Management of influenza infection in children and pregnant women in BC, an update

Immunization is the main preventive measure against influenza viruses. However, for certain patients who develop infection with influenza A or B, oseltamivir is an important treatment option.

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The 2014–2015 influenza season was very active in British Columbia and throughout Canada. Widespread influenza activity, predominantly A(H3N2), was observed throughout most regions of the province. The BC Centre for Disease Control's Influenza Surveillance Reports indicated that the proportion of visits to sentinel physicians and to the BC Children's Hospital emergency room for influenza-like illness were well above average seasonal rates.[1] One of the reasons suggested for this increase was the mismatch between influenza vaccine serotypes and circulating serotypes. With the rise in suspected or confirmed influenza cases, many clinicians have faced questions regarding the ideal management of influenza infection, particularly in the higher-risk populations of young children and pregnant women since influenza virus infection in these populations can result in significant morbidity and mortality.[2]

Immunization is the main preventive measure against influenza viruses. However, for certain patients who develop infection with influenza A or B, oseltamivir (trade name Tamiflu) is an important treatment option to reduce the severity and duration of symptoms, risk of complications, use of antibiotics, and, potentially, mortality.[3-7] Oseltamivir is an oral antiviral drug that is rapidly metabolized into its active metabolite, oseltamivir carboxylate, which inhibits viral neuraminidase, blocking release of progeny virions from infected cells and viral entry into uninfected cells.[8]

Oseltamivir was licensed primarily based on phase 3 randomized, placebo-controlled trials demonstrating a reduction in the duration of symptoms due to influenza in healthy outpatients.[9-11] No randomized trials of oseltamivir treatment have been conducted among patients hospitalized with influenza or individuals at highest risk of severe influenza disease. However, numerous cohort studies suggest even greater benefits of oseltamivir in these groups, including reductions in mortality.[12-15] Despite these data, the effectiveness of oseltamivir has been highly debated, in part due to criticisms of potential bias and incomplete release of clinical trial data from the drug's manufacturer, Roche.[16] In April 2014 the Cochrane review was updated based on full internal reports made available by Roche from oseltamivir and zanamivir trials that included over 24 000 patients, and the authors still found a benefit in patients with influenza-like illness and confirmed influenza virus infection.[17] Dobson and colleagues conducted a separate meta-analysis by an independent research group, including all available data from randomized, double-masked, placebo-controlled adult trials (n = 4328) and found that oseltamivir in adults decreases duration of symptoms and reduces risk of lower respiratory tract complications and hospital admissions but increases incidence of nausea and vomiting.[18] The great-

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est benefits of oseltamivir are seen if treatment is initiated within 2 days of symptom onset, though evidence also supports the efficacy of treatment that is started later.[2,6] Although its overall benefits are modest, oseltamivir is the most active antiviral available for influenza and is the standard of care for the treatment of influenza among high-risk or severely ill patients.[2,19,20]

Oseltamivir for treatment of influenza in children

Much less evidence exists to guide the management of children with influenza compared with adults.[20] The hospitalization rate and risk of adverse events related to influenza infection is higher in children under 5 years of age, and especially in those under 2 years of age, compared with older children. Children with certain chronic conditions or compromised immunity are also at greater risk when they contract influenza infection.[19]

A Cochrane review of 2356 children, of which 1255 had laboratory-confirmed influenza, also found that oseltamivir treatment provided a modest benefit in the duration of illness and incidence of acute otitis media but increased nausea and vomiting.[4] Benefits of oseltamivir may be more pronounced in hospitalized children and oseltamivir may decrease the length of hospital stays,[21] along with potentially preventing hospitalization in high-risk patients.[22] The Canadian Paediatric Society, Centers for Disease Control and Prevention, and American Academy of Pediatrics all recommend the empiric use of oseltamivir to manage influenza illness, particularly in hospitalized children and those at high risk for complications.[20,23,24]

No neuraminidase inhibitors are approved for children younger than 1 year of age in Canada, but oseltamivir was approved temporarily for use in this age group based on a favorable risk-to-benefit ratio during the 2009 H1N1 pandemic. Evidence and dosing studies exist for infants younger than 1 year of age,[25] and the Canadian Paediatric Society guidelines continue to recommend oseltamivir for this age group.[20]

Oseltamivir for treatment of influenza in pregnant women

Pregnant women and women up to 4 weeks postpartum are also at high risk for influenza-related complications.[2,26] Increased severity of illness, increased hospitalizations, and increased mortality have been observed, particularly in women with influenza in their third trimester.[26,27] Influenza in pregnancy has also been associated with effects on the fetus, including congenital abnormalities, low birth weight, preterm delivery, and fetal death.[2,28-30]

Oseltamivir is considered the antiviral medication of choice for pregnant women for the treatment of influenza.[2,24,31] Results from studies of pregnant women during the H1N1 pandemic in 2009 suggest that early treatment with oseltamivir may reduce ICU admissions and mortality.[6,7] Current data do not suggest any increased risk to the developing fetus if oseltamivir is taken during pregnancy.[32] Treatment guidelines from the Association of Medical Microbiology and Infectious Disease Canada, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America all recommend oseltamivir use for the treatment of suspected and confirmed influenza in the pregnant population.[2,24,31]

Local guidance for oseltamivir use in children and pregnant women

Despite being the mainstay of influenza treatment, oseltamivir has been found to be underused in BC, especially in the highest-risk age groups.[22] To promote rational use of oseltamivir the Infectious Diseases and Antimicrobial Stewardship Group from BC Children's and Women's Hospitals produced two treatment algorithms adapted from available guidelines to optimize oseltamivir use in children and pregnant women with suspected or confirmed influenza infection. Because of the availability of rapid influenza diagnostic testing in BC Children's and Women's Hospitals, the influenza protocol was designed to use oseltamivir only in confirmed influenza-positive patients with risk factors for complications, limiting empiric oseltamivir use to pregnant women and critically ill patients or as necessary according to clinical judgment. When testing with nasopharyngeal wash specimens is not feasible or rapid tests are not available, empiric therapy should be initiated in all high-risk patients with influenza-like illness without waiting for laboratory results to minimize treatment delay and maximize efficacy.

The BC Children's Hospital pediatric oseltamivir treatment algorithm (**Figure 1**) is available at http://bccwhcms.medworxx.com/Site_Published/bcc/document_render.aspx?documentRender.IdType=32&documentRender.GenericField=1&documentRender.Id=16093.

The BC Women's Hospital oseltamivir treatment algorithm for pregnant women (**Figure 2**) is available at http://bccwhcms.medworxx.com/Site_Published/bcw/document_render.aspx?documentRender.IdType=29&documentRender.GenericField=1&documentRender.Id=16922.

Competing interests

None declared. No author has any association with the manufacturers of Tamiflu.

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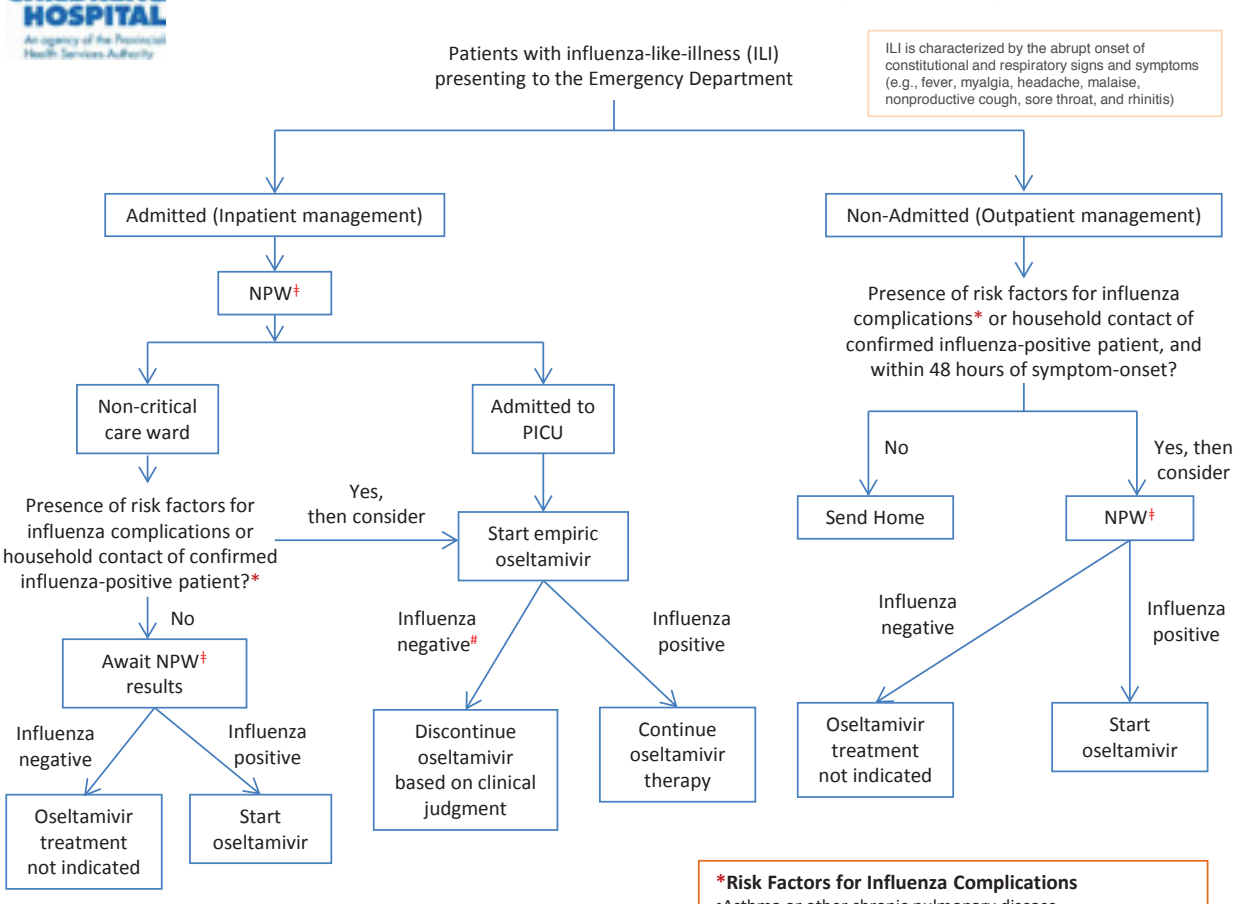
BCCH Algorithm For Oseltamivir Treatment of Influenza in Children and Youth (2 weeks to 18 years of age)



Note:

- Greatest benefit is when oseltamivir is started within 48 hours of influenza illness onset, but may still be beneficial when administered >48 hours.
- #Confirmation of a negative NPW requires a negative PCR for Influenza virus A and B.
- ‡NPW = Nasopharyngeal Wash

Oseltamivir dosing for treatment of influenza:

Children <12 months: 3 mg/kg/dose PO twice daily x 5 days

Children ≥12 months to <13 years:

•≤15 kg:	30 mg PO twice daily x 5 days
•>15 kg to ≤23 kg:	45 mg PO twice daily x 5 days
•>23 kg to ≤40 kg:	60 mg PO twice daily x 5 days
•>40 kg:	75 mg PO twice daily x 5 days
•Adolescents ≥13 years and adults:	75 mg PO twice daily x 5 days

Dose interval and duration adjustment in renal impairment:

Patients with GFR <30 mL/min: once daily x 5 days

Patients on PD/HD: once daily x 2 days

***Risk Factors for Influenza Complications**

- Asthma or other chronic pulmonary disease
- Cardiovascular disease
- Malignancy
- Immunosuppression or immunodeficiency
- First Nations, Inuit and Métis children and youth
- Diabetes mellitus and other metabolic diseases
- Hemoglobinopathies such as sickle cell disease
- Neurological disease or neurodevelopmental disorders that compromise handling of respiratory secretions
- Chronic renal insufficiency
- Chronic liver disease
- Children or youth who reside in homes or other chronic care facilities
- Individuals <18 years of age who are on chronic acetylsalicyclic acid therapy
- Obesity with BMI ≥40 kg/m^2, OR a BMI ≥3 z-scores above the mean for age and gender

(Age is not included in this list of risk factors to avoid over-testing of patients.)

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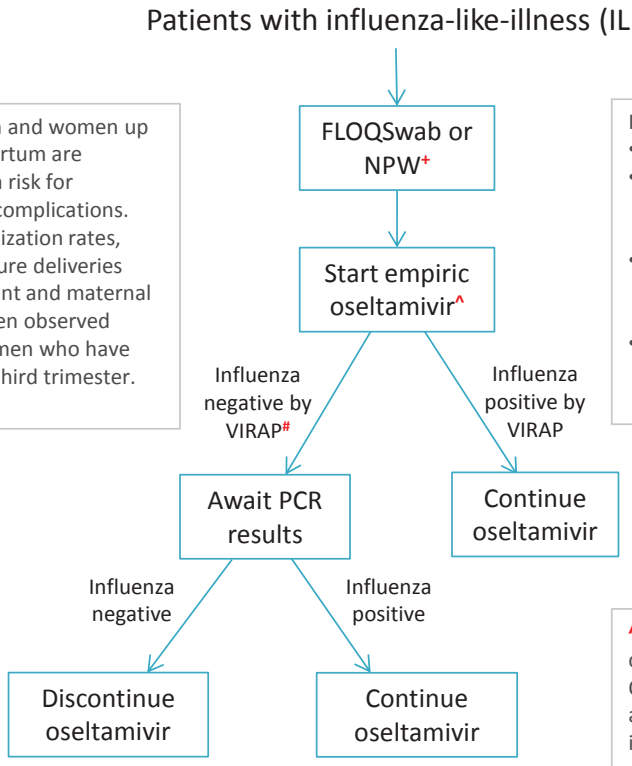
Figure 1. The BC Children's Hospital pediatric oseltamivir treatment algorithm

BC WOMEN'S HOSPITAL+ HEALTH CENTRE

BCWH Algorithm For Oseltamivir Treatment of Influenza in Pregnant Women*



*Pregnant women and women up to 4 weeks postpartum are considered at high risk for influenza related complications. Increased hospitalization rates, stillbirths, premature deliveries and increased infant and maternal mortality have been observed particularly in women who have influenza in their third trimester.

ILI is characterized by:
- Fever and cough
- Fever and gastrointestinal symptoms (nausea, vomiting, diarrhea)
- Contact with anyone with flu like symptoms in the last 7 days

PLUS

- Any of the following: muscle aches, joint pains, sore throat, extreme fatigue or weakness

^Pregnancy is NOT a contraindication to oseltamivir use. Oseltamivir is the preferred antiviral agent for the treatment of influenza in pregnant women. No adverse effects on the fetus have been observed.

To order antiviral therapy please refer to pre-printed orders **Treatment And Monitoring of Women with Influenza (WW.13.03C)**

Note:
- Oseltamivir may reduce the duration of hospitalization, ICU admissions and mortality in hospitalized patients with influenza and reduce lower respiratory tract complications in outpatients.
- Greatest benefit is when oseltamivir is started within 48 hours of influenza illness onset, but may still be beneficial when administered >48 hours.
- #Confirmation of a negative FLOQSwab/NPW requires a negative PCR for influenza virus A and B. VIRAP = Viral rapid testing program
- +FLOQSwab = flocked nasopharyngeal swab; NPW = nasopharyngeal wash

Oseltamivir dosing for treatment of influenza:
- All adults (including pregnant women): 75 mg po BID x 5 days

Dose interval adjustment in renal impairment:
- Patients with GFR 31 to 60 mL/min: 75 mg po once daily x 5 days OR 30 mg po BID x 5 days
- Patients with GFR $\leq$ 30 mL/min: 30 mg po once daily x 5 days

Please refer to **Fetal Maternal Newborn Policy Influenza Virus: Managing Women Presenting to BCW (WW.13.03A)** for further details.

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Figure 2. The BC Women's Hospital oseltamivir treatment algorithm for pregnant women

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