**Novel Avian Influenza A Virus Infections of Humans**

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**INTRODUCTION**

Influenza A viruses are RNA viruses with a segmented genome and are subtyped on the basis of the 2 virus surface glycoproteins, hemagglutinin (H) and neuraminidase (N), into 16 H and 9 N subtypes. More recently, additional virus subtypes have been discovered in bats, but these subtypes are of uncertain significance for humans. Influenza A viruses naturally circulate in a range of avian and mammalian species, including in humans. The greatest diversity of virus subtypes are found in aquatic waterfowl, which are regarded as the natural reservoir of influenza A viruses. Influenza A viruses of 3 subtypes—H1N1, H2N2, and H3N2—have been endemic in humans. Influenza A H1N1 caused the 1918 pandemic and circulated in humans...
until 1957 when a new pandemic H2N2 virus replaced it; which was in turn replaced by an H3N2 virus in 1968. The most recent pandemic was in 2009, caused by a ‘swine-origin’ H1N1 virus. Currently, influenza A subtypes H1N1 and H3N2 co-circulate in humans as seasonal influenza A viruses. Pandemics arise when novel influenza A viruses containing virus hemagglutinins from swine or birds emerge and spread efficiently and in a sustained manner among an immunologically naïve human population. In addition, avian and animal influenza A viruses may cause sporadic zoonotic human infections and disease without acquiring the ability for sustained human-to-human transmission. However, such infections cause global public health concern because they may cause significant morbidity and mortality; but the even greater concern is that they pose potential pandemic threats. Swine-origin H1 and H3 viruses have also caused zoonotic infections, but are not discussed in this article.

EPIDEMIOLOGY

Sporadic human infections with avian influenza A viruses of multiple subtypes have been increasingly detected since 1997, in part because the surveillance and laboratory capacity for molecular analyses have improved worldwide, but also because changes in poultry production marketing practices have increased the opportunity for the emergence and dissemination of potentially zoonotic viruses. The classification of avian influenza A viruses as highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) viruses is based on specific molecular criteria and pathogenicity in birds. Past pandemics have arisen from LPAI viruses. Although HPAI viruses have important agricultural and economic implications, both HPAI and LPAI virus infections have caused a wide range of mild to fatal human disease (Tables 1 and 2). Therefore, for public health impact, focus is on the virus subtype rather than virus pathogenicity in birds.

Although diverse avian influenza A virus subtypes have caused zoonotic infections (see Tables 1 and 2), virus subtypes H5N1 and H7N9 have caused the highest impact, both numerically and in disease severity. The first instance of a zoonotic avian influenza A virus causing severe disease was in 1997 in Hong Kong when 18 cases of H5N1 virus disease were detected leading to 6 deaths.1 Human cases were preceded by outbreaks in poultry. The outbreak in Hong Kong was stopped by the slaughter of all poultry in markets and farms in Hong Kong in December 1997. H5N1 viruses continued to circulate and evolve among poultry in the wider region. Zoonotic disease was again observed in early 2003 with 2 deaths among 2 confirmed and 1 probable case.2 H5N1 virus spread via the poultry trade to affect poultry in 10 countries in Asia by 2004.3 By 2005, the virus also was established in wild migratory birds and spread via bird migration to infect poultry in Central Asia, South Asia, the Middle East, and parts of Africa. Although these poultry outbreaks were stamped out successfully and repeatedly in some countries (eg, Japan, Malaysia), they became enzootic within poultry in others, evolving into antigenically distinct and genetic diverse clades leading to zoonotic disease.3 As of May 2019, 861 human cases of H5N1 virus infection and 455 deaths had been reported from 17 countries since November 2003, and the cumulative case fatality proportion among reported H5N1 cases has remained greater than 50%, although few cases have been reported worldwide since 2016.4,5 Since 2013, H5N1 viruses of clade 2.3.4.4 have undergone reassortment with other avian influenza A viruses to generate H5N6, H5N8, and other related subtypes. More recently, H5N6 has become the dominant H5 lineage virus circulating in China, sometimes causing zoonotic disease.6
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Patient Characteristics</th>
<th>Clinical Syndromes</th>
<th>Illness Severity</th>
<th>Countries</th>
<th>Years (Illness Onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H6N1</td>
<td>Young adult</td>
<td>Moderate lower respiratory tract disease</td>
<td>Moderate</td>
<td>Taiwan</td>
<td>2013</td>
</tr>
<tr>
<td>H7N2</td>
<td>Adults</td>
<td>Upper respiratory tract illness, conjunctivitis, lower respiratory tract disease</td>
<td>Mild to moderate</td>
<td>US; UK</td>
<td>2002, 2003, 2007, 2016&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>H7N3</td>
<td>Adults</td>
<td>Upper respiratory tract illness, conjunctivitis</td>
<td>Mild</td>
<td>UK; Canada</td>
<td>2004, 2006</td>
</tr>
<tr>
<td>H7N4</td>
<td>Elderly adult</td>
<td>Pneumonia</td>
<td>Moderately severe</td>
<td>China</td>
<td>2017</td>
</tr>
<tr>
<td>H7N7</td>
<td>Adults</td>
<td>Conjunctivitis</td>
<td>Mild</td>
<td>US; UK</td>
<td>1980&lt;sup&gt;b&lt;/sup&gt;, 1996</td>
</tr>
<tr>
<td>H7N9</td>
<td>All ages</td>
<td>Upper respiratory tract illness, lower respiratory tract disease, critical illness with multiorgan failure</td>
<td>Mild to severe; majority with severe to critical illness with mortality in hospitalized patients at 40%</td>
<td>China; exported cases identified in Hong Kong Special Administrative Region of China, Taiwan, Malaysia</td>
<td>2013–2018</td>
</tr>
<tr>
<td>H10N7</td>
<td>Adults</td>
<td>Conjunctivitis and upper respiratory tract illness</td>
<td>Mild</td>
<td>Australia</td>
<td>2010</td>
</tr>
<tr>
<td>H10N8</td>
<td>Middle-aged and elderly adults</td>
<td>Severe pneumonia, critical illness with multiorgan failure</td>
<td>Critical illness, fatal outcome in 2 of 3 cases</td>
<td>China</td>
<td>2013, 2014</td>
</tr>
</tbody>
</table>

As of May 2019; excludes asymptomatic infections, infections reported by sero-epidemiology studies, or infections with illness not specified in published reports.

<sup>a</sup> One case of an avian-lineage H7N2 virus was transmitted from a cat to a human causing mild respiratory illness.

<sup>b</sup> One case of conjunctivitis occurred in a researcher through close contact with a seal that was experimentally infected with a virus that was antigenically similar to an H7N7 virus of avian origin.
<table>
<thead>
<tr>
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<th>Patient Characteristics</th>
<th>Clinical Syndromes</th>
<th>Illness Severity</th>
<th>Countries</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5N1</td>
<td>All ages, primarily children and young adults</td>
<td>Upper respiratory tract illness, lower respiratory tract disease, encephalitis, respiratory failure, ARDS, multiorgan failure</td>
<td>Mild to critical illness; majority with severe to critical illness with mortality &gt;50%</td>
<td>Hong Kong Special Administrative Region of China; China; Vietnam; Thailand; Cambodia; Indonesia; China; Turkey; Iraq; Azerbaijan; Egypt; Djibouti; Nigeria; Laos PDR; Nepal; Pakistan; Myanmar; Bangladesh; Canada (imported from China)</td>
<td>1997, 2003–2017, 2019</td>
</tr>
<tr>
<td>H5N6</td>
<td>Adults</td>
<td>Upper respiratory tract illness, severe pneumonia, respiratory failure, ARDS, multiorgan failure</td>
<td>One case with mild illness; most cases with critical illness, mortality &gt;50%</td>
<td>China</td>
<td>2014–2018</td>
</tr>
<tr>
<td>H7N3</td>
<td>Adults</td>
<td>Conjunctivitis</td>
<td>Mild</td>
<td>Canada; UK; Mexico; Italy</td>
<td>2004, 2006, 2012, 2013</td>
</tr>
<tr>
<td>H7N7</td>
<td>All ages</td>
<td>Hepatitis, conjunctivitis, upper respiratory tract illness, severe pneumonia, respiratory failure, ARDS, multiorgan failure</td>
<td>Mild to critical illness with fatal outcome in one adult; majority with mild illness (conjunctivitis)</td>
<td>UK; the Netherlands, Italy</td>
<td>1959, 1996, 2003, 2013</td>
</tr>
<tr>
<td>H7N9</td>
<td></td>
<td>Pneumonia, respiratory failure, ARDS, multiorgan failure</td>
<td>Critical illness, high mortality</td>
<td>China</td>
<td>2016–2017, 2019</td>
</tr>
</tbody>
</table>

As of May 2019; does not include asymptomatic infections, infections reported by sero-epidemiology studies, or infections with illness not specified in published reports.

**Abbreviation:** ARDS, acute respiratory distress syndrome.
In 2003, an outbreak of HPAI H7N7 virus in poultry was associated with zoonotic disease affecting 89 people in the Netherlands, most of them presenting with conjunctivitis, others with influenza-like illness, and 1 fatal pneumonia in a veterinarian. There was evidence of limited human-to-human transmission to family members of persons directly exposed to infected poultry.

A novel H7N9 virus caused zoonotic disease in eastern China in the early spring of 2013. Six epidemics of human cases of H7N9 virus infection (1564 laboratory-confirmed cases and 612 deaths) occurred in China through September 2017, typically during the fall, winter, and spring months, including a very large fifth epidemic during 2016 to 2017. As of May 2019, 1568 laboratory-confirmed H7N9 virus infections acquired in China had occurred since 2013. Being an LPAI virus, H7N9 caused little or no illness in poultry and spread to multiple provinces in China. The seasonal increase in human cases corresponded with a seasonal increase in virus circulation among poultry. The cumulative case fatality proportion among reported H7N9 cases has remained approximately 40% since 2013. The H7N9 virus acquired properties of an HPAI virus in 2016 causing disease in poultry. This led to the introduction of a bivalent H5N1/H7N9 vaccination program in poultry in China leading to a decrease in virus activity in poultry and a marked reduction of zoonotic H7N9 disease since 2017. Only 2 H7N9 cases were reported in 2018, and 1 case was reported in the early spring of 2019.

Most surveillance for human infections with avian influenza A viruses has been hospital based and focused on collecting respiratory specimens for virologic testing from patients with severe disease (eg, pneumonia of unknown etiology). The recognition of clinically mild infections comes from sporadic cases identified through routine influenza surveillance among outpatients with influenza-like illness, testing of ill persons with poultry exposures during large outbreaks of avian influenza follow-up of close contacts of confirmed cases (eg, H7N9), and sero-epidemiologic studies. Therefore, asymptomatic and clinically mild illness cases of infections with avian influenza A viruses are likely underestimated, the true denominator of all infections is unknown, and the case fatality proportions for hospitalized patients are likely a substantial overestimate of the overall case fatalities for different virus infections.

Serologic studies conducted among poultry workers, persons exposed to poultry, close contacts of confirmed cases, health care providers, and the general population suggest that, although the findings vary by virus subtype, except for poultry workers, human infections with avian influenza A viruses are generally infrequent. However, because some infected persons with mild illness may not mount a detectable antibody response, and limited data on the kinetics of the antibody response for HPAI H5N1 and LPAI H7N9 virus infections suggest that antibody titers decrease over time, sero-surveys may underestimate some human infections with avian influenza A viruses.

Exported Cases

Several human cases of infection with avian influenza A viruses acquired in China have traveled overseas and were diagnosed elsewhere. A traveler who returned to Alberta, Canada, from a 3-week visit to Beijing, China, was hospitalized with pneumonia, progressed to respiratory failure with meningocencephalitis, and died. H5N1 virus was identified in this patient’s upper and lower respiratory tract and cerebrospinal fluid specimens. H7N9 virus infections acquired in China, leading to mild or critical illness, have been identified in returned travelers in Taiwan and Canada, and in a tourist in Malaysia.
Exposure Risk Factors

Most human infections with avian influenza A viruses have been sporadic and linked to recent direct contact or close exposure with domestic poultry, including raising backyard poultry or visiting a live poultry market (Table 3).55–65 Contact with dead wild swans (defeathering) was the source of infection for some cases of H5N1 virus infection in Azerbaijan.66 However, the source of exposure is not always determined for some cases of human infection with avian influenza A viruses.64,67 Live avian influenza A viruses have been identified in poultry carcasses sourced in endemic areas. Although cooking destroys virus infectivity, contamination from the carcass before cooking may contribute to some of the cases of zoonotic avian influenza A virus infection with no history of direct exposure to live poultry.58 Virologically confirmed infection with avian-lineage H7N2 virus was identified in an ill veterinarian who had exposure to ill cats.69,70 A researcher developed virologically confirmed conjunctivitis with an H7N7 virus that was antigenically related to an avian influenza A virus after close exposure to an experimentally infected seal.71

Infection of the human respiratory tract is likely initiated by inhalation of aerosolized avian influenza A viruses or contact transmission to mucus membranes, including conjunctivae, depending on the specific characteristics of the virus (eg, tropism for receptors with sialic acids attached to galactose by α2,6 linkages primarily in the upper respiratory tract vs sialic acids attached to galactose by α2,3 linkages primarily in the lower respiratory tract),72 host factors (eg, age, immune function, and underlying comorbidities) and exposure (eg, virus dose, single or multiple exposures). Some avian influenza A(H7) viruses have tropism for ocular receptors and conjunctivitis has been reported in persons with H7N2, H7N3, and H7N7 virus infections.73 In regions with enzootic poultry infections, human exposures to avian influenza A viruses such as H5N1, H5N6, and H7N9 has been extensive, but zoonotic disease is stochastic and rare. The reasons for this disconnect between exposure and disease are unclear.

Human-to-Human Transmission

Multiple clusters of epidemiologically linked human cases of H5N1 virus infection have been reported worldwide, beginning with the first outbreak described in Hong Kong.
during 1997. Most cases in clusters have had recent exposure to birds, usually domestic poultry, suggesting a common exposure source. However, some cases in clusters had close exposure to a symptomatic index case without poultry exposure. Although there is no laboratory test to confirm human-to-human transmission, epidemiologic investigations have concluded that limited, nonsustained human-to-human transmission of avian influenza A viruses likely occurred in some clusters in households or health care settings primarily among blood-related family members. Transmission has likely occurred through prolonged, unprotected close exposure to a symptomatic infected person. Similarly, at least 40 clusters of epidemiologically linked cases of H7N9 virus infection, mostly attributed to poultry exposures, were identified in China during 2013 to 2017. In some of these clusters, probable limited, nonsustained human-to-human LPAI H7N9 virus transmission likely occurred in households and in health care settings, including between blood-related family members as well as between unrelated patients. There has been no increase identified in the transmissibility of H7N9 viruses among humans since emergence in 2013. Probable, limited, nonsustained human-to-human transmission of HPAI H7N7 virus was also reported among family members in a few households in the Netherlands during 2004.

**Host Factors**

The median age for reported human cases of infection with HPAI H5N1 virus is substantially younger than for infection with LPAI H7N9 virus among hospitalized patients. It has been postulated that these different age distributions are consistent with immunologic imprinting with an individual’s first influenza A virus infection (belonging to either group 1 or group 2 virus hemagglutinin subtypes) and subsequent protection against future infection with influenza A viruses in the same hemagglutinin subtype grouping (group 1 or group 2).

Age may also influence disease severity and thus, case detection and reporting. Older age or age 60 years or older is associated with fatal outcomes from H7N9 virus infection. Among children with H5N1 virus infection, case fatality proportion was lowest in those aged 5 years or younger. Among persons with H7N9 virus infection, mild illness was observed in young children. The majority of H9N2 virus infections have occurred in children, and most cases have resulted in mild to moderate disease in patients in China, Hong Kong, Egypt, and Bangladesh.

In contrast with H5N1 virus infection, risk factors for severe H7N9 disease include having a chronic medical condition (eg, obesity, chronic obstructive pulmonary disease, immunosuppression). This finding may imply that infection in younger healthy persons occurs undetected and unreported. Epidemiologically linked clusters of H7N9 cases in China were identified in each epidemic from 2013 to 2017. Similarly, clusters of H5N1 cases have been identified in multiple countries. In zoonotic H5N1 disease, the occurrence of small clusters predominantly among blood-related family members has raised the suggestion of a genetic susceptibility.

**CLINICAL ISSUES**

**Clinical Spectrum**

The clinical spectrum of infection with avian influenza A viruses is wide and depends on the specific virus and host characteristics, ranging from asymptomatic, mild focal illness (conjunctivitis), uncomplicated upper respiratory illness, to fulminant pneumonitis with multiorgan failure and sepsis leading to fatal outcomes (see Tables 1 and 2).
Most avian influenza A virus subtypes that have infected people have resulted in mild to moderate illness. Only a few viruses (H5N1, H5N6, H7N9) have caused a high proportion of severe illness (Table 4).

Asymptomatic infections have been identified by serology for several different avian influenza A viruses, although few such infections have been confirmed virologically.\(^\text{16,96,97}\) In follow-up of household contacts of a confirmed H5N1 case, the case’s adult daughter had a throat specimen collected that yielded H5N1 virus 6 days after slaughtering a chicken, and had evidence of seroconversion without experiencing any illness symptoms.\(^\text{96}\)

Conjunctivitis has been reported for HPAI H5N1,\(^\text{74,98}\) LPAI H7N2,\(^\text{99}\) LPAI H7N3,\(^\text{100,101}\) HPAI H7N7,\(^\text{102}\) LPAI H7N7,\(^\text{103}\) HPAI H7N7,\(^\text{7,104}\) and LPAI H10N7\(^\text{105}\) virus infections. Mild to moderate uncomplicated upper respiratory tract illness has been reported for infections with HPAI H5N1 (particularly in children),\(^\text{57,74,77,106–108}\) HPAI H5N6,\(^\text{109,110}\) LPAI H7N2,\(^\text{69,111}\) LPAI H7N3,\(^\text{102}\) HPAI H7N7,\(^\text{7}\) LPAI H7N9,\(^\text{13,14}\) LPAI H9N2,\(^\text{93,94}\) and LPAI H10N7\(^\text{105}\) viruses. Lower respiratory tract disease has been reported for HPAI H5N1,\(^\text{112,113}\) HPAI H5N6,\(^\text{114,115}\) LPAI H6N1,\(^\text{116}\) LPAI H7N2,\(^\text{117}\) LPAI H7N3, LPAI H7N4,\(^\text{118}\) HPAI H7N7,\(^\text{119}\) LPAI H7N9,\(^\text{120}\) HPAI H7N9,\(^\text{121}\) LPAI H9N2,\(^\text{94}\) and LPAI H10N8\(^\text{122}\) virus infections. Respiratory failure, refractory shock, acute respiratory distress syndrome, and multiorgan failure have been reported for infections with HPAI H5N1,\(^\text{112,113}\) HPAI H5N6,\(^\text{110,115}\) HPAI H7N7,\(^\text{119}\) LPAI H7N9,\(^\text{120}\) HPAI H7N9,\(^\text{121}\) and LPAI H10N8\(^\text{122,124}\) viruses. Fatal outcomes have occurred with HPAI H5N1,\(^\text{60,112,113}\) HPAI H5N6,\(^\text{110,115}\) HPAI H7N7,\(^\text{119}\) LPAI H7N9,\(^\text{120}\) HPAI H7N9,\(^\text{121,123}\) LPAI H9N2,\(^\text{125}\) and LPAI H10N8\(^\text{109,122}\) virus infections.

**Clinical Presentation**

The clinical presentation varies by the specific virus infection, host characteristics, and time from illness onset to medical care. However, signs, symptoms, and

<table>
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<tr>
<th>Table 4</th>
<th>Summary of clinical and clinical laboratory findings reported in patients with severe disease from avian influenza A virus infection</th>
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<tr>
<td><strong>Admission clinical findings</strong></td>
<td>History of fever and cough (productive cough, shortness of breath, dyspnea, chest pain, hypoxemia are associated with severe pneumonia), myalgia; diarrhea, malaise, headache, sore throat can occur, but are less common. Radiographic findings: bilateral patchy, interstitial, lobar, and/or diffuse infiltrates, ground glass opacities, consolidation, air bronchograms</td>
</tr>
<tr>
<td><strong>Admission laboratory findings</strong></td>
<td>White blood cell count may be low or normal; lymphopenia and moderate thrombocytopenia are common; neutropenia and elevated alanine aminotransferase associated with H5N1 mortality.</td>
</tr>
<tr>
<td><strong>Clinical complications during hospitalization</strong></td>
<td>Respiratory failure, acute respiratory distress syndrome, refractory hypoxemia, pleural effusion, cardiac failure, acute kidney injury/renal failure, multiorgan failure, septic shock, rhabdomyolysis, spontaneous miscarriage in pregnant patients, disseminated intravascular coagulation, encephalitis, bacterial co-infection, fungal co-infection, pneumothorax.</td>
</tr>
<tr>
<td><strong>Laboratory findings during hospitalization</strong></td>
<td>Elevated lactate, creatinine kinase, hepatic transaminases; hypoalbuminemia, leukopenia or leukocytosis</td>
</tr>
</tbody>
</table>

Associated with H5N1, H5N6, or H7N9 virus infections.
Complications associated with avian influenza A virus infection are nonspecific and overlap with those caused by other respiratory pathogens, including seasonal influenza A and B viruses. Patients with avian influenza A(H7) virus infections can present with unilateral conjunctivitis only or also with fever and upper respiratory tract symptoms. The incubation period is not well-characterized for human infection with most avian influenza A viruses, but is estimated to be approximately 3 to 5 days after exposure to infected poultry for H5N1\cite{126,127} and H7N9\cite{127-129} virus infections, with a wider range in clusters with limited human-to-human transmission of H5N1 virus.\cite{26,77}

In early illness with H5N1, H5N6, or H7N9 virus infections, fever or feverishness is usually present; cough, and malaise, myalgia, headache, and sore throat also may be present.\cite{115,120,130} Gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea are variable,\cite{60,77,120,131} but conjunctivitis is uncommon.\cite{74,115,120} Atypical presentations have included fever and diarrhea before signs and symptoms of lower respiratory tract disease or encephalitis developed.\cite{132,133} Dyspnea, shortness of breath, tachypnea, productive cough, and chest pain are associated with severe pneumonia. Many patients with H5N1, H5N6, or H7N9 virus infections have presented to medical care with severe pneumonia and hypoxemia approximately 5 to 7 days after illness onset.\cite{4,64,112,113,115,123}

Routine laboratory findings are nonspecific and leukopenia, lymphopenia, and lymphopenia is commonly observed at admission, but white blood cell counts may be normal initially for patients with H7N9 virus infection.\cite{120} A high neutrophil to lymphocyte ratio 24 hours after hospital admission of H7N9 patients was independently associated with mortality.\cite{134} Other abnormalities reported in severely ill patients with H5N1, H5N6, or H7N9 virus infections include hypoalbuminemia\cite{77} and elevated levels of hepatic transaminases,\cite{60,112,113,115,120} creatinine kinase,\cite{98,112,115,120} and lactic dehydrogenase.\cite{112,115,120} Radiographic findings in patients with H5N1, H5N6, or H7N9 virus infections hospitalized with pneumonia include bilateral patchy, interstitial, lobar, and/or diffuse infiltrates, ground glass opacities, consolidation, pleural effusion, air bronchograms, and pneumothorax.\cite{60,112,115,120,135}

**Complications**

Respiratory complications of H5N1, H5N6, or H7N9 virus infections include pneumonia, respiratory failure, and acute respiratory distress syndrome.\cite{60,112,115,120,135} Extrapulmonary dissemination and isolation of H5N1 virus from blood, cerebrospinal fluid, brain tissues, lower respiratory tract tissues, gastrointestinal tract tissues (ileum, colon, rectum), rectal swabs, stool, ureter, and axillary lymph node have been reported.\cite{133,136,137} Detection of H7N9 viral RNA was reported in stool.\cite{138} Extrapulmonary complications owing to H5N1 or H7N9 virus infections include cardiac failure,\cite{60,112,120} acute kidney injury,\cite{60,112,120} encephalitis,\cite{51,133,139} myelitis,\cite{140} rhabdomyolysis,\cite{120,141} multiorgan failure and sepsis,\cite{112,120,142} disseminated intravascular coagulation,\cite{112,113,120,143} and spontaneous miscarriage in pregnant patients.\cite{112} A 36-week gestational infant survived after emergency Cesarean section delivery of a critically ill pregnant woman with H5N1 virus infection who died.\cite{144} Obstructive hydrocephalus,\cite{139} and Reye syndrome with aspirin administration\cite{145} have been reported in pediatric cases of H5N1 virus infection. Co-infection with bacterial pathogens has been reported at hospital admission in H7N9 patients,\cite{146} and nosocomial infection and ventilator-associated pneumonia with bacterial and fungal pathogens can occur.\cite{8,120,147,148,149} Nosocomial bacterial infections were more common in 6 fatal cases than in 6 survivors of H7N9 virus infection.\cite{138} H5N1 virus infection in persons with HIV has been reported.\cite{60,150}
Neutropenia and elevated alanine aminotransferase at admission were associated with mortality for H5N1 patients in an observational study. Septic shock with severe hypoxemia was an independent risk factor associated with mortality in H7N9 patients in another observational study. Refractory hypoxemia is a major cause of death in H7N9 patients.

Pathogenesis and pathology findings

In severe disease, the pathogenesis of H5N1, H5N6, and H7N9 virus infections is driven by high viral levels and prolonged replication in the lower respiratory tract and aggravated by innate immune dysregulation. Higher viral levels in nasal and throat swabs are associated with adverse clinical outcomes in H5N1 disease. H5N1 virus infects ciliated and nonciliated tracheal epithelial cells with tropism for α2,3-linked sialic acid receptors in the lower respiratory tract, and H7N9 virus has affinity for α2,6-linked sialic acid receptors in the upper respiratory tract, but preferentially binds to α2,3-linked sialic acid receptors in the lower respiratory tract. Patients with severe and fatal lower respiratory tract disease have prolonged H5N1 viral replication.

High-dose corticosteroid treatment is associated with prolonged detection of H7N9 viral RNA. In vitro and ex vivo studies indicate that H5N1, H5N6, and H7N9 viruses induce inflammatory mediators, and data from critically ill patients indicate that virus infection of the respiratory tract triggers a dysregulated proinflammatory cytokine and chemokine response, resulting in inflammatory pulmonary damage and multiorgan injury. H5N1 virus induces higher levels of proinflammatory cytokines and chemokines than H7N9 and seasonal influenza A viruses and infection of endothelial cells as shown in mice and ferrets may also contribute to pulmonary vascular leakage and viral pneumonia.

Limited autopsy studies have described extrapulmonary dissemination of H5N1 and H5N6 viruses, including evidence of infection of cerebral neurons, placenta, T lymphocytes in lymph nodes, cytrophoblasts of placental chorionic villi and fetal macrophages (transplacental transmission); pulmonary findings of diffuse alveolar damage and interstitial fibrosis for H5N1, H5N6, and H7N9 virus infections; and other organ findings of hepatic central lobular necrosis, acute renal tubular necrosis, lymphoid depletion, and reactive hemophagocytic syndrome for H5N1 or H7N9 virus infections.

CLINICAL MANAGEMENT

Infection Prevention and Control Measures

Prompt isolation and implementation of infection prevention and control measures is essential to decreasing the risk of nosocomial transmission of patients with avian influenza A virus infection associated with severe and fatal illness (eg, H5N1, H5N6, H7N9, H10N8 viruses). The Centers for Disease Control and Prevention recommend placement of patients with suspected avian influenza A virus infection associated with severe illness in a negative pressure respiratory isolation room and implementation of standard, contact (including goggles), and airborne (use of fit-tested N95 respirator or higher level of respiratory protection) precautions for healthcare personnel while providing care, including collecting respiratory specimens. The World Health Organization recommends personal protective equipment (medical mask, eye protection, gown, and gloves), performing adequate hand hygiene, and use of a separate adequately ventilated or airborne precaution room (isolation in mechanically or naturally ventilated rooms with 12 air changes per hour and controlled direction of airflow), and use of a respirator for aerosol-generating procedures. Patients should wear a medical mask when outside of isolation rooms.
Diagnosis

Because the signs, symptoms, and clinical findings are nonspecific, clinical suspicion of avian influenza A virus infection (all subtypes with at least 1 human infection; see Tables 1 and 2) is based on eliciting a history of (1) recent poultry exposure in a virus enzootic region, in particular, visiting a market where live poultry are sold or slaughtered, or at small farms or inside/outside homes (where poultry are raised), or (2) recent close exposure to a symptomatic person with suspected or confirmed avian influenza A virus infection (e.g., viruses in which limited human-to-human transmission has been reported, namely, H5N1, H7N7, and H7N9). The optimal respiratory specimens to collect depends on the time from illness onset to presentation, the presumed site of the major pathology and the patient’s disease severity. For example, although a nasopharyngeal specimen might be sufficient for detecting some avian influenza A viruses associated with upper respiratory symptoms, a throat swab specimen has a higher yield for detecting H5N1 virus in patients without severe lower respiratory tract disease. For hospitalized patients, the collection of respiratory specimens from multiple respiratory sites, including sputum, can increase the likelihood of detecting avian influenza A virus infection. For critically ill patients with respiratory failure receiving invasive mechanical ventilation, an endotracheal aspirate or bronchoalveolar lavage specimen should be collected for testing.

Commercially available influenza tests available in clinical settings, including molecular assays, detect influenza A and B viruses but do not specifically distinguish between seasonal influenza A viruses circulating among people worldwide and zoonotic avian influenza A viruses. Therefore, respiratory specimens must be sent to a public health laboratory for specific testing for avian influenza A virus subtypes by reverse transcriptase polymerase chain reaction (e.g., H5, H7, H9) and additional analyses, such as genetic sequencing. Antigen detection tests are less sensitive than reverse transcriptase polymerase chain reaction assays for detecting avian influenza A virus infection. Serologic testing of paired acute and convalescent sera can yield a retrospective diagnosis, but must be performed at a specialized public health or research laboratory.

Discharge Criteria

No guidelines exist on discharge criteria for hospitalized patients with avian influenza A virus infection, but key criteria are clinical recovery with demonstration of clearance of viral RNA from the respiratory tract.

Antiviral Treatment

There are no randomized controlled trials (RCTs) of antiviral treatment of patients with avian influenza A virus infection. No clinical or virologic benefit of double-dose versus standard-dose oseltamivir was found in an RCT conducted in 326 hospitalized patients with influenza, including 17 H5N1 patients.183 Mortality was very high (88%) among the enrolled H5N1 patients.183 Observational studies of patients with H5N1 or H7N9 virus infections have reported survival benefit of antiviral treatment with a neuraminidase inhibitor (NAI), usually oseltamivir monotherapy, particularly when treatment is initiated early in the clinical course.74,113,149,184–188 One observational study reported no benefit of combination NAI treatment (oseltamivir and peramivir) compared with oseltamivir for hospitalized H7N9 patients.189 Most severely ill H5N1, H5N6, and H7N9 patients have been admitted more than 5 days after illness onset, with late initiation of NAI treatment. One observational study reported that
delayed administration of NAI treatment was an independent risk factor for prolonged H7N9 viral shedding.\textsuperscript{156}

Currently, NAI treatment is recommended as soon as possible in patients with suspected avian influenza A virus infection, even before laboratory confirmation, because there may be a long delay until specific testing results are received. Recommended NAI dosing is the same as for the treatment of patients with seasonal influenza. Combination treatment with 2 NAIs is not recommended. The duration of antiviral treatment should continue until there is no evidence of viral shedding and be guided by testing results of respiratory tract specimens, particularly lower respiratory tract specimens, in ventilated patients. The emergence of antiviral resistance to NAIs should be considered in patients with prolonged viral replication with no decrease in viral load. Analyses of genetic markers associated with decreased antiviral susceptibility or resistance can be performed on viral RNA and phenotypic antiviral susceptibility testing on virus isolates at specialized public health reference laboratories.

The emergence of oseltamivir-resistant viruses containing an H275Y mutation in viral neuraminidase has been reported during oseltamivir treatment of H5N1 patients with sustained viral replication, clinical deterioration, and fatal outcomes.\textsuperscript{190} and in an H5N1 patient who had received oseltamivir chemoprophylaxis followed by oseltamivir treatment and recovered.\textsuperscript{79} Similarly, the emergence and sustained replication of H7N9 viruses with an R292 K mutation in viral neuraminidase confers resistance to NAIs.\textsuperscript{158,191–193} This mutation confers high-level resistance to oseltamivir and moderately decreased sensitivity to peramivir and zanamivir.\textsuperscript{194} Most H5N1, H5N6, and H7N9 viruses circulating among poultry are resistant to the adamantane antivirals (amantadine and rimantadine). Novel antivirals such as favipiravir and baloxavir marboxyl have not been used therapeutically in zoonotic avian influenza A virus infections, but may need to be considered in the event of NAI resistance.\textsuperscript{194}

**Adjunctive Therapy**

Immunotherapy with convalescent plasma has been administered to a very small number of hospitalized H5N1 patients. The source of the convalescent plasma was recovered survivors of H5N1 virus infection\textsuperscript{112,195} for 2 critically ill patients with respiratory failure receiving invasive mechanical ventilation and an H5N1 vaccine recipient for another patient\textsuperscript{78} with pneumonia receiving noninvasive ventilation, all of whom also received antiviral treatment and survived. Convalescent plasma from a recovered survivor has also been administered to a hospitalized H7N9 patient with respiratory failure receiving invasive mechanical ventilation with no improvement from oseltamivir treatment.\textsuperscript{196} The patient also received other medications, including methylprednisolone, and survived.\textsuperscript{196} No conclusions can be made on the clinical benefit of convalescent plasma treatment from such limited uncontrolled data, but further studies of the clinical benefit of immunotherapy as an adjunctive treatment to antiviral therapy are warranted. IVIG has been administered to some H7N9 patients on an uncontrolled basis.\textsuperscript{149}

No RCTs have been conducted of corticosteroid treatment for any patients with avian influenza A virus infection. Observational studies have suggested an increased mortality risk with corticosteroid treatment of H5N1\textsuperscript{113} and H7N9\textsuperscript{197} patients, and high-dose corticosteroids have been implicated with increased H7N9 mortality risk.\textsuperscript{155} High-dose corticosteroids were also reported to be an independent risk factor for prolonged H7N9 viral shedding in an observational study of 478 patients with H7N9.\textsuperscript{156} The clinical benefit or harm of low-dose or moderate-dose corticosteroid treatment for hospitalized patients with avian influenza A virus infection is unknown. However, given the observational data to date, high-dose corticosteroids should be avoided, and corticosteroids should only be administered for treatment of septic shock.
There are very limited and inconclusive observational data about the benefit of probiotic treatment of patients with H7N9 virus infection. Salicylates should not be administered to patients with suspected or confirmed avian influenza A virus infection because of the risk of Reye syndrome.

**Advanced Organ Support**

No RCTs are available, but advanced organ support has been administered to most critically ill hospitalized patients with H5N1, H5N6, or H7N9 virus infections, especially invasive mechanical ventilation for respiratory failure. In H7N9 patients with acute respiratory distress syndrome, extracorporeal membrane oxygenation has been administered on an uncontrolled basis. H7N9 patients with acute kidney injury have also required renal replacement therapy. Plasma exchange has been used in combination with continuous venovenous hemofiltration to reduce levels of cytokines and chemokines. Artificial liver therapy has been used in management of some H7N9 patients.

**Immune responses**

During the acute illness, most H5N1 patients typically mount a robust neutralizing antibody response 14 or more days after onset. In 4 H5N1 survivors of severe disease, although specific hemagglutination inhibition and neutralizing antibody titers increased from 15 days after illness onset and declined by 5 to 12 months, titers were detectable for 3 to 4 years after onset. A follow-up study of 11 H5N1 patients who survived severe disease reported that 70% had a positive neutralizing antibody titer after 2 weeks and all had a neutralizing antibody titer of 1:80 or greater by 3 weeks after illness, with titers peaking at 1 to 2 months and declining by 10 to 12 months.

During the acute illness, most critically ill H7N9 patients mounted a robust humoral immune response with a seroprotective titer of neutralizing antibodies (≥1:40) detected significantly earlier (median, 10.5 days) in survivors than in fatal cases (median, 14 days). Other studies in H7N9 survivors have reported variable kinetics and antibody titers after recovery declining, though still detectable at 1 year after illness. T-cell (CD8+CD4+ T-cell memory) responses are reported to play an important role in recovery from disease.

**Long-term follow-up**

Few studies have assessed long-term clinical follow-up of survivors of severe or critical illness owing to avian influenza A virus infections. During follow-up of 2 adult H5N1 patients who recovered from respiratory failure and ventilator-associated bacterial pneumonia, 1 patient had bilateral patchy, as well as fibrotic reticular and linear opacities noted at 7 months that mostly had resolved by 12 months after illness onset. However, the more severely ill patient had ground-glass shadows, reticular opacities, linear fibrotic opacities, interlobular thickening and intralobular lines at 12 months that persisted at 24 months after onset. Of 5 adult patients who survived H7N9 virus infection and were followed for approximately 5 to 7 months after diagnosis, only one reported mild respiratory symptoms, but all had bilateral lower lung abnormalities such as interlobular septal thickening, subpleural linear opacities, and some had cystic changes on a computed tomography scan. For 3 of these 5 patients who had pulmonary function testing, 1 patient had near normal pulmonary function, but 2 patients had abnormalities in forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and carbon monoxide diffusing capacity. A cohort study of 56 adult H7N9 patients followed for
2 years reported that although pulmonary function and chest computed tomography findings improved by 6 months after hospital discharge and most had returned to work, most patients had persistent abnormalities. At 1 year after discharge, 42% had pulmonary fibrosis and 52% had parenchymal opacities, with bronchiectasis noted in 24% and pleural thickening reported in 22%, and 55% had evidence of ventilation dysfunction and 78% had an abnormal carbon monoxide diffusing capacity at 24 months (Box 1).

SUMMARY

A high index of suspicion and early diagnosis of avian influenza A virus infection is essential to initiating interventions (antiviral treatment; infection prevention and control measures) as soon as possible to reduce transmission risk from symptomatic persons to close contacts, including health care personnel. Clinical suspicion relies on eliciting a history of recent exposure to poultry or to sick persons with suspected or confirmed avian influenza A virus infection. Diagnosis requires the collection of appropriate respiratory specimens, ideally from the lower respiratory tract when available, for specific testing for seasonal and avian influenza A virus subtypes at specialized public health laboratories. Patients with suspected infection should be isolated immediately and patients with lower respiratory tract disease should be placed on airborne precautions if possible, and NAI antiviral treatment should be started as soon as possible even before specific testing results are available. Corticosteroids and salicylates should be avoided and clinical management is focused on supportive care of complications, including nosocomial bacterial or fungal infections. Sporadic human infections with avian influenza A viruses resulting in mild to severe illness are expected to continue to occur in persons with close exposures to infected poultry and other birds. Options to decrease human exposure to enzootic avian influenza include interventions in live poultry markets, which serve as a major source of zoonotic infection and virus amplification. Because zoonotic avian influenza A viruses pose potential pandemic threats, it is important to risk assess these viruses to prioritize countermeasure development such as vaccines.
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