

Severe Infection with H1N1 Requiring Intensive Care – Lessons for Preparedness Programmes

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Abstract

Introduction: The influenza pandemic has generated much interest in the press and the medical world. We report our experience with 15 cases of severe novel influenza A H1N1 (2009) infections requiring intensive care. The aim of this review is to improve our preparedness for epidemics and pandemics by studying the most severely affected patients. **Clinical Picture:** During the epidemic, hospitals were required to provide data on all confirmed H1N1 cases admitted to an intensive care unit (ICU) to the Ministry of Health. We abstracted information from this dataset for this report. To highlight learning points, we reviewed the case notes of, and report, the five most instructive cases. **Treatment:** There were 15 cases admitted to an ICU from July 4, 2009 to August 30, 2009. Two patients died. **Conclusions:** The lessons we wish to share include the following: preparedness should include having intermediate-care facilities that also provide single room isolation and skilled nursing abilities, stringent visitor screening should be implemented and influenza may trigger an acute myocardial infarction in persons with risk factors.

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Introduction

Severe cases of influenza have traditionally generated much interest.¹⁻⁶ The pandemic of 1957 provided instructive materials on the subject, with publications on the pulmonary complications and histopathologic features.^{2,3,7,8} In the current H1N1 pandemic, several papers on severe influenza have been published.⁹⁻¹¹ The clinical features are thus well described, but we feel that we can also extract lessons from an administrative and preparedness viewpoint by studying the severe cases.

Since the SARS crisis of 2003, Singapore hospitals have been preparing for outbreaks of infections spread by the respiratory route. The ongoing avian influenza epidemic in the region has given these preparations a sense of urgency. In 2007 and 2008, the Ministry of Health (MOH) conducted exercises to test the preparedness of restructured hospitals.¹² The H1N1 pandemic was a true test of preparedness.

In this paper, we reviewed a series of 15 patients with infection caused by the pandemic influenza A (H1N1) 2009

virus (henceforth denoted as H1N1) who were admitted to the intensive care unit (ICU) of our hospital. Our aim is to highlight the aspects of these cases that provide teaching points from an epidemiologic, administrative and “preparedness” viewpoint.

Methods

From 4 July 2009 onwards, restructured hospitals were required to provide the Ministry of Health (MOH) with a daily report of patients with H1N1 infection who were admitted to an ICU. The report included epidemiological, demographical, patients’ symptomatology and hospitalisation management details. At the start of the outbreak, the Department of Infectious Diseases, Singapore General Hospital (SGH), dedicated one infectious disease (ID) physician by rota to H1N1 matters. This ID physician acted as a link between the ICU teams and the Epidemiology Unit, which collated the information for submission to MOH. All confirmed cases of influenza A (H1N1) treated in SGH, from 4 July to 30 August 2009 who were admitted to

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our ICU, were included in this case series. The cases were retrospectively reviewed and data from the files submitted to MOH were abstracted for the purpose of this paper. Four cases of particular interest are presented in detail. This paper is a subset of a study on respiratory viruses in immunocompromised persons, approved by the hospital's Institutional Review Board.

Case Reports

Case 1

This was a 45-year-old Chinese woman, who had received a cadaveric renal transplant and was on immunosuppressive therapy. She had hypertension, hyperlipidemia and type 1 diabetes mellitus (DM). She was admitted with a four-day history of fever, vomiting and diarrhoea. The white cell count was $11.35 \times 10^9/L$. She was treated for acute bacterial gastroenteritis and became afebrile. On the 5th hospital day, she developed fever and cough; her respiratory status deteriorated rapidly and she needed mechanical ventilation on the 7th hospital day. A chest radiograph (CXR) showed bilateral consolidation with pleural effusion. Bronchoalveolar lavage (BAL) fluid was positive for H1N1 on PCR and viral cultures. She was given empirical broad spectrum antibiotics and oseltamivir. Despite treatment, she developed Acute Respiratory Distress Syndrome (ARDS), ventilator-associated pneumonia, and barotrauma. She passed away on the 50th ICU day.

Case 2

This was a 34-year-old Chinese woman with acute myeloid leukaemia (AML), who had received chemotherapy and an allogenic bone marrow transplant in 2008. She relapsed in January 2009 and received salvage chemotherapy.

She was admitted in July 2009 with a four-day history of rhinorrhoea, breathlessness and cough. Her school-going daughter had had similar symptoms one week before. She was admitted to ICU for monitoring on the 2nd hospital day and started empirically on oseltamivir and levofloxacin. On the 7th hospital day, she developed ARDS and was mechanically ventilated.

She had *Elizabethkingiae meningoseptica* bacteraemia. In addition, BAL fluid yielded *Elizabethkingiae meningoseptica*; was positive for H1N1 via PCR and viral cultures; hyphae was also seen on microscopy with a galactomannan level of 6.8 OD. Voriconazole and amantadine were added. However, she had refractory respiratory failure and passed away on the 10th hospital day.

Case 3

A 55-year-old Chinese man, with a history of hypertension, hyperlipidemia and coronary artery disease (CAD), was admitted to the cardiac care unit (CCU) for 5 days for fever,

chills, productive cough and breathlessness.

At presentation, he had T wave inversions in the electrocardiogram (ECG), elevated Troponin T and pro-BNP levels. He was diagnosed with acute myocardial infarction (AMI) with acute pulmonary oedema (APO). His CXR revealed patchy consolidation in the lungs; a throat swab for H1N1 was positive by PCR.

He completed a five day course of oseltamivir. He did not require mechanical ventilation, inotropes or renal support during his hospitalisation. He stayed in CCU for 5 days and was discharged on the 6th hospital day.

Case 4

A 61-year-old Chinese man with DM, hyperlipidaemia and CAD, was admitted for a three-day history of fever, productive cough and breathlessness. CXR revealed bilateral alveolar shadowing. He had raised pro-BNP and troponin T levels. ECG showed ST depression and the patient was diagnosed with AMI.

He was initially managed in the general ward but worsening breathlessness led to mechanical ventilation. A throat swab was positive for H1N1 by PCR and he was started on standard dose oseltamivir. He recovered promptly and was taken off the ventilator after 3 days.

Discussion

Two of the patients in this series (Cases 3 and 7) (Table 1) did not require intensive care, although they required more than general ward care. They were admitted to an ICU because of the absence of an intermediate-care facility with single room isolation (in our hospital, all intermediate-care facilities are in shared rooms). The need to isolate patients with H1N1 infection in a single room remains a matter of debate. At the beginning of the 2009 outbreak, CDC recommended placing such patients in negative-pressure rooms, if available.¹³ As the outbreak evolved, evidence pointed to the fact that the H1N1 virus was spread, like the seasonal influenza virus, via droplets.¹⁴ On June 11, 2009, the Society for Healthcare Epidemiology of America recommended that the same infection control practices to prevent seasonal influenza be used for the prevention of H1N1. Where patient placement was concerned, single rooms were recommended, "if available". Alternatively, cohorting with other infected patients was acceptable.¹⁴

In our hospital, patients suspected or confirmed to have H1N1 infection would be nursed in single rooms. As the hospital did not have single rooms that could also provide high-dependency level care, the two patients (case 3 and 7) were managed in an ICU until their physicians felt they were suitable for the general ward. Using an ICU bed for them was not resource-efficient in an epidemic.

In our preparations for pandemics and emergencies,

Table 1. Baseline Demographics, Treatment and Outcomes of all 15 Patients with Severe H1N1 Infection

Case	Age (y)	Sex	Race	BMI	Admitting diagnosis	Medical history	ICU stay (days)	Ventilator (days)	Apache II score	Use of inotropes	Dialysis support	Hospital stay (days)	Anti-viral	Dose	Therapy (days)	Outcome
1	44	F	C	19	Sepsis	DM, hypertension, peripheral vascular disease, renal transplant on immunosuppressants	50	50	34	N	N	57	Oseltamivir	75 mg BD	5	Dead
2	34	F	C	27.4	Pneumonia	Acute myeloid leukaemia on chemotherapy	9	4	12	Y	N	10	Oseltamivir Amantide	75 mg BD 100 mg BD	9 5	Dead
3	55	M	C	24	AMI	Hypertension, IHD	5	0	8	N	N	6	Oseltamivir	75 mg OD	5	Alive
4	61	M	C	20.8	Heart failure	DM	6	3	13	Y	N	9	Oseltamivir	75 mg OD	5	Alive
5	58	F	C	18.4	Atrial fibrillation	ESRF with failed cadaveric transplant now on peritoneal dialysis, hypertension	3	0	21	N	Y	21	Oseltamivir	75 mg OD	5	Alive
6	70	F	C	26.9	Bronchitis	DM, renal transplant on immunosuppressants	5	1	27	N	Y	10	Oseltamivir	75 mg OD	3	Alive
7	66	F	I	23.1	AMI	DM	2	0	6	N	N	3	Oseltamivir	75 mg OD	3	Alive
8	58	M	C	16.2	Pneumonia	Laryngeal carcinoma, severe COPD on home oxygen	2	0	10	N	N	6	Oseltamivir	75 mg BD	5	Alive
9	45	M	M	24.9	Pneumonia	No past history of note	7	7	11	N	Y	18	Oseltamivir	75 mg OD	3	Alive
10	35	M	C	37.4	Pneumonia	Morbid obesity	14	14	10	Y	N	18	Oseltamivir	75 mg BD	5	Alive
11	43	F	I	25	Heart failure	IHD, DM, asthma	8	4	16	Y	N	9	Oseltamivir	75 mg BD	5	Alive
12	76	M	C	26.6	Pneumonia	Colonic carcinoma, hypertension, benign prostate hypertrophy	12	8	12	N	N	27	Oseltamivir	75 mg BD	5	Alive
13	59	M	C	23.9	URTI	ESRF on peritoneal dialysis, hypertension, multiple myeloma with previous bone marrow transplant	4	0	18	Y	Y	11	Oseltamivir	30 mg EOD	5	Alive
14	57	M	M	26.8	Pneumonia	Emphysema, testicular seminoma with retroperitoneal metastatic disease	18	18	14	Y	N	24	Oseltamivir	75 mg BD	5	Alive
15	52	M	C	22.5	Pneumonia	Newly diagnosed retroviral disease	11	9	19	N	N	25	Oseltamivir	150 mg BD	5	Alive

F: female; M: male; C: Chinese; I: Indian; M: Malay
AMI: acute myocardial infarction; BD: twice daily; BMI: Body mass index = height in centimeters divided by weight in kilograms; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRF: end-stage renal failure; ICU: intensive care unit; IHD: ischaemic heart disease; OD: once daily; URTI: upper respiratory tract infection

the need for ICU facilities and trained staff to man them has always been discussed.¹² However, the need for an area providing intermediate-level care to patients needing isolation has not been discussed in detail. We suggest that providing an intermediate care facility that can house patients requiring isolation will reduce the demands on ICU beds. This should come with skilled-manpower to provide a level of nursing beyond that of the general ward. The relatively low mortality of the H1N1 virus did make some of the measures adopted in our hospitals look excessive,¹⁵ but since preparedness means we should be prepared for more lethal infections (e.g., SARS), a facility that permits both single-room isolation and high-dependency nursing will relieve the pressure on ICU beds.

The renal transplant recipient in Case 1 acquired the infection while in the ward. Interestingly, the source of her infection was her own domestic helper. Once the H1N1 crisis broke, our hospital had placed limits on the number of visitors a patient could have. The hospital also required visitors to complete a screening questionnaire declaring themselves free of an influenza-like illness (ILI). It has been pointed out that persons visiting immunocompromised patients should be screened for symptoms of an upper respiratory tract infection – those with such symptoms should not be allowed to visit the patient.¹⁶ In this respect, the measures implemented locally were more stringent. Despite such measures, Case 1's domestic helper slipped through. This might be related to several factors. The staff at the screening counters might have had too many visitors to handle; some persons with an ILI may not appear ill; the domestic helper might have felt obliged to hide her symptoms to aid her ailing employer.

Case 2, who had survived a complicated course, including a bone marrow transplant and salvage chemotherapy, acquired the infection from her school-going child. One of the first clusters of infection with the current pandemic virus occurred in a school in New York.¹⁷ Schools have been described as places where “amplification” occurs.¹⁸ This case brings a human dimension to the debate on vaccine priorities. In August 2009, in anticipation of a shortfall in the supply of the H1N1 vaccine, CDC (US) recommended that the first target groups should include persons such as the pregnant, those looking after infants <6 months, etc.¹⁹ This has been questioned.²⁰ By studying five outcome measures (death, infections, years of life lost, contingent valuation, economic costs), Medlock and Galvani et al²⁰ concluded that priority for vaccination should go to schoolchildren and adults aged 30 to 39 since this group is most responsible for transmission. This mathematical model is supported by population data from Japan.²¹ From 1962 to 1987, most Japanese schoolchildren were vaccinated against influenza. In 1987, the laws were

relaxed and in 1994, repealed. Vaccination rates dropped among schoolchildren.²¹ Interestingly, deaths attributable to pneumonia and influenza rose after 1987, the rise became marked after 1994. The authors of this paper suggested that mass immunisation of schoolchildren brought about herd immunity, which was lost after influenza vaccination rates fell. The authors felt comfortable with this conclusion as none of the other social changes that Japan had witnessed over the same period had reversed after 1994.²¹ Case 2 appears to be a poignant illustration of the Medlock model and the Japanese data – if a vaccine had been available and her daughter had received it, perhaps she would not have brought the virus home.

There were two cases of H1N1 associated with AMI (cases 3 and 7). Although cardiac complications of influenza, such as myocarditis, are well recognised, the role of influenza as a trigger of AMI is less clear. In an attempt to resolve this question, Warren-Gash et al conducted a systematic review of the evidence that influenza triggered AMI or cardiovascular death.²² Seventeen studies found an increase in mortality due to cardiovascular disease or AMI during times when influenza was circulating.²² Observational studies linked acute respiratory illnesses and influenza antibodies with AMI. Although the results were mixed and the studies heterogeneous, a majority showed a statistically significant association between these factors and AMI. Two randomised studies assessed the protective effect of influenza vaccination against cardiac events in persons with cardiovascular disease. The pooled-effects estimate showed protection, though it did not reach statistical significance.²² Interestingly, an autopsy series found that influenza and acute respiratory disease epidemics were associated with a surge in CAD deaths.²³ Our two cases, plus the literature, seem to suggest that influenza may trigger an AMI.

Although obesity has been cited as a risk factor for severe H1N1 infections, morbid obesity was identified in only one patient (case 10). Only one patient (case 9) had no medical history. His illness was complicated by acute kidney injury needing renal replacement therapy. This case highlights that an immunocompetent patient without comorbidities can develop severe H1N1 infection. Human immunodeficiency virus (HIV) infected patients are at higher risk of complications from influenza.²⁴ Case 15 in this series, was a patient with *pneumocystis jirovecii* pneumonia (PCP) and was found to have H1N1 infection on BAL, but he survived his ICU course. We are unable to comment on the role that H1N1 played in his illness but we suspect that diagnosing the infection and treating it contributed to the positive clinical outcome.

Conclusion

Our review of severe cases of H1N1 suggests that

refinements to pandemic preparedness could be made. We suggest that an intermediate-care area with isolation facilities will reduce the demands on ICU beds. Although difficult to do, strict visitor screening for immunocompromised persons will help prevent a tragic case such as case 1; its implementation outside a pandemic or national outbreak should also be strongly considered. We are also in favour of more widespread vaccination, although we are aware that, in a pandemic, even getting a vaccine is not easy.

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