World Health Organization

Clinical management of human infection with avian influenza A (H5N1) virus

Updated advice 15 August 2007

Introduction

Since late 2003 the widespread occurrence across several continents of infection among poultry and birds with the highly pathogenic avian influenza A(H5N1) virus has increased the risk of human exposure to the virus and resulted in growing numbers of A(H5N1) virus-infected persons (*1*). In June 2006 WHO published recommendations on the pharmacological management of A(H5N1) virus infections (*2*, *3*). The current document reviews both commonly used pharmacological and supportive treatment modalities and provides advice on case management based on current knowledge of human influenza A(H5N1) virus infections. This guidance is based on information collected from publications as well as reports on A(H5N1) cases in affected countries that were presented at the first *WHO Consultation on Human H5N1 Infections,* Hanoi, Viet Nam, May 2005 (*4*) and at the *Second WHO Consultation on clinical aspects of human infection with avian influenza (H5N1) virus* in Antalya, Turkey, March 2007 (*5*).

This document replaces the *WHO interim guidelines on clinical management of humans infected by influenza A(H5N1)* published in 2004 and serves as a supplement to the *WHO pharmacological management guidelines* (*2* , *3*).

A working group was convened in the context of the Second WHO Consultation to provide advice and establish standards for clinical management of humans infected with the A(H5N1) virus. The group included experts in critical care medicine, pulmonary medicine, infectious diseases, paediatrics, and public health as well as clinicians with direct experience in treating A(H5N1) virus-infected patients. Due to limitations in the availability of data from human infections with the A(H5N1) virus, additional data and experience from human seasonal influenza, relevant animal models, other respiratory viral infections such as SARS, and associated syndromes, particularly acute respiratory distress syndrome (ARDS) due to other causes were used to supplement the basis of some of the recommendations.

The present advice applies to the current situation of sporadic A(H5N1) virus human infection. This advice will be modified as appropriate as more data become available or should the disease patterns change.[1]

[1] Please refer to the WHO EPR Publications web page to check for updated versions and new publications http://www.who.int/csr/resources/publications/en/index.html

General considerations

As of August 2007, more than 300 people worldwide are documented as having been infected with the avian influenza A(H5N1) virus, yet still relatively little is known about this disease. Respiratory failure is the major complication in patients hospitalized with influenza A(H5N1) virus infection. No standardized approach exists for the clinical management of A(H5N1)-infected humans, and many patients progress rapidly to ARDS and multi-organ failure. The cumulative case-fatality proportion is approximately 60% (*1*).

Standardization of clinical care and antiviral management is fundamental to improve understanding of the disease course and to identify the appropriate therapy. Developing recommendations based solely on clinical reports from humans infected with influenza A(H5N1) virus is problematic due to insufficient data currently in the public domain, and the inconsistency of data collection from A(H5N1) virus-infected individuals.

Collaborative sharing of clinical and treatment data from affected patients in different regions and countries is essential to improve understanding of this disease and to refine optimal case management. Whenever possible, clinical data and serial samples for virological monitoring should be collected on a prospective basis to determine the effects of treatment regimens. WHO can assist in these efforts. Reporting clinical findings and treatment outcomes to WHO will greatly help its work in risk assessment and in the development of management guidance. Draft reporting forms developed to assist clinicians accompany this document (available at www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html) together with contact details for submission to WHO.

Summary of clinical management advice

- Oseltamivir remains the primary recommended antiviral treatment. Observational data on treatment with oseltamivir in the early stages of the disease suggest its usefulness in reducing A(H5N1) virus infection-associated mortality. Furthermore, evidence that the A(H5N1) virus continues to replicate for a prolonged period indicates that treatment with oseltamivir is also warranted when the patient presents to clinical care at a later stage of illness.

- Modified regimens of oseltamivir treatment, including two-fold higher dosage[1], longer duration and possibly combination therapy with amantadine or rimantadine (in countries where A(H5N1) viruses are likely to be susceptible to adamantanes) may be considered on a case by case basis, especially in patients with pneumonia or progressive disease. Ideally this should be done in the context of prospective data collection.

- Corticosteroids should not be used routinely, but may be considered for septic shock with suspected adrenal insufficiency requiring vasopressors[2]. Prolonged or high dose corticosteroids can result in serious adverse events in A(H5N1) virus-infected patients, including opportunistic infection.

[1] i.e. 150 mg twice daily for adults

[2] Agent that causes vasoconstriction and maintains or increases blood pressure e.g. norepinephrine, epinephrine or dopamine

- Antibiotic chemoprophylaxis should not be used. However, when pneumonia is present, antibiotic treatment is appropriate initially for community-acquired pneumonia according to published evidence-based guidelines. When available, the results of microbiologic studies should be used to guide antibiotic usage for suspected bacterial co-infection in patients with A(H5N1) virus infection.

- Monitoring of oxygen saturation should be performed whenever possible at presentation and routinely during subsequent care (e.g. pulse oximetry, arterial blood gases), and supplemental oxygen should be provided to correct hypoxemia.

- Therapy for A(H5N1) virus-associated ARDS should be based upon published evidence-based guidelines for sepsis-associated ARDS, specifically including lung protective mechanical ventilation strategies.

Table1 . Summary of treatment modalities for clinical management of human A(H5N1) virus infection.

Recommended Modalities	Strategies
Antivirals	Oseltamivir is the primary treatment of choice. Consider modified regimens (see text).
Antibiotics	Empiric treatment[1] for community-acquired pneumonia (CAP) per published guidelines pending microbiologic results (e.g. 2-3 days);
Oxygen therapy	Monitor oxygen saturation and maintain SaO_2 over 90% with nasal cannulae or face mask.
IPPV (Invasive positive pressure ventilation)	Early intervention recommended for ARDS. Use lung protective, low tidal volume, low pressure ventilation to prevent barotrauma and conservative fluid management.
Low dose systemic corticosteroids	Appropriate for refractory septic shock complicating ARDS (e.g. hydrocortisone intra venous 200mg per day in divided doses (50 mg every 6 hours) in adults).
NSAIDs, antipyretics (Non-steroidal anti-inflammatory drugs)	Paracetamol given orally or by suppository will generally be sufficient in most cases as an anti-pyretic treatment.
Infection control	Whenever risk of infectious aerosols, use particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, gloves and an airborne precaution room or negative pressure room.

[1] Evidence-based antibiotic treatment for most likely causative pathogen.

Modalities NOT Recommended	Strategies
Adamantane monotherapy	When neuraminidase inhibitors are available, monotherapy with amantadine or rimantadine is not recommended. Combination therapy is consideration in areas where A(H5N1) virus is likely susceptible (see text).
Antibiotic chemoprophylaxis[1]	Not recommended
NPPV (Non-invasive positive pressure ventilation)	Generally not recommended (see text).
Systemic corticosteroids	Moderate to high doses of unproven benefit and potentially harmful: not recommended;
Salicylates	Avoid administration of salicylates (such as aspirin and aspirin containing products) in children and young adults (<18 years old) because of the risk of Reye Syndrome.

Case management

1. Diagnosis

The diagnosis of influenza A(H5N1) virus infection should be included in the differential diagnosis of all persons presenting with acute febrile respiratory illness in those countries or territories where influenza A(H5N1) viruses have been identified as a cause of infection in animal populations. It should also be included in the diagnosis of anyone with possible exposure to suspected or confirmed A(H5N1) virus-infected patients or to samples containing the virus. Commonly the presenting signs and symptoms of A(H5N1) illness are non-specific, and a detailed exposure history needs to be elicited, including any close/direct contact with sick or dead poultry, wild birds, other severely ill persons, travel to an area with A(H5N1) activity, or work in laboratory handling samples possibly containing A(H5N1) virus (*6*).

The use of commercially available, rapid site-of-care influenza detection tests for individual patient diagnosis is generally not recommended. Current tests have low sensitivity in A(H5N1) virus-infected patients, and a negative rapid test result does not exclude human infection with avian influenza viruses (*7*) and a positive test does not distinguish from infection by other influenza viruses. Specimens for H5N1 diagnosis should be collected according to WHO guidance (*8*) and tested at one of the laboratories recognized as capable of diagnosing H5N1, such as WHO Collaborating Centres or a H5 Reference Laboratory (*9*). Collection of multiple respiratory specimens (nasal, throat, endotracheal aspirates from intubated patients) from suspected A(H5N1)-infected patients should be done preferably before antiviral treatment has commenced but it should not delay the initiation of such treatment. Additional respiratory specimens can also be collected after treatment has started. Public health and hospital authorities should be alerted immediately.

[1] Administration of antibiotics to prevent the development of an infection.

2. Site of care

Human infection with an A(H5N1) virus often manifests as a rapid progression of pneumonia with respiratory failure ensuing over several days. Hospital care in the initial stages of the disease to monitor clinical status, including oxygenation, is warranted whenever possible. Once the patient no longer requires hospitalization, discharge to home care is reasonable. Appropriate instructions for household members on personal hygiene and infection control measures are important and should be provided (for details see *Avian Influenza, Including Influenza A(H5N1), in Humans: WHO Interim Infection Control Guideline for Health Care Facilities* and *Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care, WHO interim guidelines*) (*10, 11*). Infectious virus has been detected not only in respiratory secretions but also sometimes in blood, stools and other body fluids. Follow-up of discharged patients with home visits or telephone contact should be done to ensure there is no deterioration in the condition of the patient or occurrence of new illness in contacts. The duration of A(H5N1) viral replication in humans appears to be prolonged and has been documented to last up to 15–17 days after illness onset (*4, 12, 13*). In the absence of corticosteroid administration, immuno-competent A(H5N1)-infected persons probably cease to excrete the infectious virus 3 weeks after illness onset, but further virological shedding data are needed to verify this.

3. Antiviral Treatment

3.1 Oseltamivir

Oseltamivir, which is available only in oral formulations, remains the primary antiviral agent of choice for the treatment of A(H5N1) virus infections (*2, 3*). No data are currently available from controlled clinical trials of oseltamivir or other antivirals for treatment of A(H5N1)-virus infected patients. Limited observational evidence suggests that early oseltamivir administration may be associated with reduced mortality in patients (A Abdel-Ghafar, personal communication 2007) (*14*). It is important that patients suspected of being infected with A(H5N1) virus receive treatment as early as possible based on clinical suspicion and before confirmation of etiology. Once treatment has been initiated in a suspected A(H5N1) patient, a standard 5-day course of therapy should be administered, unless an alternative diagnosis is established. Two patients who had initial negative tests results for A(H5N1) virus infection and appeared well after receiving only a 3-day course of oseltamivir treatment developed laboratory-confirmed A(H5N1) virus-associated pneumonia several days after cessation of oseltamivir (A Naghdaliyev, personal communication, 2007). In contrast to uncomplicated seasonal influenza, oseltamivir treatment is also warranted for patients presenting late with A(H5N1) virus infection because viral replication is more prolonged than with seasonal influenza (*15*).

A(H5N1) disease is associated with higher levels and more sustained viral replication than seasonal influenza (*12,15*), and the optimal treatment regimen of oseltamivir is not currently known in A(H5N1) virus infections. The standard dose and duration of oseltamivir treatment are derived from treatment studies of outpatients with uncomplicated seasonal influenza. In adults with uncomplicated seasonal influenza, higher doses (150 mg twice daily in adults) were tolerated as well as the approved regimen but provided no greater clinical or virological benefit (*16, 17*). Animal models of A(H5N1) virus infection indicate that higher doses and more prolonged administration of oseltamivir (8–10 versus 5 days) are associated with improved control of viral replication and better outcomes (*18, 19*). However, given the lack of available

controlled clinical A(H5N1) treatment data, firm recommendations that vary from the standard regimen of oseltamivir for seasonal influenza cannot be made, and the duration of antiviral therapy should therefore be guided by the clinical course of the disease in the patient. Continued fever and clinical deterioration may suggest ongoing viral replication, although the possibilities of bacterial superinfection and other nosocomial complications should be evaluated. If no clinical improvement has been observed after a standard 5-day course, the oseltamivir therapy may be extended for a further 5 days.

Progressive disease to fatal outcome has been observed in some A(H5N1) virus-infected patients despite early administration of standard doses of oseltamivir therapy (within 1 to 3 days of illness onset) and oseltamivir-resistant virus emerged in at least one patient treated early (personal communications N Duc Hien and A Abdel-Ghafar, 2007) (*12*). In addition, there is uncertainty regarding the ability of seriously ill patients to absorb oseltamivir efficiently. Limited evidence indicates that the emergence of oseltamivir resistance during therapy appears to be associated with persistent viral replication and poor prognosis (*12*). Whether higher doses might reduce oseltamivir resistance emergence is unknown at present. Higher doses of oseltamivir may be considered on a case-by-case basis in A(H5N1) virus-infected patients, particularly if there is pneumonic disease at presentation or evidence of clinical progression. The safety of higher doses has not been examined in children. The possible risks and potential benefits of higher doses need to be considered in paediatric A(H5N1) virus-infected patients, as it is currently unclear whether oseltamivir may cause, even if rarely, severe neuropsychiatric effects in adolescents (*20, 21*).

In healthy adults oseltamivir absorption appears to be efficient after delivery to the stomach or small bowel (*22*). Although oseltamivir absorption and conversion to its active form is unaffected by uncomplicated seasonal influenza, its bioavailability is uncertain in seriously ill influenza patients, many of whom may have gastric stasis, or in those with diarrhoea or gastrointestinal dysfunction associated with A(H5N1) virus infection. In particular, no data are available on the absorption of oseltamivir oral preparations administered through a nasogastric tube. In critically ill patients with gastric stasis, placement of a naso-jejunal tube is a consideration, but it remains an invasive and technically demanding procedure of uncertain value. Collection of several timed plasma samples[1] (or residual plasma from those used for routine clinical monitoring) for later determination of oseltamivir carboxylate levels would be helpful in assessing the adequacy of oseltamivir absorption in A(H5N1) virus-infected patients with suspected gastrointestinal dysfunction[2].

3.2 Other antiviral agents

Neuraminidase inhibitors. Limited information is available about the utility of other antivirals in the treatment of A(H5N1) disease. Although highly active in vitro and in animal models of A(H5N1) virus infection, including that due to oseltamivir-resistant A(H5N1) virus (*23*), topically applied (inhaled) zanamivir has not been studied in human A(H5N1) illness. Adequacy of orally inhaled zanamivir delivery in patients with serious lower respiratory tract or extra-pulmonary disease is a major concern. Nebulized zanamivir has been used in a small number of patients hospitalized with seasonal influenza and has been shown to be adequately tolerated but

[1] Fluoride-oxalate (blood glucose) tubes should be used for oseltamivir carboxylate measurement (Lindegardh N et al. Importance of collection tube during clinical studies of oseltamivir. *Antimicrobial Agents Chemotherapy*, 2007, 5:1835–1836).
[2] WHO can help arrange testing of such samples.

of uncertain benefit (*24*). Stringent hospital infection control measures must be adhered to if any drugs are administered by a nebulizer to patients with human A(H5N1) illness to prevent possible transmission of A(H5N1) viruses by aerosol (*10, 11*). Investigational, parenterally administered neuraminidase inhibitors now in clinical development (e.g. intravenous zanamivir or peramivir) provide high drug levels and reliable delivery. Given their activity in A(H5N1) animal models, inhibitory effects for some oseltamivir-resistant variants (*25*), and good tolerability in initial human studies (*26, 27*), either parenteral zanamivir or peramivir would be a reasonable alternative to oral oseltamivir for initial treatment of human A(H5N1) virus infection, if available and approved by appropriate national regulatory authorities.

Adamantanes (amantadine and rimantadine). Early amantadine treatment of patients with adamantane-susceptible A(H5N1) virus infections in Hong Kong (SAR) in 1997 may have been associated with clinical benefit (*2, 28*). However, monotherapy of seasonal influenza with this drug is associated with a high frequency of rapid resistance emergence, and globally the majority of A(H3N2) and some A(H1N1) influenza viruses currently show resistance to adamantanes (*29, 30*). In addition, many A(H5N1) virus isolates now show primary resistance. When neuraminidase inhibitors are available, monotherapy with amantadine or rimantadine is not recommended.

Combination therapy. Preclinical studies have shown that combinations of oseltamivir and adamantanes (amantadine or rimantadine) have enhanced antiviral activity, reduced resistance emergence (*31*), and in a mouse model of amantadine-susceptible A(H5N1) virus infection, showed greater antiviral effects and increased survival compared to single drug therapies (*32*), although not when the infecting virus is adamantane-resistant. Based on these observations, in an area where A(H5N1) viruses are likely to be adamantane-susceptible, combination therapy with oseltamivir and an adamantane at standard doses may be considered if there is pneumonic disease or clinical progression. Clade 1 (Cambodia, Thailand, Viet Nam) and the majority of clade 2.1 (Indonesia) A(H5N1) virus isolates are adamantane-resistant (A Klimov, personal communication, 2007). This combination therapy should only be considered when the locally circulating A(H5N1) viruses (Clade 2.2 and 2.3) are likely to be susceptible to adamantanes and, whenever possible, with collection of serial respiratory samples for serial virological monitoring.

Immunotherapy. Administration of anti-H5N1 specific antibodies in the form of neutralizing monoclonal antibodies or of polyclonal sera (convalescent or post-immunization) shows efficacy in animal models of A(H5N1) disease (*33, 34, 35*). Early administration of convalescent blood products may have had some therapeutic value in patients with pneumonia during the 1918 pandemic (*36*). Two A(H5N1) patients who were treated with both oseltamivir and convalescent plasma from A(H5N1) virus-infected patients survived (Z. Gao, personal communication 2007)(*37*). If used, such interventions should be done preferably in the context of controlled trials with close clinical and serial virological monitoring.

3.3 Virological monitoring

Prompt reductions in upper respiratory tract A(H5N1) viral RNA loads during therapy have been associated with improved prognosis, whereas persistent replication, sometimes related to the emergence of resistance, has been associated with fatal outcomes (*12*). Real-time therapeutic monitoring of the virological response by RT-PCR testing would be desirable to help guide therapy, but this is not routinely available at present. When possible, collection of serial respiratory samples (throat swabs and, if available, tracheal aspirates) for detection of

A(H5N1)virus (before treatment, day 4–5, and day 7–8 after treatment is initiated) should be considered to analyse viral clearance or persistence and antiviral resistance. In the absence of local laboratory testing capacity, such clinical samples could be forwarded to a validated national laboratory or stored for later analysis in such a laboratory or in a WHO H5 Reference Laboratory. WHO can assist[1] in the transportation of samples and identification of an appropriate laboratory. Such samples would also be useful in later assessment of initial antiviral susceptibility and possible resistance emergence.

4. Other pharmacological interventions

4.1 Antibiotics

Most patients hospitalized with A(H5N1) virus infection have radiological evidence of pneumonia on presentation. Often the causative etiology is not evident at the time of presentation. As the diagnostic workup to establish the etiology of community acquired pneumonia (CAP) may take time, it is important to start empiric treatment with antibiotics according to the latest published national, international or expert group CAP treatment guidelines (e.g. *38*). For patients who require admission to the intensive care unit (ICU), this treatment would usually include a combination of a β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin or a fluoroquinolone (*38*). The use of fluoroquinolone monotherapy in such patients is not recommended. Treatment must be tailored by taking into consideration the likely pathogens and local susceptibility patterns. Diagnostic workup for CAP will generally include blood culture and sputum for Gram stain and culture. Additional diagnostic testing may be needed based on the local etiologies and exposure histories.

If laboratory investigation reveals no bacteriological cause of CAP and diagnostic testing confirms A(H5N1) virus infection, empiric antibiotic treatment may be stopped. However, prior use of antibiotics may confound microbiological studies and affect this decision. In those patients with a suspicion of A(H5N1) virus infection based on epidemiological and/or clinical features, but negative diagnostic testing for A(H5N1) virus and pathogens of CAP, continued therapy for both possibilities is recommended pending further microbiological studies, including repeat upper respiratory and, if possible, lower respiratory tract sampling (e.g. tracheal aspirate, sputum, or, if indicated, broncho-alveolar lavage) for laboratory testing (*8*).

In atypical cases presenting initially with fever and predominantly gastrointestinal symptoms or encephalopathy with subsequent manifestation of pneumonia (*39, 40*) or those presenting without pneumonia within the first few days of illness onset, antibiotics are not required.

Use of prophylactic antibiotics is not warranted for A(H5N1) virus-infected patients, as it is of unproven benefit and may select for resistant bacteria and cause side effects. However, influenza virus infections, including those due to A(H5N1) virus, and ventilatory support can predispose the patient to bacterial complications that may present as a clinical deterioration after initial improvement, a prolonged fever and refractory clinical course, or as a change in respiratory secretions. These infectious complications should be suspected clinically and confirmed by a Gram stain and bacterial culture of the respiratory secretions. Antibiotic choices should cover

[1] See http://www.who.int/csr/disease/avian_influenza/guidelines/labtestsMarch07web.pdf for information.

likely pathogens based on local etiologic and susceptibility patterns including *Staphylococcus*, *Streptococcus* and nosocomial Gram negative organisms.

4.2 Immuno-modulators

Systemic corticosteroids. Systemic corticosteroids have often been used for treatment of acute lung injury (ALI)/ARDS due to A(H5N1) disease, presumably for their anti-inflammatory and anti-fibrotic effects. (*4, 41, 42, 43*). However, there has been no clear clinical benefit observed, and most A(H5N1) virus-infected patients receiving corticosteroids have died, although the incompleteness of reporting, the variable dosage and timing of administration, and other confounding factors limit interpretation of these findings. One small randomized study of A(H5N1) virus-infected patients in Viet Nam found that all 4 corticosteroid recipients died (*4*). No studies of these agents in relevant animal models of A(H5N1) virus infection have been published to date. Consequently, recommendations about the use of corticosteroids can only be derived from data and publications describing their use in associated syndromes such as ARDS, sepsis, and SARS.

Corticosteroids have been used in the treatment of other respiratory viral diseases. Despite the extensive use of corticosteroids, no clear evidence of clinical benefit was evident in SARS patients (*44*), and one study found that plasma SARS-CoV RNA concentrations were higher in the second and third weeks of the illness in SARS patients given intravenous hydrocortisone than in those given placebo during the first week of the illness (*45*). Other randomized, controlled studies have found that corticosteroids are associated with delayed viral clearance in RSV[1] and rhinovirus illness (*46, 47, 48, 49*). These studies suggested that early use of corticosteroids may prolong viral replication in some respiratory viral illnesses. In addition, corticosteroid use in SARS and other conditions has been associated with adverse effects including avascular bone necrosis and psychosis (*50, 51*).

Numerous clinical trials have examined the efficacy of corticosteroids in preventing acute lung injury (ALI) / ARDS unrelated to A(H5N1) virus infection (*52, 53*) and in the treatment of both early stage and late-stage (fibrotic) ALI/ARDS. To date no consistent survival benefit has been found (*54, 55*). High-dose corticosteroids increase the risks of secondary infections (*56, 57*) and related mortality (*52*). One recent, small trial reported that prolonged, lower dose methylprednisolone therapy might be beneficial in early ARDS, although no significant increase in long-term survival was found (*58*). However, these findings require confirmation by studies conducted on a larger numbers of patients. The National Heart, Lung and Blood Institute (NHLBI)[2] of USA ARDS Network recently examined the role of methylprednisolone (MP) in the treatment of ARDS patients of at least 7 days duration in a randomized placebo-controlled study. MP therapy increased the number of ventilator-free days, shock-free days and ICU-free days in the first month but was also associated with increased 60-day and 180-day mortality rates among patients enrolled for more than 13 days after the onset of ARDS. MP recipients were more likely to return to assisted ventilation after extubation than those on placebo and also experienced neuromuscular weakness. Overall, the available evidence does not support the use of MP in treating early or late ALI/ARDS (*59*).

Hypotension and septic shock have been reported in patients with A(H5N1) virus infection (*42, 43*). High dose corticosteroids have not been shown to be beneficial in septic shock unrelated to

[1] Respiratory syncytial virus
[2] See http://www.nhlbi.nih.gov/

A(H5N1) virus infection (*52, 60*). However, several studies have reported relative adrenal insufficiency with septic shock, defined as SBP[1] < 90 mmHg despite adequate fluid resuscitation, requiring support with inotropic or vasoconstrictor drugs (*61, 62, 63*). A retrospective analysis of one prospective study found that low doses of corticosteroids for 7 days were associated with lower 28-day mortality in the subpopulation of septic shock patients with early ARDS and non-response to a short corticotrophin test, but no difference was seen in test responders (*61, 64*). Therefore, replacement dose corticosteroids (equivalent of hydrocortisone 200–300mg/day in divided doses, often combined with 50 µg fludrocortisone daily, in adults) should be considered for treatment of persisting septic shock in A(H5N1) virus-infected patients.

In summary, there is no clear benefit in treating A(H5N1) virus-associated pneumonia or ARDS with high-dose corticosteroids while there is the potential for significant harm, particularly in terms of immunosuppression leading to enhanced A(H5N1) viral replication or secondary infections, and musculoskeletal side effects. It is recommended that high dose steroids should not be given for treatment of A(H5N1) disease. Lower dose steroids should be considered in the treatment of refractory septic shock according to current best-practice guidelines, but the benefit in paediatric septic shock is unknown (*65*).

Other immunomodulating agents. A(H5N1) disease has been associated with high plasma levels of pro-inflammatory cytokines and chemokines that correlate with the levels of virus in the upper respiratory tract (*15*) Such exaggerated or dysregulated host responses have been hypothesized as causing the organ damage and severe morbidity/mortality associated with A(H5N1) disease. Cytokine dysregulation has also been invoked in the pathogenesis of sepsis and septic shock (*66, 67*). However, multiple immuno-modulating agents, including NSAIDs[2], growth hormone, anti-TNF[3] modalities amongst other therapies, have no proven benefit in the treatment of sepsis. At present, there are no human or relevant animal model data to support the use of these agents for treating A(H5N1) virus infections. Statins are currently undergoing evaluation as a treatment for sepsis, but there is at present no convincing evidence of the benefits in the treatment of CAP (*68*). There are no data available from controlled clinical trials of immuno-modulating agents for treatment of A(H5N1) virus-infected patients. Therefore, it is recommended that immune modulating agents of unproven value should not be used at present in the treatment of A(H5N1) disease. The efficacy of such interventions in the treatment of A(H5N1) disease should be explored only after preclinical studies in A(H5N1) virus infection clearly establish their potential value and safety and in the context of rigorously conducted clinical trials.

Anti-pyretic agents or pain relievers are often used to reduce fever, myalgia and arthralgia in A(H5N1) virus–infected patients. Aspirin (salicylic acid) or salicylate-containing products should not be administered to suspected influenza or A(H5N1) patients under 18 years old because of the risk of Reye Syndrome (see Table 1).

4.3 Haemophagocytosis and intravenous immunoglobulin

Several autopsies have documented reactive haemophagocytosis in fatal A(H5N1) virus-infected cases (*69, 70*), and the cytotoxic agent etoposide has been proposed as a potential therapy for A(H5N1) disease that has become complicated by haemophagocytic lymphohistocytosis (HLH) (*71*). The frequency and prognostic importance of haemophagocytosis in A(H5N1) virus-

[1] Systoric blood pressure
[2] Non-steroidal anti-inflammatory drugs e.g. paracetamol, ibuprofen.
[3] Tumour necrosis factor

infected patients are uncertain at present. Diagnostic criteria for HLH include fever, splenomegaly, bicytopenia, hypertriglyceridenia, hypofibrinogenemia, haemophagocytosis in bone marrow, spleen or lymph nodes, low/absent NK-cell activity, hyperferritinemia and increased soluble CD25 levels (*72*). These criteria should be fulfilled before using empiric therapy. In cases of A(H5N1) virus infection complicated by documented haemophagocytosis, intravenous immunoglobulin (ivIG) (if available) may be considered as a treatment option. However, it is important to consider and monitor any complications of ivIG, such as renal dysfunction and vascular thrombotic events (*73, 74, 75*). In view of their potential risks, the use of more aggressive immunosuppressive agents for A(H5N1) virus-associated haemophagocytosis should be undertaken only after close consultation with haematology experts.

5. Supportive therapy for critically ill patients

Influenza A(H5N1) virus infection often causes severe, rapidly progressive respiratory failure, and it is important to provide supportive care for A(H5N1) virus-infected patients with ALI/ARDS. Many patients also develop multiorgan failure with a high proportion of patients requiring advanced organ support. Supportive care includes effective and timely oxygenation and ventilatory support while minimizing risks of barotrauma, adequate enteral nutrition, prevention and rapid treatment of nosocomial infections, prevention of deep venous thrombosis and gastrointestinal bleeding, and good nursing care. Many of these aspects have been summarized in published guidelines for the management of patients with severe sepsis and septic shock (e.g. Surviving Sepsis Campaign (*76*); guidelines published in 2004 (*65*) and currently being updated).

5.1 Oxygen therapy

Supplemental oxygen is essential for the successful management of moderate to severe A(H5N1) illness. It is important to recognize and treat hypoxemia early in order to avoid its consequences and improve clinical outcomes. Whenever possible, pulse oximeters should be used for initial evaluation when patients present and followed by frequent serial monitoring of oxygen saturation thereafter. In settings where monitoring of oxygen saturation is not available, oxygen therapy should be administered to A(H5N1)-infected patients who have clinical signs of respiratory distress including raised respiratory rate (corrected for age) or altered conscious level (e.g. drowsiness or agitation). Special attention is required for early signs of hypoxia in paediatric patients. Where oxygen saturation monitoring is available, SaO_2 should be maintained over 90%.

Nasal cannulae do not permit high flow rates of oxygen and are only effective for management of mild hypoxemia. Patients with severe hypoxemia need high flow oxygen (e.g. 10 litres per minute) delivered by face mask. Some patients may experience difficulties with compliance and require the close involvement of nursing staff (and parents of children). Output from oxygen generators can vary in concentration and flow rate, and may be insufficient for correcting severe hypoxemia. If piped oxygen is not available in the medical ward, a supply of large cylinders will be needed. WHO has included oxygen in the Essential Medicines list since 1979 but it is still not widely available in some countries. If medical oxygen is not available, then industrial oxygen can be used (e.g. delivered by face mask) provided it conforms with national guidelines (*77*) .

5.2 Ventilatory support

Non-invasive positive pressure ventilation (NPPV). NPPV is a ventilatory option currently validated for acute exacerbation of COPD[1] and cardiogenic pulmonary edema and suggested as a bridging strategy for patients with early ALI without hemodynamic instability. However, NPPV applied via nasal or facial mask cannot be recommended for routine use for patients with respiratory failure due to A(H5N1) virus infection because of the high frequency of ARDS and the fact that hemodynamic instability and multiorgan failure are contra-indications to NPPV. In addition, this strategy is associated with an increased risk of generating potentially infectious aerosols (see section 7.1). NPPV was provided to 2 cases of human A(H5N1) virus infection as a temporary measure for respiratory failure and did not cause nosocomial infection, but the patients subsequently required invasive mechanical ventilatory support (*70*, *78*). If the clinicians decide to use NPPV and the clinical condition has not improved within 2 hours or satisfactory oxygenation levels have not been achieved with NPPV, then invasive positive pressure ventilation (IPPV) should be started as soon as possible (see below).

Invasive positive pressure ventilation (IPPV). IPPV is the preferred mode of ventilatory support for patients with A(H5N1) virus infection complicated by ARDS. The indications for IPPV in A(H5N1) disease are the same as those for other causes of pneumonia. Critically ill patients with A(H5N1) virus infection who require IPPV should be transferred to a facility and level of care commensurate with the disease. It is important to provide sufficient training to healthcare workers in the management of patients with respiratory failure and multiorgan dysfunction and in techniques for personal protection of staff and relatives.

A low-volume, low-pressure strategy for ventilation of patients with non-A(H5N1) virus infection associated ARDS has been shown to reduce mortality (*79*). Lung-protective ventilation includes minimizing tidal volume (goal of maximum 6 ml/kg of predicted body weight) and plateau pressures (maximum 30cm H_2O). Ventilatory frequency should be adjusted to control the severity of respiratory acidosis and not target a specific partial pressure of arterial carbon dioxide ($PaCO_2$). An adequate goal for arterial oxygenation may be a saturation (SaO_2, measured by pulse oximetry) of > 88 % or a partial pressure of arterial oxygen (PaO_2) > 55 mmHg (7.3kPa), achieved using whatever level of fractional inspired oxygen (FiO_2) is needed, and an appropriate level of positive end-expiratory pressure (PEEP) to recruit atelectatic alveoli. There is no evidence that high inspired oxygen concentrations in these patients causes oxygen toxicity.

There appears to be a high incidence of pneumothorax in critically ill A(H5N1) virus-infected patients (*80*), and barotrauma is a particular concern with high volume IPPV. Lung recruitment and the level of PEEP have not been proven to alter outcomes in non-A(H5N1) virus infection-associated ARDS (*81, 82, 83*). As there is no standardized approach to lung recruitment manoeuvres in the management of ARDS, no generalized recommendation regarding recruitment manoeuvres for patients with ARDS due to infection with A(H5N1) influenza virus can be made. While recruitment strategies may have a role for individual patients, judgement should be made on a case-by-case basis by the treating clinician, bearing in mind the heterogeneity of the disease process in different parts of the lung.

[1] Chronic obstructive pulmonary disease

5.3 Non-ventilatory treatments for ALI/ARDS

In the early phases of severe sepsis or septic shock, current best practice (*64,75*) includes active fluid resuscitation and early organ-system support, targeting measures of adequacy of oxygen delivery (*84*). However, in patients who develop ALI/ARDS, a conservative fluid management strategy may increase ventilator-free days and improve oxygenation compared with a fluid liberal strategy, although in one large trial overall mortality did not change (*85*). Albumin and furosemide therapy may improve lung physiology measures in the subset of hypoproteinemic patients with lung injury but data on outcomes are lacking (*86*).

Several pharmacological therapies such as surfactant (except perhaps in children with ALI (*87*)), phosphodiesterase inhibitors, and nitric oxide have been found to be ineffective in improving outcome in ARDS (*88*). Studies of other potential novel therapies for ALI, including activated protein C and alveolar fluid clearance with β- agonists, are in progress (*88*), as are studies of early goal-directed therapy for sepsis. Although the direct applicability of the results from such studies to A(H5N1) disease is uncertain, they may suggest interventions of possible benefit and identify those of unlikely utility in this disease. Until such data become available, it is recommended that agents of unproven value not be used in the treatment of A(H5N1) disease.

6. Special considerations

Limited case experience is available for A(H5N1) virus-infected patients in an immunocompromised state, such as those with HIV infection or during pregnancy. Four of six pregnant women with confirmed A(H5N1) disease died, one of whom had received corticosteroids without antiviral therapy, while two other patients experienced spontaneous abortion but survived (J Gu, A Abdel-Ghafar, and J Farrar, personal communications, 2007) (*78).* Pregnant women should be treated with antiviral therapy (*2, 3*) and appropriate supportive care should be administered.

7. Infection control considerations /Isolation facilities

All health care workers in direct or close contact[1] with suspected or confirmed A(H5N1) virus-infected patients should adhere to appropriate precaution measures[2]. During aerosol-generating procedures in A(H5N1) virus-infected patients health-care workers should wear eye protection, gowns, gloves and particulate respirators that are at least as effective as the NIOSH-certified N95, EU FFP2 or equivalent. In addition, the procedures should be undertaken in an airborne precaution room (mechanically or naturally ventilated rooms with at least 12 air exchanges/hour and safe airflow), in a single well-ventilated room, or in a negative pressure room when available.

[1] Within 1m of distance
[2] Refer to *Avian Influenza, Including Influenza A(H5N1), in Humans: WHO Interim Infection Control Guideline for Health care Facilities* for further information.
(http://www.who.int/csr/disease/avian_influenza/guidelines/infectioncontrol1/en/index.html)

7.1 Special infection control considerations during ventilatory support therapy

Earlier studies have suggested that endotracheal intubation, as well as possibly NPPV and oxygen therapy, were risk factors for SARS nosocomial transmission, although inconsistent use of PPE is a key confounding variable in such studies (*89, 90, 91*). Administration of supplemental oxygen via mask may also contribute to dispersion of potentially infectious aerosols (*92, 93*). Oxygen masks with an expiratory port and HEPA filter will reduce aerosol production (*94*). An N95 respirator can be modified by the addition of an oxygen manifold consisting of a one-way inspiratory valve, an oxygen inlet and an oxygen reservoir. The modified N95 respirator can deliver high inspired oxygen concentrations clinically equivalent to a non-rebreathing mask to the patient while maintaining its filtration and isolation capacities (*95*).

When available, HEPA filters should be attached to the expiratory ports of ventilators, and a closed tracheal suctioning system used for aspiration of respiratory secretions to reduce generation and spread of infectious aerosols. To minimize the risk of nosocomial infection, it is important to maintain adequate medical ward ventilation during application of oxygen therapy or NPPV. If NPPV is to be used, a closed system with a head helmet and an expiratory port HEPA filter is recommended whenever possible.

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