Scientific Publications

Current Research in Public Health, 2025, 5, 6156
www.scipublications.com/journal/index.phpo/crph
DOI: 10.31586/crph.2025.6156

Brief Review

Avian influenza management at bedside in Japan

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Abstract: Avian influenza is a very lethal disease caused by influenza viruses that normally circulate among birds, and contains well-known subtypes are A(H5N1) and A(H7N9). Human infection is rare and occurs through close contact with infected poultry, therefore, confirming a history of such contact is important. The same treatment as for seasonal influenza is recommended, such as the neuraminidase inhibitors, cap endonuclease inhibitors, and RNA polymerase inhibitor. The avian influenza patients are regulated by the Infectious Diseases Control Law in Japan, we should manage the avian influenza appropriately.

Keywords: Anti-influenza agents, Avian influenza, H5N1, H7N9, Infectious Diseases Control Law

1. Overview of the Disease

Avian influenza is an infectious disease caused by influenza viruses that normally circulate among birds. The most well-known subtypes are A(H5N1) and A(H7N9) of the A-type influenza virus [1]. Avian influenza A (H5N1) was first isolated from birds in Guangdong Province, China, in 1996, and infections in birds have been confirmed in various Asian countries, including Japan. As a human infection, the first case was reported in Hong Kong in 1997, and as of February 26, 2024, a total of 887 confirmed cases of A(H5N1) have been reported from 23 countries worldwide, with 462 deaths (case fatality rate of 52.1%) [2]. Since 2020, 26 cases have been reported, with 7 deaths. To date, no sustained human-to-human transmission has been confirmed [2,3].

On the other hand, cases of human infection with avian influenza A(H7N9) virus were reported by the Chinese government on March 31, 2013, and as of May 6, 2022, a total of 1,568 cases have been reported, mainly from mainland China and Hong Kong, with at least 616 deaths (39.3%) [2,3].

2. Diagnostic points

Human infection is rare and occurs through close contact with infected poultry, their excretions, carcasses, or organs. Therefore, confirming a history of such contact is of utmost importance [2].

In A(H5N1), the incubation period is generally 2–8 days, and most initial symptoms resemble those of influenza-like illness, primarily characterized by high fever and acute respiratory symptoms. Lower respiratory symptoms appear early, with respiratory distress, tachypnea, and abnormal breath sounds commonly observed, and clinically evident pneumonia is frequently seen. In cases with progressive respiratory failure, diffuse ground-glass opacities are particularly noticeable in both lungs around the third day of onset, presenting clinical findings consistent with acute respiratory distress syndrome (ARDS). Death typically occurs on average 9–10 days (range 6–30 days) after onset, with most deaths resulting from progressive respiratory failure.

How to cite this paper:
Seki, M. (2025). Avian influenza management at bedside in Japan. *Current Research in Public Health, 5*(1), 12-14.
DOI: 10.31586/crph.2025.6156

Received: June 1, 2025
Revised: June 30, 2025
Accepted: July 19, 2025
Published: July 22, 2025

In A(H7N9), the incubation period is 1–10 days (most commonly 2–5 days), and symptoms are largely similar to those of A(H5N1). However, reports of secondary infections, encephalopathy, and rhabdomyolysis have been documented. The median time from onset to death is 11 days (interquartile range 7–20 days), with many deaths attributed to progressive respiratory failure, among other causes.

In both cases, patients often present with fever of 38°C or higher, cough, shortness of breath, diarrhea, and muscle pain. Laboratory findings include peripheral leukopenia, particularly lymphopenia, thrombocytopenia, and elevated levels of AST, LDH, and CK.

Diagnosis of the pathogen is primarily made by detecting viral RNA in respiratory specimens such as sputum using RT-PCR or other genetic testing methods. Rapid diagnostic kits for influenza antigens, which are commonly used for seasonal influenza, may not reliably diagnose COVID-19 in the same manner as seasonal influenza, so caution is required.

3. My treatment approach and treatment plan

In general, the same treatment as for seasonal influenza is recommended, with the expected efficacy of traditional neuraminidase inhibitors. Due to the high incidence of severe cases, systemic administration is preferred, including intravenous infusion in addition to oral medication.

- Regarding the recently introduced cap endonuclease inhibitors, animal studies suggest efficacy against avian influenza similar to that observed with seasonal influenza [4].
- The use of favipiravir, an RNA polymerase inhibitor, is being considered in accordance with guidelines for novel influenza.
- As with seasonal influenza, severe complications due to secondary bacterial pneumonia are possible, so if yellow sputum appears or there is an increase in peripheral white blood cells, especially neutrophils, the use of antibiotics should be considered[5].
- In the most severe cases, in addition to respiratory management (including ECMO) in the ICU, steroid administration may also be considered [6].
- Treatment should be initiated as early as possible, preferably within 48 hours of onset.

4. Treatment guidelines

(Mild cases: when oral administration is initially possible)

- First-line treatment: Tamiflu® tablets (oseltamivir) (75 mg) 2 tablets, divided into two doses, for 5 days, administered orally.
- Second-line treatment: Rapiacta® intravenous infusion (peramivir) bag (300 mg) or vial (150 mg), 600 mg single dose.

(Moderate to severe cases: treatment with intravenous medications)

- First-line treatment: Rapiacta® intravenous infusion (peramivir) bag (300 mg) or vial (150 mg) 600 mg single dose.
- (More severe cases)
- In cases where there is a higher risk of life-threatening complications, additional administration of Avigan® tablets (favipiravir) or Xofluza® tablets (baloxavir marboxil) should be considered.

5. Consultation with an expert

Under the Infectious Diseases Control Law, avian influenza of subtypes A(H5N1) and A(H7N9) are classified as Category 2 infectious diseases, while other subtypes are classified as Category 4 infectious diseases in Japan [2]. Therefore, in addition to promptly

reporting the case through the public health center, patients should be transported to a hospital with an infectious disease ward capable of handling such cases as a general rule.

6. Key points for explaining to patients

- Human-to-human transmission is extremely rare but requires certain precautions.
- Avoid contact with birds and do not touch them unnecessarily.
- Do not approach markets where live birds are sold or poultry farms unnecessarily.
- Practice thorough handwashing (especially in affected regions or countries).

In conclusion, avian influenza is a lethal and life threaten disease, and regulated according to the Infectious Diseases Control Law in Japan. Although we can use several kinds of anti-influenza agents, the patients including suspected cases should be managed under appropriate understandings of the pathogenesis and severity of the avian influenza.

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