

Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza)

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We present the first six cases of H1N1 influenza 09 (confirmed by a polymerase chain reaction test from nasopharyngeal swabs) in patients requiring admission to intensive care in Australia (in three hospitals in the north-western suburbs of Melbourne). These cases highlight the small but significant risk of life-threatening respiratory failure associated with H1N1 influenza 09 infection. (MJA 2009; 191: 154-156)

Clinical records

Patient 1

A 28-year-old obese woman (body mass index [BMI], 57 kg/m²) presented to the emergency department (ED) with a history of 5 days of sore throat, lethargy and myalgias, and a clear chest x-ray, followed by 2 days of dyspnoea, productive cough, and pleuritic chest pain. She was febrile (40°C), and had tachypnoea (respiratory rate, 36 breaths/min) and hypoxia (oxygen saturation measured by pulse oximetry [SpO₂], 87% on 15 L/min oxygen via face mask). Her admission chest x-ray showed widespread alveolar infiltrates. She had a normal white cell count (WCC) of 6.3 × 10⁹/L, but an elevated serum C-reactive protein (CRP) level of 221 mg/L (reference ranges shown in Box 1). She was admitted to the intensive care unit (ICU) and, after a brief trial of non-invasive ventilation (NIV), was intubated and treated with mechanical ventilation (MV) with a fraction of inspired oxygen (FiO₂) of 1.0 and positive end-expiratory pressure (PEEP) of 20 cm H₂O for the first 24 hours to maintain an SpO₂ > 89%. She was treated with inotropes for septic shock and with renal replacement therapy for acute renal failure. Therapy with oseltamivir in addition to empiric broad-spectrum antibiotics was commenced. Bacterial cultures of blood, urine and tracheal aspirate were negative. The result of a test for urine pneumococcal antigen was negative. The patient was successfully weaned from ventilatory support on Day 14.

Patient 2

A previously well 24-year-old man (BMI, 22 kg/m²) was admitted to a regional hospital with a 1-week history of dry cough, fever, headache, abdominal pain, and vomiting. Thirty-six hours later, he was transferred to a metropolitan hospital because of worsening dyspnoea and hypoxia (SpO₂, 88% on 15 L/min oxygen via face mask). He had tachycardia (110 beats/min), tachypnoea (respiratory rate, 34 breaths/min) and was febrile (39.9°C). He had a normal WCC (4.2 × 10⁹/L) but an elevated CRP level (256 mg/L). A chest x-ray showed unilateral lobar consolidation. He was transferred to the ICU and treated with oseltamivir, broad-spectrum antibiotics, and NIV with an FiO₂ of 1.0. After 96 hours, his hypoxia remained severe (partial pressure of arterial oxygen [PaO₂] to FiO₂ ratio, < 100), another chest x-ray showed bilateral alveolar infiltrates, and he was intubated and MV was commenced with an FiO₂ of 1.0 and high-level PEEP (20 cm H₂O) for several days.

1 Reference ranges for white cell count and C-reactive protein level

	Reference range
White cell count (WCC)	4–11 × 10 ⁹ /L
C-reactive protein (CRP)	< 5 mg/L

Bacterial cultures and urine pneumococcal antigen test results were negative. Oseltamivir therapy was continued for 7 days, and MV for 15 days.

Patient 3

A 26-year-old obese man (BMI, > 40 kg/m²) with a history of mild asthma presented after 2 days of nausea without vomiting, and no fever or cough. On the day of admission, he developed shortness of breath. He was found to be hypoxic (SpO₂, 90% on an FiO₂ of 1.0) with bilateral pulmonary infiltrates showing on a chest x-ray. His WCC was 5.6 × 10⁹/L and CRP level was 137 mg/L. Therapy with broad-spectrum antibiotics and oseltamivir was commenced. He was intubated, and MV was commenced with an FiO₂ of > 0.6 and high-level PEEP (15 cm H₂O); the patient was successfully extubated after 10 days.

Patient 4

A previously well 41-year-old man (BMI, 30 kg/m²) presented with a 7-day history of cough, coryza, malaise, back pains and rigors. On the day of presentation, he became febrile (39.6°C) and developed tachypnoea (respiratory rate, 45 breaths/min) and severe hypoxia (SpO₂, 84% on 10 L/min oxygen via face mask). His chest x-ray showed widespread pulmonary infiltrates. He had a WCC of 4.4 × 10⁹/L and a CRP level of 166 mg/L. He was intubated in the ED and MV was commenced, and he was given oseltamivir and broad-spectrum antibiotics. He remained severely hypoxic (requiring an FiO₂ of > 0.8) for 10 days, and was treated with MV in the prone position and inhaled nitric oxide. His condition gradually improved, and he was extubated on Day 13.

Patient 5

A 60-year-old man presented to hospital with an exacerbation of his severe chronic obstructive pulmonary disease (COPD). He also had severe peripheral and coronary vascular disease. On examination, he had tachypnoea (respiratory rate, 36 breaths/min) but no fever. He had no prodrome of coryza or myalgias, and a chest x-ray

2 Summary of clinical recommendations for managing patients with possible H1N1 influenza 09 infection

- Maintain a high index of suspicion of possible respiratory failure in patients with risk factors such as asthma, smoking, pregnancy, obesity or chronic medical conditions.^{2,4}
- Refer patients to hospital if they have hypoxia (oxygen saturation measured by pulse oximetry [SpO_2], < 95%) and/or tachypnoea (respiratory rate, > 24 breaths/min) or pulmonary infiltrates.
- Institute respiratory and contact precautions, including personal protective equipment.^{2,4-6}
- Conduct polymerase chain reaction tests for H1N1 influenza A in patients admitted to hospital with suspected influenza.
- Start antiviral therapy early; its benefits in pregnant mothers may outweigh the risks.^{4,7}
- Refer patients for intensive care unit assessment if a fraction of inspired oxygen (FiO_2) of > 0.5 or oxygen at a rate of > 10 L/min is required to maintain the SpO_2 at > 92%.
- Non-invasive ventilation is unlikely to improve the outcome; consider intubation and mechanical ventilation.
- Complex mechanical ventilation strategies are often required. ♦

showed mild bibasal opacities. His WCC was elevated ($11.4 \times 10^9/L$), but his CRP level was 12 mg/L. He was admitted to the respiratory ward and treated with oseltamivir, broad-spectrum antibiotics, and NIV. Two days later he was intubated, and MV was commenced for hypercapnic respiratory failure. Bacterial cultures were negative. His hypoxia was mild (requiring an FiO_2 of < 0.5), but he required MV for 14 days.

Patient 6

An 18-year-old pregnant woman presented with a 4-day history of cough, fever, and persistent vomiting without diarrhoea. Oseltamivir therapy for possible H1N1 influenza infection was discussed with the patient, but not administered. After intravenous rehydration, she was discharged home, but she returned several hours later in premature labour. Her WCC was $8.2 \times 10^9/L$ but her CRP level was high (90mg/L). She was given steroids for fetal lung immaturity and transferred to a tertiary obstetric/neonatal hospital. Twenty-four hours after delivering a 26-week live infant, she developed hypoxic respiratory failure with tachypnoea (respiratory rate, 35 breaths/min) and bilateral pulmonary infiltrates. She required a high level of inspired oxygen therapy (FiO_2 , 0.6) by face mask, and monitoring in the ICU. The mother, but not her baby, had a positive polymerase chain reaction (PCR) test result for H1N1 influenza 09, and both were treated with broad-spectrum antibiotics and oseltamivir.

Discussion

Since the emergence of the novel H1N1 influenza 09 (human swine influenza) in North America and Mexico in mid April, the number of confirmed cases has increased to over 55 000 across 105 countries.¹ While most individuals will experience a mild clinical illness (coryza, fever, cough and myalgias), there have been 238 reported deaths (0.4%).² A Centers for Disease Control and Prevention (CDC) report in May provided details of the 30 patients who were hospitalised in California, of whom six required admission to an ICU and four required MV.³

At the time of writing, there have been 3912 confirmed cases of H1N1 influenza 09 in Australia.² Most reported illness has been mild, but 268 patients (6.9%) have been hospitalised, over 25 (0.6%) have been admitted to ICUs, and five deaths (0.1%) have been reported. Here, we presented the first six cases of H1N1 influenza 09 (confirmed by PCR test from nasopharyngeal swabs) in which patients required admission to intensive care in Australia. Admissions were to three hospitals in the north-western suburbs of Melbourne. These cases highlight the small but significant risk of life-threatening respiratory failure associated with H1N1 influenza 09 infection. All patients experienced a rapid (but reversible) decline in respiratory function, with most requiring complex respiratory support. The age distribution of these patients is consistent with other reports, and lower than that seen in previous influenza seasons.^{4,5}

Four of the six cases we report had risk factors, including asthma, chronic lung disease, smoking, obesity, and pregnancy; these risk factors were similar to those identified in the CDC reports.³ Patients 2 and 4 had no identifiable risk factors.

There are several possible explanations for the acute respiratory failure observed in these patients. Early onset of respiratory failure with widespread pulmonary infiltrates (Patient 3) suggests primary viral pneumonitis, whereas the delayed onset of fever with lobar signs (Patient 2) and pleurisy (Patient 1) suggest secondary bacterial pneumonia. A cytokine-mediated acute lung injury may also explain the late appearance of diffuse pulmonary infiltrates (Patients 4 and 6). The absence of a severe prodrome in Patient 5 suggests an exacerbation of the patient's COPD.

With the number of cases of H1N1 influenza 09 infection likely to increase, it is anticipated that further cases of severe respiratory failure associated with this influenza will be seen. Based on the cases reported here and other reports, we offer the recommendations shown in Box 2. A high index of suspicion that respiratory failure may ensue is warranted in patients who have risk factors⁵ or present with tachypnoea (respiratory rate, > 24 breaths/min) and/or hypoxia (SpO_2 , < 95% on supplemental oxygen), and early referral to hospital is warranted. Youth and prior good health do not preclude the possibility of severe respiratory failure.

The Victorian Department of Human Services currently recommends nasopharyngeal swabs for a PCR test for influenza A in patients admitted to hospital with suspected influenza. Empiric therapy with antiviral agents (oseltamivir or zanamivir)⁵ should be considered in addition to antibiotic treatment for community-acquired pneumonia pathogens, in consultation with an infectious diseases specialist. Patients with suspected H1N1 infection should be isolated, preferably in a negative pressure isolation room.^{6,7} Where possible, antiviral filters applied to the expiratory limb of the ventilator circuit may further reduce the risk to health care staff.

Oseltamivir (Tamiflu) and zanamivir (Relenza) reduce viral replication and shedding, and may reduce the risk of more severe illness. Their safety in pregnancy has not been investigated (Category B1 for use in pregnancy), but without treatment there may be a greater risk of premature labour (Patient 6).^{5,8} Increasing resistance to oseltamivir has been reported in other strains of currently circulating influenza A viruses, but, as yet, not in the H1N1 influenza 09 lineage.^{9,10}

Any patient with respiratory distress or severe hypoxia (requiring an FiO_2 of > 0.5) and pulmonary infiltrates on chest x-ray should be referred to an intensive care specialist for further

assessment. Mechanical ventilation for these patients is complex, and requires expertise and specialised equipment. We used restrictive tidal volumes (6 mL/kg ideal body weight), high PEEP (15–20 cm H₂O), pressure-limited modes of ventilation, alveolar recruitment manoeuvres, inhaled nitric oxide, and restrictive fluid therapy with apparent success. This is consistent with ventilation strategies used by others,¹¹ and in keeping with strategies described by the Acute Respiratory Distress Syndrome (ARDS) Clinical Network.¹² Extracorporeal oxygenation therapy has recently been used in other cases (GJD, personal communication). Based on the available data, we would not recommend NIV as the mainstay of respiratory support. The four patients who were given a trial of NIV in this series all required intubation and MV. This is consistent with published data for ARDS and pneumonia.¹³ NIV temporarily improves oxygenation and reduces the work of breathing, but does not necessarily alter the course of the disease.¹⁴ The need for NIV is an indication of severe disease and the likelihood of intubation and MV.

For the most part, H1N1 influenza 09 is a benign disease, but it may lead to severe respiratory complications in a small proportion of patients. In our series, prompt diagnosis and intensive therapy was associated with favourable outcomes.

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Competing interests

None identified.

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