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 the 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 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 in very ill hospitalized patients, nor the greater benefit of earlier treatment after onset of symptoms (4).

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°C 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

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TABLE 1
Oseltamivir and zanamivir treatment of influenza

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment (5 days)</th>
<th>Chemoprophylaxis (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 mg twice daily</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>Body weight (lbs)</td>
<td></td>
</tr>
<tr>
<td>≤15 kg</td>
<td>≤33 lbs</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt;15 kg to 23 kg</td>
<td>&gt;33 lbs to 51 lbs</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt;23 kg to 40 kg</td>
<td>&gt;51 lbs to 88 lbs</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>&gt;88 lbs</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Children ≥12 months</td>
<td>Children 3 months to &lt;12 months*</td>
<td>3 mg/kg/dose twice daily</td>
</tr>
<tr>
<td>10 mg (two 5 mg inhalations) twice daily</td>
<td>Children &lt;3 months**</td>
<td>3 mg/kg/dose twice daily</td>
</tr>
</tbody>
</table>

Zanamivir

| 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 |

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).

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).

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 should not be administered to persons with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease that increase the risk of bronchospasm.

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/hph-bgps/therapeutics/program/). If oseltamivir oral suspension is not available, zanamivir 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.
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 N1 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.

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