

Guideline on prevention and control of H7N9 avian influenza human infection

Editorial Team, Journal of Thoracic Disease

J Thorac Dis 2013;5(S2):S168-S172. doi: 10.3978/j.issn.2072-1439.2013.05.17

H7N9 avian influenza human infection is an acute respiratory infectious disease caused by Influenza A virus subtype H7N9. Up until April 20, 96 cases of H7N9 were identified in China's Shanghai City, Zhejiang Province, Anhui Province, and Jiangsu Province, among which 18 died. All these cases remain sporadic, and no human to human infection has been identified among them so far.

Aware of the severity of the situation, the related committee and experts established two guidelines on Prevention and Control of H7N9 avian influenza human infection in March. One is "Technical Guidelines on Prevention and Control of Hospital-acquired Human Infection with Influenza A (H7N9) Virus" which are developed to guide the health care providers to improve the prevention and control for hospital-acquired human infection with influenza A (H7N9) virus, lower the risk of H7N9 nosocomial infections, and standardize the behaviors and services of medical staff. The other one is "Diagnosis and Treatment Protocol for H7N9 avian influenza human infection", providing up-to-date and practical information in terms of etiology, clinical manifestations, epidemiology, diagnosis and differential diagnosis, treatment of H7N9 patient.

This is a significant first step towards our goal for prevention and control of H7N9 avian influenza human infection.

Technical guidelines on prevention and control of hospital-acquired human infection with influenza A (H7N9) virus (2013 Edition)

These technical guidelines are developed to guide the health care providers to improve the prevention and control for hospital-acquired human infection with influenza A (H7N9) virus, lower the risk of H7N9 nosocomial infections, and standardize the behaviors and services of medical staff.

1. Basic requirements

1.1 The health care providers should establish early-warning system and develop emergency preparation plan and workflow based on the following considerations: (i) the epidemiology of human infection with influenza A (H7N9) virus; (ii) the source of infection, pathways of transmission, and susceptible populations; and (iii) the local real conditions;

1.2 The health care providers should provide relevant training for the medical staff, so as to improve their awareness and capacity in identifying, reporting, and managing the hospital-acquired H7N9 infection and enable the early detection, early diagnosis, early isolation, and early report;

1.3 The health care providers should enhance their monitoring for hospital-acquired infections. Any suspects or cases with human H7N9 virus infection must be immediately reported as required and the patient should be properly managed;

1.4 The health care providers must standardize their disinfection, isolation and protection policies to provide sufficient, necessary and qualified disinfection and protection equipment to the medical staff, so as to ensure that all the disinfection, isolation, and personal protection measures are sufficiently and efficiently implemented;

1.5 The health care providers must properly clean and disinfect the medical equipment, contaminated items, item surface, and ground in accordance with the *Technical Specifications for Implementing Disinfection in Hospitals*. Also, the health care providers must improve the ventilation (and air disinfection, if necessary) in their diagnosis and treatment zones according to *Best Medical Management Practices for Air Purification*;

1.6 The medical wastes from the diagnosis and treatment of patients with human H7N9 virus infection should be properly managed and disposed according to the *Medical Waste Management Regulations and Medical Waste Management Methods in Health Care Institutions*.

2. Prevention and control of hospital-acquired infections

2.1 Fever clinic

(I) A workflow consisting of isolation, transfer, and management of the suspected and confirmed cases should be established. The building layout and workflow design should meet the relevant requirements of the *Best Medical Management Practices for*

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Submitted May 01, 2013. Accepted for publication May 22, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Isolation. Adequate hand-washing facilities must be provided at the entry and exit to a fever clinic;

(II) The medical staff should follow the standard prevention principles during the diagnosis. They must wear surgical masks when contacting each patient and implementing strict hand hygiene measures. When contacting a suspected or confirmed patient, the medical staff must wear medical protective masks;

(III) The medical staff must be aware of the epidemiology and clinical features of human infection with influenza A (H7N9) virus and are able to take immediate isolation measures for the suspected or confirmed patients and timely report every case. After a patient is transferred out, terminal disinfection should be performed according to the Technical Specifications for Implementing Disinfection in Hospitals;

(IV) Medical staff must put on or take off protective equipment correctly as required when entering or leaving a fever clinic;

(V) The patients' caregivers and patients (if their conditions allow) must wear surgical masks.

2.2 Emergency

(I) Triage system must be established. A contingency plan covering the transfer-out and rescue of the critically ill patients should be established and updated, and then strictly implemented;

(II) A specific isolation zone should be established to allow the in-site isolation and management of the suspected/confirmed patients;

(III) The medical staff must carry out personal protection and hospital environment management in strict accordance with the standard prevention principles;

(IV) The diagnosis and treatment zones must have good ventilation conditions and be cleaned and disinfected regularly.

2.3 General wards

(I) Contingency isolation rooms should be available in the general wards for the isolation and management of the suspected/confirmed cases, and relevant working policies and workflow should be established. Sufficient disinfection facilities and personal protective equipment for managing acute respiratory infections should be available in these rooms;

(II) When a suspected or confirmed case is found in the ward, the relevant contingency plans and workflow must be initiated immediately to provide timely and effective isolation and rescue for the patient;

(III) The suspected or confirmed patient should be managed and cared by a special team of medical staff. Medical staff who are not directly involved in the management should be restricted from entering the ward. If condition allows, the patients should be treated in negative pressure rooms or transferred to a special hospital with appropriate isolation or treatment capabilities. After a patient is transferred out, terminal disinfection should

be performed according to the Technical Specifications for Implementing Disinfection in Hospitals.

2.4 Special wards for patients with suspected or confirmed human infection with influenza A (H7N9) virus

(I) The building layout and workflow design should meet the relevant requirements of the Best Medical Management Practices for Isolation;

(II) All the suspected or confirmed patients should be immediately isolated, and the suspects and cases should be placed in separated rooms. The suspects should be isolated in a single room. The etiologically confirmed patients with the same disease type can be placed in the same room;

(III) According to the transmission pathways of influenza A (H7N9) virus, contact or droplet precautions should be taken in addition to the standard preventive measures. These measures may include:

(i) Medical staff must put on or take off protective equipment correctly according to the Best Medical Management Practices for Isolation when entering or leaving an isolation ward;

(ii) In principle, the patients' activities should be restricted within the isolation wards. If a patient needs to leave the isolation ward or isolation zone, he/she must take appropriate protective measures (e.g., wearing a surgical mask) to avoid cross-infection;

(iii) Stethoscope, thermometer, blood pressure monitors, and other medical devices for the suspects and cases must be used in a patient-specific manner. If the medical devices are not used in a patient-specific manner, they must be thoroughly cleaned and disinfected;

(iv) The visiting policies must be strictly implemented. In principle, no caregiver is allowed.

2.5 Protection of medical staff

(I) The medical staff should take contact and droplet precautions based on the transmission pathways of the infection in accordance with the standard protection principles;

(II) The personal protective equipment used by the medical staff must meet the relevant criteria issued by the Chinese government;

(III) The medical staff must timely perform hand hygiene before and after each contact with the patients in accordance with the Standard for Hand Hygiene for Healthcare Workers;

(IV) The medical staff must take appropriate protective measures according to the level of risk for infection:

(i) The medical staff must wear non-sterile gloves when contacting blood, other body fluids, secretions, excretions, and vomit of the patients and the contaminated items and wash their hands after taking off the gloves;

(ii) When there is a risk of spraying/splattering of blood, other body fluids, excretions or secretions, the medical staff must wear surgical masks (or respirators), goggles, and gowns;

(iii) When performing endotracheal intubation for the

suspects or cases, the medical staff must wear medical protective masks, goggles, and gowns;

(iv) The individual protective equipment such as surgical masks, medical protective masks, goggles, and gowns that have been contaminated by the patients' blood, other body fluids, and/or secretions must be timely changed;

(v) The individual protective equipment should be properly put on or taken off. After taking off the gloves or gowns, the medical staff must wash or disinfect hands immediately;

(vi) The medical staff must be protected from being accidentally stabbed by sharps;

(vii) The used medical equipment and instrument must be properly cleaned and disinfected according to the Technical Specifications for Implementing Disinfection in Hospitals.

2.6 Patient management

(I) The suspects and cases must be timely isolated, and be specifically guided to enter the isolation wards via the assigned route;

(II) If the condition allows, the patients must wear surgical masks. The patients should be instructed to cover nose and mouth with a tissue when coughing or sneezing. After contacting respiratory secretions, the patients must wash hands with regular detergent or disinfect hands with hand disinfectant;

(III) After a patient is discharged or transferred out, terminal disinfection should be performed according to the Technical Specifications for Implementing Disinfection in Hospitals;

(IV) The corpses of deceased patients must be timely handled. The corpse should be bounded with a double-layer fabric, wrapped into a double-layer plastic bag, and then sent directly by a special vehicle to a designated place for cremation. If cremation is not feasible due to ethnic or religious concerns, the corpses should be buried deep as required after having been handled as described above.

Diagnosis and treatment protocol for H7N9 avian influenza human infection (First Edition, 2013)

H7N9 avian influenza human infection is an acute respiratory infectious disease caused by Influenza A virus subtype H7N9. Since February 2013, a series of severe pneumonia cases with unknown cause(s) have been reported in China's Shanghai City, Anhui Province, and Jiangsu Province. Among them 3 were confirmed to be with H7N9 avian influenza human infection and 2 died. All these three cases were sporadic, and no epidemiological association has been identified among them.

1. Etiology

Avian influenza (AI) virus belongs to the Influenza A genus

of the orthomyxoviridae family. The viruses are highly pleomorphic and enveloped, with the spherical virions ranging in size from 80-120 nm in diameter. Their genome is a segmented negative-strand RNA. The subtypes are identified by the presence of proteins on the surface of the virus. The two proteins of importance are hemagglutinin (H) and neuraminidase (N). There are 16 different H antigens (H1 to H16) and nine different N antigens (N1 to N9). The avian influenza viruses mainly infect birds, but can also cause disease in humans, swine, equine, mink, and marine mammals. The avian influenza virus subtypes that can infect human include H5N1, H9N2, H7N7, H7N2, and H7N3. The reported subtype in China this year is H7N9. The H7N9 is a new reassortant virus, with its internal gene segments derived from an earlier H9N2 avian influenza virus.

Most avian influenza viruses are heat-sensitive. They can survive at low temperature but will be inactivated after heating at 65 °C for 30 min or boiling (100 °C) for 2 min. The viruses can survive in low-temperature faeces for one week and in 4 °C water for one month. They have certain resistance against the acidic environment (pH as low as 4.0). In the presence of glycerol, the viruses can keep alive for more than one year.

2. Epidemiology

2.1 Source of infection

The source of infection remains unclear. According to the previous experiences and the epidemiological investigations for the cases, birds carrying H7N9 avian influenza virus as well as their secretions or excretions may be the source of infections.

2.2 Route of transmission

The virus may be transmitted through the respiratory tract or by exposing to the secretions or excretions of the infected birds. Direct exposure to the virus can also result in infection. There is apparently no evidence of human-to-human transmission.

2.3 Susceptible populations

No definitive evidence has demonstrated that human is susceptible to influenza A (H7N9) virus. All the confirmed cases were adults.

2.4 High-risk populations

Currently the high-risk populations include individuals who are involved in the slaughter, processing, and sale of poultry products and those who have exposed to birds one week before disease onset.

3. Clinical manifestations

According to the incubation period for influenza and the case

investigation results, the typical incubation period of influenza A (H7N9) virus is 7 days.

3.1 General manifestations

Patients generally have flu-like symptoms such as fever and cough (with small quantities of phlegm), which may be accompanied with headache, muscle aches, and general malaise. The disease progresses rapidly in critically ill patients, manifested as severe pneumonia. Their body temperature is maintained at 39 °C, along with difficulty in breathing. Hemoptysis may occur in some patients. The patients can rapidly develop acute respiratory distress syndrome, mediastinal emphysema, sepsis, shock, unconsciousness, and acute kidney injury.

3.2 Laboratory tests

(I) Routine blood tests. WBC count is generally normal or lower. Severe cases often have decreased leukocytes and lymphocytes, and may have low platelet levels;

(II) Blood biochemistry. In most patients, the levels of creatine kinase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase elevate, C-reactive protein increases, and myoglobin may also rise;

(III) Etiological studies:

(i) Nucleic acid detection. The respiratory specimens (e.g., nasopharyngeal secretions, oral gargle, tracheal aspirate material, or airway epithelial cells) are collected to detect H7N9 avian influenza virus nucleic acid using real time PCR (or RT-PCR);

(ii) Virus isolation. The influenza A (H7N9) virus can also be directly isolated from the patients' respiratory specimens.

3.3 Chest radiograph

Chest radiograph of patients with pneumonia may display patchy changes in lungs. The disease progresses rapidly in critically ill patients, showing multiple ground-glass opacities and pulmonary consolidation in both lungs. A small amount of pleural effusion may be found in some cases. The lesions are widely distributed when ARDS occurs.

3.4 Prognosis

Human infection with influenza A (H7N9) virus has poor prognosis. Prognostic factors may include age, underlying disease, and complications.

4. Diagnosis and differential diagnosis

4.1 Diagnosis

A diagnosis of H7N9 avian influenza human infection may be made based on the epidemiological, clinical, and laboratory findings. For patients with unknown epidemiological history, the diagnosis may be made based on clinical manifestations, auxiliary examinations, and laboratory test results, particularly if the

influenza A (H7N9) virus is directly isolated from the patients' respiratory specimens or if test for H7N9 avian influenza virus nucleic acid shows positive results.

(I) History of exposure: the patient has exposed to birds and their secretions/excretions one week before disease onset;

(II) Diagnostic criteria:

(i) Suspected cases: individuals who meet the above described clinical symptoms and present the typical findings in routine blood test, blood biochemistry, and chest X-ray; positive for universal Influenza A primer and the possibility of seasonal influenza is ruled out; and has a history of exposure;

(ii) Confirmed cases: meeting the diagnostic criteria for the suspected cases; the influenza A (H7N9) virus is directly isolated from the patients' respiratory specimens; or, test for H7N9 avian influenza virus nucleic acid shows positive results.

Severe cases: patients with pneumonia accompanied with respiratory failure or other organ failure are defined as severe cases.

4.2 Differential diagnosis

H7N9 avian influenza human infection should be distinguished from human infection with the highly pathogenic avian influenza A virus (H5N1), seasonal influenza [including influenza A (H1N1)], bacterial pneumonia, severe acute respiratory syndrome (SARS), novel coronavirus pneumonia, adenovirus pneumonia, chlamydia pneumonia, and mycoplasma pneumonia. The differential diagnoses rely mainly on pathogenic examination.

5. Treatment

5.1 The clinically diagnosed and confirmed patients with H7N9 avian influenza human infection must be properly isolated and treated

5.2 Symptomatic treatment Oxygen inhalation, antipyretics, cough suppressants, and expectorants may be applied

5.3 Treatment with antiretroviral drugs Antiretroviral drugs must be applied as soon as possible

(I) Neuraminidase inhibitors: Oseltamivir or zanamivir has shown certain efficacy in treating H5N1 and H1N1 avian influenza human infections, and therefore is supposed to be effective for H7N9 avian influenza human infection. The recommended oral dose of oseltamivir for adult is 75 mg (150 mg for severe cases) twice daily for 5-7 days. The recommended dose of zanamivir for adult is 10 mg, inhaled, twice daily;

(II) Ion channel M₂ blockers: laboratory experiments have shown that the virus is resistant to both amantadine and rimantadine, and therefore the ion channel M₂ blockers should not be applied alone.

5.4 Traditional Chinese medicine

(I) The epidemic toxin invades the lung and the lung loses its

capability to disperse and descend Qi

Symptoms: fever, cough with little phlegm, headache, and muscle and joint pain.

Treatment: clearing away heat and dispersing lung.

Recommended prescriptions:

Mulberry leaves, Honeysuckle, Forsythia, Fried almonds, Gypsum fibrosum, Anemarrhena, Reed rhizome, Artemisia annua, Scutellaria, and Raw licorice.

Decoction was orally taken once or twice (every 4-6 hours) a day with water.

Addition or subtraction: for patients with severe cough, Loquat leaf and Zhejiang Fritillaria can be added.

Proprietary Chinese medicines: clearance and Detoxification Capsule, Lianhua Qingwen Capsule, and Qing Kai Ling Injection.

(II) Retention of Epidemic Toxin in the Lung; shock.

Symptoms: high fever, cough, a small amount of sputum that is difficult to spit out, breathlessness, hemoptysis, cold limbs, dripping cold sweat, uneasiness, and even coma and delirium.

Treatment: clearing Lung, detoxication, elimination of pathogen, and support of resistance.

Recommended prescriptions:

Mix-fried ephedra, Fried almonds, Gypsum fibrosum, Anemarrhena, Houttuynia, Scutellaria, Fried Gardenia, Polygonum cuspidatum, Cornus, and Heterophylla.

Decoction was orally taken or via nasogastric tube once or twice (every 4-6 hours) a day with water.

Addition or subtraction: For patients with high fever, trance, and even coma and delirium, Angongniuhuang Pill may be added. For patients with cold limbs and dripping cold sweat, Ginseng, Radix aconiti praeparata, Calcined dragon bone, and Calcined oyster may be added. For patients with hemoptysis, Radix paeoniae rubra, Agrimony, and Chinese arborvitae twig and leaf may be added. For patients with cyanotic lips, Radix notoginseng, Motherwort, Astragalus, and Angelica tail may be added.

Proprietary Chinese medicines: Shen Mai Injection may be applied.

5.5 Providing supportive care and preventing complications

Ask the patients to take good rest and drink more water. Provide sufficient nutrition, particularly easy-to-digest diets. Any potential complication must be closely monitored and prevented. The antimicrobial drugs are used only when there is confirmed secondary bacterial infection or when there is sufficient evidence prompting the presence of secondary bacterial infection.

5.6 Treatment of severe cases

The severe cases must be hospitalized. Patients with respiratory dysfunction should be provided with oxygen inhalation and other respiratory supports. Patients with other complications must be actively treated with appropriate measures.

(I) Respiratory support:

(i) Mechanical ventilation: the disease progresses rapidly in severe cases and may develop into ARDS. Mechanical ventilation for severe cases may follow the principles of mechanical ventilation for ARDS:

(a) Non-invasive positive pressure ventilation: for patients with respiratory distress and/or hypoxemia, non-invasive ventilation may be attempted at the early stage. However, the severe cases respond poorly to non-invasive ventilation and must undergo invasive ventilation as early as possible;

(b) Invasive positive pressure ventilation: since some patients may develop barotrauma during ventilation, the lung-protective mechanical ventilation strategies in ARDS should be applied.

(ii) Extracorporeal membrane oxygenation (ECMO): When the conventional mechanical ventilation can not maintain satisfactory oxygenation and/or ventilation, ECMO may be applied, if feasible;

(iii) Others: if the conventional mechanical ventilation can not maintain satisfactory oxygenation, prone ventilation or high-frequency oscillatory ventilation (HFOV) may be applied.

(II) Other treatment: in addition to respiratory support, the functional status of other organs must also be closely monitored and appropriately treated. Also, complications, particularly hospital-acquired infections, must be prevented and timely treated.

6. Miscellaneous

Measures for controlling hospital-acquired infections in health care facilities providing treatment for patients with H7N9 avian influenza human infection must be strictly standardized. In accordance with the principles of standard prevention, these health care providers must take corresponding prevention and control measures based on the routes of disease transmission. For detailed stipulations, please refer to the Technical Guidelines on Prevention and Control of Hospital-acquired Human Infection with Influenza A (H7N9) Virus (2013 Edition).

Acknowledgements

Disclosure: The authors declare no conflict of interest.



Cite this article as: Editorial Team. Guideline on prevention and control of H7N9 avian influenza human infection. *J Thorac Dis* 2013;5(S2):S168-S172. doi: 10.3978/j.issn.2072-1439.2013.05.17