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November 2022 ~ Resource #381102

Antivirals for Influenza

Getting vaccinated each year is the most effective way to prevent influenza infection.[1,2] The chart below reviews guidance on the use of antivirals for the treatment and prevention of influenza, as well as available antivirals, including place in therapy, dose, and duration. See our chart, *Flu Vaccines*, for timing considerations with antivirals and the LIVE-attenuated flu vaccine (*FluMist*).

Influenza Prevention: Antiviral prophylaxis (seasonal, pre-exposure, or post-exposure) is **not recommended** for most patients.[1]

- Per AMMI Canada, consider **pre-exposure prophylaxis** during community outbreaks only in:[7, b]
  - high-risk patients during the 14 days following administration of an inactivated influenza vaccine.
  - high-risk patients and their close contacts if circulating strains are not covered by the current year's influenza vaccine.
  - high-risk patients, their family members, and healthcare workers in close contact with unimmunized patients if they have contraindications to vaccination OR a poor response to vaccination is expected.
- Consider **post-exposure prophylaxis** for high-risk patients[b] who are not protected with vaccination. For example:[1,7]
  - within two weeks of receiving an influenza vaccination.
  - a poor response to vaccination is expected (e.g., patients on immunosuppressants).
  - there are contraindications to vaccination.
- Post-exposure prophylaxis is generally not recommended if more than 48 hours (four days per AMMI Canada) have passed since exposure.[1,7]
- During institutional outbreaks, antiviral prophylaxis, antiviral treatment, and/or inactivated vaccine administration may be considered.[1,7]
  - Per Infectious Diseases Society of America, during an institutional outbreak, all exposed residents should receive antiviral prophylaxis.[19]

Drug/Cost[a]	Dose (Pediatric)	Dose (Adult)	Comments
Oseltamivir, oral (*Tamiflu*, generics) 10-day course, capsules:[c] $25 (US) $11 (Canada)	**FDA- and Health Canada-approved**: 1 year and older.[3,8] • ≥3 months (per AAP and CDC).[1] • <3 months if they are critically ill (per CDC and AMMI Canada).[1,7] **3 months to less than 1 year**:[1,7] 3 mg/kg once daily. **1 year and older**:[3,8] ≤15 kg: 30 mg once daily. >15 kg to 23 kg: 45 mg once daily. >23 kg to 40 kg: 60 mg once daily. >40 kg: 75 mg once daily.	**13 years and older**: 75 mg once daily.[3,8] **Dosing in patients with kidney impairment**:[3,8] CrCl 31 to 60 mL/min: 30 mg once daily. CrCl 11 to 30 mL/min: 30 mg every two days. **Hemodialysis**:[3,8] 30 mg immediately, then 30 mg after alternate dialysis cycles. **Peritoneal dialysis**:[3,8] 30 mg immediately, then 30 mg once weekly.	• Neuraminidase inhibitor.[3,8] • Serious skin reactions (e.g., Stevens-Johnson syndrome) and neuropsychiatric events (e.g., hallucinations, delirium, abnormal behavior, etc) have been reported.[3,8] • Adverse reactions include nausea and vomiting. Taking with food may increase tolerability.[8] • Product labeling does not recommend for patients with CrCl of 10 mL/min or less who are not on dialysis.[3,8] • **Duration** of prophylaxis varies by indication.[c] • Intravenous oseltamivir is no longer available.[21]

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Prevention, continued			
Drug/Cost[a]	**Dose (Pediatric)**	**Dose (Adult)**	**Comments**
Zanamivir, inhaled (*Relenza*) $59 (US) $45 (Canada)	**FDA-approved**: ≥5 years.[4] **Health Canada-approved**: ≥7 years.[9] 10 mg (two inhalations) once daily for ten days.[4,9] Give for 28 days for community outbreaks.[4,9]	10 mg (two inhalations) once daily for ten days.[4,9] Give for 28 days for community outbreaks.[4,9]	• Neuraminidase inhibitor. • Avoid in patients with pulmonary disease (e.g., asthma, COPD, etc) due to risk of bronchospasm.[4,9] • Serious skin reactions (e.g., Stevens-Johnson syndrome, etc), neuropsychiatric effects (e.g., delirium, abnormal behavior, etc), and serious allergic reactions have been reported.[4,9] • Contraindicated in patients with a milk protein allergy.[4,9] • Unknown efficacy for nursing home residents.[4,9]
Peramivir (*Rapivab*) US only Note: approved but not marketed in Canada.	Not indicated.[5,6]	Not indicated.[5,6]	• Neuraminidase inhibitor.
Baloxavir (*Xofluza*) US only $155 (US) (tablets) Note: approved but not marketed in Canada.	**FDA-approved**: ≥5 years.[10] **<20 kg**:[10] single dose of 2 mg/kg. **20 kg to <80 kg**:[10] single dose of 40 mg. **80 kg or more**:[10] single dose of 80 mg.	**20 kg to <80 kg**:[10] single dose of 40 mg. **80 kg or more**:[10] single dose of 80 mg. No dose adjustments are needed in patients with moderate kidney impairment (CrCl of 50 mL/min and above) or moderate liver impairment (Child-Pugh class B).[10] No data available in patients with severe kidney or liver impairment.[10]	• Selective polymerase acidic endonuclease inhibitor.[10] • Generally well-tolerated. The most common adverse effects are vomiting (5 to 12 years old) and diarrhea.[10] Appears to have less nausea and vomiting than oseltamivir.[3,10] • Avoid taking baloxavir at the same time as products containing calcium (including dairy), iron, magnesium, selenium, or zinc due to a decrease in baloxavir absorption. Peak baloxavir absorption occurs at four hours.[10] Consider avoiding dairy and supplements until baloxavir is absorbed. • In a study (n = 752) done in Japan, baloxavir significantly reduced the household transmission of influenza compared to placebo (NNT = 9) [Evidence Level A-1].[11]

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Treatment of Influenza:

- Antivirals can be considered for otherwise healthy patients **if** the duration of symptoms is less than 48 hours. Treatment may shorten illness by about one day and reduce household transmission.[1,7]
- Antiviral treatment is recommended for patients who are hospitalized; have moderate to severe, complicated, or progressive illness; or are at high risk for influenza complications.[1,7,b]
  - In high-risk patients, some antivirals may reduce complications (e.g., otitis media in young children, pneumonia, respiratory failure), mortality in hospitalized patients, and hospital stays.[1,7]
- **Efficacy is best** when antivirals are started as early as possible after the onset of symptoms (goal should be within twelve hours).[7] However, antivirals should be initiated (even if more than 48 hours have passed since symptom onset) in patients with severe, complicated, progressive illness; who are hospitalized, and who are at high risk of complications and severe disease.[1,7,b] The decision to start therapy should not wait for diagnostic test results.[1]
- Longer durations of oseltamivir or peramivir treatment may be considered in patients who are severely or critically ill.[1,7] There are currently little data for increased efficacy with the use of baloxavir other than as a one-time dose.[10,12]
- Data do not support using a combination of antivirals for the treatment of influenza.[7,12]

Drug/Cost[a]	Dose (Pediatric)	Dose (Adult)	Comments
Oseltamivir, oral (*Tamiflu*, generics) (capsules) ~$25 (US) $11 (Canada)	**FDA-approved**: 14 days and older.[3] **Health Canada-approved**: ≥1 year.[8] AMMI Canada recommend assessing the use of oseltamivir in infants less than 1 year on a case-by-case basis.[7] CDC and AAP recommend oseltamivir for all ages.[1] AAP provides dosing guidance for both term and premature infants.[1,13] **2 weeks to <1 year, term infants (per US labeling)**:[3] 3 mg/kg/dose BID. **One year and older**:[3,8] 15 kg or less: 30 mg BID. >15 kg to 23 kg: 45 mg BID. >23 kg to 40 kg: 60 mg BID. >40 kg: 75 mg BID.	**13 years and older**:[3,8] 75 mg BID **Dosing in patients with kidney impairment**:[3,8] CrCl 31 to 60 mL/min: 30 mg BID. CrCl 11 to 30 mL/min: 30 mg once daily. **Hemodialysis**:[3,8] Initial dose of 30 mg, then 30 mg after each dialysis, not to exceed five days for most patients. **Peritoneal dialysis**:[3,8] 30 mg (single dose) prior to dialysis.	• **Duration** of treatment is five days.[3,8] • Some experts recommend 150 mg BID (in patients with normal kidney function) for immunocompromised or severely ill, hospitalized, adult patients.[1] However, limited data suggest this increased dose does not improve efficacy.[1,7,8,21] • Preferred antiviral for pregnant women.[1,7] • Product labeling does not recommend for patients with CrCl of 10 mL/min or less who are not on dialysis.[3,8] • May use adult dosage adjustments in kids >40 kg.[1] • Severely ill, hospitalized patients should be treated with oseltamivir due to insufficient data with zanamivir, peramivir, and baloxavir.[1,20] Per AMMI Canada, oseltamivir is preferred; however, zanamivir may be considered if there is no response to oseltamivir, the patient has failed oseltamivir prophylaxis, or influenza B is strongly suspected.[7] • Premature infants may a have slower clearance due to immature kidney function.[1,7] • Intravenous oseltamivir is no longer available.[21]

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Treatment, continued			
Drug/Cost[a]	**Dose (Pediatric)**	**Dose (Adult)**	**Comments**
Zanamivir, inhaled (*Relenza*) $59 (US) $45 (Canada)	7 years and older:[4,9] 10 mg (two inhalations) BID for five days.[4]	10 mg (two inhalations) BID for five days.[4,9] No adjustment necessary for kidney impairment.[4]	• CDC recommends against using inhaled zanamivir in hospitalized patients due to a lack of data.[1] Per AMMI Canada, zanamivir may be considered for patients with moderate, progressive, severe, or complicated influenza (with or without risk factors) if they have not responded to oseltamivir, failed oseltamivir prophylaxis, or influenza B is strongly suspected.[21] • Injectable zanamivir is no longer available.[1,7] • Avoid in patients with pulmonary disease (e.g., asthma, COPD, etc) due to risk of bronchospasm.[4,9] • Serious skin reactions (e.g., Stevens-Johnson syndrome, etc), neuropsychiatric effects (e.g., delirium, abnormal behavior, etc), and serious allergic reactions have been reported.[4,9] • Contraindicated in patients with a milk protein allergy.[4,9]
Peramivir, intravenous (*Rapivab*) US only $950 (US) Note: approved but not marketed in Canada.	**FDA-approved**: 6 months and older.[5] **6 months to 12 years**: 12 mg/kg (up to 600 mg) IV infusion over at least 15 to 30 minutes x one dose.[5] **Dosing in patients with kidney impairment (2 to 12 years)***:[5] CrCl 30 to 49 mL/min: 4 mg/kg (up to 200 mg) x one dose. CrCl 10 to 29 mL/min: 2 mg/kg (up to 100 mg) x one dose. *For dosing under 2 years, consult product labeling. **Canada**: not indicated under 18 years.[6]	**US**: 13 years and older. **Canada**: 18 years and older.[5,6] 600 mg (3 vials) IV infusion over 15 to 30 minutes x one dose.[5,6] **Dosing in patients with kidney impairment**:[5,6] CrCl 30 to 49 mL/min: 200 mg x one dose. CrCl 10 to 29 mL/min: 100 mg x one dose. **Hemodialysis**:[5,6] Give after hemodialysis based on kidney function.	• Generally well-tolerated.[1] The most common adverse reaction is diarrhea.[5] • Do not mix with other IV meds.[5,6] • Serious skin reactions (e.g., Stevens-Johnson syndrome, etc), anaphylaxis, and neuropsychiatric events (e.g., hallucinations, delirium, abnormal behavior, etc) have been reported.[5,6] • Consider using if a patient cannot tolerate or absorb oral/enteric oseltamivir (e.g., patients with suspected or known gastric stasis, malabsorption, or GI bleeding).[1] • There are limited data in immunocompromised patients and those over 65 years.[5,6] • Does **not** appear to have benefit compared to placebo in patients with serious influenza requiring hospitalization [Evidence Level A-1].[1,14]

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Treatment, continued			
Drug/Cost[a]	**Dose (Pediatric)**	**Dose (Adult)**	**Comments**
Baloxavir, oral (*Xofluza*), US only (tablets) $155 (US) Note: approved but not marketed in Canada.	**FDA-approved**: otherwise healthy patients: 5 years and older OR patients at high risk of developing influenza-related complications: 12 years and older.[10] **<20 kg**:[10] single dose of 2 mg/kg. **20 kg to <80 kg**:[10] single dose of 40 mg. **80 kg or more**:[10] single dose of 80 mg.	**20 kg to <80 kg**:[10] single dose of 40 mg. **80 kg or more**:[10] single dose of 80 mg. No dose adjustments are needed in patients with moderate kidney impairment (CrCl of 50 mL and above) or moderate liver impairment (Child-Pugh class B).[10] No data available in patients with severe kidney or liver impairment.[10]	• Generally well-tolerated. The most common adverse effects are diarrhea, vomiting (5 to 12 years old).[10] Appears to have less nausea and vomiting than oseltamivir.[3,10] • Avoid taking baloxavir at the same time as products containing calcium (including dairy), iron, magnesium, selenium, or zinc due to a decrease in baloxavir absorption. Peak baloxavir absorption occurs at four hours.[10] Consider avoiding dairy and supplements until baloxavir is absorbed. • Baloxavir appears to work as well as oseltamivir for the treatment of uncomplicated influenza in some high-risk outpatients [Evidence Level A-1].[10,15,16] • There is ongoing study with baloxavir in children (e.g., under one year of age).[17] • Adding baloxavir to standard-of-care treatment with a neuraminidase inhibitor (i.e., oseltamivir, zanamivir, peramivir) does NOT improve time to clinical improvement in hospitalized patients with severe influenza.[12] • Resistant strains of influenza have been detected following treatment with baloxavir (with higher rates in patients less than 5 years compared to older patients).[10,18]

Abbreviations: AAP = American Academy of Pediatrics; AMMI = Association of Medical Microbiology and Infectious Disease; BID = twice daily; CrCl = creatinine clearance; GI = gastrointestinal; IV = intravenous; NNT = number need to treat.

a. Cost is wholesale acquisition cost (WAC) of the generic product, when available, for a typical prophylaxis or treatment course in an adult. US medication pricing by Elsevier, accessed October 2022.

b. **Patients at high-risk for complications from influenza include**:[1,7]
   - children less than two years (less than five years in Canada) and adults 65 years and older.
   - **persons with chronic conditions** such as pulmonary disease (including asthma), cardiovascular disease (except hypertension alone), kidney disease, liver disease, hematological disorders (including sickle cell disease), malignancy, metabolic disorders (including diabetes mellitus),

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or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle [such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury]).
- persons who are immunosuppressed, including those on immunosuppressants and with HIV infection.
- pregnant or postpartum patients (two weeks [US] or up to four weeks [Canada] after delivery/end of pregnancy).
- persons younger than 19 years who are on long-term aspirin therapy.
- non-Hispanic Black, Hispanic or Latino, Native Americans, Alaska Natives, and Indigenous persons.
- persons who are morbidly obese (i.e., body mass index of 40 or more, or is greater than 3 z-scores above the mean BMI for age and gender).
- residents of nursing homes and other chronic care facilities.

c. For prophylaxis, product labeling for *Tamiflu* recommends a **duration** of at least 10 days.[3,8] In Canada (per labeling and AMMI), duration should be 14 days if the index case is a child or elderly person.[7,8] Give up to six weeks for community outbreaks and up to twelve weeks for immunocompromised patients.[3,8] CDC recommends prophylaxis for the duration of exposure to a person with influenza plus seven days, or for 14 days after vaccination (when using as a bridge between vaccination and the development of immunity).[1] Infectious Disease Society of America recommends a duration of seven days after the most recent exposure.[19]

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Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56.
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