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Avian influenza (H5N1): implications for intensive care

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Abstract *Background:* As influenza A/H5N1 spreads around the globe the risk of an epidemic increases. *Discussion:* Review of the cases of influenza A/H5N1 reported to date demonstrates that it causes a severe illness, with a high proportion of patients (63%) requiring advanced organ support. Of these approx. 68% develop multiorgan failure, at least 54% develop acute respiratory distress syndrome, and 90% die. Disease progression is rapid, with a median time from presentation to hospital to requirement for advanced organ support of only 2 days. *Conclusion:* The infectious nature, severity and clinical manifestations of the disease and its potential for pandemic spread have considerable implications for intensive care in terms of infection control, patient management, staff morale and intensive care expansion.

Keywords Mortality · Morbidity · Triage · Mechanical ventilation · Infection control

Introduction

The possibility of a human influenza pandemic has increased over the past few years with the emer-

gence of a highly virulent avian influenza virus, influenza A/H5N1 (H5N1). To date H5N1 avian influenza viruses have infected 165 persons and caused 88 deaths in several Asian and one European country (http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_02_06/en/index.html; accessed 6 February 2006). The continued circulation of the H5N1 virus increases the possibility of adaptive mutation or genetic reassortment with other circulating influenza viruses and increases the threat of a global pandemic which has important implications for intensive care.

To support the comments and recommendations made here we conducted a literature search using the terms “avian influenza” and “H5N1” for human studies published after 1996 in English. This search was supplemented by inspection of the reference lists of all relevant articles identified by the search. Data from case reports and case series that give individual patient data were pooled to determine the characteristics and proportion of patients requiring advanced organ support (defined as invasive mechanical ventilation or administration of inotropes or vasopressors). The following data were obtained, where possible, for each of these patients: age, sex, hospital mortality, length of ICU stay, duration of symptoms before hospital admission, and duration of hospital stay before requirement for advanced organ support. The presence of respiratory, cardiovascular, renal, hepatic, haematological, central nervous system, gastrointestinal and multiorgan failure, acute respiratory distress syndrome (ARDS) and pneumothorax was recorded. Organ failures were considered to be present if they were explicitly stated to have been present, or if the Marshall et al. [1] criterion for an organ dysfunction score higher than 2 were satisfied [1] or, in the case of haematological failure if the patient was stated to be thrombocytopenic or to have disseminated intravascular coagulation. Patients were considered to have ARDS if this was explicitly stated, or if they satisfied the consensus definition of ARDS [2]. Multiorgan failure was defined as

two or more organ failures or an explicit statement documenting multiorgan failure.

spleen, lung and liver suggests that the multiorgan failure may be mediated by cytokines [13, 14].

Epidemiology

Evidence to date suggests that close contact with dead or sick birds is the principal source of infection for H5N1 virus. There is some evidence of human-to-human transmission [3, 4], however, at present it remains inefficient, and transmission from patients to healthcare workers is rare [5, 6]. The most likely mode of transmission is via respiratory droplets, although droplet nuclei have also been implicated in the transmission of influenza virus [7]. The presence of H5N1 ribonucleic acid (RNA) in human faeces raises the possibility of faecal spread. Although controversial, humans infected with human influenza virus may be infectious for a short time when still asymptomatic [8, 9]. If this is also true of avian influenza viruses, it would have significant implications for quarantine in the event of a pandemic.

Pathogenesis

Pathogenesis of viral infections and H5N1 in particular is incompletely understood, but is likely to be caused by both direct viral infection of tissues and immunological responses. Detection of H5N1 RNA has been reported in lung, cerebrospinal fluid, blood, intestine, spleen and faeces [10, 11]. Plasma concentrations of inflammatory mediators are elevated [12, 13], and the marked lymphopenia together with the post-mortem observation of a reactive haemophagocytic syndrome in bone marrow, lymph nodes,

Clinical features

The clinical features of fever, lower respiratory tract symptoms, headache, myalgia, diarrhoea, vomiting, abdominal and chest pain, coma and bleeding from mucosal membranes are not sufficiently specific for a clinical diagnosis to be made. History of exposure to birds should be sought. Interestingly, secondary bacterial infection appears uncommon [15]. Manifestations of H5N1 are often severe, with 41 of the 65 reported cases (63%, 95% CI 51–75%) requiring advanced organ support [3, 11, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24]. However, reported cases may represent only the severe end of the spectrum as there is evidence of asymptomatic and mild infection [4, 25]. Details of patients requiring advanced organ support are given in Table 1. Important points to note are the number of children affected, short duration of hospital stay prior to requirement for advanced organ support, high mortality and high incidence of multiorgan failure, especially cardiovascular failure. These figures only provide a rough estimate as in many cases definitions of organ failures or ARDS were not documented, and patients were reported as having multiorgan failure without specific organ failures being given.

Of the 41 patients who required advanced organ support 22 (54%) developed ARDS, but this is likely to be an underestimate. Many patients with severe respiratory failure were reported with insufficient detail to establish whether they had ARDS. Pneumothorax was common (17%). All pneumothoraces occurred during mechanical ventilation.

Table 1 Characteristics of the 41 H5N1-infected patients reported in the medical literature who required advanced life support. Due to variability in reporting the sample size varies for different characteristics. Confidence intervals are not given for the proportion of pa-

tients with organ failures, ARDS or pneumothorax. These data represent only rough estimates as organ failures were poorly defined in most reports (*IQR* interquartile range, *CI* 95% confidence interval)

Characteristic	<i>n</i>	Summary data
Age, median (years)	41	13 (IQR 6–24)
Sex: M:F	41	21:20
Hospital mortality	41	90% (CI 81–99%)
Duration of symptoms prior to hospital admission, median (days)	30	5 (IQR 4–6)
Duration of hospital stay prior to requirement for advanced organ support, median (days)	16	2 (IQR 0.75–3.25)
Time from hospital admission to death, median (days)	21	6 (IQR 5–13)
Proportion with organ failures	41	
Multiorgan failure		68%
Respiratory failure		98%
Cardiovascular failure		44%
Haematological		29%
Central nervous system		2%
Renal		24%
Hepatic		7%
Gastrointestinal		41%
Proportion with ARDS	41	54%
Proportion with pneumothorax	41	17%

Investigations

Typical laboratory findings include leukopenia, lymphopenia, impaired liver function, abnormal clotting and renal impairment [15]. Radiological changes vary from diffuse bilateral infiltrates to lobar consolidation [15]. Unlike human influenza virus, H5N1 is associated with a higher frequency of virus detection in pharyngeal than in nasal samples [12]. Avian influenza (H5N1) can be confirmed by one or more of the following: a positive viral culture, a positive polymerase chain reaction assay for H5N1 RNA, a positive immunofluorescence test for antigen with the use of monoclonal antibody against H5 and a fourfold rise in H5-specific antibody titre in paired serum samples. Detection of viral RNA in respiratory samples appears to offer the greatest sensitivity for early identification of avian (H5N1) flu [15]. Commercial rapid antigen tests may help provide support for a diagnosis of influenza A infection but have a poor negative predictive value and lack specificity for H5N1 [26].

Definitive treatment

Neuraminidase inhibitors (oseltamivir and zanamivir) specifically target one of two surface structures of influenza virus, the neuraminidase protein. The presently circulating genotype Z of the avian influenza H5N1 virus carries mutations in the M2 gene and is therefore resistant to adamantanes (amantadine and rimantadine).

Oseltamivir is an orally administered prodrug with high bioavailability (90%). It undergoes hepatic metabolism to the active carboxylate. The carboxylate is 3% protein bound and is renally excreted with an elimination half life of 6–10 h. The dose should be halved in patients with creatinine clearance less than 30 ml/min [27]. There are no data to guide dosing for patients receiving continuous renal replacement therapy. Because it is a small molecule with very low protein binding, oseltamivir carboxylate should be readily filtered with a sieving coefficient close to 1 and clearance by haemofiltration should approximate the ultrafiltration rate [28]. An oseltamivir-resistant H5N1 variant has recently been isolated, leading to the suggestion that combination anti-viral therapy would be preferable [22, 24]. Current guidelines recommend that oseltamivir should be administered within 48 h at a dose of 75 mg twice daily for 5 days in adults, with weight adjusted doses for children (Table 2). In more severe cases higher doses and a longer course of therapy have been recommended [15]. The efficacy of neuraminidase inhibitors diminishes substantially if administered after 60 h of infection, and efficacy is suboptimal when instituted later in the course of illness. However, antiviral treatment could still be of benefit if there is ongoing viral replication [26].

Zanamivir is less likely to be of use in the critically ill as it is only available as a dry powder for inhalation.

Table 2 Weight-adjusted doses of oseltamivir for children under 1 year old

Weight (kg)	Twice daily dose (mg)
≤ 15	30
15–23	45
23–40	60
> 40	75

Bioavailability by this route is only 20% and may be reduced in severe pneumonia. Furthermore, drug delivery may be problematic in children, the elderly and intubated patients [29]. At present there are no data to support the use of steroids or other immunomodulatory agents in H5N1 infections [26].

Prevention and prophylaxis

No influenza (H5) vaccines are currently commercially available for human use. Although vaccination against human influenza A is unlikely to protect against avian influenza, it does reduce the risk of concurrent infection with both viruses, which may lead to an exchange in genetic material between human and avian viruses, resulting in a reassorted transmissible pandemic virus [30]. Chemoprophylaxis with 75 mg oseltamivir daily for 7–10 days is warranted for persons who have had a possible unprotected exposure [15].

Prognosis

Hospital mortality is 90% (95% CI: 81–99%) amongst those reported to require advanced organ support and 57% overall. In the 1997 epidemic risk factors for poor outcome from H5N1 avian influenza included older age, being symptomatic for a longer period before admission, pneumonia, leukopenia and lymphopenia [14]. Long-term outcome is unknown.

Implications for intensive care

The infectious nature of the disease, high incidence of multiorgan failure, ARDS, ventilator-associated pneumothorax and death, the short time between hospital and ICU admission and the age of the patient all have considerable implications for intensive care.

Even in the absence of efficient human–human transmission the consequences of transmission are potentially catastrophic because of the severity of the disease and the risk of genetic reassortment. Preparation of infection control facilities in intensive care units has been addressed in a previous publication [31]. Infection control guidelines from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend the

use of standard, contact and airborne protection, including respirators of N95 standard or higher [32, 33]. However, the United Kingdom guidelines recommend the use of surgical masks with FFP3 (N100 equivalent) respirators only for aerosol-generating procedures [34]. We believe that the WHO and CDC guidelines are more appropriate, given the frequency of aerosol generating procedures in ICU, the risk of accidental disconnection of ventilator circuits, the high mortality associated with avian influenza and the relatively ineffective filtration provided by surgical masks [35]. Furthermore, surgical masks were found to be ineffective in controlling the spread of infection during the Spanish flu pandemic of 1918–1919 [36].

Admission of all cases to an infectious diseases referral centre may have advantages in terms of ensuring adequate isolation and laboratory facilities, minimization of risk of human to human transmission and acquisition of expertise in managing the disease. However, the rapid progression of disease and requirement for advanced organ support means that the timeframe available for safe transport of the patient is short.

Once efficient human–human transmission occurs, based on data from human influenza viruses, it will have to be assumed that even asymptomatic individuals may be infectious, and quarantine of healthcare workers will be necessary.

The high incidence of ARDS and pneumothorax has implications for the type of ventilators that should be stockpiled for use in an epidemic and ventilatory management. A low-volume low-pressure strategy for ventilation of patients with ARDS has been shown to reduce mortality with a number needed to treat of 4.52 [37]. Although lung recruitment and the level of positive end-expiratory pressure (PEEP) have not been proven to alter outcome [38, 39], current expert opinion favours the use of recruitment manoeuvres and titration of PEEP to individual patient requirements [40]. It is therefore appropriate to stockpile ventilators capable of accurately measuring tidal volume, plateau pressure and intrinsic PEEP, and that allow accurate titration of extrinsic PEEP, militating against purchase of simple transport ventilators. The high incidence of pneumothorax dictates a cautious approach to lung recruitment.

Given the high incidence of ARDS, it is unlikely that non-invasive ventilation (NIV) would provide substantial benefit [41, 42, 43]. A recent multiple logistic regression analysis showing that NIV was associated with improved outcome in severe acute respiratory syndrome was flawed by failure to adjust for severity of illness and many other factors previously shown to be associated with poor outcome in the critically ill [44, 45, 46]. As there are concerns that NIV increases the risk of disease transmission [31, 47] the risk:benefit ratio does not favour use of NIV. In addition, haemodynamic instability is a relative contraindication to NIV and cardiovascular failure is common in avian flu.

A disproportionately large number of children are affected by avian influenza, making it likely that paediatric ICU services will be rapidly overwhelmed. As a result adult ICUs need to stockpile appropriate equipment for managing paediatric patients, and adult healthcare workers will need prior training in essential aspects of paediatric intensive care.

The short time between hospital and ICU admission (median 2 days) and the high requirement for advanced organ support (63% of all reported patients) means that there will be limited time for preparation in the event of an epidemic. Many preparations are time consuming and need to be made in advance [31, 48, 49]. We have previously recommended that additional staff should be trained to work in expanded ICUs, suggesting initial courses followed by refresher courses in the event of an outbreak [31]. In the case of avian influenza this may not be appropriate as there may be insufficient time to hold refresher courses once the outbreak becomes apparent.

Two recent publications have addressed the issue of expansion of intensive care in an epidemic [31, 48]. Rubinson et al. [48] have made recommendations based on the premise that provision of a lower level of intensive care to more patients is preferable to provision of a higher level of care to fewer patients. We have taken a different approach and have made recommendations on how to expand intensive care without a significant reduction in quality of care [31]. While both approaches have merits in different situations, we believe that the nature of avian influenza make the low level approach less suitable. The mortality of cases requiring advanced life support is 90%, and the incidence of multiorgan failure is high. Given the complexity of cases, it is likely that a reduction in the level of intensive care would result in a substantial rise in mortality. This could raise mortality to the point that it becomes questionable whether, on the basis of triage, patients with avian influenza should be admitted to ICU [50]. Indeed, even at the current 90% mortality diversion of resources from other critically ill patients is justified only by the young age of the patients with avian influenza. Age per se is unimportant, but it would be reasonable to expect young survivors to have a long life expectancy. Furthermore, the small benefit to patients may not justify the risk to staff. We therefore believe that ICUs have a useful role only in relatively small avian flu epidemics in which an increase in ICU capacity of 50–100% would be sufficient, and that contingency plans should be made on that basis. In larger epidemics it may be more appropriate to re-deploy ICU staff to care for less severely ill patients. There are currently insufficient data to determine which patients with avian influenza should be admitted to intensive care and which should be refused.

Staff morale is important in an epidemic and has been addressed previously [31]. Poor morale may lead to high absenteeism, which will have a severe impact on the provision of services. The high mortality rate and

the high proportion of children may exacerbate morale issues and the need for staff counselling. The need to support bereaved parents will further increase the need for counselling services, and preparations to meet this demand should be made.

Conclusion

Severe avian influenza causes a rapidly progressive disease that often culminates in ARDS, multiorgan failure and death. The already high mortality and high incidence

of multiorgan failure calls into question the usefulness of providing large numbers of ICU beds at a lower standard of care. Furthermore, the high incidence of ARDS makes it unlikely that very basic mechanical ventilators will be useful. While indicative of what can be expected, the data are limited at present, and it is possible that the genetic change that allows efficient human-human transmission of the H5N1 virus will also change the epidemiology and clinical manifestations of the disease. Nevertheless, urgent preparations to deal with an epidemic are called for as current data suggest that there will be insufficient time to prepare after the onset of an epidemic.

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