The use of antiviral drugs for influenza: Guidance for practitioners, 2012/2013; Paediatric summary

Upton D Allen; Canadian Paediatric Society, Infectious Diseases and Immunization Committee
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Abstract
This practice point summarizes the use of antiviral drugs to manage influenza illness in children and youth for the 2012/2013 season. It excerpts a recently published, full-length update of Canadian recommendations for clinicians on the use of antiviral drugs for the prevention and treatment of influenza, with a focus on paediatric antiviral therapy. Detailed information on the selective use of chemoprophylaxis can be found in the source document, which also highlights the importance of secondary bacterial infections (Streptococcus pneumoniae, methicillin-sensitive Staphylococcus aureus and methicillin-resistant S aureus) in cases of severe influenza illness.

Key Words: Antiviral therapy; Children; Influenza; Neuraminidase inhibitors


Antiviral use in children
There are fewer data to guide the management of influenza illness in children generally, and especially in infants, than for adults. Background information on this illness in children, provided in the full-length guidance document, was based on data derived from paediatric populations.[1][5] More on the strengths and weaknesses of current evidence relating to antiviral use can be found at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub3/abstract.

Significant issues include high influenza attack rates in school-aged children,[1][2] the atypical, non-specific nature of influenza illness in young children,[3] and the high risk of adverse outcomes from influenza illness among children younger than five years of age.[5] Hospitalizations occur more frequently among children younger than two years of age compared with older children, with the highest hospitalization rates being among infants younger than six months of age.[3]

These statistics do not necessarily translate into decisions to use antiviral therapy in patients younger than two years of age; children of any age with mild influenza illness do not usually require treatment.

Three currently available antiviral agents are approved for use for children in Canada. Amantadine, for seasonal influenza A, is not currently useful because of resistance. Oseltamivir (Tamiflu, Hoffman-La Roche Ltd, Canada) and zanamivir (Relenza, GlaxoSmithKline Inc, United Kingdom) are used for influenza A and B. More recent studies on the neuraminidase inhibitors (NAIs) have been reported or are in progress, and experience with their use is increasing.[6][9] However, there is a notable paucity of current data from randomized trials in infants and young children. Two recent studies provided valuable safety data[10] and data on oseltamivir use in premature newborns.[11] However, oseltamivir use for 2012/2013 seasonal influenza in children younger than one year of age should be handled on a case-by-case basis based on severity of illness. Oseltamivir is not approved for this indication in Canada, though it was temporarily approved for use in infants under one year on the basis of a favourable risk-to-benefit ratio during
the 2009 H1N1 pandemic. Published recommendations for oseltamivir dosing for babies younger than one year of age vary within a reasonably narrow range.\[12\]-\[14\]

**Treatment recommendations**

Risk factors and drug doses are summarized in **Table 1** and **Table 2**. A treatment algorithm is included as **Figure 1**. For explanation of levels of evidence, see the full guidance document.

### TABLE 1
At-risk groups and comorbid medical conditions that predispose to severe influenza illness

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asthma or other chronic pulmonary diseases, including bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis and emphysema</td>
</tr>
<tr>
<td>• Cardiovascular disease (excluding isolated hypertension; including congenital and acquired heart disease, such as congestive heart failure and symptomatic coronary artery disease)</td>
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<tr>
<td>• Malignancy</td>
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<tr>
<td>• Chronic renal insufficiency</td>
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<tr>
<td>• Chronic liver disease</td>
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<tr>
<td>• Diabetes mellitus and other metabolic diseases</td>
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<tr>
<td>• Hemoglobinopathies such as sickle cell disease</td>
</tr>
<tr>
<td>• Immunosuppression or immunodeficiency due to disease (eg, HIV infection, especially if CD4 is (&lt;200\times10^6/L), or iatrogenic, due to medication)</td>
</tr>
<tr>
<td>• Certain rheumatological diseases, such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, scleroderma, spondyloarthropathies, Sjogren’s syndrome, dermatomyositis, vasculitis, sarcoidosis and polyarteritis nodosa</td>
</tr>
<tr>
<td>• Neurological disease and neurodevelopment disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)</td>
</tr>
<tr>
<td>• Children younger than five years*</td>
</tr>
<tr>
<td>• Children or youth who reside in homes or other chronic care facilities</td>
</tr>
<tr>
<td>• Pregnant women and women up to two weeks postpartum regardless of how the pregnancy ended</td>
</tr>
<tr>
<td>• Individuals (&lt;18) years of age who are on chronic acetylsalicylic acid therapy</td>
</tr>
<tr>
<td>• Obesity with a BMI (\geq40) kg/m(^2), OR a BMI (\geq3) z-scores above the mean for age and gender</td>
</tr>
<tr>
<td>• First Nations, Inuit and Métis children and youth</td>
</tr>
</tbody>
</table>

Adapted from references 15 and 16.

* Children who are two years through four years of age have a higher rate of complications compared with older children; however, the risk for these children is lower than the risk for children younger than two years of age.

BMI: Body mass index

**General principles:**

- If the decision is made to start an antiviral drug, treatment should be initiated as soon as possible after onset of illness. The benefits of treatment are much greater with initiation at \(<12\) h than at \(48\) h. (Strong recommendation, Grade B evidence)
- Otherwise healthy patients of any age with relatively mild, self-limited influenza are not likely to benefit from neuraminidase inhibitor (NAI) therapy initiated \(>48\) h after illness onset. Clinical judgment should be used. (Option, Grade D evidence)

However, antiviral therapy should be initiated even if the interval between illness onset and
administration of antiviral medication exceeds 48 h if:
- The illness is severe enough to require hospitalization; (Strong recommendation, Grade X evidence)
- The illness is progressive, severe or complicated, regardless of previous health status; (Strong recommendation, Grade X evidence) or
- The individual belongs to a group, other than age, at high risk for severe disease. (Strong recommendation, Grade X evidence)

• Parents of children for whom antiviral therapy is not recommended should be advised of symptoms and signs of worsening illness that might warrant reassessment. (Recommendation, Grade D evidence)

• Treatment duration should routinely be five days (Strong Recommendation, Grade A evidence), but may be continued longer than five days if clinically indicated. (Option, Grade D evidence) Intubated patients with influenza illness should receive oseltamivir through a nasogastric tube. (Recommendation, Grade C evidence)

• For patients unable to tolerate or receive oral oseltamivir, inhaled or intravenous zanamivir is a suitable option. However, children younger than seven years of age are unlikely to be able to use the delivery device for zanamivir effectively. (Option, Grade D evidence)

• Zanamivir may be preferred to oseltamivir in the following situations:
  - Patients not responding to oseltamivir therapy (Recommendation, Grade C evidence); or
  - Patients with illness despite oseltamivir prophylaxis (Recommendation, Grade C evidence).

• For severely ill patients, zanamivir administered intravenously is preferred to inhaled drug. (Recommendation, Grade D evidence)

• In ventilated patients, zanamivir should only be administered intravenously. (Strong Recommendation, Grade X evidence)

• If patients are not responding to oseltamivir therapy, their virus should be tested for oseltamivir resistance and the possibility of co-infection with another pathogen considered. (Option, Grade D evidence)

Note: Grade X evidence denotes situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm.
Treating infants, children and youth with mild or uncomplicated influenza illness (Figure 1):

- For those with mild disease and no risk factors other than age:
  - Younger than one year of age: NAIs are currently not approved for the routine treatment of seasonal influenza illness. Given that infants younger than six months of age are not eligible for influenza vaccination, immunization of their household and other close contacts is important in protecting them against influenza, thereby potentially leading to reduced need for antiviral therapy. Influenza immunization of the pregnant woman may also provide protection for her infant during the first six months of life. (Option, Grade D evidence)
  - One to less than five years of age: Although children under five years of age are classified as ‘high risk’ (with those younger than two years of age having the highest risk), those who are otherwise healthy and have mild disease not requiring hospitalization do not routinely require antiviral therapy. For these children, treatment is optional. (Option, Grade D evidence)
  - Five or more years of age: Antiviral therapy is not routinely recommended for children and youth who are otherwise healthy and have mild disease not requiring hospitalization. (Option, Grade D evidence)

- For those with mild disease and risk factors other than age:
  - Younger than one year of age: NAIs are currently not approved for the routine treatment of seasonal influenza illness.
  - One or more years of age: For illness of ≤48 h duration, treat with oseltamivir or, if age-appropriate, inhaled zanamivir. (Recommendation, Grade B evidence)

- One or more years of age: For illness of >48 h duration, treat with oseltamivir or, if age-appropriate, inhaled zanamivir may be considered on a case-by-case basis. (Option, Grade D evidence)

Treating infants, children and youth with moderate, progressive, severe or complicated influenza illness with or without risk factors:

- Consider hospitalization and admission to the intensive care unit. (Recommendation, Grade C evidence)
- Start antivirals immediately. (Strong recommendation, Grade B evidence) Treat with oseltamivir or zanamivir in appropriate doses. (Table 2)
- Oseltamivir or zanamivir should be started even when the window between symptom onset and initial administration of the antiviral is >48 h. (Recommendation, Grade C evidence)
- Treatment with zanamivir instead of oseltamivir should be considered for:
  - Patients not responding to oseltamivir therapy: (Recommendation, Grade C evidence) or
  - Patients with illness despite oseltamivir prophylaxis. (Recommendation, Grade C evidence)

- Although oseltamivir was approved temporarily for use in infants younger than one year of age on the basis of a favourable risk-to-benefit ratio during the 2009 H1N1 pandemic, its use in this population for seasonal influenza should be handled on a case-by-case basis, based on severity of illness. (Option, Grade D evidence)
**TABLE 2 Oseltamivir and zanamivir treatment of influenza in children and youth (<18 years of age) – October 2012**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment (five days)</th>
<th>Chemoprophylaxis (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oseltamivir</strong> *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>75 mg twice daily</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Children ≥12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>Body weight, lbs</td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>≤33</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt;15 to 23</td>
<td>&gt;33 to 51</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt;23 to 40</td>
<td>&gt;51 to 88</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&gt;88</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Children 3 months to &lt;12 months †</td>
<td>3 mg/kg per dose twice daily</td>
<td>3 mg/kg per dose once per day</td>
</tr>
<tr>
<td>Children &lt;3 months ‡</td>
<td>3 mg/kg per dose twice daily</td>
<td>Not recommended unless situation judged critical due to limited data on use in this age group</td>
</tr>
<tr>
<td><strong>Zanamivir</strong> §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>10 mg (two 5 mg inhalations) twice daily</td>
<td>10 mg (two 5 mg inhalations) once daily</td>
</tr>
<tr>
<td>Children (≥7 years)</td>
<td>10 mg (two 5 mg inhalations) twice daily</td>
<td>10 mg (two 5 mg inhalations) once daily</td>
</tr>
</tbody>
</table>

Treatment regimens adapted from reference 17. Please note that in Canada antivirals are not authorized for the routine treatment of seasonal influenza illness in babies younger than one year of age. Such use may be considered on a case-by-case basis.*Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available in 30 mg, 45 mg, and 75 mg capsules, and as a powder for oral suspension that is reconstituted to provide a final concentration of either 6 mg/mL or 12 mg/mL. If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste or a suspension can be compounded by retail pharmacies (final concentration 6 mg/mL). When dispensing commercially manufactured oseltamivir (Tamiflu Powder for Oral Suspension [6 mg/mL or 12 mg/mL] Hoffman-La Roche Ltd, Canada), pharmacists should ensure the units of measure on the prescription instructions match the dosing device; †Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment of influenza (give two doses per day) or prophylaxis (give one dose per day) in full-term infants younger than one year of age may be necessary: 0 to 3 months = 12 mg per dose for treatment (not for prophylaxis); 3 to 5 months = 20 mg per dose; 6 to 11 months = 25 mg per dose; ‡Current weight-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of oseltamivir due to immature renal function, and doses recommended for full-term infants may lead to very high drug concentrations in this age group. Very limited data from a cohort of premature infants demonstrated that oseltamivir concentrations among premature infants given 1 mg/kg body weight twice daily were similar to those observed with the recommended treatment doses in term infants (3 mg/kg body weight twice daily). Observed drug concentrations were highly variable among premature infants. The Infectious Diseases Society of America’s 2011 recommendations for paediatric pneumonia suggest 2 mg/kg/day divided twice daily. Currently available data are insufficient to recommend a specific dose of oseltamivir for premature infants; it is strongly suggested that an infectious disease physician or clinical pharmacist should be consulted; §Zanamivir is administered by inhalation using a proprietary ‘Diskhaler’ device (Relenza, GlaxoSmithKline Inc, United Kingdom) distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered using nebulizers, ventilators or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for persons with chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease, which increase the risk of bronchospasm.
References


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