Pandemic influenza: clinical issues

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ABSTRACT

- Influenza is an acute febrile illness caused by influenza A or B viruses. It occurs mainly in winter in temperate climates, and throughout the year in tropical Australia. It is highly contagious and of considerable public health concern because of the rapidity with which epidemics evolve and the associated morbidity and mortality.
- Most influenza illnesses resolve over about 1 week without specific medical intervention.
- People at particular risk for complicated infection are those > 65 or < 5 years old, those with chronic medical comorbidities, residents of chronic care facilities (including nursing homes), and women in the second or third trimester of pregnancy.
- Complicated influenza infection most commonly manifests as primary viral pneumonia, combined viral and bacterial pneumonia, and secondary bacterial pneumonia.
- Rare but serious complications of influenza include central nervous system involvement (eg, encephalitis, transverse myelitis, aseptic meningitis, and Guillain–Barré syndrome).
- The recent emergence of avian influenza A/H5N1 and confirmation of sporadic cases of human H5N1 infection have heightened concern about an impending human influenza pandemic, either from a human form of H5N1 or a primary new human influenza strain.
- H5N1 infection in humans has been associated with severe illness and a > 50% mortality rate, with high mortality in people aged 10–39 years.

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Influenza is an acute febrile illness caused by influenza A or B viruses. It occurs mainly in winter in temperate climates, and throughout the year in tropical Australia. Influenza is highly contagious and of considerable public health concern because of the rapidity with which epidemics evolve and the associated morbidity and mortality.

Uncomplicated influenza

Uncomplicated influenza is typically characterised by acute onset of symptoms of an upper respiratory tract infection (eg, dry cough, sore throat) accompanied by a constitutional illness (eg, various combinations of fever, headache, chills, myalgias, anorexia and malaise). The typical incubation period for influenza is 1–4 days, with an average of 2 days.[1] In the context of a declared influenza pandemic, the presence of cough and fever may be diagnosed as influenza infection with a reasonable degree of certainty.[2]

History

Adults

Adults are infectious from the day before symptoms begin until about 5 days after. People who are severely immunocompromised can shed virus for weeks to months.[3-5]

Children

School-aged children have the highest attack rates of influenza and are major sources of virus dissemination.[6] This increased infectiousness is accounted for by the shedding of higher titres of virus for a longer period than other patient groups (≥ 10 days after onset of symptoms).[7,8] During the influenza season, about 50% of hospitalisations for lower respiratory tract infections in children are influenza-related, and affect predominantly the 6–12-months-old group.

Unexplained fever may be the only manifestation of influenza infection in young children; they may develop high temperatures (> 39.5° C) and have febrile seizures. Presentations may include laryngotracheobronchitis ("croup"), bronchiolitis, and pneumonia. Gastrointestinal manifestations such as nausea, vomiting, diarrhoea and abdominal pain are much more frequent in children than adults (up to 50% of patients), especially in children less than 3 years old.

Children may develop middle ear infections and sinusitis as complications of influenza.[9]

Neonates have non-specific features of sepsis such as lethargy, poor feeding, apnoea and poor peripheral circulation. A variety of central nervous system findings, including apnoea, opisthotonos and seizures, can occur in up to 20% of infants, who may also manifest meningeal irritation.

The elderly

In the elderly, influenza infection may not present characteristically, but with undifferentiated syndromes of sepsis in old age, such as delirium, falls, immobility and incontinence. Those living in nursing homes are at greater risk of developing influenza-related complications.[10]

Examination and investigation

Abnormal physical findings are sparse in patients with uncomplicated influenza. One hospital series found that only half the patients with proven influenza satisfied the criteria for influenza-like illness (temperature > 37.8° C, cough or sore throat), so a high index of suspicion is required to recognise influenza.[11] Examination of the chest is usually unremarkable. The respiratory rate, estimated haemoglobin oxygen saturation (assessed by pulse oximetry) and chest x-ray are usually normal.

The full blood examination in uncomplicated influenza may be normal or consistent with the presence of a viral infection — that is, the blood haemoglobin concentration will likely be normal; the platelet count and total white cell count may be normal, decreased, or raised; and a blood film will probably suggest infection, with a neutrophil "left shift", "band forms", and "toxic" changes. In general, the serum urea, creatinine and electrolytes will be normal, or exhibit mild, clinically insignificant abnormalities. Liver function tests may demonstrate a mild hepatitis (raised serum alanine aminotransferase or asparagine aminotransferase concentrations) or non-specific cholestatic changes (eg, raised serum gamma glutamyl transferase and alkaline phosphatase concentrations). Study of C-reactive protein (CRP) in assessment of respiratory viral

infections suggests that uncomplicated infection with influenza A or B viruses tends to produce higher CRP levels when compared with other upper respiratory viruses.[12,13] However, it is neither sufficiently sensitive nor specific to support its use as a marker of influenza infection.

Immunopathogenesis

The major target of influenza infection is the ciliated epithelial cells in the mucous layer of the respiratory tract, leading to their necrosis, with oedema and infiltration by lymphocytes, plasma cells, histiocytes and neutrophils. In uncomplicated infection, repair starts about 3–5 days after illness, corresponding with the time of defervescence. However, restoration of ciliated cell function and normal mucous production may be delayed for 2 or more weeks after the onset of the illness. In fatal cases of influenza pneumonia, there have been varying degrees of interstitial cellular infiltrate, alveolar oedema and hyalin membrane deposition described. The virus may also infect neutrophils and lymphocytes, resulting in a reduced response to chemotactic stimuli and cellular function in general. This, together with necrosis and desquamation of the ciliated epithelial cells and abnormal mucus secretion, favours the development of secondary bacterial infection, including bronchitis and pneumonia, as well as other complications such as middle ear infections and sinusitis.[14,15]

The severity of clinical disease during an influenza pandemic is determined by intrinsic properties of the virus and the immunological status of the affected individual. For instance, the "cleavability" of the haemagglutinin (HA) glycoprotein has an association with viral pathogenicity. Anti-HA antibodies are the primary neutralising antibodies, and participate in complement-mediated lysis of infected cells, aggregation of virions, and cell cytotoxicity. Anti-neuraminidase reduces the number of infectious particles released from infected cells, and may reduce disease severity. The replication of influenza in a new host activates an inflammatory cytokine cascade, which leads to the febrile response and symptoms. Lavage specimens of nasal secretions typically contain interleukin 6 (IL-6), tumour necrosis factor (TNF), interferon γ, interleukin 10, monocyte chemotactic protein 1, and macrophage inflammatory proteins. While these cytokines may be associated with decreases in viral titre, very high levels of cytokines (eg, IL-6 and TNF) have been found in patients who manifest complicated disease.[14,16,17]

Management

Commencement of antivirals within 48 hours of symptom development is indicated in people with a high probability of influenza infection during a declared influenza pandemic. Collection of appropriate diagnostic specimens should be performed beforehand, but this should not delay therapy.[18,19]

Complicated influenza

There are a number of individuals who are at increased risk for complicated influenza infection. They are:

- People with chronic cardiac or pulmonary disorders (eg, cystic fibrosis, asthma, asthma/chronic airways limitation, cor pulmonale, and bronchopulmonary dysplasia);
- Residents of chronic care facilities, including nursing homes;
- People with chronic medical conditions (eg, diabetes mellitus, renal insufficiency, haemoglobinopathy, immunodeficiency and immunosuppression);
- Women in the second or third trimester of pregnancy; and
- People older than 65 years or younger than 2 years.

Primary influenza pneumonia

Primary influenza pneumonia occurs when influenza virus infection directly involves the lung parenchyma. It is a manifestation of severe influenza infection, and the least common of the pneumonic complications. It occurs predominantly in high-risk patients, but has been occasionally described in otherwise healthy adults. Presentation is often abrupt and dramatic, progressing within 24 hours to severe pneumonia with respiratory failure and shock. Non-fatal cases recover 5–16 days after pneumonia onset, but residual lung damage is frequent. Mortality is in the order of 10%–20%.

Combined viral–bacterial pneumonia

Combined viral–bacterial pneumonia is at least three times more common than viral pneumonia, from which it is clinically indistinguishable. Clinical examination, including chest x-ray, frequently shows pleural effusions, and areas of consolidation or cavitation. The diagnosis requires isolation of pathogenic bacteria. The most frequently implicated agents are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*. Mortality is about 10%.

Secondary bacterial pneumonia

Clinically, secondary bacterial pneumonia may be easier to differentiate from combined viral–bacterial pneumonia, as patients typically improve as expected and then deteriorate with symptoms or signs suggestive of bacterial pneumonia, including chills, rigors, increased productive cough, pleuritic chest pain and dyspnoea. Examination and chest x-ray may reveal areas of consolidation; repeat full blood examination may reveal a new leukocytosis and elevated CRP level. Mortality is about 7%.

Other pulmonary complications

In children, pneumonia is less common, although bronchitis or bronchiolitis may occur. It may be difficult to distinguish influenza from other forms of viral respiratory infection (eg, respiratory syncytial virus or parainfluenza virus).

Acute exacerbations of chronic obstructive airways disease or chronic airways limitation, asthma, bronchitis and cystic fibrosis may occur in adults.

Non-pulmonary complications

Non-pulmonary complications are rare. They include:

- Myositis and rhabdomyolysis. These are more common in children. The acute myositis may present with extreme tenderness of the affected muscles, most commonly in the legs. Markedly elevated serum creatine phosphokinase concentrations are seen, and myoglobinuria with associated renal failure has been reported.[20]
- Central nervous system involvement, including encephalitis, transverse myelitis, aseptic meningitis, and Guillain–Barré syndrome.[21-23] Psychiatric complications, including depression, have been recognised.

- Reye syndrome. Children between the ages of 2 and 16 years seem preferentially affected, and the syndrome usually occurs after a seemingly unremarkable case of influenza.[24] An epidemiological association with aspirin use has been described.[25]
- Myocarditis and pericarditis were reported in the 1918 influenza pandemic, but have been infrequently reported since. However, during the Asian epidemic in 1957, signs of focal or diffuse myocarditis were found in a third of autopsies.

Avian influenza A/H5N1 in birds and humans

In 1997, an epizootic avian influenza A/H5N1 virus of high pathogenicity began to cross the species barrier from birds to humans. This first epidemic occurred in China and Hong Kong, and 18 human infections were described (six deaths), which ceased after a mass cull of the entire Hong Kong chicken population. In mid 2003, the H5N1 virus began to circulate widely in poultry in the South-East Asian region as a result of the commercial flow of poultry stocks between neighbouring countries. Its adaptation to migratory birds in 2005 has allowed widespread dissemination of the virus, which is now present in at least 50 countries in Asia, the Indian subcontinent, Africa and Europe.

Since December 2003, 10 of those 50 countries have reported a total of 256 laboratory-confirmed human cases of H5N1 influenza, of which two were asymptomatic cases detected on contact screening.[26] The case fatality rate (of symptomatic cases) was 59%. Although this mortality rate is high, it must be recognised that the extent of subclinical infection or mild illness is not certain — it cannot be assumed that these confirmed cases are representative of all human H5N1 infections. However, recent epidemiological surveys have detected only very low rates of asymptomatic seropositive cases of H5N1 virus among health care contacts of patients with documented H5N1 infection, suggesting a substantial symptomatic infection rate.[27]

Most cases of confirmed human H5N1 influenza to date have been in previously healthy young children or adults, probably reflecting the age-related behaviours that increase risk of exposure to infected birds (ie, poultry workers in the affected countries often tend to be young women). Median duration from symptom onset to hospitalisation was 4–5 days. The median time from symptom onset to death was 9 days. Case fatalities have been highest in those aged 10–39 years, lowest among those older than 50 years, and intermediate among children younger than 10 years. This age profile differs from the typical age-related case fatality for seasonal influenza, in which the highest mortality is seen among people at the extremes of age. The age distribution is similar to that described for the 1918 "Spanish flu" epidemic, in which fatality rates were higher among young adults.[28]

The clinical presentation of H5N1 infection has been with fever (typically > 38° C) and an influenza-like illness, with lower respiratory tract symptoms more frequent than upper respiratory tract symptoms. Most patients (> 88%) have had pulmonary infiltrates at time of diagnosis.[29] Limited microbiological data gathered to date suggest that this pneumonic process is a primary viral pneumonia. Gastrointestinal manifestations have been a relatively prominent aspect of the presentation; watery diarrhoea has preceded respiratory manifestations by up to 1 week.[29] The fatality rate of hospitalised patients since 2003 is 78%.[26]

Common laboratory findings have included leukopenia (particularly lymphopenia), mild to moderate thrombocytopenia, and mild to moderately elevated serum aminotransferase levels. In Thailand, an increased risk of death was associated with decreased leukocyte, platelet, and, particularly, lymphocyte counts at admission.[30]

H5N1 infection may be associated with a higher frequency of viral detection and higher viral DNA levels in pharyngeal than in nasal samples.[17] Commercial rapid antigen tests have been less sensitive than reverse transcription polymerase chain reaction assays in detecting H5N1 influenza.[30]

Most hospitalised patients with H5N1 influenza have required ventilatory support within 48 hours of admission, and intensive management for multiorgan failure.[30,31] Empirical therapy has generally consisted of broad-spectrum antibiotics and antiviral agents, alone or with corticosteroids; the emergency situation has not allowed a rigorous assessment of their effectiveness. Initiation of antibiotics and antivirals relatively late in the disease course has not resulted in any apparent reduction in mortality, although early initiation of antivirals does appear to be of some benefit.[27,30,31] After treatment with oseltamivir, it has not been possible to culture the virus from patients who survived, and reductions in pharyngeal viral load have been described within 72 hours of oseltamivir initiation. However, clinical deterioration and eventual death have occurred despite these observations. Observations like this, as well as the apparent risk of serious disease in the otherwise healthy, have suggested a possible role of the innate immune response in the pathogenesis of H5N1 influenza. Elevations of various cytokines, including IL-6, TNF-α, interferon γ, soluble interleukin 2 receptor, interferon-inducible protein 10, monocyte chemoattractant protein 1, and monokine induced by interferon γ, have been described. In one study, the average levels of plasma interferon α in people who died of H5N1 influenza were about three times that found in healthy controls. Such responses may account, at least in part, for the sepsis syndrome, acute lung injury and multiorgan failure seen in many patients who died.[17,27]

Applying the clinical knowledge of influenza to an H5N1 pandemic

The presentation of H5N1 influenza in humans is similar to that of severe seasonal influenza, with signs of lower respiratory tract involvement. Many patients will have chest x-ray changes at presentation. A prodrome of gastrointestinal symptoms (particularly diarrhoea) may be more frequent than that observed in seasonal influenza.

In the setting of an influenza pandemic, the positive predictive value of acute onset of cough and fever for influenza will be high. Rapid diagnostic testing can yield results in a clinically useful time frame. Nevertheless, if the clinical pre-test probability of influenza is high, then management should be instituted on the basis of the clinical impression alone.

There is likely to be a high rate of serious and complicated disease and a high case fatality rate.

The possibility of H5N1 infection should be considered in any patients presenting with serious febrile illness (eg, encephalopathy or diarrhoea) during a declared H5N1 pandemic.

Specific age groups at particular risk of serious and complicated disease may include healthy young adults as well as the usual "at risk" spectrum of the elderly, young children, and other specific risk groups.

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Competing interests

Mark Boyd has received grants to attend conferences from Merck, Sharpe and Dohme, Roche, and Gilead Sciences, and is an advisor to Roche. Rodney Pearce is an Executive Member of the Influenza Specialist Group, which receives funding from various companies, including CSL, GlaxoSmithKline, Merck, Sharpe and Dohme, and Aventis, but operates as an incorporated independent body. He has received travel expenses from the Influenza Specialist Group, and Roche paid travel expenses for him to attend the *Lancet* pandemic influenza meeting in Singapore, April 2006. Richard Lindley has received a donation of oseltamivir (Tamiflu) from Roche for a research project.

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