

Guidance on the use of antiviral drugs for influenza in acute care facilities in Canada, 2014-2015

H Grant Stiver MD¹, Gerald A Evans MD², Fred Y Aoki MD³, Upton D Allen MBBS⁴, Michel Laverdière MD⁵

The purpose of this document is to provide an update on the management of patients in the acute care setting infected with influenza viruses circulating in Canada during the 2014-2015 influenza season.

A. PROCESS STATEMENT

The development of this updated guidance arose in November 2014 from information provided by the Public Health Agency of Canada regarding early data indicating a mismatch of the influenza vaccine H3N2 component to an emerging H3N2 seasonal strain. This created a need to update recommendations for the use of antiviral drugs for this year's seasonal influenza. The concept was then approved by Association of Medical Microbiology and Infectious Disease (AMMI) Canada. A first draft was cowritten by all the authors (HGS, FYA, UDA, GAE and ML). Subsequently, all the authors reviewed, revised and approved the document before a further review from the AMMI Canada Guidelines Committee and the Infectious Diseases and Immunization Committee of the Canadian Paediatric Society. AMMI Canada approved the final document before submission to the Journal for publication.

B. WHY THE NEED FOR AN UPDATE?

Clinical trials with the neuraminidase inhibitors (NIs) oseltamivir and zanamivir and meta-analyses of oseltamivir therapy administered within 36 h to 48 h of symptom onset to low-risk outpatients with influenza (where placebo-controlled trials were ethically safe) have shown that overall, these agents shorten the duration of symptoms by 1 to 1.5 days (1-4). Systematic reviews of studies investigating the efficacy of NIs in treating mild to moderate influenza illness in outpatients have not adequately addressed the significantly greater benefit of NI treatment in very ill hospitalized patients, nor the greater benefit of earlier treatment after onset of symptoms (4). Earlier therapy with oral oseltamivir administered within 12 h of symptom onset was shown to reduce symptoms by 3.6 days (5). Inhaled zanamivir shortened the duration of major influenza symptoms by 3 days compared with placebo in individuals who were febrile at enrollment and received zanamivir within 30 h (3). In low-risk outpatients, NI treatment of mild influenza illness may be considered but is optional (6).

On the other hand, observational cohort-controlled studies of patients with severe influenza due to the H3N2 subtype and H1N1 pandemic subtype treated in hospital with oseltamivir clearly demonstrate reduction in mortality, and this benefit was still observed if oseltamivir was started up to 4 to 5 days after the onset of symptoms (7,8). The majority of these patients usually had pre-existing risk factors for severe influenza, but approximately 30% were healthy younger persons with no discernable risk factors.

In the current 2014-2015 influenza season, A(H3N2) influenza has accounted for the majority of influenza cases documented by testing. In addition, a significant antigenic drift has occurred in the majority of H3N2 influenza strains obtained from ill patients, resulting in a clinically relevant mismatch between the predominant circulating H3N2 influenza virus and the H3N2 vaccine strain. The WHO Global Influenza Surveillance and Response System laboratories have tested >96,535 specimens: 23,421 were positive for influenza viruses, of which 22,129 (94.5%) were typed as influenza A and 1292 (5.5%) as influenza B. Of the subtyped influenza A viruses, 163 (1.7%) were influenza A (H1N1) pdm09, and 9211 (98.3%) were influenza A (H3N2) (9).

Although the vaccine may still provide partial protection, it is not expected to be optimal. Therefore, vaccinated individuals may present to acute care facilities with influenza-like illness (ILI) and require treatment with NI.

To date, the majority of the predominating H3N2 virus isolates of influenza are susceptible to oseltamivir and zanamivir. All isolates of H1N1 are oseltamivir- and zanamivir-susceptible. Almost all isolates of influenza B are also susceptible to oseltamivir and zanamivir.

C. WHAT INVESTIGATIONS ARE REQUIRED TO DIAGNOSE INFLUENZA IN A PATIENT PRESENTING WITH ILI TO AN ACUTE CARE FACILITY?

During peaks of influenza activity in the community, a case definition in older children and adults of fever >38 °C with cough has a positive predictive value of 86% and a negative predictive value of 39.3% for influenza in patients attending an outpatient clinic (10). Of course, these values vary depending on the prevalence of influenza in the community relative to other respiratory infections. In older patients with chronic obstructive pulmonary disease, who have been vaccinated for influenza, only the presence of fever >37.8° and myalgias correlated with influenza, but with a lower positive predictive value of 41% (11). Other respiratory viruses, including but not limited to: respiratory syncytial virus (RSV), adenovirus, parainfluenza, rhinovirus, coronavirus or human metapneumovirus infection, may account for those with non-influenza infection. The use of influenza polymerase chain reaction (PCR) is preferred to direct fluorescent antigen detection (DFA) due to its greater sensitivity. A nasopharyngeal swab is preferred for influenza PCR testing, particularly if the patient requires hospital admission. If the patient is intubated, an endotracheal aspirate can be substituted for an NP swab. If an NP swab has been performed and is negative, and the patient is subsequently intubated, an

¹Professor Emeritus of Medicine, Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, British Columbia; ²Professor of Medicine, Biomedical & Molecular Sciences and Pathology & Molecular Medicine; Chair, Division of Infectious Diseases, Department of Medicine, Kingston General Hospital, Queen's University, Kingston, Ontario; ³Professor of Medicine, Medical Microbiology and Pharmacology & Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba; ⁴Professor, Department of Pediatrics & Institute of Health Policy, Management and Evaluation; Senior Associate Scientist, Research Institute; Chief, Division of Infectious Diseases, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario; ⁵Department of Microbiology-Infectious Disease, Hôpital Maisonneuve-Rosemont, Montreal, Quebec

Correspondence: Dr Gerald A Evans, Division of Infectious Diseases, Room 3013, Etherington Hall, Queen's University, 94 Stuart Street, Kingston, Ontario K7L 3N6. E-mail evansg@queensu.ca



This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact support@pulsus.com

TABLE 1
Oseltamivir and zanamivir treatment of influenza

Updated from: The use of antiviral drugs for influenza: A foundation document for practitioners (6)

Medication	Treatment (5 days)		Chemoprophylaxis (10 days)
Oseltamivir ¹	Adults		
	75 mg twice daily	75 mg once daily	
	Children ≥12 months		
	Body weight (kg)	Body weight (lbs)	
	≤15 kg	≤33 lbs	30 mg twice daily
	>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily
	>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily
	>40 kg	>88 lbs	75 mg twice daily
	Children 3 months to <12 months^{2*}		
		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
Children <3 months^{3*}			
	3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group	
Zanamivir ⁴	Adults		
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
	Children (≥7 years for treatment and chemoprophylaxis)		
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

*Please note that antivirals are not authorized for the routine treatment of seasonal influenza illness in infants <1 year of age. Such use may be considered on a case-by-case basis.

1. 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 15 mg/mL).

When dispensing commercially manufactured Oseltamivir (TAMIFLU) Powder for Oral Suspension (6 mg/mL or 12 mg/mL), pharmacists should ensure the units of measure on the prescription instructions match the dosing device.

2. The above dosage provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults (13-15). The American Academy of Pediatrics recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants aged 9–11 months for the 2013-14 season. However, it is unknown whether this higher dose will improve efficacy (14)

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 <1 year of age may be necessary: 0–3 months = 12 mg per dose for treatment (not for prophylaxis); 3–5 months = 20 mg per dose; 6–11 months = 25 mg per dose.

3. It is strongly suggested that an infectious disease physician or clinical pharmacist be consulted in the case of premature infants for whom treatment with oseltamivir is being considered. The current weight-based dosing recommendations are not appropriate for premature infants as they might have slower clearance of oral oseltamivir because of immature renal function. The following dosing is recommendations from the CDC and the AAP [14] and is based on data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group using the infants' postmenstrual age (gestational age + chronological age): 1.0 mg/kg/dose, orally, twice daily, for those <38 weeks postmenstrual age; 1.5 mg/kg/dose, orally, twice daily, for those 38 through 40 weeks postmenstrual age; 3.0 mg/kg/dose, orally, twice daily, for those >40 weeks postmenstrual age.

4. Zanamivir is administered by inhalation using a proprietary "Diskhaler" device 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 that increase the risk of bronchospasm.

endotracheal aspirate specimen for PCR should also be performed. Multiplex PCR testing allows for the diagnostic confirmation of other respiratory viruses, although unlike influenza, there are presently no antiviral agents available to treat them.

D. WHAT IS THE ROLE OF ANTIVIRALS IN THE MANAGEMENT OF INFLUENZA IN THE ACUTE CARE SETTING?

Treatment of patients with mild illness without risk factors for severe or complicated influenza with antiviral drugs is not recommended if >48 h have passed since the onset of influenza-like symptoms. However, in severe illness requiring hospitalization, oseltamivir treatment has been shown to reduce mortality even if treatment is started up to 96 h after the start of symptoms (7,8). Following initial clinical assessment and collection of appropriate specimens for virus testing, treatment should be started immediately, most frequently with oseltamivir orally. For adults with normal renal function, the typical regimen is 75 mg every 12 h for five days. In ventilated patients, oseltamivir should be administered by nasogastric tube. If zanamivir is required in a severely ill patient,

intravenous zanamivir is recommended at a dose of 600 mg every 12 h. If intravenous zanamivir is needed, it can be obtained by request to the Government of Canada Health Protection Branch, Special Access Program, Ottawa. (Web access at <http://www.hc.sc.ca/hpb-dgps/therapeut> telephone 613-941-2108 (0830-1630 weekdays), 613-941-3061 (after hours and weekends), fax 613-941-3194). Inhaled zanamivir is not advised in a severely ill patient because the inhaled powder deposits chiefly in the upper airways. Zanamivir powder administered through ventilator circuits is contraindicated.

The recommended dose of oral oseltamivir suspension for pediatric patients is shown Table 1, as are doses required for patients with renal impairment in Table 2. Oseltamivir oral suspension may also be used by adult patients who cannot swallow a capsule. If oseltamivir oral suspension is not available, oseltamivir capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. For children old enough to safely swallow capsules, the 30 mg and 45 mg capsules can also be taken as outlined in Table 1.

Patients with severe immunodeficiency, and very ill patients on ventilators may not improve and continue to shed influenza viruses for

TABLE 2
Recommended oseltamivir regimens for prevention and treatment of adult patients with renal impairment (Tamiflu® Product Monograph, 2014)

Creatinine clearance	Treatment for five days	Prophylaxis (10–14 days)
>60 mL/min	75 mg twice daily	75 mg once daily
>30–60 mL/min	30 mg suspension twice daily OR 30 mg capsule twice daily	30 mg once daily
10–30 mL/min	30 mg once daily	30 mg on alternate days
<10 mL/min (renal failure)	Single 75 mg dose for the duration of illness	No data
Dialysis patients	Low-flux HD: 30 mg after each dialysis session	30 mg after alternate dialysis sessions
	High-flux HD: 75 mg after each dialysis session	No data
	CAPD dialysis: 30 mg once weekly	30 mg once weekly
	CRRT high-flux dialysis: 30 mg daily or 75 mg every second day	No data

The following dosing regimen has been suggested for children based on limited data: In children >1 year of age, after alternate hemodialysis (HD) sessions (7.5 mg for children weighing >15 kg; 10 mg for children weighing 16–23 kg; 15 mg for children weighing 24–40 kg, and 30 mg for children weighing > 40 kg). While this may provide a framework for guidance, it is strongly suggested that an infectious disease physician, a specialist in renal insufficiency or clinical pharmacist be consulted

prolonged periods, even after five days on antiviral therapy. In these circumstances, repeat endotracheal samples should be sent for viral PCR and susceptibility testing for oseltamivir resistance. Suspected oseltamivir resistance should prompt a switch to intravenous zanamivir until results of antiviral susceptibility testing are available. Repeated viral testing should be performed if the clinical condition fails to improve.

E. IS THERE ANY ROLE FOR THE USE OF ANTIBIOTICS IN A PATIENT WITH SUSPECTED INFLUENZA?

A detailed discussion of the appropriate antibiotic management of patients with suspected bacterial pneumonia is beyond the scope of this document. However, if a patient presents with an acute respiratory infection on a background of an influenza outbreak, and a chest radiograph demonstrates pulmonary infiltrates, primary influenza or secondary bacterial pneumonia, or both, are possibilities. Primary influenza pneumonia typically presents with severe shortness of breath and occurs within one to three days of initial symptom onset (12). Clinicians should be aware that the presentation of a biphasic illness with reappearance of fever after defervescence from a typical influenza illness might represent a complicating secondary bacterial pneumonia. Bacterial pneumonia should be strongly suspected when a typical influenza illness is resolving, usually around the fifth day, and then there is a recurrence of fever and productive cough, often but not always with purulent sputum. In severely ill patients, appropriate antibiotics for community-acquired or nursing home-acquired pneumonia should be instituted immediately, as well as NI antiviral drug treatment, pending an etiologic diagnosis.

F. WHAT ARE THE APPROPRIATE INFECTION CONTROL MEASURES FOR A PATIENT WITH SUSPECTED INFLUENZA?

A detailed discussion of the appropriate infection control measures for the management of patients with suspected influenza is beyond the scope of this document. However, the following measures are generally employed.

Patient isolation

During an influenza outbreak, all individuals with ILI admitted to the emergency department or the hospital should be placed on Droplet and Contact precautions pending the results of testing on the NP swab.

Personal protective equipment (PPE)

All medical personnel should use appropriate PPE for droplet and contact precautions prior to contact with persons with ILI. Influenza virus can be transmitted through large droplet spread from coughing or mucosal contact with contaminated surfaces or fomites.

Whether vaccinated or unvaccinated, health care workers (HCW) should wear a mask, gown and gloves when caring for an individual with ILI.

G. WHAT SHOULD A HCW DO IF THEY DEVELOP AN ILI?

All HCWs who develop ILI symptoms should immediately be sent home if working, or told to remain at home. Guidelines from the institution's occupational health service should be consulted to determine when the HCW can return to work. HCWs should use their personal health care provider for care and additional information.

H. WHAT IS THE ROLE OF ANTIVIRAL PROPHYLAXIS FOR PATIENTS AND HCWs?

Post-exposure prophylaxis:

Secondary cases of influenza in family members of an index case can be reduced by early institution of post-exposure prophylactic oseltamivir or zanamivir (16). Hospitalized patients and HCW, regardless of their vaccine status, who have had unprotected close contact with a patient with ILI, may be offered either oseltamivir at a dose of 75 mg once daily or zanamivir inhalation, two puffs (10 mg) once daily for seven (oseltamivir) to 10 (zanamivir) days to reduce the chance of influenza illness. This is especially important this influenza season in the face of the vaccine mismatch. Post-exposure prophylaxis is less likely to be effective if started >48 h after the exposure. In high-risk patients, the use of post-exposure prophylaxis, even >48 h, may be justified. In HCWs and low-risk hospitalized patients identified >48 h after exposure, observation and early treatment if symptoms arise is the preferred strategy.

Close observation and early treatment is recommended for individuals who choose not to receive post-exposure antiviral prophylaxis.

Pre-exposure prophylaxis

Pre-exposure prophylaxis with either oseltamivir or zanamivir for hospitalized patients or staff is not routinely recommended. This recommendation differs from that for residents and staff in long-term or chronic care facilities. Pre-exposure prophylaxis for patients may be considered in specific circumstances (eg, in high-risk semi-closed hospital units such as transplant units) when at least one laboratory-confirmed case occurs on a hospital unit. The end of a unit outbreak is generally considered when no new cases of ILI have appeared for ≥7 days after the onset of the last case. Pre-exposure prophylaxis increases the risk of long-term use, and the development of resistance.

ACKNOWLEDGEMENTS: The authors acknowledge the review and endorsement of the document by the Infectious Diseases and Immunization Committee of the Canadian Paediatric Society.

DISCLOSURES: Dr Fred Y Aoki: Honoraria: Merck; Research: Biocryst Inc. Dr Upton D Allen: Research: Hoffmann La Roche Inc. Dr H Grant Stiver: Honoraria: Hoffman La Roche Inc; Advisory Board: Hoffman La Roche Inc. Dr Gerald A Evans: Research: Biocryst Inc. Dr Michel Laverdiere: None.

REFERENCES

1. Nicholson K, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: A randomized controlled trial. *Lancet* 2000;355:1845-50.
2. The MIST (Management of influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 1998;352:1877-81
3. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A virus infections. *New Engl J Med* 1997;337:874-80.
4. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: Systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2545.
5. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Ther* 2003;51:123-9.
6. Aoki FY, Allen UD, Stiver HG, Laverdière M, Evans GA. The use of antiviral drugs for influenza: A foundation document for practitioners. *Can J Infect Dis Med Microbiol* 2013;24(Suppl C):1C-15C.
7. McGeer A, Green K, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.
8. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza (H1N1) pdm09. *Clin Infect Dis* 2012;55:1198-1204.
9. World Health Organization. Influenza update. 12 January 2015 – Update number 228. <www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/en> (Accessed January 13, 2015).
10. Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with the use of a clinical case definition. *Clin Infect Dis* 2000;31:1166-9.
11. Neuzil KM, O'Connor TZ, Gorse GJ, Nichol KL. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. *Clin Infect Dis* 2003;36:169-74.
12. Bisno AL, Griffin JP, Van Epps KA, Niell HB, Rytel MW. Pneumonia and Hong Kong influenza: A prospective study of the 1968-1969 epidemic. *Am J Med Sci* 1971;261:251-63.
13. Kimberlin DW, Acosta EP, Prichard MN, et al. Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 years with influenza. *J Infect Dis* 2013;207:709-20.
14. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. <www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm> (Accessed January 13, 2015).
15. US Food and Drug Administration. Drug Approval Package. TAMIFLU (oseltamivir phosphate) 30, 45 and 75 mg capsules and TAMIFLU (oseltamivir phosphate) 6 mg/mL powder for oral suspension. <www.accessdata.fda.gov/drugsatfda_docs/nda/2012/021246Orig1s045_021087Orig1s062_tamiflu_toc.cfm> (Accessed January 13, 2015).
16. Halloran ME, Hayden FG, Yang Y, Longini IM Jr, Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: Observation-based trials. *Am J Epidemiol* 2007;165:212-21.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

