .................................................................................................................. 3
RECOMMENDATIONS.................................................................................................... 4
METHODOLOGY............................................................................................................. 6

TABLE 1. ADULT DOSING OF ENTERAL AND INHALATION ANTIVIRAL MEDICATIONS USED TO TREAT AND PREVENT INFLUENZA .................................................. 10
TABLE 2. PEDIATRIC DOSING OF ENTERAL AND INHALATIONAL ANTIVIRAL MEDICATIONS USED TO TREAT AND PREVENT INFLUENZA ....................................... 11
TABLE 3. WEIGHT-BASED OSELTAMIVIR DOSING FOR PEDIATRIC PATIENTS AGED 1 TO 12 YEARS ................................................................................................. 12
REFERENCES................................................................................................................. 13
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Introduction
Influenza is an infectious virus causing illness characterized by fever, malaise, headache, nonproductive cough, sore throat and rhinitis. Uncomplicated illness usually resolves in three to seven days, however, complications from influenza can be severe and may require hospitalization. Complications from influenza include pneumonia, secondary bacterial co-infection, respiratory failure, shock, and death. Globally, influenza results in 250,000 to 500,000 deaths each year. Influenza is spread from person to person through respiratory droplet transmission. Large-particle respiratory droplets typically do not travel more than six feet through air, therefore transmission requires close contact. Contaminated surfaces may also serve as a vehicle for transmission, although this is less common. Influenza virus has an incubation period of one to four days and can be shed from one day prior to symptom onset through five to ten days after symptom onset.

Vaccination against influenza is the best method for prevention and is recommended annually for all individuals six months of age and older.

Scope
Intended Users: Prescribers (physicians, nurse practitioners, physician assistants) and pharmacists.

Objective: To provide information and guidance in the evaluation, diagnosis, and treatment of suspected or diagnosed influenza.

Target Population: Adult and pediatric patients at risk for or diagnosed with influenza.

Clinical Questions Considered:
- Who should receive post-exposure chemoprophylaxis to prevent influenza?
- When and in which patients should treatment with antivirals be initiated?
- How should antivirals be dosed for prophylaxis against or treatment of influenza?

Definitions
Risk factors for complications from influenza:
- Children < 2 years of age
- Adults ≥ 65 years of age
- Patients with chronic pulmonary conditions (including COPD and asthma)
- Cardiovascular disease (excluding hypertension alone)
- Renal or hepatic disease
- Hematological disease (including sickle cell disease)
- Metabolic disorders (including diabetes mellitus)
- Neurologic or neurodevelopmental conditions (including cerebral palsy, epilepsy, stroke, developmental delay, muscular dystrophy etc.)
- Patients with immunosuppression (including HIV infection or immunosuppression caused by medications)
- Women who are pregnant, or within 2 weeks postpartum
- Patients < 19 years of age receiving chronic aspirin or salicylate-containing medication therapy
- American Indians/Alaskan Natives
- Morbidly obese patients with a BMI ≥ 40
- Residents of nursing homes and other chronic-care facilities
Recommendations

Post-exposure Prevention (See Tables 1, 2, and 3)

1. The neuraminidase inhibitors, oseltamivir (Tamiflu®) and zanamivir (Relenza®), may be used for preventing influenza in patients with suspected exposure to the influenza virus and are the preferred agents for chemoprophylaxis.2,8,10,11 (UW Health Conditional Recommendation, Moderate Quality of Evidence)

   1.1. These antiviral medications are approximately 70% to 90% effective in preventing influenza.9,12
   1.2. Ideally, post-exposure prophylaxis should be started within 48 hours of influenza exposure.2,8-10 (UW Health Conditional Recommendation, Very Low Quality of Evidence)
   1.3. Prophylaxis with oseltamivir is dosed 75 mg PO once daily for 7 days after the most recent exposure to a close contact with influenza in the community (e.g., household contact). (UW Health Strong Recommendation, Moderate Quality of Evidence)

   1.3.1. Prophylaxis with oseltamivir may be given for a duration of 14 days (and continued for at least 7 days after symptom onset in the last identified case) for residents on outbreak-affected institutional units.10 (UW Health Conditional Recommendation, Low Quality of Evidence)

   1.3.2. Dosage adjustments are required for patients with CrCL below 30 mL/min and patients receiving hemodialysis, CAPD, or CRRT (Tables 1 and 2).13-16 (UW Health Strong Recommendation, Moderate Quality of Evidence)

1.4. Prophylaxis with zanamivir is dosed 10 mg inhaled once daily for 7 days.10,16

1.5. Peramivir (Rapivab®) should not be used for influenza prophylaxis. (UW Health Conditional Recommendation, Very Low Quality of Evidence)

2. The decision to administer antiviral medication for prophylaxis of influenza should be weighed against the patient’s risk for influenza complications (see Definitions), the extent of possible viral contact, the time since symptom onset, and clinical judgment.2,8 (UW Health Conditional Recommendation, Very Low Quality of Evidence)

2.1. Judicious use of antiviral medications for chemoprophylaxis is recommended to prevent antiviral resistance.2,8,9 (UW Health Conditional Recommendation, Very Low Quality of Evidence)

2.2. Situations where chemoprophylaxis may be warranted include2,8: (UW Health Conditional Recommendation, Very Low Quality of Evidence)

   2.2.1. Patients with high risk for influenza complications exposed to potential infection during the two weeks following influenza vaccination;
   2.2.2. Patients with severe immune deficiency exposed to potential infection;
   2.2.3. Patients with high risk for influenza complications exposed to potential infection and who cannot receive influenza vaccine due to contraindications;
   2.2.4. Residents of institutions (long-term care facilities or jails) during an influenza outbreak at the institution.

3. Adamanatanes, amantadine and rimantadine, have limited use in preventing influenza due to widespread resistance to influenza A virus strains and lack of efficacy against influenza B virus strains. They generally should not be used for chemoprophylaxis.2,8,10,17 (UW Health Conditional Recommendation, Moderate Quality of Evidence)

4. Influenza prophylaxis does not eliminate the risk for influenza and is not a substitute for influenza vaccination.2,8 (UW Health Strong Recommendation, Very Low Quality of Evidence)

Diagnosis

5. Diagnosis of influenza should be made through clinical assessment and diagnostic tests including viral PCR and rapid influenza diagnostic tests (RIDTs).2,8,10 (UW Health Conditional Recommendation, Moderate Quality of Evidence)

5.1. The viral PCR is the most accurate and sensitive test for detecting influenza viruses and is preferred over RIDTs in hospitalized patients to improve detection.2,8,10 (UW Health Conditional Recommendation, Moderate Quality of Evidence)

5.2. Rapid diagnostic tests have lower sensitivities (40% to 70%) than viral PCR resulting in a high rate of false negative results.2,8
6. In patients with a high clinical suspicion for influenza, treatment with antiviral agents should not be withheld while viral PCR results are pending.\textsuperscript{2,8,18} (UW Health Strong Recommendation, High Quality of Evidence)

Treatment (See Tables 1, 2, and 3)
7. Treatment with antiviral agents is recommended as soon as possible for patients requiring hospitalization even if the time from exposure is greater than 48 hours.\textsuperscript{2,8,10,18-21} (UW Health Conditional Recommendation, Moderate Quality of Evidence)

7.1. Oseltamivir use is associated with a reduction in influenza-related complications and pneumonia, faster alleviation of influenza symptoms, and reduced antibiotic use.\textsuperscript{22-25}

7.2. Earlier antiviral treatment within 48 hours of illness onset is associated with less severe disease progression and may lead to reduced complications due to influenza and reduced length of hospital stay.\textsuperscript{18,26} However, for hospitalized patients, or those with severe complicated illness, antiviral treatment administered greater than 48 hours from illness onset may reduce morbidity and mortality.\textsuperscript{18,19,27,28}

7.3. Several studies have demonstrated improved survival in critically ill patients treated with antiviral agents within 5 days of symptoms compared to those receiving no treatment.\textsuperscript{18,19,27,28}

8. Begin treatment with oseltamivir 75mg twice daily for the critically ill and non-critically ill patient. Treatment duration should last for five days.\textsuperscript{2,8,29} (UW Health Strong Recommendation, Moderate Quality of Evidence)

8.1. The duration of treatment may be extended to longer than five days in patients with severe protracted illness or those with immunosuppression.\textsuperscript{2,8-10} (UW Health Conditional Recommendation, Low Quality of Evidence)

8.2. Dosage adjustments are required for patients with CrCl below 30 mL/min and patients receiving hemodialysis, CAPD, or CRRT (Tables 1 and 2).\textsuperscript{13-15,29} (UW Health Strong Recommendation, Moderate Quality of Evidence)

8.2.1. In patients receiving CRRT, doses of 150 mg twice daily resulted in supratherapeutic oseltamivir carboxylic acid concentrations when effluent rates of 3300 ±919 mL/hour. A dose of 75 mg once daily is recommended, however, a higher dose may be needed when using higher effluent rates.\textsuperscript{13}

8.3. Some evidence suggests doses of 150 mg twice daily may be beneficial in the treatment of influenza B but not influenza A.\textsuperscript{30} There is some evidence that suggests this practice is not beneficial.\textsuperscript{31} If patients are not improving and have documented influenza B, 150 mg twice daily may be appropriate.\textsuperscript{8,30} Oseltamivir is well tolerated in severely ill patients with influenza.\textsuperscript{32,33} (UW Health Conditional Recommendation, High Quality of Evidence)

8.4. In patients unable to take oral medications, oseltamivir may be administered via nasogastric or nasojejunal tube. Capsules should be opened and dissolved in 10 mL to 30 mL of water. After administration, the tube should be flushed with water.\textsuperscript{13,14,34} (UW Health Strong Recommendation, Moderate Quality of Evidence)

9. Oseltamivir doses probably do not need to be adjusted for obesity as pharmacokinetic disposition of oseltamivir is similar between obese and non-obese patients.\textsuperscript{35} (UW Health Conditional Recommendation, Low Quality of Evidence)

10. Oseltamivir is probably safe to use in pregnancy.\textsuperscript{36} (UW Health Conditional Recommendation, Moderate Quality of Evidence)

10.1. Some experts recommend an oseltamivir dose of 150 mg twice daily for severe illness during pregnancy due to altered pharmacokinetics.\textsuperscript{10}

11. Oseltamivir is associated with nausea/vomiting and potentially psychiatric events.\textsuperscript{23,25}

12. Injectable peramivir is reasonable for influenza treatment in patients who are unable to take oral or other enteral oseltamivir (e.g. strict NPO, unable to reliably take enteral medications) (UW Health Strong Recommendation, Moderate Quality of Evidence)

12.1. UWCHC peramivir use is restricted to Infectious Disease approval AND to patients unable to take oral oseltamivir (e.g. strict NPO, unable to reliably take enteral medications) AND patients presenting with influenza symptoms within 48 hours of onset AND the suspected phenotype is peramivir susceptible. Peramivir restriction details may be found at the Lexicomp peramivir monograph.
13. Baloxavir may be considered for treatment of influenza as it is noninferior to oseltamivir in time to symptom resolution but baloxavir possesses a low barrier to resistance.\textsuperscript{37,38} (UW Health Conditional Recommendation, Moderate Quality of Evidence)

13.1. Baloxavir should not be crushed. (communication with manufacturer)

13.2. Baloxavir is only FDA approved for patients 12 years of age or older who have been symptomatic for no more than 48 hours.\textsuperscript{10}

14. Antiviral treatment in patients with confirmed or suspected influenza who are at high risk for complications (see Definitions) is recommended as soon as possible post-exposure.\textsuperscript{2,8,10,11} (UW Health Strong Recommendation, Moderate Quality of Evidence)

15. Treatment of influenza with adamantanes (amantadine and rimantadine) is not recommended due to high rates of resistance against influenza A viruses and lack of activity against influenza B viruses.\textsuperscript{2,8,10,17} (UW Health Strong Recommendation, Moderate Quality of Evidence)

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology
Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline authors and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- Electronic database search (e.g. PubMed)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 2014 to 2018

Search Terms:
- Influenza prophylaxis
- Influenza treatment
- Neuraminidase inhibitors
- adamantanes

Methods Used to Select the Evidence:
Expert opinion, clinical experience, and regard for patient safety/experience were considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.
Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).
Figure 1. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

**GRADE Ranking of Evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

**GRADE Ratings for Recommendations For or Against Practice**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (S)</td>
<td>Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)</td>
</tr>
<tr>
<td>Conditional (C)</td>
<td>May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)</td>
</tr>
</tbody>
</table>

**Recognition of Potential Health Care Disparities:** No potential disparities identified.
Collateral Tools & Resources
The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics
• Oseltamivir and peramivir use per influenza season
• Morbidity and mortality rate with influenza infection

Patient Resources
Lexicomp Patient Education - Oseltamivir

Protocols
• IP – Renal Function-Based Dose Adjustment - Adult – Inpatient/Ambulatory [8]
• Influenza Screening and Treatment – Adult/Pediatric – Ambulatory [133]

Companion Documents
• Influenza and Pneumococcal Vaccination – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline
• Renal Function-Based Dose Adjustments – Adult – Inpatient Clinical Practice Guideline
Table 1. ADULT dosing of enteral and inhalation antiviral medications used to treat and prevent influenza

<table>
<thead>
<tr>
<th>ADULT dosing of enteral and inhalation antiviral medications used to treat and prevent influenza</th>
<th>Oseltamivir (Tamiflu®)</th>
<th>Zanamivir (Relenza®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCL &gt;30 mL/min</strong></td>
<td>Treatment</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Adult General Care: 75 mg PO twice daily x 5 days</td>
<td>75 mg PO once daily x 7 days</td>
<td>2 inhalations twice daily x 5 days</td>
</tr>
<tr>
<td>Adult Critical Care: 75mg PO twice daily x 5-10 days</td>
<td>75 mg PO every other day x 7 days</td>
<td>2 inhalations once daily x 7 days</td>
</tr>
<tr>
<td>(150mg PO twice daily if not improving with influenza B)</td>
<td>OR</td>
<td>(each inhalation delivers 5 mg, total dose of 10 mg)</td>
</tr>
<tr>
<td><strong>CrCL ≤30 mL/min</strong></td>
<td>75 mg PO once daily x 5 days</td>
<td>75 mg PO every other day x 7 days</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>75 mg PO after each HD session x 5 days</td>
<td>OR</td>
</tr>
<tr>
<td>(each inhalation delivers 5 mg, total dose of 10 mg)</td>
<td>30 mg once daily x 7 days</td>
<td>(each inhalation delivers 5 mg, total dose of 10 mg)</td>
</tr>
<tr>
<td>CAPD</td>
<td>30 mg PO once weekly after a dialysate exchange</td>
<td>30 mg PO once weekly after a dialysate exchange</td>
</tr>
<tr>
<td>CRRT</td>
<td>75 mg PO once daily</td>
<td>30 mg PO once daily</td>
</tr>
<tr>
<td><strong>Obesity (BMI &gt;40)</strong></td>
<td>No adjustment needed: 75 mg PO twice daily x 5 days</td>
<td>No adjustment needed: 75 mg PO once daily x 7 days</td>
</tr>
<tr>
<td><strong>Liver dysfunction</strong></td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Respiratory disease</strong></td>
<td></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

A Dosing recommendation deviates from package insert. Oseltamivir therapeutic window is wide and availability of 30 mg capsule product may be limited in the ambulatory pharmacy setting.

B Consider switching therapy to 150mg PO BID if critically ill and influenza B positive.

C Prophylaxis with oseltamivir may be given for a duration of 14 days (and continued for at least 7 days after symptom onset in the last identified case) for residents on outbreak-affected institutional units.
### Table 2. PEDIATRIC dosing of enteral and inhalational antiviral medications used to treat and prevent influenza

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oseltamivir (Tamiflu®)</th>
<th>Zanamivir (Relenza®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td><strong>CrCL &gt;30 mL/min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥13 years</td>
<td>Follow adult dosing</td>
<td>≥13 years</td>
</tr>
<tr>
<td>1-12 years</td>
<td>Weight-based, follow Table 3</td>
<td>1-12 years</td>
</tr>
<tr>
<td>2 weeks to &lt;1 year</td>
<td>3 mg/kg** PO twice daily⁹</td>
<td>2 weeks to &lt;1 year</td>
</tr>
<tr>
<td><strong>CrCL ≤30 mL/min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥13 years</td>
<td>Follow adult dosing</td>
<td>≥13 years</td>
</tr>
<tr>
<td>1-12 years</td>
<td>Weight-based, follow Table 3</td>
<td>1-12 years</td>
</tr>
<tr>
<td>2 weeks to &lt;1 year</td>
<td>3 mg/kg** PO once daily</td>
<td>2 weeks to &lt;1 year</td>
</tr>
<tr>
<td><strong>Hemodialysis</strong></td>
<td></td>
<td>Dose after each HD session¹⁰:</td>
</tr>
<tr>
<td>≤15 kg</td>
<td>7.5 mg</td>
<td></td>
</tr>
<tr>
<td>16-23 kg</td>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td>24-40 kg</td>
<td>15 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>30 mg</td>
<td></td>
</tr>
<tr>
<td><strong>CAPD</strong></td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>CRRT</strong></td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Obesity (BMI &gt; 40)</strong></td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td><strong>Liver dysfunction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory disease</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** There is no data in pediatric patients for doses greater than 75 mg.
Table 3. Weight-based oseltamivir dosing for pediatric patients aged 1 to 12 years

<table>
<thead>
<tr>
<th>Weight</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCL &gt; 30 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15 kg</td>
<td>30 mg PO twice daily x 5 days</td>
<td>30 mg PO once daily x 7 days</td>
</tr>
<tr>
<td>15 to 23 kg</td>
<td>45 mg PO twice daily x 5 days</td>
<td>45 mg PO once daily x 7 days</td>
</tr>
<tr>
<td>23 to 40 kg</td>
<td>60 mg PO twice daily x 5 days</td>
<td>60 mg PO once daily x 7 days</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>75 mg PO twice daily x 5 days</td>
<td>75 mg PO once daily x 7 days</td>
</tr>
<tr>
<td>CrCL &lt; 30 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15 kg</td>
<td>30 mg PO once daily x 5 days</td>
<td>30 mg PO every other day x 7 days</td>
</tr>
<tr>
<td>15 to 23 kg</td>
<td>45 mg PO once daily x 5 days</td>
<td>45 mg PO every other day x 7 days</td>
</tr>
<tr>
<td>23 to 40 kg</td>
<td>60 mg PO once daily x 5 days</td>
<td>60 mg PO every other day x 7 days</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>75 mg PO once daily x 5 days</td>
<td>75 mg PO every other day x 7 days</td>
</tr>
</tbody>
</table>
References


