Diagnostic and treatment protocol for human infections

with avian influenza A (H7N9)

(2nd edition, 2013)

Human infections with avian influenza A (H7N9) are known to cause acute and severe respiratory illness and death. The first known human case became ill on February 19, 2013 and through April 11, 2013 38 cases with nine deaths have occurred, all in Anhui, Jiangsu, Shanghai, and Zhejiang. The cases are distributed in a sporadic manner.

It is recommended to detect early, report early, diagnosis early and treat early severely ill patients with efficacious medicines, emphasizing the comprehensive effects from both traditional Chinese medicine and Western medicine. These measures play a vital role in effective prevention and control, improving the cure rate, and reducing mortality related to avian influenzas A (H7N9).

Ⅰ. Etiology

Avian influenza viruses belong to the family Orthomyxoviridae of the influenza A virus genus. Avian influenza A virus particles are pleomorphic, its spherical diameter is between 80 to 120 nm with the presence of an envelope. The genome consists of eight segments of negative-sense single-stranded RNA molecules. Based on the antigenic properties of the hemagglutinin (HA) and neuraminidase (NA) glycoproteins, influenza A viruses are classified into 16HA（H1～H16）and 9 NA (N1～N9）subtypes. In addition to infecting birds, avian influenza A viruses also are known to have infected humans, swine, horses, mink, and various marine mammals. While many different subtypes of avian influenza A viruses have infected humans, the subtypes known to more commonly cause human disease include H5N1, H9N2、H7N7、H7N2、and H7N3. This reported subtype is H7N9; this is a novel genetic reassortment from an internal gene of an avian influenza A (H9N2) virus.

Avian influenza viruses are sensitive to heat and strongly resistant to low temperature. They can be inactivated either by heating for 30 minutes at 65℃ or boiling for two minutes. The virus can survive in feces for 1 week at low temperatures, and also can survive in 4℃ water for 1 month. It has some resistance to alkaline environments, and can survive at pH4.0. The virus can survive more than 1 year if it is preserved with glycerol.

Ⅱ Epidemiology

1. **Origin of transmission**. Avian influenza A (H7N9) has been isolated from the bodily fluids and excreta of poultry. These viruses are highly congenetic with human

infections with avian influenza A (H7N9) virus. The source of transmission may be avian influenza A (H7N9) infected poultry. Through April 11, 2013, there has been no definitive case of human-to-human transmission.

2. **Route of transmission**. Influenza A viruses can be transmitted through the respiratory tract, and can also be contracted through close contact with the bodily fluids and excreta of poultry, or direct contact with the virus.

3. **High risk population**. Persons with ILI and a history of contact with poultry within 1 week of the onset of illness, especially a history of having worked on poultry feeding, transportation, selling, slaughter, or processing are more likely to be infected with avian influenza A (h7N9).

Ⅲ Clinical Manifestations

Based data from investigations of avian influenza A (H7N9) cases through April 11, 2013, the incubation period is generally within seven days.

1. Symptoms, physical signs and clinical characteristics

Patients typically present with influenza-like illness (ILI) with symptoms such as fever, cough with little to no sputum production, and accompanied by headache, muscular soreness, and general malaise. Patients can develop severe disease rapidly. In those who develop it, severe pneumonia occurs in 5-7 days. Most of these cases with severe pneumonia have a persistent temperature over 39℃, difficulty breathing, and may be accompanied by hemoptysis. Some rapidly progress to acute respiratory distress syndrome (ARDS), sepsis, shock, and multi-organ dysfunction syndrome. Complications to date have included pneumomediastinum and pleural effusion.

2. Laboratory examination

2.1 Blood tests The total number of white blood cells is generally neither extremely high or low, but most patients with severe disease have exhibited leukopenia, lymphopenia and thrombocytopenia.

2.2 Blood chemistries Most patients have had an increase of creatine kinase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and C react protein. Myoglobin may rise also.

2.3 Etiology and related testing Respiratory tract samples (such as nasopharyngeal secretions, concentrated oral rinse culture, tracheal aspirates and respiratory epithelial cells) must be collected before antiviral treatment is started., Medical Institutions who have a laboratory that can test for avian influenza A (H7N9) infection should do so as soon as possible. If on site testing is not available, then should send the clinical samples to the institution designated to test their samples.（1）Influenza A virus antigen screening: Can use a rapid test kit in the clinic to test for the presence of influenza A viruses. Only a screening test.（2）Nucleic acid testing PCR testing is done in specialized, designated laboratories and can detect avian influenza A (H7N9) virus.（3）Viral isolation Viral isolation is performed on respiratory tract specimens in

specialized, designated laboratories. This is the gold standard for diagnosing infection with avian influenza A (H7N9) virus.（4）Serology Two paired sera collected at least four weeks apart that demonstrate a four-fold or greater increase in the titer of the antibody against avian influenza A (h7N9) indicates acute infection with this virus. Again, this is done in specialized, designated laboratories.

3. Chest radiographs Pneumonia caused by influenza A (H7N9) infection results in abnormal chest radiographs. Abnormalities seen include a ground glass appreanceof the lung, severe patients Lesions progress quickly, A double lung multiple ground glass shadow and the image of consolidation of the lung, accompanied by a small amount of pleural effusion, Lesions are widely distributed when in ARDS.

4. Prognosis. People infected with avian influenza A (H7N9) virus who become critically ill have an extremely poor prognosis. Prognostic factors may include the patient's age, underlying diseases and complications.

Ⅳ. Diagnosis and differential diagnosis

1.Diagnosis: Infection with avian influenza A (H7N9) virus is suspected on the basis of clinical presentation and a history of exposure to persons with an acute respiratory infection. As of this writing other high risk factors for infection are not well understood. The clinical presentation is that of any of a number of acute febrile respiratory diseases including influenza caused by other influenza viruses; i.e., fever, cough, coryza, difficulty breathing. Infection with avian influenza A (H7N9) virus is confirmed with a positive laboratory test. A naso-pharyngeal swab should be collected and it can be tested for avian influenza A (H7N9) virus using PCR or viral isolation. Dynamic paired sera can be collected at least four-weeks apart and tested for avian influenza A (H7N9) virus specific antibody levels. A four-fold or greater increase in these antibody levels is diagnostic.

1.1 Epidemiologic history. Record exposure history to persons ill with an acute respiratory infection and exposure history to poultry their blood and bodily fluids.

1.2 Diagnostic criteria

a) Suspected case: clinical symptoms consistent with acute influenza (fever, cough, coryza, difficulty breathing) and a laboratory test positive for infection with an untyped influenza A virus or with a history of contact with a confirmed or suspected case.

b) Confirmed case: clinical symptoms consistent with acute influenza (fever, cough, coryza, difficulty breathing) or with a history of contact with a confirmed or suspected case and a laboratory test positive for avian influenza A (H7N9) virus; PCR, viral isolation or a four-fold or greater increase in serum antibodies specific for this virus isolated in paired sera.
Severe case: a confirmed case with pneumonia complicated by respiratory failure or other organ failure.

2. Differential diagnosis: The differential diagnosis is the same as for other influenza viruses; all causes of acute respiratory infection should be considered. but the more

likely ones are other influenza viruses including highly pathogenic H5N1 avian influenza and seasonal influenza (including pH1N1 2009), other viral cause such as coronoviruses and adenoviruses and bacterial causes including mycoplama and chlamydia. The patient's age, underlying medical state and exposure history determine the likelihood of each diagnosis. The diagnosis depends ultimately on the results of tests for specific pathogens.

Ⅴ. Treatment

1. Suspect and confirmed cases should both be placed in an isolation room with respiratory and enteric precautions.
2. Symptomatic treatment. Oxygen, antipyretics and expectorants as indicated.
3. Anti-viral treatment. An appropriate antiviral drug regimen for influenza should be administered as soon as the diagnosis of avian influenza A (H7N9) is entertained. Do not wait for the results of definitive tests for infection with this virus to initiate therapy. (see attached file).

3.1 Principles of anti-viral treatment

(1) Before the use of antiviral drugs, respiratory specimens should be collected.

(2) Antiviral drugs for influenza should be initiated within 48 hours of symptom onset. Focus on the following populations:

①Patients infected with avian influenza A (H7N9) virus;

②ILI cases with a rapid test for influenza A positive;

③ILI cases with a negative rapid test for influenza A or without a test, but having one or more of the following:

A. Close contacts including health care workers; one of a cluster of ILI cases of unknown etiology or exposure to poultry within the last week.

B. An underlying medical condition associated with a higher risk of severe disease from infleunza, including but not limited to cardiopulmonary disease, old age or pregnancy;

C. Rapid progression of the illness. and

D. Pneumonia of unknown etiology consistent with influenza.

(3) If more than 48 hours have passed since symptom onset, anti-viral drugs may still provide some benefit and should be considered in cases with severe disease or deterioration.

3.2 Neuraminidase inhibitors (please see the links below for more complete information on the drugs below)

(1) Oseltamivir: adult dose is 75mg twice daily, in severe cases the dose may be doubled, for 5-7 days. For children one year and older dose by body weight as follows:

less than 15 KG 30mg twice daily; 15-23kg 45mg twice daily; 23-40kg 60mg twice daily; 40kg and more 75mg twice daily. For children with difficulty swallowing capsules, may use oseltamivir suspension.

奥司他韦（Oseltamivir）

Chinese

http://www.roche.com.cn/fmfiles/re7185004/Tamiflu_approved.pdf

English

http://www.tamiflu.com/tamiflu-for-adults;jsessionid=C71B61A4C5676C22330B4BA0F299D8E0.gxeTam-m1

(2) Zanamivir: For persons seven years and above, the dose is10 mg twice daily (every 12 hours) inhaled.

扎那米韦（Zanamivir）

Chinese

http://www.gsk.tw/PDF/medicines/RELENZA-2.pdf

English

http://www.gsk.ca/english/docs-pdf/product-monographs/Relenza.pdf

(3) Peramivir: In severe or refractory cases or when oral administration is not possible, may use peramivir sodium chloride injection. The daily adult dose is 300-600mg via intravenous infusion, and it is administered for 1-5 days of treatment. There is limited clinical experience with peramivir so extra vigilance monitoring for adverse reactions is indicated.

帕拉米韦（Peramivir）

Chinese

http://wenku.baidu.com/view/b4ae4f3cee06eff9aef80776.html

English

http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm187811.pdf

Mild cases should be prescribed oseltamivir or zanamivir. Whether to extend the course of treatment should be based on the individual patient's response to therapy, his condition and laboratory results suggesting drug resistance.

3.3 ***Ion channel M2 blockers:*** is not recommended to use amantadine or rimantadine monotherapy because of widespread resistance.

4 Chinese traditional medicine treatment

4.1 For patients with fever, cough, scanty sputum, dyspnea and leukopenia, as well as suspect and confirmed cases of avian influenza A (H7N9):
These symptoms indicate a pulmonary infection and result in compromised pulmonary function.

Syndromes: fever, cough, scanty sputum, headache, muscle and joint pain.

Signs: red tongue with thin tongue coating, slippery and rapid pulse.

Treatment: clear heat and poison from the body, diffuse the lungs to relieve cough.

Reference prescription and dosage: Yin Qiao San and white tiger elixir.
Honeysuckle 30g, forsythia 15g, fried almonds 15g, raw gypsum 30g
Anemarrhena 10g, 15g mulberry leaves, reed rhizome 30g, 15g

Artemisia annua Scutellaria 15g, raw licorice 6g
Dissolve and boil in water, 1-2 does daily, take orally every 4-6 hours.
Modified prescription for cases with severe cough: add loquat leaf, Fritillaria.
Synthetic traditional medicine: Shufeng detoxification capsules, Lianhuaqingwen capsules, Jinlianqingre effervescent tablets can provide treatment of clear heat and poison in the body, diffuse the lung to suppress cough.

Chinese medicine injection: Xiyanpin injection, Reduning injection, Shen Mai injection.

4.2 For patients with high fever, Acute Respiratory Distress Syndrome (ARDS), or septic shock:

These symptoms indicate toxins have accumulated in the lungs and result in compromised pulmonary function.

Syndromes: High fever, cough, scanty sputum with difficulty coughing, stuffiness and shortness of breath, hemoptysis, or cough with pink frothy sputum, with cold hands and feet, convulsions, and even delirium and coma.

Signs: Dark red tongue, weak or undetectable pulse.
Treatment: detoxification to relieve the burden of lung, maintain and support body functions
Reference prescription and dosage: Xuanbai Cheng Qi Tang decoction and Senate dogwood decoction.
Raw rhubarb 10g, Trichosanthes 30g, fried almonds 10g to fry Tinglizi 30g
Raw gypsum 30g, Raw gardenia 10g, Polygonum cuspidatum 15g, radish seed 15g, Cornus 15g, American ginseng15g
Dissolve and boil in water, 1-2 doses daily, take orally or nasal feeding every 4-6 hours.

Modified prescription:
For patients with high fever, altered consciousness, and even delirium or coma, add An Gong Niu Huang Pill ;
For patients with cold extremities or profuse sweating, add gun aconite, calcined keel, calcined oyster;
For patients with hemoptysis, add red peony root, Agrimony, credit leaves;
For patients with cyanotic lips, add motherwort, astragalus, angelica.
Synthetic traditional medicine: Shen Mai injection, Shenfu Injection, Xiyanping injection, Reduning injection.

4.3 The above mentioned Chinese traditional medical decoctions, synthetic medicines and injections should not be used to prevent disease.

5 Strengthen supportive treatment and prevent complications.

Rest, drink plenty of water, and eat nutritious food. Observe and monitor patients vigilantly to prevent complications. Antimicrobial drugs should be used when there is sufficient evidence of secondary bacterial infection only.

6 Treatment of severe cases: for patients with respiratory dysfunction, inspired oxygen and other respiratory support should be provided. Proper treatment for other complications must also be provided.

6.1 Respiratory support:

6.1.1 Mechanical ventilation: Severe cases can progress rapidly and sometimes develop acute respiratory distress syndrome (ARDS). Mechanical ventilator support is usually indicated once ARDS develops.

6.1.1.1 Noninvasive positive pressure ventilation: For patients at an early stage of respiratory distress and / or hypoxemia, noninvasive ventilation can be considered, but for severe cases that do not improve with noninvasive ventilation, invasive mechanical ventilation should be considered.

6.1.1.2 Invasive positive pressure ventilation: Given that some patients are more prone to barotrauma, the ARDS protective ventilation approach should be adopted.

6.1.2 Extracorporeal membrane oxygenation (ECMO): ECMO is recommended when oxygenation and / or ventilation cannot be maintained by conventional mechanical ventilation.

6.1.3 Other methods: Prone position ventilation or high-frequency oscillatory ventilation (HFOV) should be considered when oxygenation cannot be maintained by conventional mechanical ventilation.

6.2 Circulatory support: Continuous monitoring of the patient's cardiovascular state is required to detect shock (severe hypotension with ineffective circulation) in a timely manner. Early volume resuscitation and proper usage of vasoactive

drugs should be considered. Hemodynamic monitoring should be continuous, because treatment should be guided by the patient's hemodynamic status.

6.3 Other treatment: The functional status of all other organs should be checked during respiratory and circulatory support. This increases the prevention of complications and allows for timely treatment when they do occur. Special attention must be paid to prevent hospital acquired infections.

Ⅵ.Others

Hospitals should adopt measures to reduce the incidence and severity of hospital acquired infections in patients infected with avian influenza A (H7N9) in accordance with "Technical Guidelines on the Prevention and Control of Hospital Infections in Patients Infected with Avian Influenza A (H7N9) (2013)"

《人感染 H7N9 禽流感医院感染预防与控制技术指南（2013 年版）》

http://www.moh.gov.cn/mohyzs/s3586/201304/25a6ba8ff2214f6e89d9683cce25b2fc.shtml

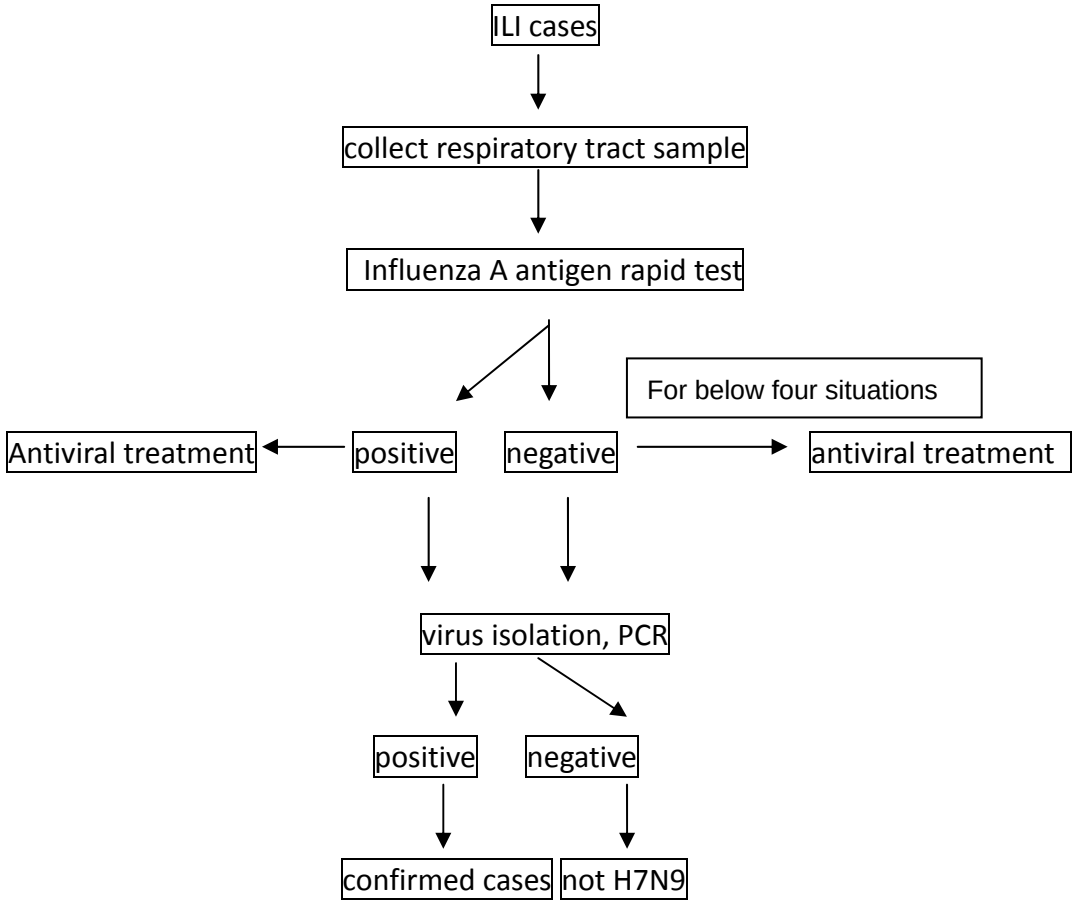
Ⅶ. Transfer or discharge standards

1. For patients with chronic underlying disease or severe comorbidities, if two consecutive PCR tests are negative, the patients can be transferred out from an isolation room to the appropriate unit for further treatment as indicated.

2. For patients who defervesce, whose clinical symptoms disappear, and have two consecutive negative PCR tests, they can be discharged from hospital.

Annex: Flow chart for early detection and treatment of avian influenza A (H7N9) cases in an epidemic area. (As of 11 April 2013, Anhui, Jiangsu, Shanghai and Zhejiang).

Annex: **Flow chart for early detection and treatment of avian influenza A (H7N9) cases in an epidemic area. (As of 13 April 2013, Anhui, Jiangsu, Shanghai and Zhejiang).**



A. ILI case who is a close contact (including health care workers) one of a cluster clustered of ILI cases or exposed to poultry within the last week;

B. ILI case who has an underlying disease such as chronic pulmonary disease, heart disease, old age, pregnant women;

C. ILI case that progress rapidly or one prescribed antiviral drugs; or

D. ILI case with pneumonia of unknown etiology.