Clinical Care Summary and Algorithm for Sporadic Human Cases of Influenza A H5N1

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This guideline and algorithm were put together by the Clinical Care Working Group for the Canadian Pandemic Influenza Committee. The document is intended to provide front-line clinicians with guidance on how to handle patients who may present with the Asian strain of highly pathogenic Influenza A H5N1 infection during the inter-pandemic period (Phase 3). This is ***not*** a guidance document for an influenza pandemic (Phase 6). If human-to-human transmission of H5N1 were to occur (Phase 4/5), public health authorities would provide updated guidelines. This clinical care summary is based on a review of the literature, current nationally approved guidance documents on emerging respiratory infections,[1] the new International Health Regulations,[2] and recommendations from infectious disease, public health and laboratory experts.

H5N1 is largely an infection of birds and is not highly contagious in humans. Until now, human cases of H5N1 have occurred sporadically in South East Asia, the Middle East and Africa and have almost always been associated with people coming in close contact with ill birds or their excreta. There have been no reports to date of medical or nursing staffs developing clinical H5N1 disease after caring for these patients.

How could sporadic cases occur?

There are at least 4 ways that a sporadic case could appear in Canada:

1. **A person infected with avian influenza from an H5N1-affected area could travel to Canada and present with illness.** The incubation period for H5N1 can be up to 10 days, so it is possible that someone could be asymptomatic when travelling from an affected area, and only show symptoms after arriving in Canada. This is the most likely route of infection.
2. **A farmer, veterinarian, culler, or others could have direct contact with infected domestic poultry, which had contact with H5N1 infected wild birds.** If the wild bird population in Canada were infected with H5N1 this could then spread to domestic poultry, especially free-range chickens. Canada has routine surveillance of the wild bird population. To date, surveillance has not detected the Asian strain of highly pathogenic H5N1 in the wild bird population in Canada, but it remains a risk.
3. **A hunter, wildlife researcher, those living in remote communities, or others could have direct contact with an H5N1 infected wild bird.** Wild birds infected in affected areas may transfer H5N1 through their migration flyways to wild birds in Canada. Once H5N1 is in the wild

[1] See the Public Health Agency of Canada's Emerging Respiratory Infections website for Health Professionals at: http://www.phac-aspc.gc.ca/eri-ire/index.html

[2] See the World Health Organization's International Health Regulations website at: http:/ www.who.int/csr/ihr/en/

bird population, it could be transferred to humans. However, to date, there has been no documentation of transmission from wild birds directly to humans.

4. **A person infected by an illegally imported bird with H5N1 (or contaminated bird products).**

What follows is the information clinicians need to know, so that when a patient who has a history and clinical presentation consistent with a sporadic case of H5N1, appropriate clinical and public health actions can be taken.

Maintain routine infection prevention and control practices

First and foremost, when seeing anyone with cough and a fever, ensure routine infection prevention and control practices are taken:

1. Screen all patients for cough and fever at reception.
2. If they have these symptoms, they should be:
    a. Given a surgical mask.
    b. Directed to clean their hands with soap and water or alcohol based hand rub.
    c. Seated at least a metre away from others or placed directly in an examining room.
3. Before examining the patient, protect yourself with *droplet precautions*:
    a. Clean your hands before and after examining the patient.
    b. Wear a mask and eye protection
4. After the patient has left, clean affected surfaces with a disinfectant.

Take a travel and contact history

Although highly unlikely, anyone who presents with a severe respiratory infection or influenza like illness could potentially have H5N1. This can be assessed by taking a travel and contact history according to the Canadian screening guidelines. To do so, **determine if either of the following occurred in the 10 days prior to onset of symptoms:**

1. **Travel to an affected area AND residence in or visit to an area/setting where sick or dead domestic poultry or wild birds have been reported**
2. **Close contract (within 1 metre) with an ill traveller from an affected area with known H5N1 in domestic poultry or wild birds**

To confirm where the current H5N1 affected areas are, visit the Public Health Agency of Canada website.[3]

Understand the pathology:

Avian influenza attacks the respiratory system first, but H5N1 can also be found in the blood, GI tract, liver, and kidneys. Death is usually by respiratory distress and multiple organ failure. The world-wide death rate of diagnosed cases has been about 60%. Most people were young and previously healthy.

[3] See: http://www.phac-aspc.gc.ca/h5n1/index-eng.php

Know the common clinical presentation

Typically, patients with H5N1 present with a new or worsening cough and an abrupt onset of fever over 38° Celsius. The clinical features of the initial human cases of H5N1, are summarized below:

Table 1: Clinical and Common Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission[4]

Clinical and Common Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission.*

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Age — yr					
Median	14–22	18.5	30	12.5	16.5–10.0
Range	2–58	1.5–45.0	12–41	1–75	5–20
Male sex — no./total no. (%)	19/41 (46)	33/54 (61)	3/8 (38)	12/38 (32)	9/16 (56)
Contact with poultry within previous 2 weeks — no./ total no. (%)	31/36 (86)	41/54 (76)	8/8 (100)**	31/38 (82)	8/8 (100)††
Time from onset of symptoms to hospitalization — days					
Median	6–8	5	6	3	5–6
Range	3–8	1–14	3–11	0–14	1–12
Clinical presentation — no./ total no. (%)					
Fever	41/41 (100)	54/54 (100)	8/8 (100)	34/38 (89)	15/16 (94)
Dyspnea	33/37 (89)	51/54 (94)	4/8 (50)	14/38 (37)	7/16 (44)
Cough	40/41 (98)	50/54 (93)	7/8 (88)	27/38 (71)	12/15 (80)
Pneumonia	41/41 (100)	54/54 (100)	8/8 (100)	23/38 (61)‡‡	14/16 (88)
Coryza	9/27 (33)	NR	NR	NR	2/14 (14)
Sore throat	13/41 (32)	NR	NR	26/38 (68)	14/16 (88)
Vomiting	5/31 (16)	6/54 (11)	NR	3/37 (8)	0/7 (0)
Diarrhea	16/31 (52)	6/54 (11)	NR	2/37 (5)	4/14 (29)
Depressed consciousness	NR	NR	NR	3/38 (8)	4/8 (50)
Seizures	NR	1/54 (2)	NR	NR	2/7 (29)
Headache	5/14 (36)	7/54 (13)	NR	19/38 (50)	7/15 (47)
Conjunctivitis	0/22 (0)	NR	NR	14/38 (37)	1/8 (12)
Myalgia	11/37(30)	7/54 (13)	NR	17/38 (45)	4/15 (27)
Leukopenia	17/22 (77)	41/49 (84)	NR	10/37 (27)	11/15 (73)
Lymphopenia	16/24 (67)	16/29 (55)	NR	4/25 (16)	7/13 (54)
Thrombocytopenia	13/24 (54)	29/45 (64)	NR	8/26 (31)	9/13 (69)
Increased aminotransferase levels	20/28 (71)	NR	NR	15/27 (56)	6/8 (75)
Deaths — no./ total no. (%)	32/41 (78)	41/54 (76)	7/8 (88)	15/38 (39)	9/16 (56)
Time from onset of symptoms to death — days					
Median	8–12	9	9	11.5	10–13
Range	4–30	5–19	8–19	6–32	9–17

* The presumed clade or subclade assignment is based on the known geographic distribution of the viruses and is not verified by individual patient data. Few sequences are available for human isolates in the public database for some countries. Multiple clades and subclades have circulated in China in poultry. NR denotes not reported.
† Data are from the WHO Writing Committee.[1]
‡ Data are from Sedyaningsih et al.[24]
§ Data are from Yu et al.[35] and Yu et al.[51]
¶ Data are from Abdel-Ghafar A (unpublished data). The lower mortality among Egyptian patients as compared with Indonesian patients in 2006–2007 could be related to the approximately 2-day shorter time to presentation and lower frequency of pneumonia among the Egyptian patients.
‖ Data for Turkey are from Oner et al.[21] Data for Azerbaijan were provided by the Ministry of Health.
** This number includes six of eight patients who visited live-bird markets but did not have known direct exposure to poultry.
†† Only one of eight patients had contact with poultry in Azerbaijan; exposures were to dead swans.
‡‡ Pneumonia did not develop in 2 of 12 adults (17%) and 13 of 26 children (50%) in Egypt.

Notify your local medical officer of health (MOH)

[4] Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus (2008) Current Concepts: Update on Avian Influenza A (H5N1) Virus Infection in Humans NEJM, vol.358 No.3.

If the person has a positive travel or contact history and you conclude that your patient may have H5N1, contact your local medical officer of health (MOH) immediately. It is a general requirement for all physicians to know the contact number of their local MOH .[5] Public health will conduct a more in-depth assessment to establish whether there is a significant epidemiologic link or not. If public health determines this is a possible or suspect case then further clinical and public action is required.

Work with public health to arrange for viral samples and oseltamivir

Managing a patient with H5N1 requires close collaboration of both the clinician and public health . It is considered a **joint responsibility** to ensure that:

- Throat and nasopharyngeal samples and serology are rapidly sent to the public health laboratory. Include the travel and contact history as well as contact information for yourself and the local medical officer of health.
- Oseltamivir treatment is started as soon as possible.

How these two actions are conducted will vary depending on the province or territory. However, the principle of a joint responsibility and clinicians working with public health to address H5N1 is applicable across Canada. Duplicate throat, nasopharyngeal and blood samples are recommended. If gastro-intestinal symptoms are present, submit a fecal sample for virology as well. Public health can help you obtain the right virology testing kit and get it to the appropriate public health laboratory. Point of care test kits or "rapid tests" are not effective for diagnosis. Timing is important; samples should not be sent to a commercial lab. Generally, samples sent by transport should be triple packaged and marked as a diagnostic specimen. [6] Alternatively, swabs may be collected in hospital.

Coordinate clinical and public health actions

The first suspect case of H5N1 in a person in Canada will need to be hospitalized to facilitate thorough investigation and management and will merit the involvement of an infectious disease specialist. When arranging for transfer to hospital, you will need to notify the paramedics and the hospital infection control staff beforehand of the provisional diagnosis, so that appropriate infection prevention and control measures may be taken. The initial diagnostic work-up includes a chest x-ray and a complete blood count. Sputum and blood cultures, electrolytes, urinalysis, AST, and stool samples for influenza should be ordered as indicated. Investigations should commence to rule out other causes. In light of the limited data on H5N1 patients, draft reporting forms from WHO should be used to collect data. [7]

Public health will take a detailed exposure history, conduct contact tracing, liaise with the public health laboratory and report to provincial or territorial health authorities. As with any severe respiratory illness of unknown origin, provincial public health authorities will notify the Public Health Agency of Canada (PHAC). It is PHAC's responsibility to report infectious diseases of potential international public health risk to the World Health Organization, as outlined in the International Health Regulations.

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[5] Local public health contact information can be obtained from: www.pandemic.cpha.ca/en/offices.html

[6] Consult your nearest public health laboratory for the latest transportation guidelines.

[7] Available at: http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html

Summary of clinical management

Clinical management is based on recent WHO guidelines.[8] Procedures should be undertaken in an airborne precaution or negative pressure room. During aerosol-generating procedures health care workers should wear eye protection, gowns, gloves and particulate respirators, such as an N-95 mask.[9] Real-time therapeutic monitoring of the virologic response by RT-PCR testing will help guide therapy.

Oxygen: Supplemental oxygen is essential to treat moderate to severe A (H5N1) illness. It is important to detect and treat hypoxia early to improve clinical outcome. Serial monitoring of oxygen saturation is indicated; if not available, oxygen therapy should be administered if there are signs of respiratory distress including an increased respiratory rate or an altered level of consciousness. SaO_2 should be maintained over 90%.

Antivirals: Oseltamivir is the primary treatment of choice based on trial evidence for seasonal influenza (when used within 48 hours of symptom onset) and observational data on H5N1 patients. The usual adult dose of oseltamivir is 75 mg twice a day for 5 days (a child's dose is determined by weight) and should be started as soon as possible. Based on evidence of prolonged viral shedding, oseltamivir treatment is still warranted when a patient presents after 48 hours of symptoms. Double dosage and longer duration (such as 150 mg twice a day for 10 days) may be considered, especially in patients with pneumonia or progressive disease. There is a concern that seriously ill patients may not be able absorb oseltamivir efficiently due to gastric stasis. In such patients, it may be worthwhile to consider the Special Access Programme for release of investigational intravenous neuraminidase inhibitors, such as intravenous zanamivir or peramivir.[10]

Antibiotics: If the patient has radiologic evidence of pneumonia, empiric treatment with antibiotics according to the latest guidelines for community-acquired pneumonia is indicated.[11] For patients who require admission to the intensive care unit this would usually include a combination of a β-lactam plus either azithromycin or a fluoroquinolone. Diagnostic work-up would include blood culture and sputum for Gram stain and culture. If no bacterioloic cause is found, empiric antibiotic treatment may be stopped. Use of prophylactic antibiotics is not warranted, but ventilatory support can increase the risk of a secondary bacterial infection. A prolonged fever and refractory clinical course may suggest a secondary pneumonia and should be confirmed by Gram stain and culture.

Ventilatory support: Invasive positive pressure ventilation (IPPV) is the preferred method of ventilatory support for patients with A(H5N1) infection complicated by acute respiratory distress syndrome (ARDS).

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[8] Ibid.

[9] Refer to Avian Influenza, Including influenza A(H5N1) in Humans: WHO Interim Infection Control Guideline for Health care Facilities at: http://www.who.int/csr/disease/avian_influenza/guidelines/infectioncontrol1/en/index.html

[10] Information on Health Canada's Special Access Programme can be obtained at: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3_e.html

[11] Mandell L, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27-S72.

Other: Acetaminophen given orally or non-steroidal anti-inflammatory drugs (NSAIDS) given orally or by suppository will help to reduce fever and provide comfort. Corticosteroids have not been shown to be of clinical benefit with the possible exception of low doses systemic corticosteroids for refractory septic shock complicating ARDS. Immunotherapy remains experimental.

Algorithm for Clinical Care of Sporadic Influenza A H5N1 Infection in Humans (Interpandemic Period)