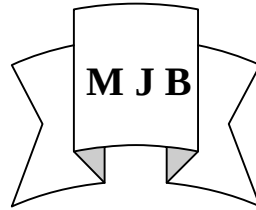


Facts of Bird Flu

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Review Article

Abstract

Every day, millions of billions of virus particles are silently replicating, swapping genes, mutating and evolving in waterfowl. Occasionally, an otherwise mild avian influenza virus changes to become a highly pathogenic virus that can infect, kill and start epidemics in domestic poultry. In 1997, the H5N1-type avian virus emerged in Hong Kong by gene-swapping between bird viruses, not in itself a particularly unusual event. But for the first time, this new virus began to infect and cause illness in humans. Subsequently the virus continued to evolve by acquiring different genes from other bird viruses and ignited epidemics among domestic poultry and ducks throughout the world.

This activity of reviewing articles, try to throw some lights on this greatly important subject aiming to prepare the health authorities to girds for the bird flu battle, discussing: history, pathology, epidemiology, transmission, clinical features, investigation, treatment, and prevention of the disease

الخلاصة

عدد لا بأس به من فايروس الانفلونزا يتعرض الى تحولات بحيث يصبح أكثر مرضية حيث يقتل من يصبه من الطيور وكذلك الإنسان ويمكن ان ينتقل بصورة سريعة بين الحالات نوع يسمى (H5N1 افين) وجد في هونكونغ وللمرة الأولى ومن هناك انتشر الى باقي انحاء العالم هذه المقال تسلط الضوء على أهمية هذا الموضوع وخطورة هذا الفايروس والمرض المسبب له (انفلونزا الطيور) حيث نتاقش تأريخ المرض ، تطوره ، انتشاره ، حالة المريض الفحوصات لتشخيص المرض وطرق العلاج والوقاية منه

Historical Review

Bird flu and human flu have a complex and likely inter-related story. The three influenza A viruses associated with the 20th century human pandemics all appear to have genetic components originally housed in viruses in birds, the 1918 H1N1 virus killed 20 to 40 million people worldwide, the 1957 H2N2 and 1968 H3N2 viruses were far less lethal, but still were each responsible for more than 1 million deaths[1]. Now, in 2005, all eyes are focused on H5N1, more commonly known as bird flu [2]. It was first identified in South African wild terns in 1961(3). It spread naturally throughout global bird populations over the next four decades, appearing dramatically in poultry populations in 2003, that outbreak

occurred in eight countries in Asia – Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand and Vietnam – and resulted in the loss of more than 100 million domestic birds, the outbreak appeared under control until June of 2004 when it reappeared in four of the same countries and Malaysia [3, 4].

In humans, the appearance was less dramatic. H5N1 first infected a human population in Hong Kong in 1997. There were 18 documented cases and six deaths. It reappeared in 2 cases, causing one death in 2003, but shortly thereafter broke out in Vietnam, Thailand and Cambodia. As of June 2005, there were 100 documented human cases with a 54 percent mortality rate. Most transmission has been the result of direct contact with infected poultry [3, 4].

Pathology

The influenza viruses are segmented genome RNA viruses classified in the family Orthomyxoviridae, they constitute 3 of the 5 genera of the family and are designated influenzavirus A, influenzavirus B, and influenzavirus C, each is represented by single virus species: influenza A virus, influenza B virus, and influenza C virus [5]. The influenza A viruses exist as several distinct subtypes, defined by the hemagglutinin (H) and neuraminidase (N) surface antigens, which infect humans and a range of avian and mammalian species, the influenza B viruses do not exhibit subtype variation and appear to infect humans only, causing epidemics but not pandemics-presumably because there is no reservoir of novel antigenic variation in nonhuman hosts, influenza C viruses infect humans and have also been isolated from pigs in China, but these viruses are not associated with either epidemic or pandemic disease in the human population[6].

The influenza A viruses exist in greatest profusion in waterfowl, at present, 15 distinct H and 9 distinct N antigenic types are recognized, all of which occur in waterfowl in virtually all combinations, it is generally accepted that feral aquatic birds are the reservoir for influenza A viruses and that influenza in aquatic birds has achieved "evolutionary stasis" [7], meaning that the internal genes of the viruses show little genetic variation even over many decades, unlike those of the influenza viruses present in other species. A recent survey of influenza A viruses isolated from feral Canadian ducks over a period of 17 years confirmed the stability of the gene pool and, at the same time, revealed that extensive reassortment of genes was occurring more or less at random, so that all combinations of H and N subtype genes in mammalian influenza viruses and avian influenza viruses present in domestic fowl are strictly limited [6]. The avian influenza viruses causing disease in domestic poultry are

predominantly viruses of H5 and H7 subtypes, strains of low- (LPAI) and high- (HPAI) pathogenicity avian influenza virus of each subtype exist[6]. Pathogenicity is determined in part by the presence of multiple basic amino acids (arginine and lysine) at the cleavage site of the H protein [8]. Cleavage of the H molecule is necessary for infectivity of the virus, and the susceptibility of the H molecule to specific cellular proteases determines the tissue tropism and virulence of the virus [6]. Conversely, the resistance or susceptibility of different varieties of domestic fowl may be determined by the specificity of their cellular proteases [6].

Epidemiology

In 1989 and 1990, there were severe outbreaks of equine H3N8 virus influenza in northeast China that were caused by an influenza virus in which 6 of the 8 genes were of recent avian origin [9]. Subsequent cases of an avian-like H3N8 virus involved other species, including humans [10].

A new phenomenon has been the appearance of severe sporadic cases of avian H5N1 subtype viruses in humans, occurring first in the Hong Kong Special Administrative Region of China and later in Thailand and Vietnam [11-13]

The avian influenza A (i.e., H5N1) virus cases in eastern Asia were preceded in 2003 by a devastating outbreak of avian influenza in poultry in The Netherlands that was caused by an H7N7 virus [14]. This virus was responsible for the death of a veterinarian and extensive conjunctivitis among those employed in disposal of diseased birds [14]. Approximately 500 people were infected either directly from their relatives or from colleagues, but no one who had indirect contact with diseased birds showed symptoms of infection [15]. A smaller outbreak of H7 virus (N subtype unconfirmed) occurred in British Columbia early in 2004 with little impact on the human population [16].

In 1997, H5N1 HPAI viruses were circulating in poultry farms and markets in

the Hong Kong Special Administrative Region of China, and 18 cases of human disease were confirmed, 6 of which resulted in death [17], In February 2003, a similar H5N1 strain again infected humans, causing illness in a family group of 3 individuals who were visiting southern China from Hong Kong, 2 of whom died [17]

As of 28 September 2004, the World Health Organization (WHO) had confirmed, by laboratory testing, a total of 42 human cases of infection resulting in 30 deaths in Thailand and Vietnam (the cumulative number of avian A virus cases and deaths can be accessed at the WHO Web site [18].

Serological test results positive for H9N2 avian strains with isolation from the throats of some patients with mild influenza-like illnesses were reported from China in 1999 [19,20]. In an outbreak of H7N7 virus in poultry in The Netherlands in 2003, the virus was demonstrated in 78 poultry workers with conjunctivitis and 7 with influenza-like illnesses, as well as in 4 with other symptoms [21]. Three of 83 contacts were found to have evidence of infection, 1 of whom developed an influenza-like illness [14]. All illness was mild, except in the case of 1 of the patients with an influenza-like illness who developed evidence of primary viral pneumonia and acute respiratory distress syndrome and died [21]. In past years, H7N7 virus has caused isolated cases of infection in humans, including laboratory acquired infections; all infections were mild and were isolated to the eyes [22-27].

There has been a single probable case of human-to-human transmission of clinical disease with H5N1 virus, from a child to a mother who cared for her during her illness, both individuals died [27].

In humans, infection with H5N1 virus has been deadly, in 1997 and then again starting in December of 2003 and continuing to the present, there have been severe cases of H5N1 infection in humans in Asia, with devastating outcomes, in

1997, in Hong Kong, there were 18 documented cases involving 6 deaths in people exposed to live poultry [13, 28, 29], eleven of the 18 patients developed viral pneumonia, and 6 of them died of acute respiratory distress syndrome and/or multiorgan failure. Although there were no clinical cases in a survey of poultry workers, 10% had serological evidence of infection [13]. Most of the 42 reported cases and 30 deaths among patients with H5N1 disease (from December 2003 through 28 September 2004) have been in children and young adults; however, the mortality rate has been higher in older adults, most of the individuals who died had no obvious underlying disease[27, 31].

Transmission

Human influenza is transmitted by inhalation of infectious droplets, by direct contact, and perhaps, by indirect (fomite) contact, with self-inoculation onto the upper respiratory tract or conjunctival mucosa[32,33].

Animal to Human

In 1997, exposure to live poultry within a week before the onset of illness was associated with disease in humans, whereas there was no significant risk related to eating or preparing poultry products or exposure to persons with influenza A (H5N1) disease [34].

Exposure to ill poultry and butchering of birds were associated with seropositivity for influenza A (H5N1) [35]. Plucking and preparing of diseased birds; handling fighting cocks; playing with poultry, particularly asymptomatic infected ducks; and consumption of duck's blood or possibly undercooked poultry have all been implicated. Transmission to felids has been observed by feeding raw infected chickens to tigers and leopards in zoos in Thailand [36, 37] and to domestic cats under experimental conditions [38]

Human to Human

Bird Flu can jump from person to person [39-41]. Human-to-human transmission of influenza A (H5N1) has been suggested in several household

clusters [42] and in one case of apparent child-to-mother transmission [43]. In 1997, human-to-human transmission did not apparently occur through social contact [44], and serologic studies of exposed health care workers indicated that transmission was inefficient [45]. To date, the risk of nosocomial transmission to health care workers has been low, even when appropriate isolation measures were not used; however, one case of severe illness was reported in a nurse exposed to an infected patient in Vietnam [46, 47]

Environment to Human

Oral ingestion of contaminated water during swimming and direct intranasal or conjunctival inoculation during exposure to water are other potential modes, as is contamination of hands from infected fomites and subsequent self-inoculation, the widespread use of untreated poultry feces as fertilizer is another possible risk factor[48].

Clinical Features

The incubation period in the reported cases seemed to be 2-4 days (similar to that in cases of human influenza) , followed in most patients by fever, cough, and dyspnea[49, 50]. Diarrhea was variably reported, and sore throat and runny nose were noted in some of the patients [49, 50]. Nevertheless, the isolation of virus from a rectal specimen is a major source of concern, since it highlights a potential route of human-to-human transmission, especially in combination with crowded living conditions and diarrhea [51]. In those individuals with severe disease, there was rapid progression with increasing dyspnea; this is very much like what is seen in cases of primary influenza virus pneumonia caused by human viruses[51]. However, unlike in cases of human influenza (in which primary viral pneumonia has been rare since the 1957-1958 epidemic, and in which secondary bacterial pneumonia has been a much more common complication), in the H5N1 avian virus cases, primary viral pneumonia was common, whereas

secondary bacterial pneumonia has not been reported.[52]

The marked lymphopenia-together with the observation in a limited number of autopsies of a reactive hemophagocytic syndrome in bone marrow, lymph nodes, spleen, lungs, and liver-suggested to some investigators that a cytokine-driven condition might explain multiorgan failure in some patients [53-55]

Watery diarrhea without blood or inflammatory changes appears to be more common than in influenza due to human viruses [56] and may precede respiratory manifestations by up to one week [57]. Diarrhea, vomiting, abdominal pain, pleuritic pain, and bleeding from the nose and gums have also been reported early in the course of illness in some patients[58-61] One report described two patients who presented with an encephalopathic illness and diarrhea without apparent respiratory symptoms[62]

Clinical Course

Lower respiratory tract manifestations develop early in the course of illness and are usually found at presentation, in one series, dyspnea developed a median of 5 days after the onset of illness (range, 1 to 16)[59] Respiratory distress, tachypnea, and inspiratory crackles are common, sputum production is variable and sometimes bloody, almost all patients have clinically apparent pneumonia, multiorgan failure with signs of renal dysfunction and sometimes cardiac compromise, including cardiac dilatation and supraventricular tachyarrhythmias, has been common[58-61]. The mortality of influenza A (H5N1) infections have caused high rates of death among infants and young children, the case fatality rate was 89 percent among those younger than 15 years of age in Thailand, death has occurred an average of 9 or 10 days after the onset of illness (range, 6 to 30), and most patients have died of progressive respiratory failure [59, 60].

Investigations

Laboratory findings leukopenia, particularly lymphopenia; mild-to-

moderate thrombocytopenia; and slightly or moderately elevated aminotransferase levels may be found, marked hyperglycemia, perhaps related to corticosteroid use, and elevated creatinine levels also occur[60]

Radiographic findings

Radiographic changes include diffuse, multifocal, or patchy infiltrates; interstitial infiltrates; and segmental or lobular consolidation with air bronchograms[59] Radiographic abnormalities were present a median of 7 days after the onset of fever in one study (range, 3 to 17)[59] . Progression to respiratory failure has been associated with diffuse, bilateral, ground-glass infiltrates and manifestations of the acute respiratory distress syndrome (ARDS) [59].

Virological investigations

Laboratory confirmation of influenza A (H5N1) requires one or more of the following: a positive viral culture, a positive PCR assay for influenza A (H5N1) RNA, a positive immunofluorescence test for antigen with the use of monoclonal antibody against H5, and at least a fourfold rise in H5-specific antibody titer in paired serum samples[63]. Avian influenza A (H5N1) infection may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. In Vietnam, the interval from the onset of illness to the detection of viral RNA in throat-swab samples ranged from 2 to 15 days, and the viral loads in pharyngeal swabs 4 to 8 days after the onset of illness were at least 10 times as high among patients with influenza A (H5N1) as among those with influenza A (H3N2) or (H1N1). Earlier studies in Hong Kong also found low viral loads in nasopharyngeal samples [64].

Management

Most hospitalized patients with avian influenza A (H5N1) have required ventilatory support within 48 hours after admission, as well as intensive care for multiorgan failure and sometimes

hypotension. In addition to empirical treatment with broad-spectrum antibiotics, antiviral agents, alone or with corticosteroids, have been used in most patients, although their effects have not been rigorously assessed [59, 60].

Patients with suspected influenza A (H5N1) should promptly receive a neuraminidase inhibitor pending the results of diagnostic laboratory testing. The optimal dose and duration of treatment with neuraminidase inhibitors are uncertain, and currently approved regimens likely represent the minimum required. These viruses are susceptible in vitro to oseltamivir and zanamivir[65,66]. Oral oseltamivir [65]and topical zanamivir are active in animal models of influenza A (H5N1)[67,68]. Recent murine studies indicate that as compared with an influenza A (H5N1) strain from 1997, the strain isolated in 2004 requires higher oseltamivir doses and more prolonged administration (eight days) to induce similar antiviral effects and survival rates[69].

Although approved doses of oseltamivir (75 mg twice daily for five days in adults and weight-adjusted twice-daily doses for five days in children older than one year of age- twice-daily doses of 30 mg for those weighing 15 kg or less, 45 mg for those weighing more than 15 to 23 kg, 60 mg for those weighing more than 23 to 40 kg, and 75 mg for those weighing more than 40 kg) are reasonable for treating early, mild cases of influenza A (H5N1), higher doses (150 mg twice daily in adults) and treatment for 7 to 10 days are considerations in treating severe infections, but prospective studies are needed[70-72].

Agents of clinical investigational interest for treatment include zanamivir, peramivir, long-acting topical neuraminidase inhibitors, ribavirin[73,74] and possibly, interferon alfa [75]

Prevention

Immunization

A new viral-vectored vaccine has been developed to facilitate vaccine efficiency

against avian influenza. Development of new vaccines will help to protect birds and humans in the event of an outbreak of avian influenza [76].

Earlier H5 vaccines were poorly immunogenic and required two doses of high haemagglutinin antigen content[77]or the addition of MF59 adjuvant[78] to generate neutralizing antibody responses. A third injection of adjuvanted 1997 H5 vaccine variably induced cross-reacting antibodies to human isolates from 2004[79] Reverse genetics has been used for the rapid generation of nonvirulent vaccine viruses from recent influenza A (H5) isolates[80,81]and several candidate vaccines are under study. One such inactivated vaccine with the use of a human H5N1 isolate from 2004 has been reported to be immunogenic at high haemagglutinin doses[82]. Studies with approved adjuvants like alum are urgently needed. Live attenuated, cold-adapted intranasal vaccines are also under development. These are protective against human influenza after a single dose in young children [83].

Heat inactivation of avian influenza [84, 85]

The H5N1 avian influenza virus is not transmitted to humans through properly cooked food. The virus is sensitive to heat. Normal temperatures used for cooking (so that food reaches 70°C in all parts) will kill the virus. To date, no evidence indicates that any person has become infected with the H5N1 virus following the consumption of properly cooked poultry or poultry products, even in cases where the food item contained the virus prior to cooking. In countries with outbreaks, thorough cooking is imperative. Consumers need to be sure that all parts of the poultry are fully cooked (no “pink” parts) and that eggs, too, are properly cooked (no “runny” yolks)

Hospital-Infection Control.

The efficiency of surgical masks, even multiple ones[86], is much less than that of N-95 masks, but they could be used if the

latter are not available. Chemoprophylaxis with 75 mg of oseltamivir once daily for 7 to 10 days is warranted for persons who have had a possible unprotected exposure [87, 88]

Household and Close Contacts [48]

Household contacts of persons with confirmed cases of influenza A (H5N1) should receive postexposure prophylaxis as described above. If evidence indicates that person-to-person transmission may be occurring, quarantine of exposed contacts should be enforced. For others who have had an unprotected exposure to an infected person or to an environmental source (e.g., exposure to poultry) implicated in the transmission of influenza A (H5N1), postexposure chemoprophylaxis as described above may be warranted.

Conclusion

A common saying in medicine is this: When you hear hoof beats, think of horses, not zebras. In the case of bioterror events, however, it may be a zebra. The challenge posed to healthcare executives is to ensure that their organization is alert, vigilant, and prepared to strategically respond to a bioterror event. Preemptive strategies are key.

Our current capacity to diagnose and manage an H5N1 pandemic is less than adequate. To prevail, we need excellent surveillance that relies on clinical, scientific and technologic capacity. We need knowledge sharing and the will to act, and act quickly, at the first signs of facilitated human-to-human transmission. Specific concerns are that H5N1 is already resistant to two of four common anti-viral drugs. But there is some good news – on Aug. 7, health officials announced success in an initial test of a human vaccine. They cautioned, however, that the existence of a vaccine in itself would not be enough to prevent a worldwide pandemic.

Human transmission of bird flu is predictable and therefore manageable. Failure to take action could be a mistake of historic proportions

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