

3 CLINICAL FEATURES

3.1 How reliable is a clinical diagnosis of influenza infection during a pandemic?

The clinical manifestations of infection by influenza viruses are diverse, ranging from asymptomatic infection to fulminant respiratory distress leading to respiratory failure and death. Furthermore, the presence of an influenza-like illness (ILI) comprising of a combination of fever, cough, sore throat, myalgia and headache is not specific for influenza infection. Other respiratory pathogens that may present with an ILI include viruses such as respiratory syncytial virus (RSV), adenovirus, rhinovirus and parainfluenza virus, as well as bacterial pathogens such as *Chlamydia pneumoniae*, *Legionella* sp., *Mycoplasma pneumoniae* and *Streptococcus pneumoniae*.(14-16)

Studies that have examined the value of a clinical definition of ILI in the diagnosis of influenza infection have not always used the same clinical definition for an ILI and have included different study populations, making comparison between studies complicated. A systematic review of the literature in this area identified the three-fold combination of the presence of fever, cough and acute onset to be the most predictive clinical features. The accuracy of this clinical definition was higher in persons aged 60 years and above compared to patient groups without age restrictions (positive likelihood ratio (95% CI) 5.4 (3.8 to 7.7) vs 2.0 (1.8 to 2.1)).(17) The probability of influenza infection also increases with increasing level of fever.(18;19)

Importantly, the predictive value of clinical definitions based on an ILI increases when influenza virus is known to be circulating in the community.(15;17;20) In cohort studies, correlation of ILI with laboratory-confirmed influenza infection ranges from 25 – 45% while in clinical trials, rates of 70% have been consistently reported.(15;21-23)

These findings relate to influenza infections during interpandemic periods. During a global influenza pandemic, when a pandemic strain is known to be circulating locally in an immunologically susceptible population, the presence of an ILI would be expected to be highly predictive for influenza infection. (However, the extent to which a clinical diagnosis of ILI becomes predictive during a pandemic will also be determined by the behaviour of the public- if many, who would not normally present to a health professional, are prompted to present, then the predictive value of a clinical diagnosis of ILI will be reduced.)

Box 3.1 Clinical Case Definition (October 2005):

The presence of fever and new (or, in those with chronic lung disease, worsening) cough of acute onset in the context of influenza circulating in the community.

(Important note - This definition may be modified once a pandemic occurs.)

3.2 What are the clinical features of uncomplicated influenza?

The following description will relate mainly to interpandemic influenza A infections. Influenza B and C are not considered pandemic threats. Different strains may be associated with different clinical presentations and disease severity. For instance, there is evidence to suggest that the H3N2 subtype causes more severe disease than H1N1 subtype.(24) **The spectrum of clinical disease associated with a new influenza A subtype (eg. a pandemic strain) cannot be determined currently and may differ from that described for interpandemic influenza.**

The incubation period prior to the onset of symptoms is commonly 2 – 4 days (range 1 – 7 days). In adults, the illness typically presents as an abrupt onset of fever accompanied by other a range of other symptoms as listed in Box 3.2. (25-29)

Box 3.2 Range of symptoms associated with uncomplicated influenza infection

- cough (~85%)
- malaise (~80%)
- chills (~70%)
- headache (~65%)
- anorexia (~60%)
- coryzal symptoms (~60%)
- myalgia (~53%) and
- sore throat (~50%).

Fever is the paramount symptom and may reach 41°C although more usually it ranges between 38 – 40 °C. The peak occurs within 24 hours of onset and lasts typically for 3 days (range 1 – 5 days).(25-29) The cough is generally dry although in up to 40% of cases it may be productive. A productive cough together with chest tightness and substernal soreness is more common in patients with underlying chronic lung disease. Myalgia affects mainly the back and limbs. Gastrointestinal symptoms such as vomiting and diarrhoea are uncommon (<10%) in adults. Abdominal pain is rare.

Clinical findings include a toxic appearance in the initial stages, hot and moist skin, a flushed face, injected eyes and hyperaemic mucous membranes around the nose and pharynx. Tender cervical lymphadenopathy is found in a minority (~10%) of cases. Wheezing or lung crackles are recognised findings (~10%) more commonly noted in patients with coexisting chronic lung disease.

Although the overall clinical picture of uncomplicated influenza in any specific age group is similar for different influenza A subtypes, the frequency of certain symptoms may vary. For instance, during the 'Asian' pandemic of 1957 (H2N2), headache and sore throat were frequent initial symptoms.(30)

In uncomplicated infection, the illness usually resolves in 7 days although cough, malaise and lassitude may persist for weeks.

3.3 What complications are associated with influenza infection?

Influenza virus infection has been associated with worsening in the clinical condition of patients with a range of existing medical conditions, such as, heart failure, diabetes, coronary heart disease, asthma and chronic obstructive airways disease (COPD).

In addition, specific complications associated with influenza infection regardless of co-existing medical conditions are recognised (Table 3.1). Based on data from interpandemic influenza, certain persons are identified as being at high risk from influenza-related complications. Such patients are similar to the group currently recommended for influenza vaccination by the Department of Health. These include those of all ages with chronic respiratory disease including asthma, chronic heart disease, chronic renal disease, chronic liver disease, immunosuppression due to disease or treatment, or diabetes mellitus, and all those aged 65 years or older, or those in long stay residential care (see Appendix 2).

In the course of a pandemic, it may emerge that the patient group at high risk of complications differs from the group currently identified. In such circumstance, details of the 'high risk' patient group will be altered according to relevant clinico-epidemiological data.

Table 3.1: Complications associated with influenza infection in adults

Complication	Incidence	Comments
<u>Respiratory</u>		
Acute bronchitis	Common	More common in elderly and those with chronic medical conditions.
Primary viral pneumonia	Uncommon	Onset within 48 hours of start of fever.
Secondary bacterial pneumonia	Common	Typically occurs 4 – 5 days after onset of illness.
<u>Cardiovascular</u>		
ECG abnormalities	Common	Non-specific T wave and rhythm changes, ST segment deviation. Mostly not associated with cardiac symptoms.
Myocarditis	Rare	
Pericarditis	Rare	
<u>Muscle</u>		
Myositis	Uncommon	Occurs during early convalescence
Myoglobinuria and renal failure	Rare	
<u>Central Nervous System</u>		
Encephalitis/ encephalopathy	Rare	Occurs within first week of illness. More common in children and in Japan.
Transverse myelitis	Very rare	
Guillain-Barre syndrome	Very rare	
<u>Others</u>		
Otitis media	Uncommon	Much more common in children
Toxic shock syndrome	Rare	
Parotitis	Very rare	

3.3.1 Influenza-related pneumonia

The incidence of pneumonia (defined as a combination of respiratory symptoms and signs supported by chest radiographic changes consistent with infection) complicating influenza infection varies widely, from 2% to 38%, and is dependent on viral and host factors.(25-27) Pneumonia generally occurs more frequently and with greater severity in patients with pre-existing chronic cardiac and respiratory conditions.

Patients who develop pneumonia may present with symptoms and signs indistinguishable from pneumonia related to other viral and bacterial pathogens. In the context of an influenza pandemic, the presence of an ILI *and* new or worsening dyspnoea should prompt a careful examination for the presence of complicating pneumonia. Two main types of influenza-related pneumonia are recognised; primary viral pneumonia and secondary bacterial pneumonia.(25-28)

(A) *Primary viral pneumonia.*

Patients with primary viral pneumonia typically become breathless within the first 48 hours of onset of fever. An initially dry cough may become productive of blood-stained sputum. Cyanosis, tachypnoea, bilateral crepitations and wheeze on chest examination and leucocytosis are usual. The commonest chest radiographic abnormality is of bilateral interstitial infiltrates predominantly in the mid-zones, although focal consolidation is also well recognised. Rapid clinical deterioration with respiratory failure may ensue.(31) The mortality in hospitalised patients is high (>40%) despite maximum supportive treatment on intensive care.(25-28) In the majority of fatal cases, death occurs within 7 days of hospital admission.

(B) Secondary bacterial pneumonia

Secondary bacterial pneumonia is more common (up to four times) than primary viral pneumonia. Typically, symptoms and signs of pneumonia develop during the early convalescent period (4 – 5 days from onset of initial symptoms). In others, symptoms of pneumonia blend in with the initial symptoms of influenza. Chest radiography usually demonstrates a lobar pattern of consolidation. Mortality rate ranges from 7% to 24%,(25-29;32) although some small studies report higher mortality rates

The spectrum of pathogens implicated is similar to that observed in CAP and includes *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and Groups A,C and G beta-haemolytic streptococci.(27;28;33-35) Different pathogens have predominated at different times. For instance, in the 1918 pandemic, *H influenzae*, beta-haemolytic streptococci and *S pneumoniae* were the predominant pathogens isolated. In contrast, during the 1957 pandemic, *Staphylococcus aureus* was the predominant organism isolated (up to 69% of cases) (25) In 1968, *Streptococcus pneumoniae* was the predominant pathogen (48%) followed by *Staph aureus* (26%) and non-typeable *H influenzae*(11%).(34) Importantly, *Staphylococcus aureus* was identified two and a half times more frequently during the 1968 pandemic compared to pneumonia occurring in the interpandemic period.(34;36)

Secondary staphylococcal pneumonia is associated with a higher incidence of lung abscess formation (14% vs 2%) and carries a poorer prognosis compared to non-staphylococcal pneumonias (mortality 47% vs 16%).(25;29;32;37)

(C) Mixed viral bacterial pneumonia

Bacterial and viral pneumonia can occur concurrently. In these instances, the chest radiograph may demonstrate lobar consolidation superimposed on bilateral diffuse lung infiltrates. The mortality rate in mixed viral – bacterial pneumonia is high (>40%), as for primary viral pneumonia.(25-28)

3.3.2 Cardiovascular

Minor abnormalities on ECG such as ST segment deviation, T wave changes and rhythm disturbances have been described in uncomplicated influenza illness. They have been reported in up to 81% of patients hospitalised with influenza.(25) Most do not have cardiac symptoms. Myocarditis and pericarditis are occasionally encountered in severe illness.(38;39) Post mortem evidence of necrotising myocarditis has been reported in patients without clinically significant myocarditis in the antemortem period.

3.3.3 Myositis

In contrast with myalgia affecting the back and limbs which is common on initial presentation, myositis generally develops after the subsidence of the acute upper respiratory tract symptoms. The gastrocnemius and soleus muscles are typically involved with pain and tenderness to palpation. Complete recovery usually occurs in 3 days. Elevation in serum creatine phosphokinase is recognised.(40;41) Rarely, this is associated with myoglobinuria and renal failure.(42;43) Myositis is more commonly described in children than adults.

3.3.4 Central Nervous System

Central nervous system (CNS) involvement in adults is uncommon. Most reports originate from Japan and occur in children.(44;45) The main clinical syndrome is an encephalitis or encephalopathy manifesting in the form of decreased consciousness and seizures about 3 days (range 0 – 7 days) following the onset of upper respiratory tract symptoms. Focal neurological signs such as paresis, aphasia, choreoathetosis and cranial nerve palsies are less common. Cerebrospinal fluid (CSF) examination may be normal or reveal an elevation in protein or white cell count. Imaging by CT or MRI may be normal and if so, is indicative of a good prognosis and full recovery may be anticipated.(46) Young age and abnormal CT/MRI findings are associated with a poor outcome including death or recovery with severe neurological sequelae. [A fuller description is given in Section 11.2.6]

Acute necrotising encephalopathy is a rare fulminant syndrome associated with multifocal brain lesions that is described mainly in Japan.(46) Other rare manifestations include transverse myelitis and Guillain-Barre Syndrome (47;48)

Reye's syndrome, characterised by an encephalopathy, acute fatty liver, association with aspirin use and high mortality (~40%), is a special situation that is almost exclusively seen in children and adolescents.(46) Nevertheless, physicians managing adults are advised to be aware of this complication. [A fuller description is given in Section 11.2.6]

3.3.5 Others

Other complications rarely encountered in adults with influenza A infection include toxic shock syndrome in conjunction with secondary *Staphylococcus aureus* infection(49;50) and parotitis.(51) Otitis media is more commoner encountered in children than adults.

3.4 What are the clinical features associated with human infection by avian influenza A (H5N1)?

The first recorded instance of human infection by avian influenza H5N1 occurred in May 1997 in Hong Kong. The first patient was a 3 year old child who presented initially with symptoms of fever, sore throat and abdominal pain. He later developed Reye's syndrome, ARDS, multi-organ failure and eventually died.(52) A total of 18 persons were subsequently infected before the outbreak ended in December 1997.(53;54) Half the patients were aged 18 years and below and only 2 were aged over 50 years. Abdominal symptoms, such as diarrhoea, vomiting and abdominal pain, were described in a number of patients 10(56%). Eleven (61%) had a severe illness characterised by pneumonia occurring within 14 days of symptom onset, lymphopenia, deranged liver function tests and a high mortality (6 (55%) of 11 patients with pneumonia). Secondary bacterial infections were not identified as the cause of the pneumonias.

The clinical features of patients infected by the re-emergent avian influenza A (H5N1) in 2004 were very similar to those described in 1997. (Table 3.2) Once again, children and young adults were the main groups affected. Gastrointestinal symptoms were common. The presence of lymphopenia and deranged liver function tests were again associated with the development of a severe primary viral pneumonia.(55)

From 26 December 2003 to 10 October 2005, 117 cases had been reported to the WHO, 91 cases occurring in Viet Nam, 17 in Thailand, 5 in Indonesia and 4 in Cambodia. In the initial period, mortality was very high (December 2003 to March 2004, 24 (68%) of 35 cases). In latter months, crude mortality rate has been lower (December 2004 to October 2005, 28 (38%) of 73 cases.) (56).

3.4.1 Summary

The spectrum of human illness associated with avian influenza A (H5N1) infection is not fully known. The proportion of persons with asymptomatic or mild illness compared to those with illness warranting hospital admission is difficult to determine. Recent evidence suggests that mild or subclinical infections are not very common.

In patients who are symptomatic, an ILI similar to that associated with inter-pandemic influenza A (H1N1 or H3N2) infection is recognised. In addition, gastrointestinal symptoms are present in a relatively large proportion of both adult and paediatric cases. This contrasts with the relatively low incidence of gastrointestinal symptoms in seasonal influenza. The majority of patients develop a severe primary viral pneumonia usually associated with lymphopenia, thrombocytopenia and deranged liver function tests. Renal failure and multi-organ failure may develop subsequently. Mortality is high.

Should influenza A (H5N1) acquire efficient human-to-human transmission capabilities, it may result in an influenza pandemic. In such an event, the clinical features of human disease may alter.

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Table 3.2: Clinical features of human H5N1 infection (adapted from refs (54;57))

	Children (16 years and under)			Adults (>16 years)		
	1997 Hong Kong	2004 Vietnam	Total (%)	1997 Hong Kong	2004 Vietnam	Total (%)
Number	7	7	14	5	3	8
Male	3	3	6 (43)	1	3	4 (50)
Mean age (years)	4.1	10.3	-	36.4	21.7	-
Fever	7	7	14 (100)	5	3	8 (100)
Headache	1	NK	1 (7)	1	NK	1 (13)
Sore throat	2	NK	2 (14)	1	NK	1 (13)
Rhinorrhoea	4	NK	4 (29)	2	NK	2 (25)
Dyspnoea	NK	7	7 (50)	NK	3	3 (38)
Cough	4	7	11 (79)	4	3	7 (88)
Sputum	0	2	2 (14)	2	3	5 (63)
Diarrhoea	1	4	5 (36)	1	3	4 (50)
Vomiting	2	NK	2 (14)	2	NK	2 (25)
Abdominal pain	1	NK	1 (7)	1	NK	1 (13)
Deranged LFTs	2	5 of 5	7 of 12 (58)	4	1 of 1	5 of 8 (63)
Raised ALT	1	5 of 5	6 of 12 (50)	3	1 of 1	4 of 8 (50)
Thrombocytopenia	1	6	7 (50)	3	3	6 (75)
Lymphopenia	5	7	12 (85)	5	3	8 (100)
Leucopenia	2	7	9 (64)	2	3	5 (63)
Bacterial infection			0 (0)			0 (0)
CXR pneumonia	1	7	8 (57)	4	3	7 (88)

NK = not known or reported