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A review on current trends in the treatment of human infection with H7N9-avian influenza A

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ABSTRACT

The H7N9 subtype of avian influenza is an enzootic and airborne virus which caused an influenza outbreak in China. Infected individuals mostly worked with poultry, suggesting H7N9 virus-infected poultry as the primary source of human infection. Significantly increased levels of proinflammatory mediators (chemokines, cytokines) during virus infection could hamper the immune system and aggravate the infection. Severe cases are marked by fulminant pneumonia, acute respiratory distress syndrome (ARDS) and encephalopathy. Left untreated, the condition may rapidly progress to multi-organ failure and death. Reverse transcription polymerase chain reaction (rRT-PCR) is the gold standard diagnostic test for H7N9 avian influenza. Use of neurominidase inhibitor antivirals remain the main treatment. New antivirals are developed to counteract neurominidase inhibitor resistance H7N9 viral strains. Corticosteroid use in viral pneumonia may provoke mortality and longer viral shedding time. Subjects at high risk of contracting avian influenza H7N9 infection are recommended to receive annual seasonal influenza vaccination.

Contents

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Introduction

The H7N9 subtype of avian influenza is an enzootic virus that was not known to infect human until 31st March 2013 where the first case of infection was reported to the Chinese centre for disease control and prevention [1]. As of March 28th, 2018 there were 1625 confirmed cases with 623 deaths; an overall fatality ratio of ≈38% [2]. Initial data shows confirmed cases clustered around the Yangtze River delta (YRD). Cases were then reported in neighbouring provinces to the north and south of YRD. By the October 2016, avian influenza spread overseas as 5 cases were reported in Taiwan, twenty in Hong Kong, one in Macau, two in Canada and one in Malaysia [3] (Fig. 1).

Since the first recorded outbreak of H7N9 infection, five seasonal outbreaks have occurred in China in the peak season during spring and winter [1,4]. The fifth outbreak of human infection occurred earlier than anticipated with a steep increase in number infected compared to cases in previous seasons, causing increased domestic and international concern. Notable features of the fifth outbreak were that a quarter of those affected are farmers, and those staying in urban areas who reported exposure to live poultry [1]. Under experimental conditions, Brown et al. showed that viruses persisted in low temperatures (<17 °C), at alkaline pH (7.4–8.2) and in freshwater conditions. Avian influenza virus optimal temperature for persistence is 4 °C for more than 200 days [4].

Influenza virus is spread between humans through exposure to droplets expelled during sneezing or coughing. Droplets may be categorised into larger droplets that settle to the ground, and small droplets (<5 μm) that can remain airborne [5]. Small particles are also referred to as aerosols that can retain infectivity, thus can transmit influenza virus across rooms. This implicates hospital settings during the influenza season [6]. Viruses can also survive on non-porous surfaces for long periods, whereas not on hands, thus, hand hygiene is essential to reduce environmental contamination [7]. It is also found that aerosol transmission accounts for approximately half of all transmission events. Thus, by only reducing transmission by contact of larger droplets among individuals is not sufficient to control the spread of Influenza A virus among household members [5].

Humans infected by avian influenza A (H7N9) viruses develops pneumonia which may progress to severe pulmonary and acute respiratory distress syndrome (ARDS) within 5–7 days, then multi-organ failure and death [7,8]. Clinical criteria are (i) acute respiratory illness with fever >38 °C, cough and/or sore throat, (ii) pneumonia, and (iii) death from unexplained acute respiratory illness [8]. Unlike other influenzas outbreaks, patients who are more susceptible to this disease are older individuals with underlying comorbidities. Healthy young individuals have milder symptoms, and may potentially be asymptomatic. Patients infected with H7N9 virus are also reported have peripheral hypercytokinemia [9], and raised angiotensin-II levels [10]. These substances may act as biomarkers [9]. Other markers such as Macrophage Migration Inhibitory Factor (MIF) [11], Stem Cell Factor (SCF) [12], Monocyte Chemoattractant Protein (MCP-1) [13], and Hepatocyte Growth Factor (HGF) [14] are also elevated, and may serve as dynamic biomarkers and predict fatal outcome with better accuracy than angiotensin-II [9].

As avian influenza A (H7N9) does not cause illness or death in infected animals, it is difficult to eradicate or destroy sources of avian infection, to prevent infection in human [15]. To prevent spread, China's premier, Li KeQiang asked provincial officers in affected areas to close live poultry markets and disinfect their premises. Measures such as upgrading China's poultry industry by raising livestock on larger scale, centralised slaughter, cold chain transport and sale of chilled meat would be implemented [1].

Influenza H7N9 virus belongs to the genus *Orthomyxoviridae*. This virus is highly pleomorphic, enveloped with the spherical virions and the family has 3 genera, namely A–C, which are characterised based on antigenic differences in their core proteins. The two important proteins for the characterisation of virus subtype are surface hemagglutinin (HA) and neuraminidase (NA). For Influenza A virus, there are 16 different HA and 9 different NA subtypes [6]. The HA and NA genes were derived from H7 virus found in domestic ducks: H7N3 strain (A/duck/Zhejiang/11/2011), and N9 virus circulating in migratory birds [6,14,15]. According to phytogenetic analysis, it is found that the remaining six internal sequence of Influenza (H7N9) virus has 98% similarity with A/chicken/Zhejiang/Q1D4/2011(H9N2) strain [16]. Certain mutations in genes such as Q226L in HA shows a possible shift from avian to human receptor binding of the H7N9 virus [8]. Substitution of E627K gene found in PB2 increases the ability of replication and transmission of H7N9 virus in mammals [6,7]. Furthermore, substitution of S31N gene present in M2 of the novel H7N9 avian influenza virus results in drug resistance to Amatidine. R29K mutation present in NA of H7N9 virus shows a potential resistance to NA inhibitors. Thus, many therapeutic benefits of NA inhibitors in particular Oseltamivir are compromised due to the emergence of resistant virus variants. Influenza vaccines should also be updated regularly due to the antigenic drift and sporadic shift present in viral surface [6].

Epidemiology

According to the World Health Organisation, human cases of novel avian influenza A H7N9 infection were found in late March and April 2013 in eastern China. However, the first case was identified on February 19, 2013 [1–3]. In addition, most of the cases have occurred in the mainland of China. In December 1, 2013, in the mainland China, total 139 laboratory-confirmed cases and one suspected case were determined in 10 provinces and 2 municipalities [15]. Among the confirmed cases in the mainland China, 50 cases were found in Zhejiang, 33 cases in Shanghai, 28 cases in Jiangsu, 6 cases in Jiangxi, 5 cases in Fujian, 4 cases in both Anhui and Henan, 2 cases in Hunan, Beijing, Shandong and Guangdong respectively and 1 case in Hebei and Jilin [17].

Based on the epidemiological data from the cases, the median age of patients with positive H7N9 virus infection was 61 years old, 58 cases (42%) happened in the age of 65 years or older, and 4 cases (3%) occurred in children younger than 5 years old, given that all of them had clinically mild upper respiratory illness [15]. Moreover, males have the highest prevalence of the confirmed cases with 71%, 73% of the confirmed cases are residents living in urban areas, and 79 of 108 patients (73%) had underlying medical conditions [17]. From the 70 patients among the 79 patients having underlying medical conditions which had sufficient data for more specific classification of underlying conditions, 54 of them (77%) were considered to be at high risk of developing influenza complications due to age (less than 5 years or 65 years old or older) or prevalence of specific underlying medical conditions. According to the epidemiological data, 9 patients with confirmed cases (6%) worked as poultry workers [17]. Therefore, it was suggested that H7N9 virus has been transmitted from poultry to humans as H7N9 virus is detectable from live poultry and also from environmental samples. In short, H7N9 virus-infected poultry might be the primary source of human infection [7]. Among the 139 patients with confirmed cases, 137 of them (99%) were hospitalised, and 125 of them (90%) had pneumonia or respiratory failure [17]. In addition, avian influenza virus H7N9 is said to cause severe respiratory infections with 30% of case fatality rate [7].

Fig. 1. Avian influenza A(H7N9) virus infection distribution among human cases and positive avian in environmental samples of China.
Source: Food and Agriculture Organization of the United Nations (FAO), Emergency Prevention System for Transboundary Animal Diseases (EMPRES), Rome, Italy [2].

In mainland China, 1372 hospitalised patients with pneumonia of unexplained origin was tested for H7N9 virus infection using their respiratory specimens from March 25 through December 1, 2013 and the results showed that 104 patients (7.6%) were tested positive for H7N9 virus infection [17]. In May 12, 2014, there are 437 laboratory-confirmed cases of human infection related to H7N9 virus in the mainland China. Among the 437 cases, 146 death were reported [7]. Therefore, it is suggested that the H7N9 virus infection have occurred in two waves in which the first wave happened in February through May, 2013, followed by sporadic cases in July and August whereas the second wave has been happening from October 2013. Based on the reports received, it can be observed that there is increase in number of new cases after January 2014 [7]. During the interval of Feb 19, 2013, to Feb 23, 2017, there were 1220 laboratory-confirmed human infections with H7N9 virus reported in mainland China. Among the 1220 confirmed cases, 134 cases were reported in the spring of 2013, 306 cases were reported from year 2013 to year 2014, 219 cases were reported from year 2014 to year 2015, 114 cases were reported from year 2015 to year 2016 and 447 cases were reported from year 2016 to year 2017 [18]. From the data shown, it suggested that from year 2016 to year 2017, H7N9 virus began to spread to more district and therefore more provinces were affected and had more confirmed cases as compared to the previous year.

Besides, percentage of confirmed cases in middle-aged adults increased from 41% (55 of 134) to 57% (254 of 447) from the first epidemic to the epidemic from year 2016 to 2017. In addition, percentage of confirmed cases in semi-urban and rural areas in year 2015–2016 and in year 2016–2017 which were 63% (72 of 114) and 61% (274 of 447) respectively, were both higher than the first three epidemics which are 39% (52 of 134), 55% (169 of 306) and 56% (122 of 219) respectively [18]. In terms of the clinical severity of the patients admitted to the hospital, epidemic in year 2016 to 2017 was similar to the previous epidemics [14,18]. Not only in the mainland of China, in other countries such as Hong Kong, the first case of human infection with H7N9 virus was confirmed on 2 December 2013. In addition, during winter season of 2013–2014, 10 confirmed cases were reported and from December 2014 to February 2015, another three confirmed cases were reported [8]. On February 22, 2017, based on Disease Outbreak News issued by World Health Organisation (WHO), total of 1223 laboratory-confirmed cases of human infection with H7N9 virus were reported since early 2013 [19]. In fact, the human cases of H7N9 infection that has been developing since year 2013, accounted for approximately one-third of all the human cases of H7N9 infection reported since year 2013, including five cases in Taiwan, 20 cases in Hong Kong, one case in Macau, two cases in Canada and one case in Malaysia [19]. Moreover, on February 23, 2017, there were at least 425 cases reported during the fifth outbreak in China, which started in October, 2016 and increased suddenly in December, 2016 [1].

Based on National Health and Family Planning Commission (NHFPC) of China, since January 2017, total of 192 cases of H7N9 infection including 79 deaths were reported and most of the cases occurred around the Yangtze and Pearl River deltas [1]. On 28 September 2016 in Zhejiang Province, there was illness onset reported from the first case of the fifth epidemic. Following by October and November 2016, there were total of eight cases reported in four provinces including Jiangsu, Zhejiang, Fujian, and Guangdong [3]. However, the number of cases has gradually increased since 1 December 2016, with total of 106 cases reported in December 2016 alone. The number of reported cases in the fifth epidemic was 11.4, 2.7 and 6.1 times greater than that observed during the second (10 cases), third (31 cases) and fourth (16 cases) epidemics respectively [3,5].

Pathophysiology

Avian influenza A H7N9 viruses isolated during the first four waves contain a hemagglutinin (HA) cleavage site with a single basic amino acid, indicating that these are low-pathogenicity influenza virus strains. This allows the virus to spread silently among poultry causing no or only mild illness to indicate its presence [20].

Receptor and tissue tropism

The virus HA is the viral protein that mediates attachment to cell receptors and fusion of viral and cellular membranes releasing viral

RNA into the host cell. The uncleaved precursor form is known as HA0 and needs to be cleaved by a host cell protease into the subunits HA1 and HA2 to be active as fusion proteins [20,21].

The amino acid sequence of the HA receptor-binding site affects the preference for avian-type (α-2,3-linked galactose) or human-type (α-2,6-linked galactose) receptors. Certain mutations in HA (i.e. the Q226L mutation) enhances HA binding of avian influenza viruses to human-type receptors [24]. A study has shown that recombinant avian influenza A H7N9 viruses possessing the Q226I or Q226L mutation bind preferentially to human-type receptors, while a recombinant virus lacking these mutations bind equally well to both avian-type and human-type receptors [22].

Human upper airways and trachea express mainly α-2,3-linked galactose receptors, whereas human lung tissues contain both α-2,3-linked galactose and α-2,6-linked galactose receptors. H7N9 viruses appear binds to human-type receptors, indicating that they display tropism for cells in both upper and lower airways and that human to human transmission is possible [22,23]. However, another study showed that H7 HA preferentially binds the avian-type receptors(α2-3) over human-type receptors [23].

Analysis of infected human tracheal explant sections and lung tissues showed that H7N9 can invade epithelial cells in the lower respiratory tract and type-II alveolar cells via the expression of viral nucleoprotein [23]. Influenza virus HA binds to cellular receptor of the host and is subsequently responsible for the fusion of viral envelope with host endosomal membrane [24]. To mediate fusion, influenza virus HA must go through post-translational cleavage by host protease. Transmembrane protease S2 (TMPRSS2) is a host protease that cleaves and activates the influenza virus HA in the human respiratory tract. In a genome-wide association study, a polymorphism that upregulates TMPRSS2 expression was associated with severe H7N9 influenza infection [24].

Chemokines and cytokines

Although cytokine storms reflect a host defense response against pathogens, the highly elevated levels of inflammatory mediators could cause immunity damage and contribute to severity of infection. However, the underlying immunopathological mechanism of H7N9 infection is still remains unclear [25].

In a study that measured the serum concentrations of chemokines and cytokines in patients infected with avian influenza A H7N9, the levels of several chemokines and cytokines (i.e. monocyte chemoattractant protein-1 [MCP-1], Macrophage Inflammatory Protein-1 beta [MIP-1β], interferon inducible protein-10 [IP-10], interleukin [IL]-6, IL-8) were elevated compared to that of healthy individuals [23].

In another study, serum concentrations of IP-10, IL-6, IL-17, and IL-2 were increased in avian influenza A H7N9 infected patients, with severely ill patients exhibiting significantly higher levels of IL-6 and IP-10 [9].

- MCP-1 and MIP-1β which come from the CC chemokine ligands (CCL) family are two chemokines that mainly promote the recruitment of monocyte/macrophages to inflammatory sites [25,26], hence mediating host innate immunity and expanding inflammatory effects.
- IP-10 is a proinflammatory cytokine that is secreted by several cells, including endothelial cells, monocytes, fibroblasts and hepatocytes. IP-10 belongs to the CXC chemokine family, and is capable of recruiting and activating T-cells, natural killer (NK) cells, monocytes/macrophages, dendritic cells and eosinophils [27].
- IL-17 can be produced by γd T-cells, Th17 lymphocytes, CD8+ T-cells and NK T-cells (NKT). IL-17 stimulates proinflammatory chemokines and recruits' neutrophils into the respiratory tract. IL-17A plays an important protective role in host defense in various infections, including asthma [23,27].
- Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), also known as CCL5 is a small 68-amino acid protein that belongs to a rapidly growing chemokine family. It can be strongly induced by viral and bacterial infections and recruits T-cells, dendritic cells, eosinophils, NK cells, mast cells, and basophils to sites of inflammation and infection [23,25,27].
- EOTAXIN is a potent chemokine which act as a chemoattractant for eosinophils to sites of inflammation by selectively stimulates the agonist activity for CC chemokine receptor 3 [25].

Significantly increased levels of proinflammatory mediators in human lung endothelial cells during virus infection provides evidence that H7N9 viruses can induce elevated levels of proinflammatory mediators in pulmonary endothelial cells, although these cells do not promote productive viral replication of this virus. Endothelial and epithelium cells are the main cell structures in the human lungs [26,27]. It was found that H7N9 infection in epithelial cells resulted in the release of a large amount of virus with cleaved HA and damaged epithelial monolayer from cell death, especially by necrosis. Therefore, following the release from neighbouring epithelial cells, pulmonary endothelial cells become accessible to infection with H7N9 virus. Subsequently, the viruses elicit elevated levels of cytokines and chemokines recruiting lymphocytes to the lung and facilitate viral clearance. However, a cytokine cascade can result in enhanced lymphocyte infiltration and lung inflammation and damage, leading to pneumonia and acute respiratory distress syndrome [28].

Clinical manifestations

The sign and symptoms of Avian Influenza A H7N9 presented in patients are similar to those with other respiratory tract infections [18]. The most common symptoms presented in patients were fever, cough and myalgia [29]. Moreover, many of them have rapidly progressed to severe pneumonia. Patients may also present sign and symptoms of headache, lymphocytopenia, thrombocytopenia, and shortness of breath [26,29].

Other than the respiratory manifestation, the uncommon clinical manifestations may also can be seen in severe cases, such as fulminant pneumonia, respiratory failure, heart failure, acute septic shock, multi-organ failure, respiratory distress syndrome (ARDS), alteration of thrombohemostasis, renal impairment, and encephalopathy [17,29].

Diagnosis of new H7N9 influenza infection

Currently, limited diagnostic tests are available to identify H7N9. Therefore, reverse transcription polymerase chain reaction (rRT-PCR) has become the gold standard for avian influenza A H7N9 [30].

In clinical practice, patients with body temperature more than 38.3 °C and have the history of recent close contact with confirmed cases of human infection with H7N9 or travel to the area where H7N9 viruses are known to be circulating in animals should be primarily screened by influenza rapid test. If the screening result is positive, starting the antiviral drug treatment is recommended. Moreover, further confirmation test for H7N9 should be done at the same time [29,30].

Treatment

The treatment of H7N9 avian influenza virus infection mainly consist of antiviral drugs and corticosteroids and the main goals of

these treatment are to reduce viral replication, reduce inflammation and pain management.

Antivirals

Initial enthusiasm for this therapeutic approach, primarily using a combination of neurominidase inhibitors (oseltamivir) and fibrates (fenofibrates) has been validated and data show that this combination has the potential to inhibit viral replication and normalizing the aberrant immune response [31].

However, the emergence of neuraminidase mutations poses a problem for clinical care. Virus variants that carry markers of decreased susceptibility to neuraminidase mutations may indicate a poor prognosis [32]. Fludase (DAS181), a recombinant sialidase fusion protein has the ability to potently inhibit replication of wild-type influenza A (H7N9) and its oseltamivir-resistant variants. Promising data from animal studies have prompted ongoing small clinical studies in humans [33]. Nitazoxanide (NTZ) is a novel thiazolide that inhibits the replication of influenza A (H7N9) virus by impairing hemagglutinin transportation into the host cell plasma membrane, preventing mature virions from leaving the host cell [34]. As NTZ is a broad-spectrum antiviral that covers all virus variants/strains, it is defined as the first line therapy for influenza A (H7N9) patients. Existing data show that NTZ 600 mg twice daily for 5 days could reduce the duration of clinical symptoms viral shedding [35].

Another novel anti-influenza drug, favipiravir (T-705) is also a broad-spectrum antiviral which covers resistant influenza strains. With the addition of purine nucleic acid onto the surface of T-705, viral RNA polymerase mistakenly recognises this complex as a purine nucleotide, conferring T-705 its viral RNA polymerase inhibitory properties [36]. However, favipiravir is still in phase II/III clinical studies.

Corticosteroids

Viral pneumonia treated with methylprednisolone (40–80 mg) for 7 days is associated with a significant increment in mortality and longer viral shedding time. Existing data from case-control analyses do not demonstrate benefit from corticosteroids [37].

Patient management

Patients must be advised to wear respirators (e.g. N95 masks) to prevent the spread of virus particles. If they have contact with respiratory secretions, hand disinfectants must be used to disinfect the hand. If patient is experiencing respiratory dysfunction, oxygen should be initiated alongside with other respiratory support to prevent or minimise disease progression. Patients should rest well and drink more water. Adequate nutrition (easy-to-digest diets) should also be provided and maintained [38].

Monitoring

Any potential complications, particularly hospital acquired pneumonia must be closely monitored and prevented. Close monitoring of the functional status of other organs is equally important to ensure vigorous and appropriate treatment. The severe cases must be hospitalised. 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 [36,38].

Prevention

To prevent infection with influenza A (H7N9) virus, sources of exposure should be avoided. For instance, infected bird's saliva, mucous and faeces. Biosecurity and infection control practices such as hand hygiene and use of appropriate personal protective equipment should be adhered by poultry workers [39]. In the meantime, poultry workers should also receive annual seasonal influenza vaccination. Although vaccinations such as A/Anhui/1/2013-like virus [40] will not prevent infection with influenza A (H7N9) virus, the risk of co-infection with human and the virus could be reduced [39].

Post-exposure prophylaxis

Oseltamivir or inhaled zanamivir chemoprophylaxis is recommended in close contacts of a probable H7N9 case patient. Administration of chemoprophylaxis should be within 48 h upon clinical judgement, with regards to the type of risk of exposure. Oseltamivir 75 mg once daily or zanamivir 10 mg (2 inhalations) twice daily regime is usually recommended for 5–10 days [40].

H7N9 subtype of Avian Influenza is an enzootic virus which is first reported in China [17,25]. Till date, there were 1552 confirmed cases, with its fifth wave occurred earlier than expected, affecting mainly farmers that are exposed to live poultry [17,23]. It is transmitted through infected respiratory droplets that remains airborne as well as at porous surfaces [1,2].

Reverse transcription polymerase chain reaction (rRT-PCR) is the gold standard for Avian Influenza A H7N9 diagnosis. Initially, a combination of antiviral neurominidase inhibitor (oseltamivir) and fibrates (fenofibrates) was primarly used to inhibit viral replication and normalises the immune response [1]. However, with the recent emergence of influenza A (H7N9) virus with neuraminidase mutations it renders the previous treatment to decrease in efficiency [2].

Few novel drugs that are being studied on its antiviral efficacy are such as Fludase, Nitazoxanide (NTZ) and Favipavir, with NTZ showing the most promising results. It is a thiazolide anti-infective drug which inhibits the replication of H7N9 virus, and it is used as the first line therapy for H7N9 patients [2–5]. From a case control analysis of corticosteroids for the treatment of H7N9 viral pneumonia, there was no significant benefit found, with one research showing higher mortality instead [5]. Patients are also recommended to wear N95 masks, disinfect hands regularly, and to rest well. To prevent contracting the virus, it is recommended to receive annual seasonal influenza vaccination to reduce risk of infection, albeit some studies shows that vaccinations such as A/Anhui/1/2013-like virus does not prevent infection of influenza A (H7N9) virus [6,7].

Conclusion

Early diagnosis is very important in the management of avian influenza H7N9 for reducing its viral replication. Along with antiviral therapies, symptomatic treatments are also suggested to improve patient's pain related symptoms and quality of life. Early vaccination of avian influenza A (H7N9) is warranted to prevent the spread of this disease in global population. Personal hygiene also plays a vital role in preventing the spread of virus infection.

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Competing interests

None declared.

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