Clinical Guidance for the Management of Influenza-Like Illness in the Context of Pandemic H1N1 Influenza Virus in Adult Intensive Care Units

Introduction

This guidance has been developed for clinicians managing adult patients with severe influenza infections requiring Intensive Care Unit (ICU) admission, in the context of pandemic (H1N1)2009 Influenza (pH1N1).

On September 2 & 3, 2009, The Public Health Agency of Canada (PHAC), in collaboration with Manitoba Health, the University of Manitoba, and the Critical Care Society of Canada, hosted a conference bringing together more than 175 national and international critical care, public health, and primary care experts to discuss the clinical care and management of severe H1N1 disease and to prepare for the anticipated fall pandemic wave. As an outcome of that conference, a need for a clinical guidance document for the management of Influenza Like Illness (ILI) in the context of pandemic H1N1 influenza virus in adult intensive care units was identified.

The following document was developed by a nationally representative group of critical care, infectious disease and public health experts in collaboration with PHAC.

Because of the short time frame for the development of guidelines following the appearance of the pH1N1 virus, the clinical trials that would inform these recommendations are still in progress. Thus, the recommendations made herein are based on the data available at the time of writing. As new data become available, adjustments may be made to the guidance provided. Many of the recommendations in the document are based on level III evidence (opinion of scientific and medical experts). As new knowledge is gained about this novel virus recommendations will be updated as appropriate.

Severe pH1N1 Infection Warranting Consideration of ICU Care

ICU admission and care may be indicated for patients presenting with Severe Respiratory Illness (SRI) or other complications associated with pH1N1 infection.

The presentation of severe pH1N1 infection may include:

1) rapidly progressive diffuse pneumonitis associated with severe, refractory hypoxemia, often in young, relatively healthy teens/adults and immunocompromised patients
2) acute and prolonged exacerbation of chronic obstructive pulmonary disease and asthma in those with pre-existing disease
3) decompensation of chronic underlying disease in those patients with serious comorbidities including congestive heart failure, chronic renal failure, end-stage liver disease, poorly controlled diabetes, etc.
4) bacterial pneumonia (frequently with gram positive pathogens including *Streptococcus pneumoniae, Staphylococcus aureus* and Group A Streptococcus) on a background of mild or severe pH1N1 infection
5) bronchiolitis and croup in infants and young children which may require hospitalization but not, in most cases, ICU care

Based on clinical experience to date, the **signature clinical syndrome** requiring ICU care among all age groups appears to be diffuse bilateral, four quadrant pneumonitis that can be rapidly progressive in the absence of antiviral therapy. Such patients may require extraordinary advanced ventilatory/oxygenation modalities (high frequency oscillation (HFO), inhaled nitric oxide and/or extracorporeal membrane oxygenation [ECMO] therapy)(1). Presentation of this syndrome has been associated with increased mortality: although lower in Canada (17.3%), than the original spring 2009 outbreak in Mexico (41.0%)(1;2). Pregnancy, female gender, aboriginal ethnicity, obesity and chronic immunocompromise may represent significant risk factors for severe disease.

Diagnostic Considerations

- Shortness of breath is a cardinal clinical symptom suggesting the possibility of severe disease and warrants a more thorough assessment including oximetry/blood gas and chest radiograph
- All patients with diffuse pneumonitis need to be closely monitored as the risk of rapid deterioration is high
- Initial testing for pH1N1 infection should consist of paired nasopharyngeal and tracheal aspirate specimens for Reverse Transcription Polymerase Chain Reaction (RT-PCR) for intubated patients. Testing of clinically/ epidemiologically high risk patient should be repeated within 48-72 hours if initial tests are negative
- Antiviral therapy is recommended in patients with progressive or severe infection even if the initial test for H1N1 is negative (unless an alternate pathogen is isolated)

The initial diagnosis and trigger for initiation of antiviral therapy may need to be presumptive.
Clinical features of an influenza-like illness:

- Usually: Sudden onset of cough and fever
- Common: Sore throat, coryza, fatigue, malaise, prostration, myalgias, arthralgias, headache, decreased appetite
- Sometimes: vomiting, diarrhea, nausea

Shortness of breath is not typical of uncomplicated influenza virus infection, and is suggestive of severe disease. All patients with clinical symptoms consistent with influenza virus infection (as noted above) and new onset shortness of breath warrant rapid and close evaluation and initiation of antiviral therapy. Where possible, oximetric assessment of blood oxygenation should be performed and arterial blood gas evaluation of PO2 may be considered. Clinical evidence of significant hypoxemia should trigger further assessment by a physician and testing to include a chest radiograph where possible. The chest radiograph frequently demonstrates bilateral if not four quadrant mixed alveolar/interstitial infiltrates that may be rapidly progressive and may require urgent intubation.

Other clinical signs noted in patients with severe disease have included hemoptysis, frothy pink sputum and purulent sputum with diffuse lung crackles, encephalopathic central nervous system dysfunction (including seizures and decreased level of consciousness), severe dehydration, renal failure, multiple organ failure, shock, severe rhabdomyolysis and myocarditis. Complicated infection may include exacerbation of underlying disease including asthma, chronic obstructive pulmonary disease, chronic liver disease, renal failure, diabetes, ischemic heart disease, congestive heart failure, etc. Laboratory findings typically found at presentation with severe disease include normal or low normal leukocyte counts (in the absence of bacterial superinfection) and evidence of rhabdomyolysis with elevated creatine kinase(1;2).

Early laboratory diagnosis of pH1N1 infection currently requires RT-PCR testing. In addition to standard testing of a nasopharyngeal swab, RT-PCR testing of tracheal aspirates is recommended for intubated patients to increase yield. A negative result in a severely ill patient warrants repeat testing within 48-72 hours. Rigid adherence to sample acquisition protocols is recommended even in the most severely ill patients.

Emerging surveillance evidence suggests that the occurrence and severity of life-threatening pH1N1 infection may be mitigated by initiation of antiviral therapy ideally within the first 48 hours. Initial treatment decisions should be based on clinical presentation and epidemiological data and should not be delayed pending laboratory confirmation.

Antiviral therapy

- Oseltamivir is the recommended first line antiviral agent for neuraminidase-sensitive influenza virus infection, ideally within the first 48 hours
- Antiviral therapy is recommended for all severely ill patients, even those presenting late (>48 hrs) after the onset of symptoms

- 10 days of antiviral therapy should be considered for severe pH1N1 infection requiring intubation
- An oseltamivir dose of 75 mg BID is appropriate; higher doses may be considered but are not specifically recommended.
- Zanamivir is recommended as the 2nd line anti-viral treatment for severe cases since it does not offer systemic therapy

Patients at high risk for progressive, complicated or severe infection and those presenting with progressive, complicated or severe infection require prompt initiation of antiviral therapy. pH1N1 is resistant to amantadanes but generally sensitive to neuraminidase inhibitors including oseltamivir and zanamavir.

Practitioners experienced in the treatment of severe pH1N1 infection have observed that, in the absence of early antiviral therapy, patients with diffuse pneumonitis progress rapidly following presentation and require intubation within 24 hours. Antiviral therapy has been shown to ameliorate influenza progression even when started >48 after symptom onset(3;4). Clinical experience to date also suggests that duration of treatment longer than 5 days may be required. Continuation of antiviral therapy for 10 days in critically ill patients should be considered unless clinical or virological data suggest otherwise.

A major concern has been the adequacy of gut absorption of oseltamivir among the critically ill who may frequently exhibit significant disruptions of bowel function including ileus. However, published studies(5) and unpublished research communications (courtesy, A Kumar) suggest consistent adequacy of gut absorption with blood levels comparable to those found in ambulatory patients receiving the same dose.

Zanamivir is inhaled and cannot be administered to patients unable to use the supplied inhalation device, and is not recommended for people with reactive airway disease. Product monographs will contain additional prescribing information. Zanamivir is not intended to be used in a nebulizer or mechanical ventilator as this has been associated with ventilator malfunction and the potential for fatal outcomes.
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/relenza_nth-aah-eng.php

Supportive Care

- No standard recommendation can be made for ventilatory support. Therapy must be highly individualized for a given patient at different time points in their disease evolution
- Standard pressure/volume limited, lung protective strategies are recommended as initial therapy
- Clinical experience suggests severely ill patients that do not respond to conventional volume cycled modes of ventilation may respond to pressure-cycled ventilatory modes and high frequency oscillation (HFO)
- Some centers have identified a potential role for ECMO but convincing evidence to support its use is not yet available
- Use of extraordinary strategies such as HFO or ECMO should only be considered by clinicians or centers experienced in their use
- A conservative or fluid restrictive strategy may be of benefit in the management of acute lung injury

Most elements of supportive care for patients with severe pH1N1 infection are similar to that for any critically ill patient in the ICU. Almost all patients with severe pH1N1 infection in ICU will have deficits in oxygenation and ventilation, and the duration of ventilation required in such patients may be prolonged (two to three weeks median time (1;2). A subset may also have shock and renal failure which may occur in part as a consequence of efforts to optimize oxygenation and effective mechanical ventilation(1;2). Based on previous experience with severe influenza infections (in addition to current pH1N1 infection reports), other significant but less frequently seen clinical disorders at presentation may include encephalitis (with or

without decreased level of consciousness or seizure activity)(6-10), cardiac injury (myocarditis, pericarditis, conduction defects)(11;11-14) and rhabdomyolysis(15-18).

Among ventilatory techniques, controlled mandatory ventilation may be less useful in severe cases. Experienced clinicians have noted the utility of pressure-cycled modes including pressure support at very high levels (25-35 cm of water), pressure control with inverse ratio, airway pressure release ventilation and HFO. However, the utility of any of these modalities at any given time point appears to be unpredictable at present, and should only be considered by clinicians and centers experienced in their use.

Another notable observation is that severely hypoxemic patients may require extraordinary doses of sedating agents for prolonged periods of time(19). Clinical experience suggests that this extraordinary need for sedation may persist in ventilated patients for weeks. In view of the rapid depletion of short-acting agent stores, long acting benzodiazepines, narcotics and major tranquilizers may be useful in moderating short-acting agent consumption.

Further, although paralytic agents may enable more effective ventilation, experience from several centers has suggested significant untoward effects with prolonged use of paralytic agents, such as prolonged muscle weakness requiring prolonged mechanical ventilation and rehabilitation. For this reason, paralytics are not generally recommended and if required should only be used only for short periods.

A conservative strategy of fluid management has been shown to be of benefit in the management of acute lung injury(20). Furthermore, experienced clinicians in one Canadian center have noted that diuretic therapy generating a degree of modest hypovolemia may be of benefit in treating refractory hypoxemia early in the course of severe diffuse pneumonitis(21).

ECMO is one modality that has seen a remarkable degree of clinical use. A recent paper has shown that use of ECMO in severe ARDS is associated with improved survival(22). Clinicians in Australia have recommended aggressive use of ECMO for H1N1 infected patients based on their recent experience(23). Canadian experience with this modality is limited and research continues to evolve(24). Use of ECMO would not be recommended by clinicians or in centers not experienced in its use.

Secondary Bacterial Pneumonia:

- Initial empiric antimicrobial therapy of suspected pH1N1 pneumonia/pneumonitis should include both oseltamivir and community-acquired pneumonia antibiotic therapy
- Discontinuation of antibiotic therapy may be considered if no bacterial pathogen is isolated within three days

With respect to progressive or severe pH1N1 infection, data is limited on the issue of bacterial co-infection as a cause of morbidity and mortality. Recent reports have suggested bacterial pneumonia caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* and Group A streptococci as major causes of death in two large sets of autopsy material examined(25;26). A significant minority of total *Staphylococcus aureus* isolates in the two reports were methicillin-resistant. Data on timing of secondary bacterial pneumonia was not available in these reports.

In a large Canadian series of progressive or severe pH1N1 infections requiring ICU admission, secondary bacterial pneumonia was seen in 24.4% of cases with *Staphylococcus aureus*, *Streptococcus pneumoniae*, Group A streptococci and *Escherichia coli* being the dominant pathogens(1). Examination of a subset of Manitoba data with more detailed information reveals that *Staphylococcus aureus* and *Streptococcus pneumoniae* were equally common at any point in the ICU stay. However, Group A streptococci species were usually seen at admission while gram negatives including *E. coli,* were typically seen after several weeks in ICU. The majority of secondary bacterial infections were seen after several weeks of being ventilated.

Infection control in ICU

- General guidance on infection prevention and control measures for health care workers can be found in the document entitled: **Guidance: Infection prevention and control measures for Health Care Workers in Acute Care Facilities** http://www.phac-aspc.gc.ca/alert-alerte/h1n1/hp-ps/ig_acf-ld_esa-eng.php. This guidance should be used in concert with existing infection control guidelines developed for or specific to each ICU setting

Viral shedding, as determined by the taking of NP swabs from previously confirmed pH1N1 cases after seven days following the onset of illness and testing these for influenza by RT-PCR, has been shown to be prolonged in hospitalized patients with seasonal influenza (27) and in pH1N1 infections(28;29). In one study, approximately 1/3 of patients continued to shed live virus at least one week after symptom onset (29). In another, 47% of patients continued to shed virus for 7 days or more and 8% for > 10 days following symptom onset despite therapy with oseltamivir(28).

Existing institution specific guidelines on infection control issues should be reviewed and adapted as required to ensure they reflect clinical realities in acute care settings (e.g. emergency rooms, ICU). Ventilators differ greatly, therefore health care workers need to be aware of the exhaust system functionality as filters are not always present. Appropriate personal protective equipment should be worn, and N95 respirators should be used during aerosol generating medical procedures (AGMP).

Infection prevention and control staff may consider discontinuation of isolation procedures when non-immunocompromised patients are PCR or viral culture negative and have demonstrated clinical improvement.

Other Critical Care Resources

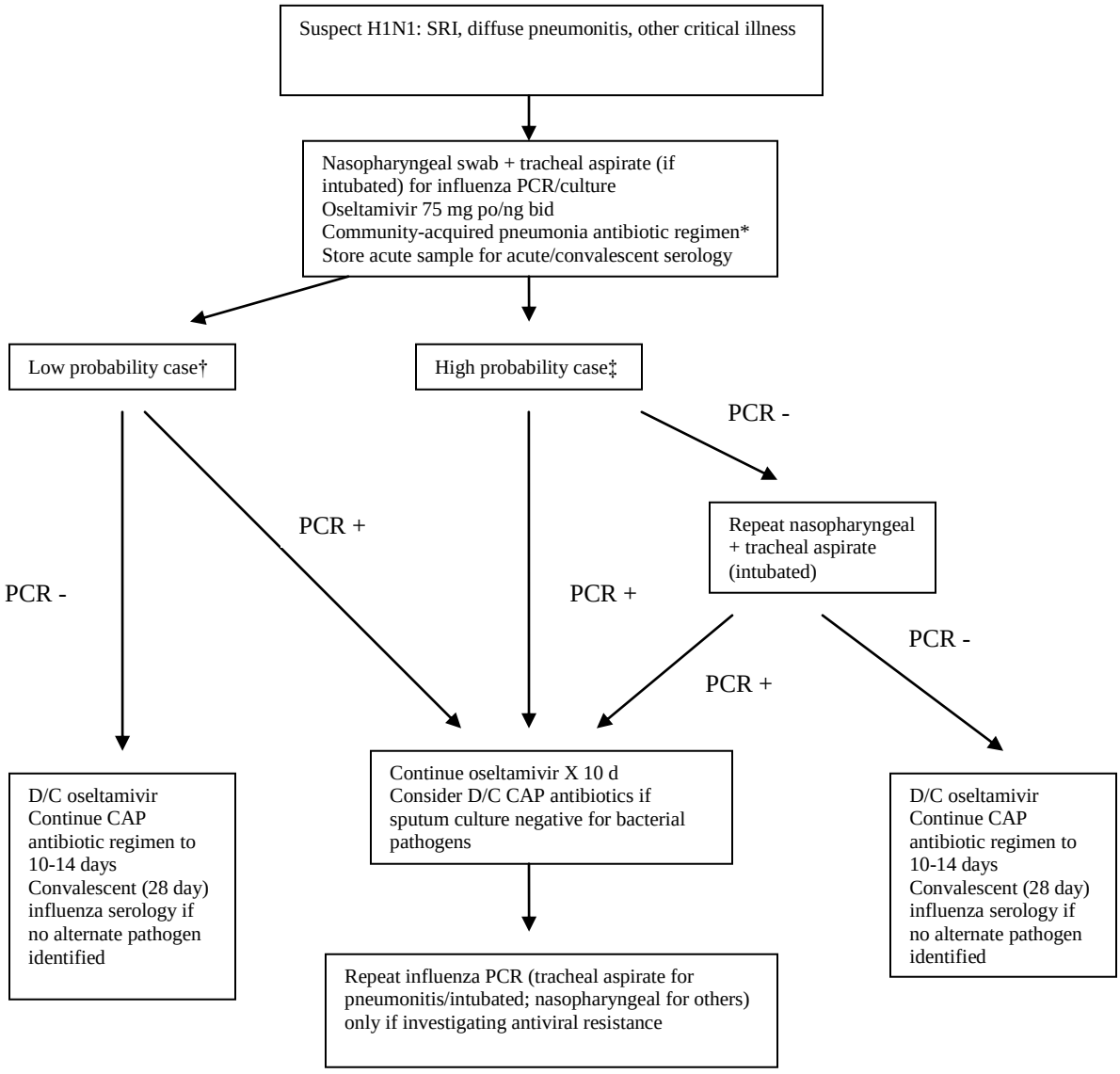
http://canadiancriticalcare.org/h1n1_index.htm

http://www.icu-pandemic.org

http://www.thoracic.org/sections/clinical-information/critical-care/salvage-therapies-h1n1/index.html

http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf

Figure 1: Clinical Management Recommendations for ICU



* recommended CAP antibiotic regimen should include a moderate to high level of activity for Staphylococcus aureus. Selection of antibiotics to cover methicillin-resistant Staphylococcus should be based on the prevalence of this organism in the community.

† Low probability case as per epidemiologic or clinical presentation

‡ High probability case as per epidemiologic or clinical presentation

Reference List

(1) Kumar A, Zarychanski R, Pinto R, Cook D, Marshall J, Lacroix J et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA*. In press.

(2) Dominguez-Cherit G, Lapinsky SE, Espinosa-Perez L, Pinto R, Macias AE, de la Torre A et al. Critically ill patients with influenza A (novel H1N1) in Mexico. *JAMA*. In press.

(3) Toovey S. First results from an Avian Influenza Registry. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy V533. 2009.
Ref Type: Abstract

(4) Zarychanski R, Stuart TL, Doucette S, Elliot L, Kumar A, Kettner J et al. Treatment delay, First Nation ethnicity and comorbidities are correlates of severe disease in patients infected with pandemic influenza A (H1N1). *CMAJ*. In press.

(5) Taylor WR, Thinh BN, Anh GT, Horby P, Wertheim H, Lindegardh N et al. Oseltamivir is adequately absorbed following nasogastric administration to adult patients with severe H5N1 influenza. *PLoS ONE 3(10):e3410* 2008.

(6) Horner FA. Neurologic disorders after Asian influenza. *New England Journal of Medicine 258(20):983-5,* 1958.

(7) Mellman WJ. Influenza encephalitis. *Journal of Pediatrics 53(3):292-7,* 1958.

(8) Blattner RJ. Neurologic complications of Asian influenza. *Journal of Pediatrics 53(6):751-3,* 1958.

(9) Neurological complications of Asian influenza. *Lancet 2(7036):32,* 1958.

(10) Thiruvengadam KV. Disseminated encephalomyelitis after influenza. *British Medical Journal 2(5161):1233-4,* 1959.

(11) Rowan T, Coleman FC. Myocarditis and adrenal failure in influenza. Report of a fatal case. *Journal 49:632-6,* 1959.

(12) Clough PW. Cardiac disturbances during the pandemic of influenza of 1918 to 1920. *Annals of Internal Medicine 49(5):1267-72,* 1958.

(13) Coltman CA, Jr. Influenza myocarditis. Report of a case with observations on serum glutamic oxaloacetic transaminase. *JAMA 180:204-8,* 1962.

(14) Hilderbrandt HM, Maassab HF, Willis PW, III. Influenza virus pericarditis. Report of a case with isolation of Asian influenza virus from the pericardial fluid. *American Journal of Diseases of Children 104:579-82,* 1962.

(15) Middleton PJ, Alexander RM, Szymanski MT. Severe myositis during recovery from influenza. *Lancet 2(7672):533-5,* 1970.

(16) Morton SE, Mathai M, Byrd RP, Jr., Fields CL, Roy TM. Influenza A pneumonia with rhabdomyolysis. [Review] [38 refs]. *Southern Medical Journal 94(1):67-9,* 2001.

(17) Simon NM, Rovner RN, Berlin BS. Acute myoglobinuria associated with type A2 (Hong Kong) influenza. *JAMA 212(10):1704-5,* 1970.

(18) Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. [Review] [87 refs]. *American Journal of Medicine 121(4):258-64,* 2008.

(19) Gin A, Kumar A, Zarychanski R, Honcharik N. Increased sedative and antibiotic use in H1N1 ICU Patients. Canadian Medical Association Journal . 2009.
Ref Type: Electronic Citation

(20) Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, DeBoisblanc B et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354(24):2564-2575.

(21) Funk DJ, Siddiqui F, Wiebe K, Miller RR, Bautista E, Jimenez E et al. Practical lessons from the first outbreaks: Clinical problems, obstacles and management strategies for severe pandemic (H1N1) 2009 influenza. *Crit Care Med*. In press.

(22) Peek M, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *The Lancet*. In press.

(23) Webb S. ECMO in ICU for H1N1. *JAMA*. In press.

(24) Freed DH, Henzler D, White CW, Fowler R, Zarychanski R, Arora RC et al. Extracorporeal lung suport for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. *Can J Anesthesia*. In press.

(25) anonymous. Surveillance for pediatric deaths associated with 2009 pandemic influenza A(H1N1) virus infection---United States, April--August 2009. *MMWR* 2009; 58((34)):941-947.

(26) anonymous. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A(H1N1)--United States, May--August 2009. *MMWR* 2009; 58:1-4.

(27) Lee N, Chan PKS, Hui DSC, Rainer TH, Wong W, Choi KW et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *JID* 2009; 200:492-500.

(28) Lye D, Chow A, Tan A, et al. Oseltamivir therapy and viral shedding in pandemic (H1N1) 2009. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy V1269c. 2009.
Ref Type: Abstract

(29) De Serres G, Rouleau I, Hamelin ME, et al. Shedding of novel 2009 pandemic H1N1 (nH1N1) virus at one week post illness onset. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy K1918a. 2009.
Ref Type: Abstract