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REVIEW OF THERAPEUTICS

Update and narrative review of avian influenza (H5N1) infection in adult patients

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Abstract

The avian influenza is a serious infection caused by influenza virus that is native to birds. Avian influenza remains a global challenge due to high transmission and mortality rates. The highly pathogenic strain of H5N1 resulted in significant outbreaks and deaths globally since the late 1800s. The most recent outbreaks in wild birds, domestic birds, and cows with some genetic variations and mutations among H5N1 strains has raised major concerns about potential transmission and public health risks. Symptoms range from asymptomatic to mild flu-like illness to severe illness that requires hospitalization. There are multiple vaccines in development for humans to protect against avian influenza, specifically the H5N1 virus. This includes a cell-based vaccine approved by the FDA for people aged 6 months and older who are at higher risk of exposure to the H5N1 virus called Audenz. Chemoprophylaxis against avian influenza following a suspected exposure should be started as soon as possible or no later than 48 h, and it is recommended to be continued for 7 days. The majority of avian influenza viruses are susceptible to neuraminidase inhibitors and cap-dependent endonuclease inhibitor. Neuraminidase inhibitors are the mainstay of the avian influenza treatment and includes oseltamivir, peramivir, and zanamivir. Baloxavir marboxil is a cap-dependent endonuclease inhibitor. This clinical review aims to highlight the background, epidemiology, clinical presentation, complications and current treatment and prevention strategies for avian influenza H5N1.

KEYWORDS
avian flu, bird flu, clinical pharmacy, H5N1, influenza, outbreak, pandemic

1 | INTRODUCTION

Highly pathogenic avian influenza (HPAI) raises concern for a looming public health crisis due to its ongoing spread among bird populations and its potential for human transmission, leading to severe illness.[1,2] Since 1997, there have been over 800 cases of confirmed avian influenza H5N1 in humans with a significant case fatality rate of 50%–53%.[1,2] In the wake of the COVID-19 pandemic, which began with the first reported cases in December 2019 and escalated to pandemic status by April 2020, affecting over 1 million people, the prospect of a new pandemic should be approached with utmost caution.[3] While a novel influenza A (H5N1) virus has the potential to become pandemic, the Centers for Disease Control and Prevention (CDC) reports as of June 5, 2024, that the risk to public health remains low as there are only four confirmed cases in 2024 thus far.[4–6] Avian influenza was discovered back in 1878; however, the highly pathogenic strain was later discovered in the mid-1990s.[4–6]

In infectious disease, the terms pandemic and endemic are used frequently. Pandemic is defined as a widespread of an infectious disease over a specific country or the world at a specified time.[3] While endemic refers to a disease that is regularly occurring and native within an area or community.[3] Pharmacists, as essential healthcare professionals, play a crucial role in managing public health through medication management, patient education, and administering vaccines and tests. During the COVID-19 pandemic, pharmacists facilitated point-of-care testing, vaccinations, and medical therapies to more than 150 million Americans.[7] Their expertise and preparedness will be critical in addressing a potential avian influenza pandemic, helping to prevent a recurrence of the challenges faced during COVID-19.[7] This clinical review highlights the background, epidemiology, clinical presentation, complications and current treatment and prevention strategies for avian influenza H5N1.[7] The goal of this narrative review was to highlight the background, epidemiology, clinical presentation, complications and current treatment and prevention strategies for avian influenza H5N1. The literature search was done using the following: avian flu, avian influenza, bird flu, and H5N1 in combination with drugs or treatment or pharmacotherapy using PubMed and google scholar to identify relevant articles.

2 | HISTORY AND EPIDEMIOLOGY OF AVIAN INFLUENZA PANDEMIC

Avian influenza, historically referred to as "fowl plague virus" (FPV), was first documented in Northern Italy in 1878. By 1955, Werner Schafer determined that FPV was an influenza A subtype, resembling human and swine viruses.[8] Of the A, B, C, and D subtypes, influenza A viruses are specifically known to infect a variety of birds and mammals, and have caused numerous global outbreaks.[8] Notorious influenza A-related pandemics include the 1918 "Spanish flu," which was responsible for the deaths of nearly 50 million people, followed by pandemics in 1957 (United States of American and People's Republic of China), 1968 (Hong Kong), and the most recent 2009 (mostly in Mexico) swine flu.[9]

Influenza subtype A H5N1, now commonly known as avian or avian flu, was more appropriately qualified in 1959, with the discovery of an antigenically different, highly pathogenic avian influenza (HPAI) strain in a Scottish chicken farm.[8,9] A LPAI variant was isolated in ducks and turkeys approximately 10 years later.[8,9] The first reported case of human H5N1 infection was in 1997 in Hong Kong, China.[8,9] H5N1 has since been found in humans in more than 50 countries, and there have been five reported cases in the United States since 2022 in Colorado, Texas, Michigan, and Missouri.[8,9]

3 | VIROLOGY

Avian influenza viruses are caused by influenza A viruses and belong to the family Orthomyxoviridae.[10] The RNA genome of the influenza A virus encodes for different viral proteins which include hemagglutinin (HA), neuraminidase (NA), matrix proteins (M1 and M2), and polymerase complex proteins (PB1, PB2, NP, and PA), and nuclear export protein/nonstructural protein 2 (NEP/NS2), NS1.[10–12] Each component has a different mechanism of action (see Table 1).[11]

The surface protein HA subtypes are numbered H1 through H18 and the surface protein NA subtypes N1 through N11.[10–14] The influenza A virus has one H antigen and one N antigen, and are named in this manner (e.g., H5N1).[13,14] The viral proteins also contribute to the pathogenicity of the virus.[12] Influenza A viruses to the HA and NA surface proteins mutating—both antigenic drift and antigenic shift.[13,14] Antigenic drift causes a mutation that can alter the antibody-binding sites of HA and NA, making it hard for the immune system to recognize the virus.[11–13] Antigenic shift, occurring less, causing a shift in the RNA genome of the virus (i.e., changing segments or combinations of HA and NA), and therefore, can cause new hosts to be affected.[11,13] It is the variations in HA and NA that are important in the determination of the virus's ability to infect other species and cause outbreaks in humans.[10–14]

The avian influenza viruses are further subcategorized based on their infectivity and viral characteristics as: highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI).[10–14] This categorization is based on the disease severity in poultry.[11,13] The reservoir for the avian influenza viruses are wild aquatic birds, such as geese or shore birds, but show limited signs of disease in these types of birds and have LPAI.[11,12,14] However, domestic poultry can be affected by both LPAI and HPAI.[12,14] This is the probable link for zoonotic transmission between birds and humans.[13] Most avian influenza viruses are of the LPAI; however, H5 and H7 have been associated with the HPAI and thought to seriously affect birds and humans.[11,12,14]

TABLE 1 Viral components of influenza A.

Viral component (protein)	Type of protein	Mechanism of protein
Hemagglutinin (HA)	Surface protein	Facilitates viral entry into host cells
Neuraminidase (NA)	Surface protein	Essential for viral particle release, facilitates spread of virus
Matrix proteins (M1 and M2)	Structural protein (M1) Ion channel protein (M2)	Involved with viral assembly and release; structural support (M1 only)
Polymerase complex proteins (PB1, PB2, PA, and NP)	Complexes with viral RNA	Involved with viral replication and transcription
Nuclear export protein/ nonstructural protein 2 (NEP/ NS2), NS1	Other proteins that exist in virus	Promote viral RNA replication

4 | TRANSMISSION

As of September 2024, there are more than 100 million poultry affected by this Highly Pathogenic Avian Influenza A (H5N1) Virus.[15] The virus impacts not only poultry species but also pet birds, wild birds, cows, and occasionally, humans.[16,17] Influenza A virus was categorized and recognized by hemagglutinin HA subtypes.[16,17] The HA initiates the infection by connecting the virus to the host cell membrane by modulating sialic acid receptors.[18] Avian influenza primarily affects the upper respiratory system due to the prevalence of the sialic receptors on the epithelial cells on the respiratory tract.[18] As a result, respiratory failure often manifests as a predominant feature in avian flu-infected individuals.[19,20]

Avian influenza can be transmitted by several mechanisms.[21] Infected birds release the virus through their saliva and feces.[21] Direct contact, contaminated environment, and respiratory droplets can facilitate disease transmission among birds as migratory birds often interact with domestic or wild birds.[21,22] The interactions are crucial in spreading the virus over long distances.[22] Local transmission happens through the movement of migratory infected birds, movement of feces, contaminated feeding, and agricultural or human activities in poultry settings.[23] Since the infection originated from birds, the risk of contracting the disease is highest in areas with a high prevalence of poultry farming. Nonetheless, exposure to birds should be avoided during the outbreak regardless of proximity to the endemic area as there is risk of exposure to the infected bird due to bird migration.[23]

Among humans, the virus spread via infected droplets inhalation and direct or indirect contact.[24] Infected birds to humans or environment to humans have been proposed as mode of transmission.[24] In previous outbreak, disease transmission between birds and human or birds to other animals were less likely or sporadic to mammals (bears, bobcats, minks, mountain lions, raccoons, and skunks).[24] However, in the current outbreak in 2024, H5 in dairy cows was first reported in Texas and Kansas by the U.S. Department of Agriculture (USDA).[24] Unpasteurized milk from infected cows from farms in Kassas and Texas tested positive for H5 viruses with the same genetic clade that is widespread among infected birds globally.[25] The transmission was presumably due to wild birds since there were reported deceased wild birds on the premise.[25] According to the CDC, pasteurization of milk is required for any interstate commerce; therefore, this poses no risk to consumers in the United States.[25] Pasteurization is effective at inactivating avian influenza in milk and other dairy products.[25] Further, milk from infected cow had been diverted and destroyed, so it did not enter commercial distribution.[25] Regardless, consuming unpasteurized dairy products such as cheese or raw milk should be avoided in the areas of outbreak.[25]

Transmission from birds to dairy cows in 2024 is new and unexpected of the H5N1 virus since influenza A virus infection in bovine species is exceptionally rare.[26] The spread among cows indicates a sign that the virus is mutating, making it easier for it to spread to other animals or potentially humans.[26] Avian influenza virus is transmitted to mammals through infected birds, poultry, or other animals and following environmental exposure.[26] While the transmission of H5N1 from birds to humans is regarded as uncommon, and humans to humans transmission is rare, a limited number of human cases have been documented in several countries since 2003 with high mortality rates.[27] Humans to humans transmission has been reported in multiple countries among close, prolonged, unprotected household exposure to infected family members from 2004 through 2007.[28] Since 2007, all cases have involved exposure to infected animals. In 2024 thus far, reports of transmission to humans have been limited to a few cases.[25] Human cases were reported in the United Sates of America, Ecuador, Mexico, Cambodia, and People's Republic of China.[25] Currently, CDC employs a close monitoring to indicate unusual level of influenza virus and illness activity.[2,3,6] Since the outbreak in early 2024, at least 4900 people who have exposure risk were monitored (at least 70 persons were exposed to dairy cows and at least 2600 persons were exposed to birds and other animals including poultry).[2,3,6] Two hundred forty persons were screened for Avian influenza. Only 14 persons were tested positive.[2,3,6]

5 | CLINICAL PRESENTATION AND COMPLICATIONS

Clinical presentations of H5N1 infection are typically only reported and documented in patients who required hospitalization since routine testing for H5N1 infection is usually not performed.[21] Symptoms ranges from no asymptomatic to mild flu-like illness to severe illness that requires hospitalization.[21] The clinical presentation of avian influenza can vary widely, from asymptomatic cases to severe disease.[7,29] Mild symptoms include conjunctivitis, fever, sore throat, fatigue, and cough, while severe infections can lead to fulminant pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure.[4,30] The onset of symptoms is 2–4 days after the exposure, although in some cases, it can occur over 7 days after disease transmission.[31] Infected patients often exhibit signs of elevated body temperature, flu-like symptoms, chills, shortness of breath, myalgia, vomiting, diarrhea, headache, and abdominal pain.[31] In some severe cases, patients can present with pneumonia.[31] Radiographic changes such patchy, multifocal, or diffused infiltrates, or consolidation can be observed.[31] Respiratory failure, multiorgan failure have also been reported with the mortality exceeds 50% of all hospitalized H5N1-infected patients.[28,32,33] When compared to seasonal influenza, patients with avian influenza most frequently present with a high-grade fever, greater and more pronounced respiratory distress, and conjunctivitis.[28,32,33]

Avian influenza complications include heart failure exacerbation, asthma and chronic obstructive pulmonary disorder exacerbation, lower or upper respiratory tract disease infection, neurologic deterioration, and multiorgan failures.[34–36] Individuals at risk of developing avian influenza complications include any patients older than 65 years old or younger than 2 years old, pregnancy, patients with chronic lung disease, any chronic illness (cardiac, renal, hepatology,

neurologic, and hematologic) obese, and immunocompromised patients.[34–36]

6 | DIAGNOSIS

Avian influenza should be considered in individuals presenting with influenza-like illness or acute respiratory infection, especially if they have had recent exposure (within the past 10 days) to animals with known or suspected avian influenza.[6] Thus, conducting an exhaustive history taking and obtaining an accurate patient's history is pivotal for an accurate diagnosis. Radiographic findings may show diffuse, multifocal or patchy infiltrates, interstitial infiltrates or lobular consolidations, although pleural effusions are uncommon in avian influenza (H5N1) infections.[30,37] The differential diagnosis for suspected avian influenza infection should include other acute respiratory illnesses, such as coronaviruses, rhinoviruses, seasonal influenza, respiratory syncytial virus, and bacterial pneumonia, consistent with local epidemiology and circulating pathogens.[6,38] Unlike seasonal influenza, avian influenza patient's chest X-ray shows bilateral diffuse infiltrates or consolidation.[6,38] Chest X-ray among seasonal influenza patients shows mild diffuse interstitial infiltrates.[6,38] Data from epidemiological studies show that bacterial coinfections can occur in a significant proportion of patients with vial influenza, with estimates 10%–50%.[39,40]

Individuals should be tested for avian influenza if they meet specific epidemiologic criteria and either clinical or public health response criteria.[4] Preferred respiratory specimens should ideally be collected within 7 days of symptom onset and sent to a local or state health department laboratory.[6,41] Collection should be done using a nasopharyngeal swab, nasal aspirate, or nasal wash, either alone or in combination with an oropharyngeal swab.[41] For patients with severe lower respiratory tract illness, an endotracheal aspirate or bronchoalveolar lavage fluid should be obtained.[41] Testing for suspected avian influenza is conducted via real-time reverse-transcriptase polymerase chain reaction (rRT-PCR), which can differentiate between seasonal and avian influenza.[31] The sensitivity and specificity of rRT-PCR for diagnosing avian influenza are between 95% and 99%.[42,43] Rapid antigen detection tests are not recommended due to their unknown sensitivity and specificity for novel influenza A viruses.[4,37] Serology testing is also not recommended for the acute diagnosis of avian influenza.[31] Serology testing does not provide timely results, and is dependent on antibodies produced that are minimally present during the early acute phase of infection.[31] Respiratory specimens sent to the local/state health department will be confirmed by the CDC's Influenza Division Laboratory or a CDC designated laboratory for the diagnosis of avian influenza A virus.[44] Commercially available rapid influenza antigen tests (RIDTs) have moderate sensitivity and high specify. Tests with moderate sensitivity and high specify generate false negative results. Clinicians should consider a confirmatory test among negative results patients with high suspension and pandemics.[45]

7 | TREATMENT

Table 2 summarizes the mechanism of action, dose, dosage form, and side effects of all antivirals effective for avian influenza treatment and post-exposure prophylaxis. The mainstay of avian influenza treatment is similar to the seasonal influenza treatment modality.[34–36] The majority of avian influenza viruses are susceptible to neuraminidase inhibitor and cap-dependent endonuclease inhibitor.[34–36] The avian influenza is often resistant to amantadine and rimantadine.[34–36]

7.1 | Neuraminidase inhibitor

This class of antivirals work through the inhibition of viral surface neuraminidase enzyme.[34–36] This enzyme enables the virus to leave the host cell neuraminidase inhibitors that are FDA-approved antivirals and effective against influenza A include oseltamivir, peramivir, and zanamivir.[34–36] Neuraminidase inhibitors are the mainstay of the avian influenza treatment.[34–36] A meta-analysis found the use of any neuraminidase inhibitor for confirmed influenza A infections resulted in a 29%–43% significantly lower odds of developing complications requiring antibiotics use.[46] The initiation of antiviral treatment is recommended for any patient with confirmed or suspected avian influenza who is hospitalized, or showing severe, complicated, or progressive viral illness, or at risk of influenza complications.[34–36] The antiviral treatment should preferably start within 48 h of symptoms onset.[34–36] Although this open label clinical trial only included patients with seasonal influenza, it is likely the effect will be similar among avian flu patients due to a similar virology.[47] This open label clinical trial demonstrated that patients who were started on antiviral therapy within 12 h from fever onset had significantly lower duration of illness by 3.1 days compared to those initiated on antiviral therapy between 12 and 48 h from fever onset.[47]

When oral administration is feasible, the use of oral oseltamivir is recommended for hospitalized and outpatients avian influenza treatment.[34–36] A landmark trial was published in 2000 by Nicholson KG et al. demonstrated that oral oseltamivir is safe and effective for influenza A acute treatment.[48] The use of oseltamivir resulted in a significant reduction in the duration of illness by 29 h for the dose of 75 mg twice daily and by 35 h at a dose of 150 mg twice daily.[48] The use of intravenous (IV) peramivir is recommended over oral oseltamivir when gastrointestinal absorption is compromised, gastrointestinal bleeding or perforation.[49,50] An open-label clinical trial showed IV peramivir when oral oseltamivir is contraindicated resulted in a reduction of viral shedding and in clinical improvement.[49] This was demonstrated by a significant reduction in virus titer from baseline by 1.47–1.66 $TCDI_{50}$/mL.[49] There was no significant difference in clinical outcomes.[49] Although included all patients with influenza A and utilized a lower dose peramivir IV, time to clinical stability was similar between peramivir 400 mg IV daily, peramivir 200 mg IV daily and oral oseltamivir at 37, 23.7, and 28.1 h, respectively.[50]

TABLE 2 FDA-approved antivirals for avian flu treatment and post-exposure prophylaxis.

Antiviral agent	Mechanism of action	Dosage form	Treatment dose	Prophylaxis dose	Side effects	Dose adjustments	Pregnancy class	Drug interaction
Neuraminidase inhibitor								
Oseltamivir. Prodrug that is converted to oseltamivir carboxylate by liver esterase	Acts through the inhibition of viral surface neuraminidase enzyme. This enzyme enables the virus to leave the host cell	PO capsule and PO suspension	75 mg PO BID	75 mg PO QD	N/V	• Treatment; CrCl 10–30 mL/min: 75 mg PO QD • Prophylaxis; CrCl 10–30 mL/min: 75 mg every other day or 30 mg PO QD	Considered safe	• Avoid the use of LAIV within 2 weeks before or 48 h after oseltamivir • Oseltamivir is excreted through OAT1/3; probenecid increases oseltamivir concentration
Peramivir		IV	600 mg IV QD over 15 min	NR	SJS, hypersensitivity, and diarrhea	• CrCl 30–49 mL/min: 200 mg IV QD • CrCl 10–29 mL/min: 100 mg IV QD	Human data are not available	Avoid the use of LAIV within 2 weeks before or 48 h after peramivir
Zanamivir		INH	Two inhalation (10 mg) BID	Two inhalation (10 mg) QD	Sore throat, cough, asthma, and COPD exacerbation	–	Human data are not available	Avoid the use of LAIV within 2 weeks before or 48 h after zanamivir
Cap-dependent endonuclease inhibitor								
Baloxavir marboxil. Prodrug that is converted to baloxavir via UGT1A3 and CYP3A4	Viral endonuclease inhibitor of the polymerase acidic protein. This leads to inhibition of the viral gene transcription, and replication	PO tablet and PO suspension	• Weight < 80 kg; 40 mg PO QD • Weight ≥ 80 kg; 80 mg PO QD	Same as the treatment dose	N/V	–	Human data are not available	Polyvalent cation (calcium, iron, magnesium, selenium, or zinc); decreases the concentration of baloxavir marboxil

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; INH, oral inhalation; IV, intravenous; LAIV, live attenuated influenza vaccine; N/V, nausea and vomiting; NR, not recommended; OAT1/3, organic anion transporter1/3; PO, by mouth; QD, once daily; SJS, Stevens–Johnson syndrome; UGT1A3, UDP-glucuronosyltransferase 1A3.

The FDA-recommended dose of oral oseltamivir for influenza A treatment is 75 mg twice daily by mouth.[51] A higher dose of oseltamivir 150 mg twice daily by mouth was studied for influenza A treatment, however, currently not approved.[51] Two randomized clinical trials concluded that a higher dose of oseltamivir was not associated with a significantly lower mortality rate when compared to the standard dosing (7.3% vs. 5.6%) or virologic improvement (44.7% vs. 40.2%) when used among patients with influenza A.[52,53] The higher dose of oseltamivir failed to show better clinical and virologic improvement among immunocompromised patients.[54] Additionally, oseltamivir resulted in a similar reduction rate of infection, complications, and symptoms alleviation irrespectively of the dose administered.[55] Data also suggests against the oseltamivir dose adjustment among obese patients.[56] A pharmacokinetic study demonstrated that a dose of 75 mg by mouth twice daily and 150 mg twice daily among obese patients achieved comparable therapeutic levels to nonobese patients.[57] The C_{max} for the 75 mg twice daily and 150 mg twice daily for nonobese versus obese patients were 74.4 versus 78.9, and 192 versus 153 ng/mL, respectively.[57] This study suggests that a higher dose for obesity is not warranted.[57]

Lastly, inhaled zanamivir has demonstrated efficacy and safety when used for uncomplicated avian influenza treatment.[58–60] Due to the lack of oral bioavailability, zanamivir is available as an powder with a lactose vehicle.[53] It is administered orally with the use of an inhalation device (Diskhaler, Glaxo Wellcome).[53] Currently, there are no data that supports the use of inhaled zanamivir among high risk patients or complicated avian influenza cases.[58–60] Similar to oral therapy, inhaled zanamivir therapy must be initiated within 48 h of symptoms.[58–60] When initiated early, it resulted in a significant reduction of respiratory events leading to the use of antibiotics versus placebo at a rate of 11% and 17%, respectively.[61] When zanamivir was studied among patients with influenza A and B, it significantly lowered the duration of illness and time needed to return to normal activity by 2.5 and 3 days, respectively.[62] The combination therapy of inhaled zanamivir plus oral oseltamivir is not recommended.[63] Published data suggests this combination therapy is less efficacious than oral oseltamivir monotherapy.[64,65] Although data are conflicting, when zanamivir was administered via inhaled and intranasal combination therapy, it resulted with a significantly shorter time to symptoms alleviation by 1 day.[66] Inhaled zanamivir could exacerbate asthma and chronic obstructive pulmonary disease (COPD).[58–60] Severe cases of bronchospasm were reported following the inhaled zanamivir among patients with and without respiratory disease.[58–60] The safety and efficacy of inhaled zanamivir among patients with decompensated asthma and COPD have not been established.[58–60]

7.2 | Cap-dependent endonuclease inhibitor

Cap-dependent endonuclease inhibitors result in inhibition of viral enzymes needed for mRNA capping and decay.[67] This prevents the initiation of mRNA synthesis.[67] This leads to inhibition of transcription and replication of the viral gene. The oral administration of baloxavir marboxil is approved for influenza A and B treatment.[67] Similar to oseltamivir, it is approved to be used within 48 h of symptoms onset.[67] A single dose of baloxavir marboxil was safe and effective in the treatment of influenza A.[67] It resulted in a significantly lower time to symptoms alleviation compared to placebo of 53.7 h versus 80.2 h, respectively.[67] The CAPSTONE-2 trial demonstrated that early initiation of a single dose baloxavir marboxil was superior to placebo and equivalent to oseltamivir among high risk influenza A patients.[68] Time to improvement in influenza symptoms among patients treated with baloxavir marboxil, placebo and oseltamivir were 73.2, 102.3, and 81 h, respectively.[68] Although was tolerated, the combination of baloxavir marboxil and neuraminidase inhibitor was not superior to the neuraminidase inhibitor monotherapy in the FLAGSTONE trial.[69] Time to clinical improvement in the combination group was 97.5 h compared to 100.2 h in the monotherapy group.[69] However, the combination therapy was associated with a significantly lower viral shedding compared to neuraminidase inhibitor monotherapy (23.9 h vs. 63.7 h).[69] However, the CDC recommends against the use of baloxavir marboxil among immunocompromised patients with suspected avian influenza solely based on the lack of randomized clinical trials and due to the risk of developing sever avian influenza complications.[63]

8 | INVESTIGATIONAL THERAPIES

8.1 | Convalescent plasma

Convalescent plasma therapy is the use of plasma from a patient who obtained antibodies after recovering from a viral infection, which is then transfused to another patient suffering from the same viral infection.[1,70] This therapy was first established and used in 1880 for the treatment of diphtheria.[1,70] A large systemic review and meta-analysis suggested that convalescent plasma significantly reduced mortality among patients with primary or secondary immunospressions.[71] The use of convalescent plasma therapy for avian influenza could possiblly has benefits, however, data are limited.[72]

Data obtained from a small study during the influenza A pandemic showed that convalescent plasma therapy increased survival rates by reducing respiratory tract viral loads, and serum cytokine response among patients with severe influenza A viral infections compared to patients who did not receive the treatment.[73] When convalescent plasma was used in combination with oseltamivir resulted in a reduction in the density of pulmonary lesions, a negative result on RT-PCR and enhanced patient recovery.[74] Due to the lack of research on the use of convalescent plasma for avian influenza, specific dosing regimens are not yet established.[72] According to the FDA, guidelines state 200 mL as an initial infusion are recommended and additional doses are based on the patient's response and clinical judgment.[75] Although generally considered safe, convalescent plasma still has risk of use including allergic reactions, infusion reactions, and potential for transmission of other infections.[72,74] Other

challenges associated with convalescent plasma therapy include the process of obtaining, processing, and administering the plasma, and the need for inpatient care level.[72,74]

8.2 | Corticosteroids

Steroids have been widely used for their role in inhibition of inflammation and immunosuppressive properties.[76,77] In cases of severe avian influenza cases, steroids are thought to mitigate the severe inflammatory response that can lead to the development of acute respiratory distress and organ failure.[76] The potential role of corticosteroids for the treatment of avian influenza (H5N1) is not yet established due to lack of research.[72] To date, there are no published randomized clinical trials that evaluated the use of corticosteroids among influenza patients.[72] Steroids could have the potential to help manage the severe inflammatory response that occurs with the avian influenza with early intervention.[72,76]

Early administration, if necessary, may help reduce inflammation and prevent cytokine storm that can occur in severe cases.[76] However, a recent meta-analysis and systemic review showed that corticosteroids significantly resulted in a higher mortality rate among influenza patients.[78] With the use of steroids for any influenza virus, important aspects should be considered including timing of administration, duration of treatment, monitoring of side effects, appropriate dosing, and tapering off.[72,76] The use of steroids for treatment of any indication requires careful consideration due to the side effects associated with short-term and long-term use of steroids.[76] Short-term use of side effects include but are not limited to hyperglycemia, pancreatitis, electrolyte abnormalities, hypertension, hirsutism, and hematologic effects.[79] While the long-term use bring more significant side effects and risk including osteoporosis, adrenal insufficiency, increased risk of infection, and weight gain.[79] A major risk associated with the use of steroids long term with abrupt discontinuation is adrenal suppress which can lead to adrenal crisis due to the suppression of the hypothalamic–pituitary–adrenal axis.[79] A systematic review and meta-analysis that included 10 trials and 6548 patients demonstrated that corticosteroids were associated with higher mortality.[80] Based on a limited data, the routine use of corticosteroids for influenza treatment cannot be recommended.

9 | POST-EXPOSURE PROPHYLAXIS

The aim of post-exposure prophylaxis (PEP) is to prevent the likelihood of developing avian influenza infection following a known or suspected exposure.[81] The prevention measures of administrating the proper pharmacologic intervention should be implemented against suspected poultry and human-to-human transmission.[25,81] Being in proximity (2 m) of an infected person, secretions or infected bird without the proper personal protective equipment qualifies for a PEP.[25,81] The ideal time to administer antivirals for PEP and chemoprophylaxis is as soon as possible (no later than 48 h), and recommended to be continued for 7 days.[25,81] Oral oseltamivir, oral baloxavir marboxil, and inhaled zanamivir are approved for chemoprophylaxis.[25,81] For outbreaks in long-term facilities and hospitals, the CDC recommends either oral oseltamivir or inhaled zanamivir for at least 2 weeks and to be continued for at least 1 week following the detection of last identified case.[25,81]

10 | INFECTION CONTROL AND PREVENTION

The best preventative measure is to avoid sources of exposure. All individuals should avoid unprotected exposure to sick or deceased animals such as wild birds, migratory birds, poultry, wild or domesticated animals (including cows), as well as with animal carcasses and feces of confirmed or suspected H5N1 infection.[6] Uncooked food products such as raw milk, cheeses from animals with confirmed or suspected H5N1 should be avoided.[6] Individuals with frequent exposure to poultry or livestock should utilize appropriate personal protective equipment.[6] Individuals should be isolated at home and monitored for signs and symptoms of infection for 10 days after an exposure to suspected or confirmed H5N1 animals.[6]

11 | VACCINATION

Types of influenza vaccines include live attenuated, inactivated, subunit, epitope-based, and mRNA vaccines.[11,82] Vaccines are divided into live and inactivated vaccines; however, how vaccines are now being developed has evolved tremendously and include many methods for manufacturing vaccines.[11,82] Traditionally, the influenza vaccine are egg-based vaccines.[11,82] In egg-based vaccines, a fertilized chicken egg is used to grow the virus, and then inactivated or attenuated, and then manufactured into a vaccine for use.[11,82,83] This process can be time consuming and can take up to 6 months in some cases and can have issue with egg allergy.[11,83] There is some thought that newer mRNA technology may offer a streamlined solution to the time delay and egg allergy issues.[83]

In the United States, the currently available able seasonal influenza "flu" vaccine will not work against the HPAI (specifically H5N1 virus); however, the US government in developing a candidate vaccine virus (CVV) for the HPAI or H5 candidate vaccine viruses (CVVs).[72] The vaccine in development is thought to work against the clade in circulation causing issue in humans, birds, and other mammals.[72,84] The United States also has the National Pre-Pandemic Influenza Stockpile (NPIVS) that works to ensure rapid development of vaccines, specifically influenza A.[85] More recently, there are multiple vaccines in development for humans to protect against avian influenza viruses, specifically the H5N1 virus.[85] This includes a cell-based vaccine approved by the FDA for people aged 6 months and older who are at higher risk of exposure to the H5N1 virus called Audenz.[86] There is an experimental mRNA vaccine also being studied.[83] Other avian influenza vaccines approved in Europe.[87]

12 | CONCLUSION

The avian influenza infection remains challenging worldwide. Neuraminidase inhibitors (oseltamivir, peramivir, and zanamivir) remain backbone for avian influenza treatment. Patients presenting with avian influenza can vary widely, from asymptomatic cases to severe disease. The cap-dependent endonuclease inhibitor, baloxavir marboxil, also FDA-approved treatment. The use of convalescent plasma and steroids should be carefully considered due to the late of data and possible complications. Pharmacists play a major role in vaccination advocacy among patients prior to discharge and provide care that includes evaluation of vaccination status, and the proper use of antiviral.

CONFLICT OF INTEREST STATEMENT

W Anthony Hawkins—see conflict of interest disclosure form submitted with manuscript.

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