The Use of Antiviral Drugs for Influenza: Guidance for Practitioners, 2010-11

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Index

SUMMARY

This Guidance addresses the use of antiviral drugs in the management of seasonal influenza illness for the 2010-11 season. It updates our document published in 2006. Noteworthy changes include:

- Recognition that the 2009 oseltamivir-susceptible influenza A pandemic H1N1 virus has become the seasonal H1N1 virus in 2010.
- Recommendations for antiviral drug use that are accompanied by assessment of the level of supporting evidence based on the GRADE System.
- Recommendations limited to oseltamivir and zanamivir. Amantadine is no longer considered an option because of widespread resistance.
- Recognition of the wider range of co-morbid conditions that predispose individuals to an increased risk of influenza complications.
- Recognition that antiviral therapy initiated more than 36 to 48 hours after illness onset appears to be beneficial in those with complicated influenza and/or more serious illness.
- Treatment and prophylaxis recommendations that differ depending on the severity of illness and the presence of risk factors for complicated influenza.
- Further limitations on the use of oseltamivir for prophylaxis due to a perceived increased risk of resistance emergence.
- Recognition of the strategy of early presumptive therapy as an alternative to post-exposure prophylaxis in individuals at high risk of complications who have been exposed to persons with proved or suspected influenza.
- New off-label oseltamivir dose regimens for:
    - Infants less than one year of age
    - Patients with dialysis-dependent renal failure

I. PURPOSE OF THIS GUIDANCE

The purpose of this document is to provide recommendations for clinicians on the use of antiviral drugs for the prevention and treatment of influenza during the 2010-2011 influenza season in Canada. Other aspects of influenza management such as laboratory diagnosis, infection control, immunization and non-pharmacological interventions are beyond the scope of this article.

II. GRADING OF RECOMMENDATIONS

The GRADE system is used to qualify recommendations based on the quality of evidence and the determination of benefit vs. harm arising from the recommendation as defined below.[1] In situations where high-quality evidence is not available but anticipated benefits strongly outweigh the harm, the recommendation could be based on lesser evidence. See Table 1 for categories of evidence and their relationship to recommendations.

Definitions of the strength of evidence for the recommendations

Strong Recommendation: Benefits of treatment approach clearly exceed harms; quality of evidence is high (Grade A).

Recommendation: Benefits exceed harms, but quality of evidence is moderate (Grade B) or low (Grade C).

Option: Quality of evidence is very low (Grade D) or well-done studies (Grade A, B or C) show little clear advantage.

No Recommendation: There is a lack of pertinent evidence or quality is very low and there is an unclear balance between benefits and harms.

Impact of recommendation strength on practicing clinicians

Strong recommendations should be followed unless a clear and compelling reason for an alternate approach is present.

Recommendations should generally be followed, but clinicians should remain alert to new information and patient preferences.

Option reflects flexibility in decision-making regarding appropriate practice, but clinicians may set bounds on alternatives. Patient preference should play a substantial influencing role.

No recommendation reflects no constraints on decision-making, and clinicians should remain alert to new evidence that clarifies the balance of benefit and harm. Patient preference should play a substantial influencing role.

III. THE DISEASE

Influenza Virus

For the 2010-2011 influenza season, it is expected that the circulating influenza strains will be those contained in the trivalent inactivated vaccine: 1. Pandemic H1N1 [A/California/07/2009 (H1N1)-like], hereafter referred to as pH1N1, 2. A/Perth/16/2009 (H3N2)-like, and 3. B/Brisbane/60/2008-like.[2] The influenza strain that will predominate, is unknown. Influenza A/Brisbane/59/H1N1-like viruses (so called seasonal influenza A/H1N1 viruses) appear to have been completely displaced during and since the 2009-2010 pandemic by the pH1N1 virus.

Antiviral drug resistance of influenza viruses demonstrated *in vitro* generally correlates with treatment outcomes. No oseltamivir resistance was reported in A/H3N2 viruses and influenza B in 2009.[3] Oseltamivir resistance rates remain low in all pandemic H1N1 viruses at approximately one percent of isolates tested in the United States between September 2009 and

August 2010. Resistant viruses were isolated from patients who were receiving oseltamivir prophylaxis,[4] or longer term oseltamivir treatment (usually in critical care units),[5] and immunosuppressed patients who had prolonged virus shedding during oseltamivir therapy.[6] All pH1N1-like strains remain susceptible to zanamivir. Globally, as of August 2010, 304 oseltamivir-resistant, zanamivir susceptible pH1N1 viruses have been reported to WHO, representing approximately 1% of tested isolates.[7] Based on these *in vitro* data, oseltamivir and zanamivir are likely to be similarly efficacious in the management of pH1N1 disease.

The susceptibility of current seasonal influenza viruses to the neuraminidase inhibitor drugs, oseltamivir and zanamivir, and amantadine are shown in Table 2.[8] Since all three strains (A/pH1N1, A/H3N2, influenza B) are resistant to amantadine, subsequent discussion is limited to the neuraminidase inhibitor drugs. Recommendations for laboratory testing of influenza viruses for antiviral resistance testing have been published. (Available at: http://www.cphln.ca/pdf/EN_H1N1_Best_Practice_Final_Version.pdf)

Clinical aspects

Seasonal influenza A viruses share similar clinical features with the recently described pH1N1 virus.[9]

The transmission characteristics of the above two groups of influenza virus are similar. Virus is transmitted from infected to susceptible persons through respiratory secretions containing suspensions of virus, especially airborne droplets generated by coughing and sneezing. The relative contributions of small particle aerosols and fomites in transmission are uncertain. The basic reproductive number [R_o] (mean number of secondary cases transmitted by a single index case to susceptible contacts) ranges from 1.3 to 1.7.

The incubation period of seasonal influenza A illness is 1 to 4 days with a mean of 2 days, which is generally similar to pH1N1.[10] However, in a minority of pH1N1 cases, the incubation period was observed to be up to 7 days. This may also apply to seasonal influenza illness.

In otherwise healthy patients with uncomplicated illness, virus in nasopharyngeal secretions is shed beginning 24 hours (1 day) before onset of symptoms, peaks with the onset of symptoms and declines over 5 to 7 days although it is commonly accepted that some persons, particularly young children and immunocompromised persons, may shed virus for longer periods.

For purposes of post-exposure prophylaxis, the infectious period is considered to extend from 1 day before onset of symptoms until 24 hours after fever ends.

Illness caused by influenza virus can range from asymptomatic to mild, uncomplicated, self-limited upper respiratory tract infection to serious complicated illness dominated by exacerbation of a co-morbid, underlying medical condition or severe viral lower respiratory tract infection (pneumonia) with or without multiorgan failure.

In adults, influenza typically begins with fever, respiratory symptoms such as cough or sore throat and systemic symptoms, such as myalgia, arthralgia and headache. Gastrointestinal symptoms, notably diarrhea, have been described uncommonly as manifestations of seasonal influenza A. However, as many as 25% of persons with pH1N1 reported diarrhea and up to 32%, abdominal pain or vomiting.

Severe lower respiratory tract disease encompasses diffuse primary viral pneumonia which often develops directly from progression of initial symptoms, and a secondary bacterial pneumonia which may arise after a period of initial improvement. Acute respiratory distress syndrome (ARDS) may develop several days after illness onset. The importance of secondary

bacterial infections in influenza is further illustrated by the fact that among cases of pH1N1, concomitant bacterial infection with organisms including *S. pneumoniae* and MRSA was demonstrated in 20-30% of cases of pH1N1 disease with pneumonia.

While the typical clinical features of influenza illness appear in older children and youth, among those less than 10 years of age, the clinical features may be atypical. Indeed, among children less than 5 years of age, influenza illness is often non-specific and may be indistinguishable from illness due to other respiratory viruses. Young infants may present with a sepsis-like picture. Infants younger than six months of age are more likely to present with rhinorrhea and dehydration than cough and pneumonia and among those less than 3 months of age, fever alone or fever with dehydration are common presenting features.[10] Diarrheal illness may be observed. Some clinical signs in infants, children and youth warrant urgent medical attention. Familiarity with these signs is advised (Table 3).

Conditions that place individuals (including infants, children and youth) at risk of severe outcomes from influenza illness are shown in Table 4, which is adapted from recommendations of the WHO[11] and the Canadian National Committee on Immunization.[12] Table 4 has been added since our 2006 document[22] and includes pregnancy and morbid obesity as risk conditions plus First Nations, Inuit and Metis heritage as a risk factor. Influenza-related complications in infants, children and youth include severe hemorrhagic viral pneumonia, secondary bacterial pneumonia (due to *Streptococcus pneumoniae*, *Staphylococcus aureus,* or group A Streptococcus), mixed viral and bacterial pneumonia, localized viral pneumonia, severe laryngotracheobronchitis (croup) and exacerbation of chronic pulmonary disease. Non-pulmonary complications include acute myositis, myocarditis or pericarditis, toxic shock-like picture (due to invasive secondary bacterial sepsis) and neurologic complications. The latter

include febrile seizures, status epilepticus, encephalitis/encephalopathy, Reye's syndrome and Guillain-Barré syndrome.[13]

Clinical diagnosis of influenza illness

Clinical suspicion and the accuracy of diagnosis vary substantially. However, when influenza is circulating in the community the presence of cough and a fever of 37.8^0C or higher in otherwise healthy adults has a positive predictive value of 86.8% for a laboratory-confirmed diagnosis of influenza, although the negative predictive value is poor at 39.3%.[14] Among non-immunized young healthy adults, the combination of a fever of 37.8^0C or higher plus at least one respiratory symptom (sore throat, cough or nasal symptoms) and one constitutional symptom (myalgia, headache, sweats, chills or fatigue) are predictive of influenza by laboratory testing in 60% to 71% of cases.[15,16] Among immunized patients 60 years of age and older, the combination of fever, coughing and acute onset have a predictive value of 44% for laboratory-confirmed diagnosis of influenza.[17]

Diagnosing influenza illness by clinical criteria in children is more problematic than in adults because they cannot articulate their symptoms as readily. Studies evaluating the sensitivity and specificity of a clinical diagnosis of influenza in children compared with a laboratory gold standard are limited.[18] The common presenting findings of fever, cough and rhinorrhea do not distinguish influenza illness from that due to other respiratory viruses.[18] Thus, in diagnosing influenza in a patient and arriving at a treatment decision, practitioners should be guided by knowledge of whether influenza virus is circulating in their community as well as their clinical assessment of the individual patient, taking into account factors that may influence the presentation such as extremes of age, co-morbid conditions and immunocompetence.

IV. TREATMENT OF INFLUENZA ILLNESS

Antiviral drugs

1. Oseltamivir – The neuraminidase inhibitor (NAI) drug oseltamivir (Tamiflu^{R}) is approved by Health Canada for the treatment of uncomplicated influenza in patients one year of age or older who have been symptomatic for no more than 2 days. Oseltamivir is also approved in Canada for prevention of influenza in adults and children $\geq$ 1 year old who are close contacts of an individual with characteristic symptoms of influenza.

Oseltamivir is formulated as oseltamivir phosphate in capsules containing 30, 45 or 75 mg per capsule or as a suspension containing 12 mg/ml. No injectable formulation is currently approved for use.

Oseltamivir phosphate is well absorbed and extensively converted by hepatic and intestinal epithelial cells to oseltamivir carboxylate, which is the active antiviral molecule. It is eliminated almost completely as unchanged drug in the urine by glomerular filtration and renal tubular secretion.

In part due to lack of further metabolic transformation, oseltamivir carboxylate has little potential for drug-drug interactions and this expectation has been borne out by limited clinical studies.

Treatment and prophylaxis regimens of oseltamivir and zanamivir for adults and for children by age and weight are detailed in Table 5.[19] Dose reduction is advised for pharmacokinetic reasons in persons with creatinine clearance < 10 ml/min although the drug has a wide margin of safety and causes no serious, dose-related adverse effects. Mild, rapidly reversible nausea and/or vomiting have been observed in approximately 5-10% more persons ingesting oseltamivir than an identical placebo.

Oseltamivir was widely used during the 2009 H1N1 pandemic. Such use included treatment with higher doses administered for longer periods than the approved 5-day regimen of 75 mg BID. In critically ill ventilated patients with pH1N1, oseltamivir administered via a gastric tube was well absorbed, yielding plasma concentrations that exceed the inhibitory concentration of influenza A virus.[20] Preliminary analysis from a randomized comparison of 150 mg BID and 75 mg BID oseltamivir for treatment of patients seriously ill with influenza, including pH1N1 viruses, suggested that the larger dose was safe but offered no additional benefit over the standard dose regimen, as evaluated by reductions in viral shedding at day 5 of treatment.[21]

A review by the drug manufacturer identified no additional safety issues associated with the extensive use of oseltamivir during the H1N1 pandemic compared to the prepandemic period.[22]

More details regarding safety, tolerance, drug interactions and formulations were detailed in our previous guideline.[23]

2. Zanamivir – Zanamivir (Relenza^{R}) is approved by Health Canada for the treatment of uncomplicated influenza in patients 7 years of age or older who have been symptomatic for no more than 2 days. It is also approved for the prevention of influenza in patients 7 years of age or older.

Zanamivir is marketed as a drug powder in a proprietary device that delivers a dose of 5 mg zanamivir by oral inhalation. Approximately 80% of an inhaled dose is deposited onto the upper respiratory tract lining and 13% in the bronchi and lungs, where it exerts its antiviral effect.

Less than 2% of an oral dose is absorbed into the systemic circulation from which it is eliminated unchanged into the urine.

Since inhaled zanamivir may induce bronchospasm, Health Canada advises against its use in persons with severe asthma or COPD.

No dose reductions are recommended for any patient population.

In seriously ill patients with pH1N1 influenza receiving mechanical ventilation, zanamivir prepared by the diskhaler powder in water and administered by nebulizer resulted in bronchospasm and obstruction of ventilator filters.[24]

Intravenous zanamivir may be obtained through the Special Access Programme of Health Canada (613-941-2108).

Benefits of antiviral treatment

Neuraminidase inhibitor therapy of patients ill with infection due to seasonal influenza viruses ameliorates the duration and severity of uncomplicated, self-limited laboratory-confirmed influenza in otherwise healthy children greater than 1 year of age and adults.[25,26] NAIs reduce the frequency of otitis media as a complication of influenza in pediatric patients.[26] Treatment of hospitalized patients with seasonal influenza may reduce the duration of hospitalization and mortality.[27]

While there are no comparable randomized controlled trials describing the benefits and risks of treating patients with influenza due to the pH1N1 virus, in a number of observational studies of patients with pH1N1 infection, it was reported that treatment with NAIs, chiefly oseltamivir, was effective in reducing the progression and severity of illness in the general population as well as vulnerable groups. These groups include pregnant women and solid organ transplant recipients.[28]

Inasmuch as a number of respiratory tract viral pathogens can cause an influenza-like illness, anti-influenza drug therapy will invariably result in treatment of some persons whose

influenza-like illness (ILI) is not due to influenza virus *per se*. At present, there are no data to suggest that such treatment is ecologically harmful. Since NAIs are specific inhibitors of only influenza virus neuraminidase, such treatments are unlikely to engender resistance in other microorganisms. Moreover, influenza viruses are not constituents of the normal flora of humans. However, it has been speculated that a theoretical risk exists that widespread use of neuraminidase inhibitor drugs resulting in high concentrations in urine and human sewage effluent and the environment may select for resistant viruses in water fowl that ingest the medication while harboring replicating influenza virus in their gastrointestinal tract.[29]

Indications for treatment

The indications for treatment may be structured around the following considerations:

A. Severity of illness,

B. Membership in at-risk groups and presence of co-morbid conditions,

C. Interval between onset of illness and diagnosis,

D. Likely influenza type(s) causing infection (see Section III)

A. Severity of illness:

Useful definitions of the range of clinical illness caused by influenza viruses have been adapted from those published by the CDC[19]:

- **Mild or uncomplicated illness** is characterized by typical symptoms like fever (although not everyone with influenza, especially at the extremes of age, will have a fever), cough, sore throat, rhinorrhea, muscle pain, headache, chills, malaise, sometimes diarrhea and vomiting, but no shortness of breath and little change in chronic health conditions.

- **Moderate or progressive illness** is characterized by typical symptoms plus signs or symptoms suggesting more than mild illness: chest pain, poor oxygenation (e.g. tachypnea, hypoxia, labored breathing in children), cardiopulmonary insufficiency (e.g. low blood pressure), CNS impairment (e.g. confusion, altered mental status), severe dehydration, or exacerbations of chronic conditions (e.g. asthma, chronic obstructive pulmonary disease, chronic renal failure, diabetes or other cardiovascular conditions).
- **Severe or complicated illness** is characterized by signs of lower respiratory tract disease (e.g., hypoxia requiring supplemental oxygen, abnormal chest, radiograph, mechanical ventilation), CNS findings (encephalitis, encephalopathy), complications of low blood pressure (shock, organ failure), myocarditis or rhabdomyolysis, or invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond three days).

B. Membership in at-risk groups and presence of co-morbid medical conditions:

- Risk groups include patients with co-morbid medical conditions based on extensive experience during seasonal influenza outbreaks and recent experience during the pH1N1 pandemic (see Table 4).

Notwithstanding the above association of the aforementioned medical conditions as risk factors for severe influenza, 20-40% of patients with severe pH1N1 influenza admitted to intensive care units were previously healthy persons not belonging to any known high-risk group. The corollary is that practitioners must be vigilant in their evaluation of otherwise healthy individuals in whom seasonal influenza illness appears to be mild but may be progressing.

C. Interval between onset of illness and initiation of antiviral therapy.

Initiation of treatment of uncomplicated seasonal influenza in healthy adults with neuraminidase inhibitors within 36-48 hours of illness onset is efficacious. Optimal benefits are obtained if treatment is initiated as early as possible during this 36- to 48-hour window.[30] Thus, starting treatment within 12 hours of illness onset should be a practice ideal.

Antiviral therapy should be initiated even if the interval between illness onset and administration of antiviral medication exceeds 48 hours if:

- The illness is severe enough to require hospitalization,
- The illness is progressive, severe or complicated, regardless of previous health status,
- The individual belongs to a group at high risk for severe disease.

Otherwise healthy patients with relatively mild, self-limited influenza caused by seasonal influenzas are not likely to benefit from neuraminidase inhibitor therapy initiated more than 48 hours after illness onset. However, clinical judgment is always an essential part of the decision to treat with antiviral drugs.

Patients for whom antiviral therapy is not recommended should be advised of symptoms and signs of worsening illness that might warrant reassessment.

D. Likely influenza type(s) causing infection:

As discussed in Section III, it is uncertain what will be the predominant strain of influenza causing illness in the 2010-11 influenza season. Practitioners should be mindful of reports in PHAC *FluWatch* and reports from their provincial or territorial public health departments. This may be important in case oseltamivir-resistant seasonal H1N1 viruses reappear.

V. RECOMMENDATIONS FOR TREATMENT

A. Treatment of adults with mild or uncomplicated influenza illness:

A treatment algorithm is provided as **Appendix A**.

- Treatment should be initiated as rapidly as possible after onset of illness as the benefits of treatment are much greater with initiation at less than 12 hours than at 48 hours. **(Strong recommendation, Grade B evidence)**
- Treatment duration should be 5 days. **(Strong Recommendation, Grade A evidence)**
- For individuals with mild disease, no risk factors and:
    - illness of less than 48 hours' duration, treat with oseltamivir or inhaled zanamivir. **(Recommendation, Grade A evidence)**
    - illness of more than 48 hours' duration, antiviral treatment is not recommended. **(Recommendation, Grade C evidence)**

- For individuals with mild disease, risk factors and:
    - illness of less than 48 hours' duration, treat with oseltamivir or inhaled zanamivir. **(Strong Recommendation, Grade C evidence)**
    - illness of more than 48 hours' duration, treatment with oseltamivir or inhaled zanamivir is recommended. **(Option, Grade D evidence)**

B. Treatment of adults with moderate, progressive, severe or complicated influenza illness with or without risk factors

A treatment algorithm is provided as **Appendix B**.

- Hospitalize and consider admission to ICU **(Recommendation, Grade C evidence)**

- Oseltamivir 75 mg every 12 hours orally or by nasogastric tube should be started immediately. **(Recommendation, Grade C evidence)**
- Oseltamivir should be started even though the window between symptom onset and initial administration of antiviral is longer than 48 hours. **(Recommendation, Grade C evidence)**
- Zanamivir is recommended in preference to oseltamivir in the following situations:
    i. Patients not responding to oseltamivir therapy **(Option, Grade D evidence)**
    ii. Patients with illness despite oseltamivir prophylaxis **(Option, Grade D evidence)**
    iii. Severely immunosuppressed patients **(Option, Grade D evidence)**
- Zanamivir administered intravenously is preferred to inhaled drug. **(Option, Grade D evidence)**
- In ventilated patients, zanamivir should only be administered intravenously **(Option, Grade D evidence)**
- Treatment should be continued longer than 5 days in patients if clinically indicated **(Option, Grade D evidence)**
- If patients are not responding to oseltamivir therapy, their virus should be tested for oseltamivir resistance **(Option, Grade D evidence)**

C. Treatment of children

A treatment algorithm is provided as **Appendix C.**

This section of the document addresses recommendations for infants (<1 year of age), children (1 to <12 years) and youth (12-18 years). While some aspects of influenza prevention and treatment in adults can be extrapolated to children, there are several areas where special pediatric considerations are necessary. In general, when compared to adults, there are less available data to guide the management of children, notably young infants.

The attack rates for seasonal influenza in healthy children range from 3% to 30% with 1% requiring hospitalization.[31,32] During community outbreaks of seasonal influenza, the highest attack rates occur in school-age children. Children are a common source from which infection is spread to other household members. While the shedding of virus usually starts 24 hours prior to the onset of overt symptoms and ceases at 7 days, prolonged viral shedding may be seen in infants and young children.

The atypical and non-specific nature of influenza illness in young children is evidenced by Canadian surveillance data that suggest that among hospitalized children, fever and cough are the most common presenting features.[33] Furthermore among those less than 5 years of age, influenza illness may be indistinguishable from illness due to other respiratory viruses.

The pulmonary and non-pulmonary influenza-related complications in infants, children and youth are generally similar to those in adults with the exception that some conditions are more likely to be seen in children (sepsis-like illness, diarrhea, otitis media, severe laryngotracheobronchitis (croup), febrile seizures, Reye's syndrome, and refusal to walk due to myositis.[31]

Children at the highest risk of adverse outcomes from influenza illness include those less than 5 years of age.[34] However, among infants, children and youth, hospitalizations occur more frequently among those less than 2 years of age compared with older children, with the highest

hospitalization rates being among those less than 6 months of age.[33] This does not necessarily translate into a decision to uniformly use antiviral therapy in those less than 2 years of age; such children with mild influenza illness might not necessarily need treatment.

Among the currently available antiviral agents, three are approved for use for children in Canada: amantadine, for influenza A; oseltamivir and zanamivir, for influenza A and B. Clinical trials supporting the role of the NAIs in children were previously summarized and have been the subject of recent meta-analyses.[26, 35] One meta-analysis suggested that the neuraminidase inhibitors shorten the duration of illness in children with seasonal influenza and reduced household transmission, but that they have little effect on asthma exacerbations or the use of antibiotics.[35] The challenges of pooling data from disparate studies have been acknowledged.[36] Indeed, data from the only double-blind, randomized, controlled trial on oseltamivir for the treatment of influenza in previously healthy children, indicated significant reductions in physician-diagnosed complications requiring antibiotic therapy (relative risk-reduction 40%) and in the likelihood of developing otitis media (relative risk reduction 44%).[37] Another randomized trial among children aged 1-3 years, indicated an 85% reduction in acute otitis media when oseltamivir was started within 12 hours after the onset of influenza illness, but no reduction when treatment was started at > 24 hours after the onset of symptoms. [38] A benefit on asthma exacerbations among oseltamivir-treated children has also been demonstrated in a randomized controlled trial.[39]

Since the earlier studies on NAIs, additional studies have been reported and are in progress and experience with their use has increased.[40-44] However, there exists a relative paucity of new data from randomized trials in infants and young children. Thus, the use of antiviral agents in infants (including premature newborns) continues to pose a challenge. Oseltamivir was approved temporarily for use in infants under 1 year of age on the basis of a

favourable risk-to-benefit ratio during the recent 2009 H1N1 pandemic. However, its use for seasonal influenza in infants should be handled on a case-by-case basis, based on severity of illness as it is not approved for this indication in Canada. During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing for infants less than one year of age varied within a reasonably narrow range and have been updated for seasonal influenza.[8,45,46] Current dosing recommendations are shown in table 5. [19]

Recommendations

1. The following treatment recommendations apply:
   - Treatment should be initiated as rapidly as possible after onset of illness as the benefits of treatment are likely much greater with initiation at less than 12 hours than at 48 hours. **(Strong recommendation, Grade B evidence)**
   - Treatment duration should be 5 days. **(Strong Recommendation, Grade A evidence)**
   - For children with mild disease, no risk factors and:
     i. illness of less than 48 hours' duration, treat with oseltamivir or if age appropriate, inhaled zanamivir. **(Recommendation, Grade A evidence)**
     ii. illness of more than 48 hours' duration, treatment with oseltamivir is not recommended (Recommendation, Grade C evidence).
   - For children with mild disease, risk factors and:
     i. illness of less than 48 hours' duration, treat with oseltamivir or if age appropriate, inhaled zanamivir (see comment below for children < 2 years of age). **(Recommendation, Grade B evidence)**

ii. illness of more than 48 hours' duration, treatment with oseltamivir or if age appropriate, inhaled zanamivir may be considered on a case-by-case basis.**(Option, Grade D evidence)**

2. Antiviral therapy is indicated for the following children and youth with influenza illness:

- Those with moderate, progressive, severe or complicated illness:

a. Consider hospitalization and admission to ICU **(Recommendation, Grade C evidence)**

b. Start treatment immediately **(Strong recommendation, Grade B evidence)**

c. Treat with oseltamivir or inhaled zanamivir in appropriate doses (see Table 5)

d. Treatment with zanamivir is recommended in preference to oseltamivir in the following situations:

i. Patients not responding to oseltamivir therapy **(Option, Grade D evidence)**

ii. Patients with illness despite oseltamivir prophylaxis **(Option, Grade D evidence)**

iii. Severely immunosuppressed patients **(Option, Grade D evidence)**

e. Zanamivir administered intravenously is preferred to inhaled drug. **(Option, Grade D evidence)**

3. Although classified as high risk, children under 2 years of age who are otherwise healthy and have mild disease not requiring hospitalization do not routinely require

antiviral therapy. The same applies to children 2 to < 5 years of age in whom the risk of complications is even lower than those less than 2 years of age. **(Option, Grade D evidence)**

4. Antiviral therapy is not routinely recommended for children and youth ≥ 5 years of age who are otherwise healthy and have mild disease not requiring hospitalization. **(Option, Grade D evidence)**

5. In infants less than one year of age, NAIs are currently not approved for the routine treatment of seasonal influenza illness. Although oseltamivir was approved temporarily for use in infants under 1 year of age on the basis of a favourable risk-to-benefit ratio during the recent 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)**

6. Given that infants less than 6 months of age are not eligible for influenza vaccination, immunization of their household and other close contacts, the so-called cocoon strategy, may be important in protecting them against influenza, thereby potentially leading to reduced need for antiviral therapy. **(Option, Grade D evidence)**

7. Early therapy is preferred over routine pre-exposure prophylaxis. However, during community outbreaks of influenza illness, some experts recommend the selective use of pre-exposure prophylaxis for the following scenarios. **(Option, Grade D evidence)**

   i. As a bridge to vaccine-induced immunity during the 14-day period after immunization of high-risk individuals.

   ii. Protection of children for whom vaccination is contraindicated.

   iii. Protection of children at high risk and their family members and close contacts when circulating strains of influenza virus in the community are

not matched with trivalent seasonal influenza vaccine strains, based on current data from the local or national public health laboratories

iv. Protection of family members or health care workers who are likely to have ongoing close exposure to unimmunized children at high risk or infants and toddlers who are younger than 24 months of age, if vaccination is contraindicated (e.g., known anaphylaxis to chicken or egg protein).

8. Early therapy is preferred over post-exposure chemoprophylaxis due to concerns regarding drug resistance. **(Option, Grade D evidence)** In selected circumstances, chemoprophylaxis might be considered for the following scenarios.

i. Exposures in closed institutional settings

ii. Selectively in family settings, notably where the patient who is being considered for post-exposure chemoprophylaxis cannot be protected/reliably protected by immunization (e.g., age less than 6 months, immunocompromised or vaccine is contraindicated).

D. Treatment recommendations for special patient populations

1. Treatment of influenza in the immunocompromised patient

This group includes individuals with immunodeficiency states ranging from congenital immunodeficiencies, selective acquired deficiencies and immunodeficiencies secondary to organ/tissue transplantation and immunoablative, immunosuppressive or myelosuppressive chemotherapy. The heterogeneity of populations of immunocompromised hosts is well recognized. This results in varying degrees of risk of adverse outcomes from influenza illness. In this context, Table 6 summarizes selected

clinical, laboratory and other markers that help to categorize various immunodeficiency states and identify patients who might be at the greatest risk of adverse outcomes from influenza illness.[47] The presence of these markers suggest increased risk for acquisition of infection, progression to more severe and potentially life-threatening consequences of infection, and for an impaired ability to develop immunity to infection following subsequent exposure to influenza virus.[47]

In addition to the well-recognized variability in the clinical manifestations of influenza illness, atypical clinical features may be present in immunocompromised individuals. For example, immunocompromised individuals may present with fever as the sole manifestation of influenza illness.[48] In addition, immunocompromised persons may present without fever.[49]

The complications seen among persons with normal immune systems may also be seen in immunocompromised hosts. Invasive secondary bacterial infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and other bacterial pathogens may occur and can be devastating for the immunocompromised host. For example, asplenic individuals are known to be at increased risk of severe invasive pneumococcal disease.

Prolonged illness and viral shedding are features of infection in immunocompromised individuals. Indeed, in some of the more immunocompromised individuals, the virus may be persistently present in the respiratory tract for several weeks or months.[50,51] This persistent shedding may be accompanied by periodic exacerbations of illness.[50,51] Cell-mediated immunity is important in mediating protection from influenza illness, viral clearance and recovery from illness.[51-55] Thus, reductions in T-cell number or function as a result of acquired or congenital

immunodeficiency states may result in an increased likelihood of a more severe and prolonged illness and an increased risk of antiviral resistance.[51,52] The risk for immunocompromised persons is compounded if they have co-morbid states that are themselves risk factors for adverse outcomes from influenza illness (e.g., underlying chronic lung disease). The risk among these individuals may be variable due to differences in the nature and intensity of their immunosuppressive therapies (e.g. corticosteroids).[56]

Recommendations

1. Immunocompromised individuals who have uncomplicated influenza illness are at risk of developing severe or complicated illness and thus should be treated with oseltamivir as soon as possible without regard to the duration of illness. **(Recommendation, Grade C evidence)**
2. Immunocompromised patients should be treated with zanamivir if they have recently received or are currently receiving oseltamivir as prophylaxis. **(Option, Grade D evidence)**
3. Prolonged antiviral therapy should be avoided in immunocompromised individuals if possible due to the potential for antiviral resistance. **(Option, Grade D evidence)**
4. Early initiation of therapy for symptomatic infection in immunocompromised patients is preferred over post-exposure prophylaxis. In the setting of a defined, significant exposure (e.g. household contact or healthcare associated exposure such as shared hospital accommodation) of an immunocompromised patient to

a proven or suspect case of influenza, post-exposure prophylaxis may be considered. **(Option, Grade D evidence)**

2. Treatment of patients with renal impairment

Recommended oseltamivir regimens for treatment of patients with renal impairment or failure are presented in Table 7.[57,58]

No dosage adjustments are required for inhaled zanamivir treatment in patients with renal impairment.

3. Treatment of pregnant women

During seasonal influenza epidemics, healthy pregnant women with influenza, especially those in the third trimester of pregnancy, experienced rates of hospitalization in excess of those observed in age-matched non-pregnant women with influenza.[59] Moreover, the rates of hospitalization were comparable to those observed in individuals with other recognized co-morbid conditions that increase the risk of influenza-related complications.[59] As a result of such data, pregnancy came to be considered a risk factor that warrants annual influenza immunization. During the 2009 pH1N1 pandemic, not only were increased rates of hospitalization again observed in healthy pregnant women, most in the the second and third trimester, but also increased rates of death compared to non-pregnant women.[60] Such excess mortality had previously been observed during the 1918 and 1957 pandemics. These observations taken together, support the recommendation to treat influenza in pregnant women with antiviral drugs.

Both oseltamivir and zanamivir are listed by the FDA as Pregnancy Category C drugs, reflecting the fact that no clinical studies have been done to assess their safety during pregnancy. No adverse effects on the pregnant woman or fetus have been observed as a result of treatment with oseltamivir during pregnancy.[61]

Some authorities recommend oseltamivir in preference to zanamivir because it is systemically absorbed.[62] Systemically absorbed oseltamivir would likely be delivered to virus-infected respiratory tract tissues more consistently than inhaled zanamivir, especially in the later stages of pregnancy when diaphragmatic excursion, limited by the gravid uterus, may impair necessary distribution of inhaled zanamivir through the respiratory tract. On the other hand, we have previously recommended zanamivir because lack of systemic absorption might limit any adverse effect on the fetus and protecting the fetus in utero against influenza illness seems unnecessary since influenza in the fetus has not been reported.[23]

Recommendation

- Pregnant women with influenza illness should be treated with oseltamivir. **(Option, Grade D evidence)**

4. Treatment of patients who are unable to ingest oseltamivir or inhale zanamivir

Some patients, such as those who are intubated to permit mechanical ventilation, will not be able to ingest oseltamivir capsules or suspension nor receive inhaled zanamivir powder. In such individuals, administration by gastric tube yields plasma concentration in excess of those observed in healthy adults with influenza who ingest 75 mg capsules twice daily with beneficial therapeutic effects.[20]

Recommendations

- Intubated patients with influenza illness should receive oseltamivir by nasogastric tube. **(Recommendation, Grade C evidence)**

- For patients unable to tolerate or receive oral oseltamivir, inhaled or intravenous zanamivir is a suitable option. **(Option, Grade D evidence)**

E. Off-label use

For both approved NAIs, these guidelines are recommending some uses that are off-label and not approved by Health Canada. Accordingly, it remains incumbent on the prescribing clinician to apprise the patient of such use.

VI. CHEMOPROPHYLAXIS VERSUS EARLY THERAPY

An algorithm for prophylaxis is provided as **Appendix D**.

Antiviral prophylaxis with NAIs has been demonstrated to be efficacious and well tolerated. Three chemoprophylactic strategies were detailed in our previous guideline: [23] (i) Seasonal prophylaxis including bridging prophylaxis to protect individuals for two weeks after receipt of inactivated injectable influenza vaccine until vaccine-induced immunity developed, (ii) post-exposure prophylaxis (PEP) or contact exposure and (iii) outbreak control. Antiviral chemoprophylaxis is no longer recommended other than in very selected circumstances, such as to control outbreaks in nursing homes and other long-term care facilities that house large numbers of patients at high risk of influenza complications.[8]

In the above context, in the appropriate setting, PEP is an efficacious strategy when initiated in the first 48 hours after exposure to an infectious ill contact. Contacts are considered infectious for the interval beginning 24 hours before illness onset until the time fever ends.

However, it is now recommended that the strategy of early treatment be used as an alternative to PEP because of reports of oseltamivir resistance arising during PEP. Early presumptive therapy with treatment doses of oseltamivir or zanamivir twice daily initiated

after exposure to an infectious contact even before symptoms begin may be appropriate for situations where influenza infection appears prevalent and persons at higher risk of influenza complications are exposed.[8]

For less vulnerable contacts, an early treatment strategy entailing counseling about early symptoms and signs of influenza combined with advice that they seek treatment immediately if influenza-like illness develops may be appropriate. Such contacts could be provided a prescription they could fill so as to have medication on hand for early initiation of therapy.

Recommendations

1. Prophylaxis, combined with treatment, is indicated to control outbreaks in nursing homes and other long-term care facilities with large numbers of patients at high risk of acquiring infection due to their housing arrangements and influenza complications. **(Strong Recommendation, Grade C evidence)**
2. In general, early treatment of symptomatic illness is recommended in preference to post-exposure prophylaxis after contact with infectious individuals. **(Option, Grade D evidence)**
3. In exposed, susceptible, profoundly immunosuppressed individuals at very high risk of complications, presumptive treatment should be initiated prior to the onset of symptomatic illness. **(Option, Grade D evidence)**
4. For early and presumptive treatment, oseltamivir is preferred. **(Option, Grade C evidence)**
5. Early treatment is recommended in place of seasonal prophylaxis for all situations including that in which protection is to be provided to individuals who have just

received vaccine until vaccine-induced immunity develops, or persons who are unable to receive vaccine. **(Option, Grade D evidence)**

6. An early treatment strategy should involve counseling together with arrangements for contacts to have medication on hand. **(Option, Grade D evidence)**
7. Neither early treatment nor PEP should be prescribed:
    - For groups of healthy individuals based on possible exposure in the community
    - If the close contact did not occur during the infectious period of the person with suspected or confirmed influenza
    - If > 48 hours have elapsed since the last infectious contact

    (Option, Grade D evidence)

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CONFLICT OF INTEREST DECLARATION:

Dr. Fred Y. Aoki: Honoraria: Hoffmann La Roche Inc., GlaxoSmithKline and Merck; Advisory Board: GlaxoSmithKline, Hoffmann La Roche Inc.; Research: GlaxoSmithKline, Hoffmann La Roche Inc., Biocryst, Merck

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

Table 1 GRADE Evidence Quality vs. Benefit to Harm Ratio and Recommendation Grading

Quality of Evidence	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well-designed, randomized, controlled studies or diagnostic studies on relevant populations	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case control or cohort design)		
D. Expert opinion, case reports, reasoning from first principles	Option	No Recommendation
X. Exceptional situations where validating studies cannot be done and there is a clear preponderance of benefit or harm	Strong Recommendation / Recommendation	

Table 2.[8] Susceptibility of influenza viruses to oseltamivir, zanamivir and amantadine as of December, 2010

	Oseltamivir	Zanamivir	Amantadine
pH1N1	S	S	R
Seasonal H1N1	R	S	S
Seasonal A H3N2	S	S	R
Influenza B	S	S	R

S = susceptible; R = resistant

Table 3. Clinical signs warranting urgent medical attention in infants, children and youth with suspected or proved influenza

Infants and Toddlers (< 1 year and 1-3 years, respectively)
Rapid breathing and difficulty breathing
Bluish skin colour or change in skin colour
Not drinking enough fluids
Not waking up or not interacting
Being so irritable that child does not want to be held
Flu-like symptoms improve but then return with fever and a worse cough
Fever with a rash
Seizures
Children and Youth (>3 to < 12 years and 12-18 years, respectively)
Rapid breathing, difficulty breathing or shortness of breath
Bluish skin colour, bloody or coloured sputum
Flu-like symptoms improve but then return with fever and worse cough
Confusion, listlessness, altered consciousness
Severe or persistent vomiting
Fever with a rash
Severe chest pain or abdominal pain
Seizures

Table 4. At-risk groups and co-morbid medical conditions that predispose to severe influenza (Adapted from 11,12)

- Asthma and other chronic pulmonary disease, including bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis and emphysema
- Cardiovascular disease (excluding isolated hypertension; including congenital and acquired heart disease such as congestive heart failure and symptomatic coronary artery disease)
- Malignancy
- Chronic renal insufficiency
- Chronic liver disease
- Diabetes mellitus and other metabolic diseases
- Hemoglobinopathies such as sickle cell disease

- Immunosuppression or immunodeficiency due to disease (e.g. HIV infection, especially if CD_4 is < 200 x 10^6/L), or iatrogenic, due to medication
- Certain rheumatologic diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, scleroderma, spondyloarthropathies, Sjogren's syndrome, dermatomyositis, vasculitis, sarcoidosis, polyarteritis nodosa
- Neurologic disease and neurodevelopmental disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)
- Children younger than 2 years of age*
- Individuals 65 years of age or older
- People of any age who are residents of nursing homes or other chronic care facilities
- Pregnant women and women up to 2 weeks post partum regardless of how the pregnancy ended
- Individuals < 18 years of age who are on chronic aspirin therapy
- Morbid obesity (BMI $\geq$ 40)
- First Nations, Inuit and Metis Canadians

* Children who are 2 years through 4 years of age also have a higher rate of complications compared to older children; however, the risk for these children is lower than the risk for children younger than 2 years

Table 5. Oseltamivir and zanamivir regimens adapted from: http://www.cdc.gov/h1n1flu/recommendation.htm and European Medicines Agency[18]

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	≤33lbs	30 mg twice daily	30 mg once daily
> 15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	45 mg once daily
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	60 mg once daily
>40 kg	>88 lbs	75 mg twice daily	75 mg once 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
*Please note that antivirals are not approved for the routine treatment of seasonal influenza illness in infants less than 1 year of age.			
Zanamivir[4]			
Adults			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 years or older for treatment, ≥5 years for 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 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. Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment (give two doses per day) or prophylaxis (give one dose per day) of influenza in full-term infants younger than 1 year of age may be necessary: 0-3 months (treatment only) = 12 mg (1 mL of 12 mg/mL commercial suspension); 3-5 months = 20 mg once daily (1.6 mL of 12 mg/mL of commercial suspension), 6-11 months = 25 mg (2 mL of 12 mg/mL commercial suspension) once daily).
3. Current weight-based dosing recommendations are <u>not</u> 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. These data are insufficient to recommend a specific dose of oseltamivir for premature infants.
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.

Table 6. Selected Surrogate Indices of Immunocompromised states

Laboratory-based Indices	Clinical States	Treatment-related Indices
Significant Risk • Severe neutropenia (ANC < 0.5 x 10^9/L), and/or, • Severe lymphopenia (ALC < 0.5 x 10^9/L)	Significant but Variable Risk Due to Heterogeneity in Clinical States • Individuals with malignancies receiving active cytotoxic chemotherapy • Acute leukemia patients • HSCT recipients • SOT recipients (e.g. lung, heart, kidney) • Individuals with congenital immunodeficiency states • Individuals with acquired immunodeficiency states (e.g. Human Immunodeficiency Virus infection, plasma cell dyscrasias, B-lymphocyte malignancies) • Individuals with rheumatic diseases or autoimmune disorders (e.g. RA or SLE) • Individuals with GI diseases receiving immunosuppressive drugs (e.g. IBD), • Individuals on renal dialysis • Individuals with asthma or COPD receiving corticosteroid therapy.	Significant but Variable Risk Due to Heterogeneity in Nature and Intensity of Treatments A history of ongoing myelosuppressive and/or immunosuppressive therapies such as: • Corticosteroid therapy[56] (i.e., among adult patients > 700 mg cumulative dose of prednisone equivalent on an ongoing basis and at the time of clinical evaluation) • Cytotoxic therapy* • Immunomodulator therapies**:

*Examples of cytotoxic therapy include, but are not limited to:	**Examples of immunomodulator therapy include, but are not limited to:
(e.g., *anthracyclines* such as doxorubicin or epirubicin; *purine analogues* such as azathiaprine, thioguanine, mercaptopurine, fludarabine, pentostatin, or cladribine; *pyrimidine analogues* such as flurorouracil, cytarabine, capecitabine, or gemcitabine; *anti-folate agents* such as methotrexate or premetrexed; *alkylating agents* such as the nitrogen mustards (cyclophosphamide or ifosphamide), nitrosoureas (carmustine, lomustine, semustine, streptozotocin), and platinum analogues (cis-platin, carboplatin, or oxaliplatin); *taxanes* (e.g., docetaxel, paclitaxel); *topoisomerase I inhibitors* (e.g., irinotecan).	*Calcineurin inhibitors* (e.g., cyclosporine, tacrolimus, sirolimus), *Guanine synthesis inhibitors* (e.g., Mycophenolate mofetil), *Anti-B lymphocyte therapy* (e.g., rituximab), *Anti-T lymphocyte therapy* (e.g., anti-thymocyte globulin or anti-CD3), *Anti-B and T cell therapy* (e.g., alemtuzumab, basiliximab, daclizumab), *Anti-TNF therapy* (e.g., infliximab or etanercept), Alpha-interferon therapy

Adapted from: Allen U, Doucette K, Bow E, in reference 47

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant; RA, rheumatoid arthritis; SLE, systemic lupus

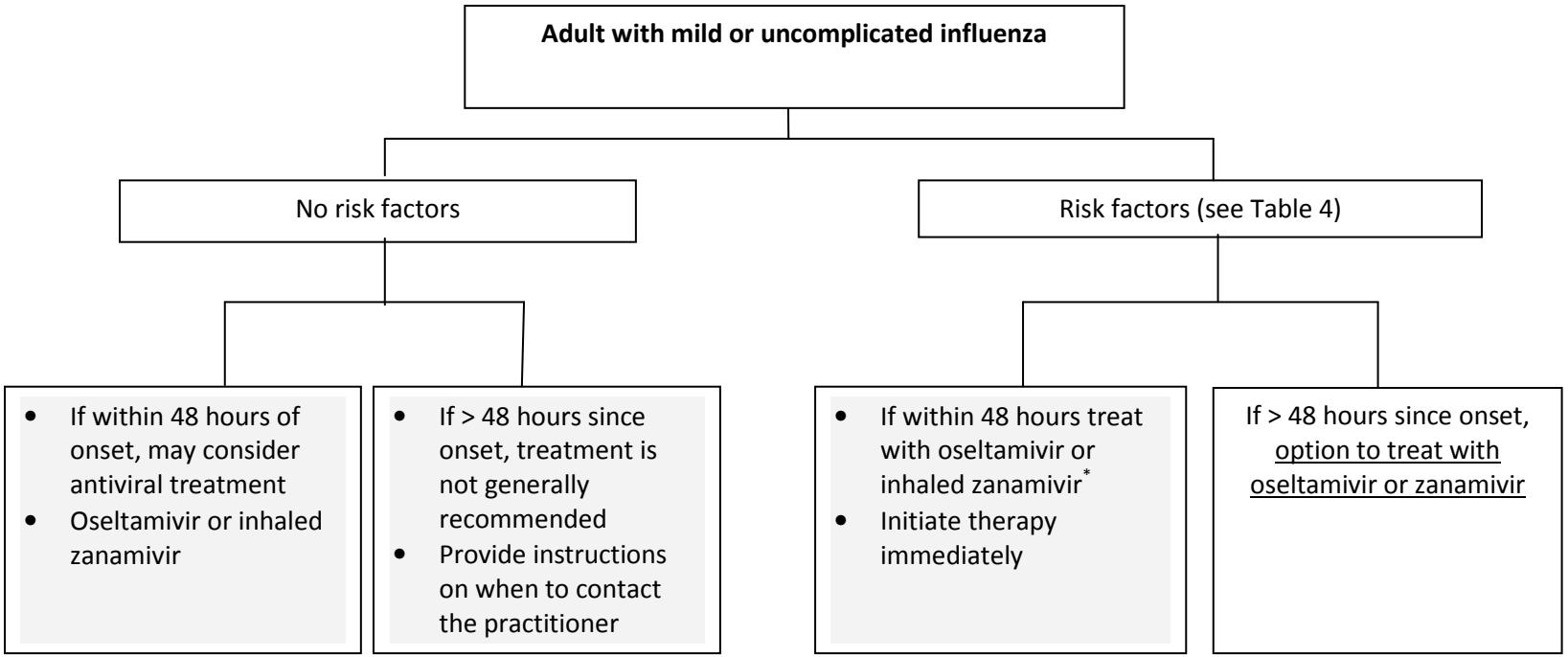
erythematosis; GI, gastrointestinal; IBD, inflammatory bowel disease; COPD, chronic obstructive airways disease; TNF, tissue necrosis factor

Table 7. Recommended oseltamivir regimens for treatment of patients with renal impairment or failure

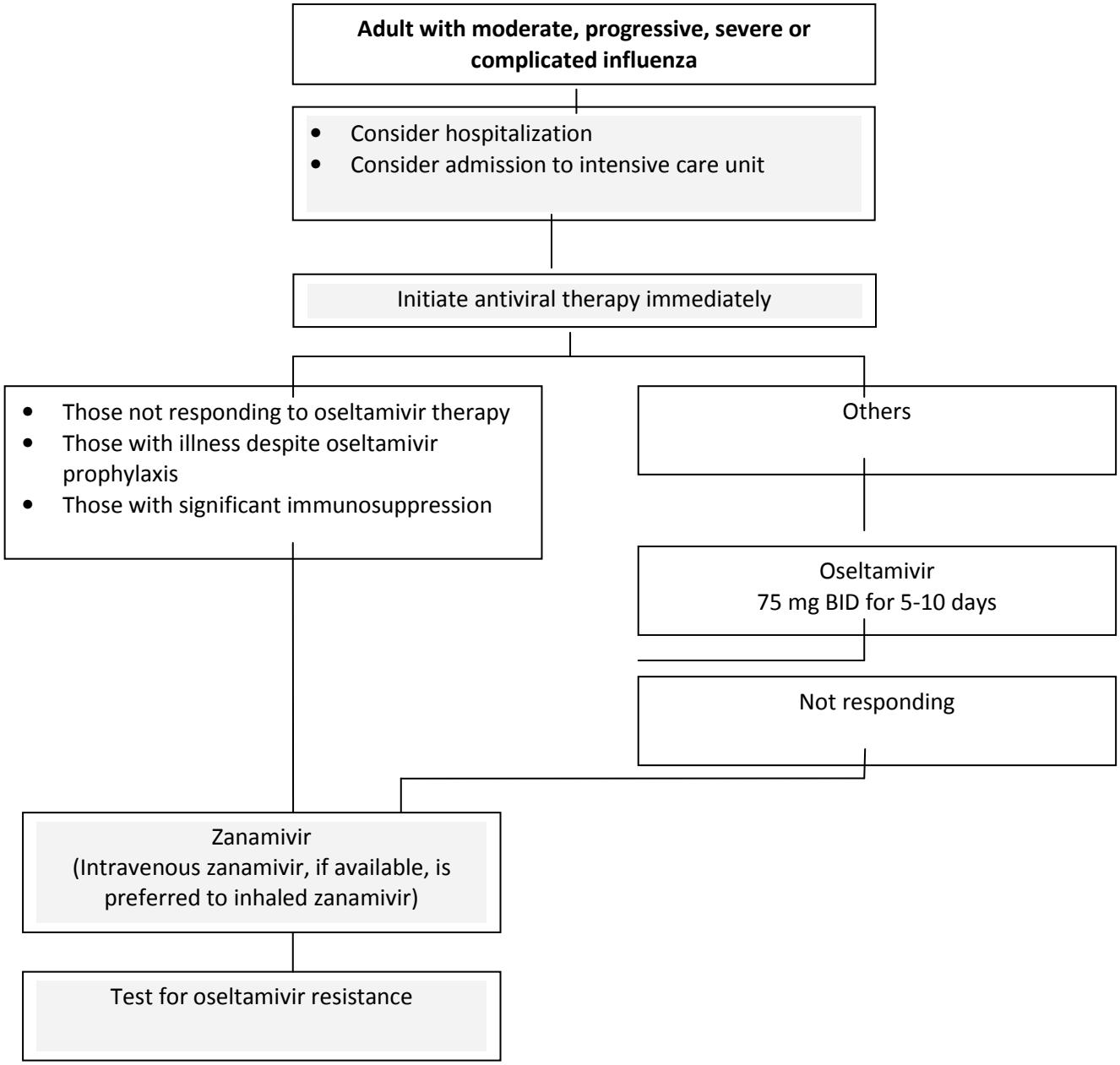
Creatinine clearance	**Treatment**
>30mL/min	75mg twice daily
>10–30mL/min	75mg once daily OR 30mg suspension twice daily OR 30mg capsule twice daily
≤10mL/min (renal failure)*	Single 75mg dose for the duration of illness
Dialysis patients*	Low-flux HD: 30mg after alternate dialysis sessions High-flux HD: 75mg after each dialysis session CAPD dialysis: 30mg once weekly CRRT high-flux dialysis: 30mg daily or 75mg q48hrs

*Experience with the use of oseltamivir in patients with renal failure is limited, however these regimens have been suggested based on the limited available data[57,58]

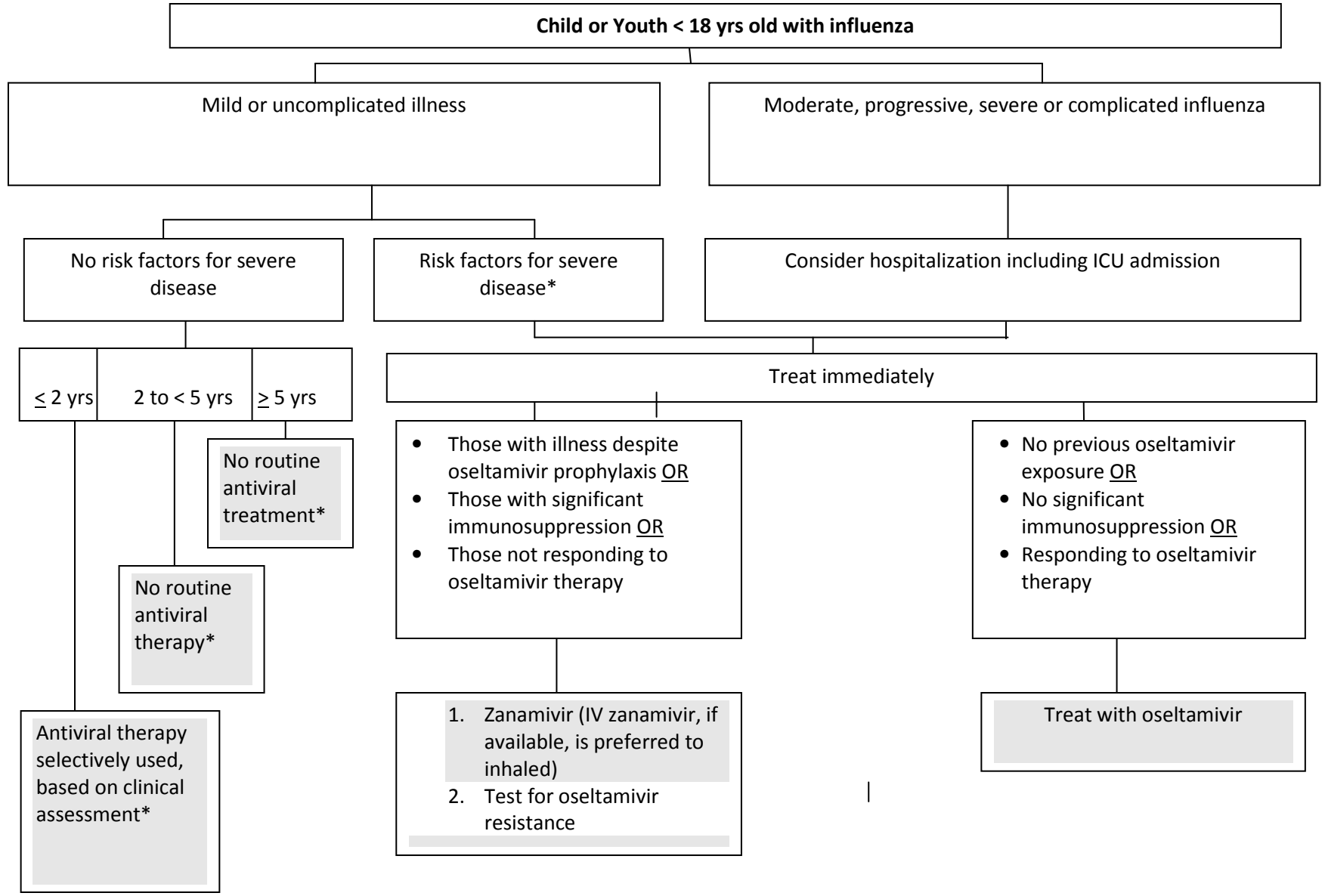
Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in adults



Algorithm for oseltamivir and zanamivir treatment of moderate, progressive, severe or complicated influenza in adults

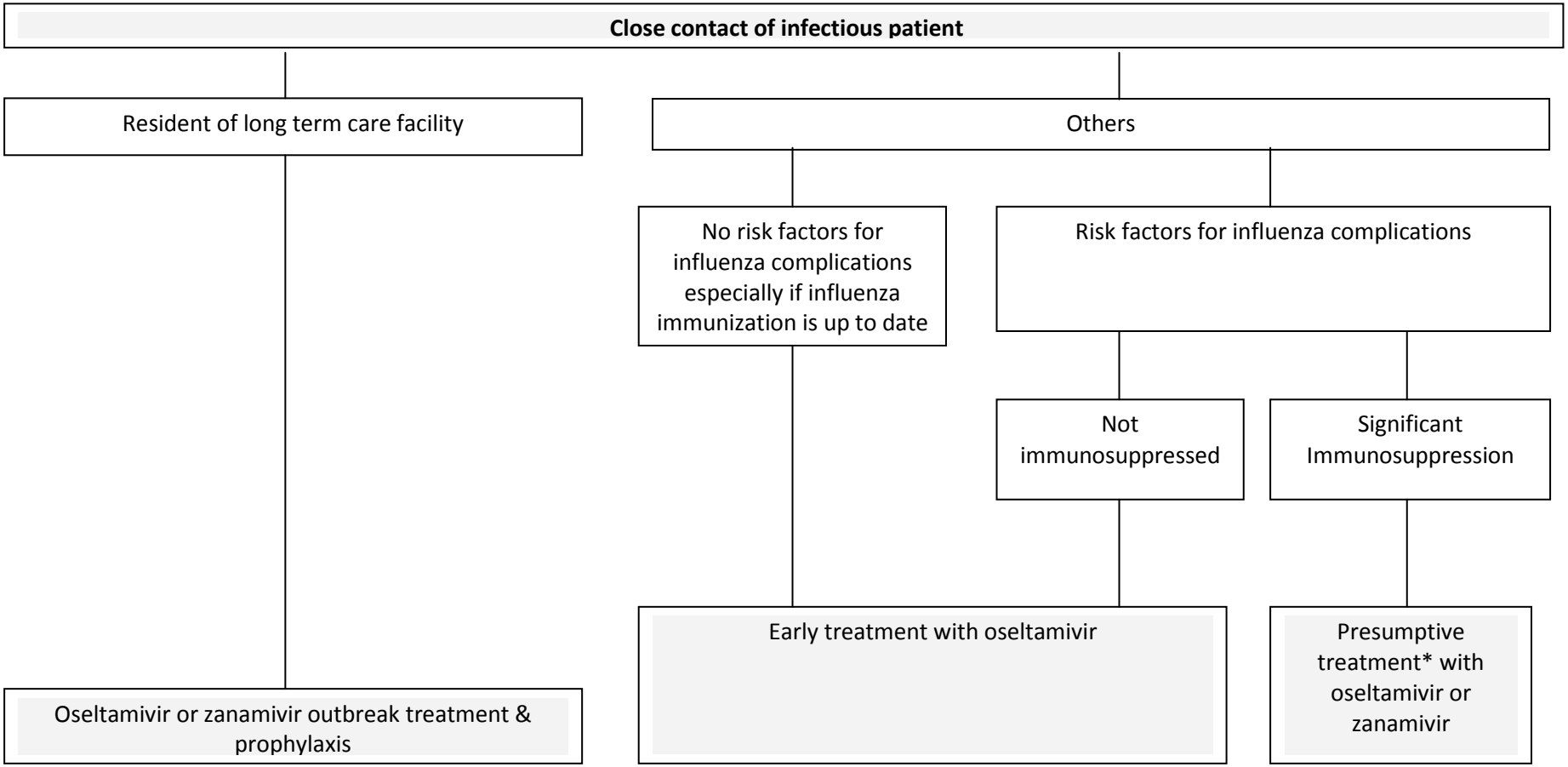


Algorithm for oseltamivir and zanamivir treatment of influenza in children and youth (< 18 yrs old)



In the above scenarios, treatment is not routinely recommended if ill for > 48 hrs.

Algorithm for oseltamivir and zanamivir prophylaxis or early therapy in close contacts of infectious patients



*Presumptive treatment is therapy with twice daily doses of oseltamivir or zanamivir initiated before the onset of influenza symptoms in close contacts of individuals with suspected or proved influenza illness

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