TIBDN Toronto Invasive Bacterial Diseases Network

FREQUENTLY ASKED QUESTIONS (Appendix to TIBDN newsletter January 2010, volume 4, Issue 2)

As with any novel or emerging pathogen, the management of pandemic H1N1 2009 Influenza can sometimes be confusing, especially when new information about the virus results in changes to guidelines. Answers to questions from physicians in Ontario can be found in the on-line version of this newsletter at www.pandemicwatch.ca/. In addition, we encourage health care providers to consult publicly available resources on pandemic H1N1 2009 influenza, such as the Public Health Agency of Canada (www.phac-aspc.gc.ca/alert-alerte/h1n1/index-eng.php), the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/h1n1flu/), and their provincial health ministry websites), for further information and direction.

1. A patient comes to the clinic with relatively mild influenza. The physician on duty decides not to treat because the patient has no risk factors for complicated infection. Two to three days later, their symptoms have worsened and now they present quite ill, possibly requiring hospitalization. Should the physician have started treatment when the patient first presented? If a patient presents on day 5 with worsening disease is an antiviral effective?

As always, clinical judgment is needed to guide treatment decisions. Most patients with pandemic H1N1 2009 influenza have a self-limited respiratory illness similar to typical seasonal influenza. For these patients, the benefits of using antivirals are modest. There are two recently published meta-analyses on neuraminidase inhibitors and influenza: 1 in adults published in *Lancet Infectious Diseases*[1], and 1 in children published in *BMJ*[2]. For healthy adults with influenza like illness, duration of symptoms was reduced by 0.55 days for oseltamivir, and for "at-risk" adults, symptom duration was reduced by 0.98 days. There were insufficient data to give a reliable number for averted complications, but antibiotic use was reduced when either zanamivir or oseltamivir were prescibed. For children, symptom duration was reduced by 0.5-1.5 days, but there was little effect on the rate of asthma exacerbation or antibiotic use. Therefore, healthy adults with mild disease will not benefit substantially from treatment. During a week with high influenza activity (whether seasonal or pandemic), treatment should be considered for persons who are at risk for complications. Treatment is recommended for anyone ill enough to require hospitalization. As the CDC notes, "persons presenting with suspected influenza and more severe symptoms such as evidence of lower respiratory tract infection or clinical deterioration should receive prompt empiric antiviral therapy, regardless of previous health or age".

Treatment, if offered, should be initiated as soon as possible after the onset of symptoms. Evidence for benefit is strongest when treatment is started within 48 hours of illness onset. However, studies on treatment of hospitalized patients with seasonal influenza and pandemic H1N1 influenza have indicated benefit, including reductions in mortality or duration of hospitalization, in patients whose treatment was started more than 48 hours after illness onset. Thus, if a patient presents with worsening symptoms of influenza, it is reasonable to start antivirals even if symptoms have been present for more than 48 hours.During influenza seasons, patients who require hospital admission for influenza-like illness or pneumonia should receive empiric antivirals.

2. An otherwise healthy patient comes into the walk in clinic with an influenza-like illness (ILI). Physicians are often not asking about others in the household (eg, children < 1-2 years of age, immunocompromised family members, etc). Should the physician treat the patient if there are "at risk" family members (ie, will this reduce transmission)? Should the physician be considering a preventative treatment for the 'at risk' household member? What is the best/ideal way to handle this situation?

The highest risk of influenza transmission occurs in households: with pandemic H1N1 2009 influenza, the risk that a second household member will become infected is 15-35%. We also know from laboratory studies that viral shedding is greatest on the first and second day of illness, and declines significantly thereafter. Practically speaking, then, it is unclear exactly how much of a reduction in household transmission would be achieved by starting treatment in such a scenario, especially since most patients don't seek or receive care within 48 hours of symptom onset. If the household includes a child <2 years of age, a pregnant woman, or another person at high risk of complications, such as a person with immune suppression, prophylaxis for household contacts may be considered. However, in general, the benefits of prophylaxis are relatively small, and most physicians would recommend non-pharmaceutical prevention measures combined with early therapy if symptoms develop. Non-pharmaceutical measures include frequent hand washing/use of handrub, good respiratory etiquette, maintaining distance (>6 feet) between ill and well family members, and surface cleaning. A recently published randomized controlled trial in the *Annals of Internal Medicine*[3] demonstrated a significant reduction in household influenza transmission when enhanced hand hygiene and face masks were implemented within 36 hours of symptom onset in the index patient. Most of the effect appeared to be associated with increased hand hygiene, but face masks may also be appropriate in households where an "at-risk" person resides.

Ideally, this situation should be avoided by strongly and repeatedly recommending influenza vaccination for all persons who live in households where an at-risk person is present.

3. Some people are not feeling better after 5 days of therapy. Should a physician consider extending the treatment days from 5 to 7-10? What are the thoughts on duration of therapy?

The standard duration of antivirals for the treatment of pandemic H1N1 2009 influenza is 5 days, although longer durations have been used for severely ill, hospitalized patients. There are no data on the potential benefits of prolonged antiviral therapy in outpatients with influenza.

Fatigue, cough, and green nasal discharge/post-nasal drip commonly persist for longer than 5 days, but will not benefit from further treatment with antivirals or from antibacterial therapy.

In patients with persisting fever, or increasingly productive cough, consideration must be given to the possibility of complicating bacterial infections. If bacterial infection is thought not to be present, teaching about warning signs that may indicate a worsening infection and require appropriate referral to an escalated level of care is likely a superior approach to extension of antiviral treatment. Warning signs and symptoms that should prompt urgent medical attention in adults include persistently high fever after day 5, increasing fever/chills, tachypnea, dyspnea, pain or pressure in the chest or abdomen, confusion, sudden dizziness, and severe or persistent vomiting. In children, additional warning signs include laboured breathing, cyanosis, severe somnolence and difficulty rousing, dehydration, and severe irritability.

4. Why are women more likely to get sick longer and/or need hospitalization more often then men? Does it have to do with body fat composition and the virus' ability to build up toxins in females?

In a study of 168 Canadian patients with pandemic H1N1 2009 influenza admitted to the ICU and reported in *JAMA*[4], 67.3% were female. Thus, there appeared to be an association between female gender and severe influenza. This excess has not been seen in other studies,and, during the second wave of the pandemic in Canada, 49% of 4,843 patients hospitalized with H1N1, 47.6% of cases admitted to the ICU,and 47.9% of the deaths due to H1N1 have been female. It seems likely that the overrepresentation of women during the first wave was a result of a large number of cases from aboriginal communities in Manitoba, which have relatively high rates of both pregnancy and underlying chronic illnesses such a diabetes. There is no evidence that body fat composition increases the risk of severe influenza, due to this pandemic virus, or other influenza strains.

5.Can you provide information on prescribing antivirals in pregnancy?

Pregnant women, particularly in their second and third trimester of pregnancy and up to 6 weeks post-partum, are at elevated risk of complicated influenza infection. For this reason, the **Society of Obstetricians and Gynecologists of Canada** (www.sogc.org) recommends that pregnant women speak to their doctors about a plan for prompt treatment with antivirals should they develop an influenza-like illness during peaks of influenza activity. It is not recommended that the drug be taken in the absence of symptoms, but it is recommended to start treatment as early as possible after development of symptoms (preferably within 48-hours of symptom onset). Early treatment of influenza in pregnant women can help reduce the risk of severe or complicated infection.

Both oseltamivir (Tamiflu) and zanamivir (Relenza) are active against the pandemic H1N1 2009 influenza virus, however, zanamivir is not reliably available in pharmacies. Tamiflu is usually well tolerated, but can cause nausea and vomiting, both of which may be reduced by taking the medicine with food. Zanamivir comes as an inhaled formulation and can induce bronchospasm; thus, it is not recommended for treatment of patients with underlying lung disease. Oseltamivir and zanamivir are class C drugs, with limited safety data on their use during pregnancy. The US Centers for Disease Control and Prevention and the Public Health Agency of Canada recommend oseltamivir treatment of all pregnant women with laboratory confirmed or suspected pandemic H1N1 2009 influenza. The few studies that are available suggest that Tamiflu is safe to use during pregnancy. This was reiterated in a recently published study in the *Canadian Medical Association Journal*[5]. Treatment dosing in pregnant women is the same as for other adults: oseltamivir (Tamiflu) 75 mg twice daily for 5 days or zanamivir (Relenza) two 5-mg inhalations (10 mg total) twice daily for 5 days.

During periods of high influenza activity, empiric therapy of influenza-like illness in pregnant women may be warranted. When little influenza activity is occurring, treatment should not be offered to those without laboratory confirmation of disease.

References:
[1]Burch J et al. Lancet Infect Dis 2009;9:537-545, available at: http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(09)70199-9/abstract
[2]Shun-Shin M et al. BMJ 2009;339:b3172, available at: http://www.bmj.com/cgi/content/full/339/aug10_1/b3172?view=long&pmid=19666987
[3]Cowling B et al. Ann Intern Med 2009;151:437-446, available at: http://www.annals.org/content/151/7/437.full
[4] Kumar A et al. JAMA 2009;302:1872-1879, available at: http://jama.ama-assn.org/cgi/content/full/302/17/1872?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=h1n1+icu&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT
[5]Tanaka T et al. CMAJ 2009;181:55-58, available at: http://www.cmaj.ca/cgi/content/full/181/1-2/55?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=neuraminidase&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=date&resourcetype=HWCIT