Severe refractory hypoxaemia in H1N1 (2009) intensive care patients: initial experience in an Asian regional hospital

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ABSTRACT

Introduction: The management of Influenza A (H1N1) patients with acute respiratory distress syndrome (ARDS) is an emerging challenge, especially during the 2009 pandemic. These patients frequently require advanced mechanical ventilation (MV) and on occasion, rescue therapy. We describe the demographics, presentation, course and outcomes of the first 12 H1N1 patients with ARDS who were admitted to our institution.

Methods: This was a retrospective chart review of H1N1 patients with ARDS who were admitted to our intensive care unit (ICU) between July and September 2009.

Results: Seven of the 12 patients were female. The median age was 46 (range 27–66) years. 25 percent of the patients had good health prior to the infection. The presenting symptoms were mainly cough (100 percent), fever (92 percent) and dyspnoea (64 percent). The median times from symptom onset to both hospitalisation and ICU admission were five (range 2–9) days. Ten (83 percent) patients required invasive MV within 24 hours of presentation. The mean PaO_2/FiO_2 ratio was 87.9 +/− 37.3 mmHg, with a mean positive end expiratory pressure at 16.1 +/− 7.3 cm H_2O. Three patients required either unconventional MV and/or prone positioning, inhaled nitric oxide or nebulised prostacyclin. The mean Acute Physiology and Chronic Health Evaluation II score was 12.7 +/− 9.1. Among survivors, the median number of ventilator days was 7.5 (range 5–11), with a median length of ICU stay of ten (range 6–14) days. The median length of hospitalisation was 13.5 (range 9–31) days. The mortality rate in our case series was 50 percent.

Conclusion: Unlike patients of seasonal influenza, our severe H1N1 patients were of a younger age. A significant proportion had no underlying risk factors. Despite high ventilatory requirements, unconventional MV and adjunct therapy, the mortality rate remained high.

Keywords: H1N1, acute respiratory distress syndrome, influenza pandemic, primary viral pneumonitis

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INTRODUCTION

In March 2009, an outbreak of severe pneumonia was reported in conjunction with the isolation of a novel Influenza A (H1N1) virus in Mexico.[1] Since then, the World Health Organization had raised the influenza pandemic alert to Phase 6, with an estimate of over 378,223 laboratory confirmed cases and 4,525 reported fatalities.[2]

In Singapore, the first case of H1N1 was diagnosed on 27 May, 2009,[3] with evidence of community transmission emerging by 19 June, 2009.[4] While most patients had mild illnesses, cases of severe H1N1 pneumonitis began to appear locally by early July 2009. These patients appeared to have a relatively rapid progression of the disease, with a short duration between hospital admission and respiratory failure.

We report the first 12 H1N1 patients with acute respiratory distress syndrome (ARDS) who were admitted to our intensive care unit (ICU). We believe that this is the first case series of H1N1 patients with refractory hypoxaemic respiratory failure from tropical Southeast Asia.

METHODS

Our institution is a 790-bed regional hospital. It does not provide inpatient neonatal/paediatric or obstetric services. From June to September 2009, a total of 153 H1N1 patients were admitted to our institution. As such, an independent pandemic ICU was operationalised, with a surge capacity of 18 negative pressure isolation beds. This augmented the existing combined ICU capacity of 32 beds in our medical and surgical units.

The ICU admission criteria and treatment modalities,

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Table I. Baseline characteristics of case series.

Patient no.	Age (yrs)	Gender	Comorbid chronic disease	Initial symptoms	Duration (days)		Initial CXR Score*
					Symptom onset to hospitalisation	Illness onset to ICU admission	
1	51	Male	DM, hypertension, smoker	Fever, sore throat, cough, sputum, dyspnoea	3	3	4
2	49	Male	DM, hypertension, hyperlipidaemia, smoker	Fever, cough, sputum, dyspnoea	5	5	3
3	42	Female	Impaired glucose tolerance	Fever, sore throat, cough, sputum, dyspnoea	5	5	3
4	34	Male	Down's syndrome	Fever, sore throat, cough, rhinorrhea	6	9	2
5	27	Female	None	Fever, cough, dyspnoea, myalgia	5	5	3
6	29	Female	Obesity	Fever, cough, rhinorrhea	8	9	3
7	52	Female	DM, hyperlipidaemia hypertension, end-stage renal failure, smoker	Cough, dyspnoea, pleuritic chest pain	2	3	3
8	43	Female	None	Fever, cough, PEA	7	7	4
9	38	Female	None	Fever, cough	3	3	3
10	66	Male	COPD, bronchiectasis, hypertension, chronic hepatitis B	Fever, cough, dyspnoea, vomiting	2	7	2
11	53	Male	DM, hypertension, chronic hepatitis B	Fever, cough, dyspnoea	7	7	3
12	53	Female	Hypertension, obesity	Fever, cough	3	4	2

* The number of quadrants of alveolar consolidation noted on the presenting CXR: 0 = no alveolar consolidation, 1 = alveolar consolidation confined to one quadrant, 2 = alveolar consolidation confined to two quadrants, 3 = alveolar consolidation confined to three quadrants, 4 = alveolar consolidation confined to four quadrants.
CXR: chest radiograph; ICU: intensive care unit; PEA: pulseless electrical activity; COPD chronic obstructive pulmonary disease; DM: diabetes mellitus

including the need for mechanical ventilation, rescue/adjunct therapy, empirical antibiotics and antiviral agents, were determined by the attending physician. The diagnosis of H1N1 was confirmed on reverse transcriptase-polymerase chain reaction (RT-PCR) testing of samples from the upper respiratory tract. All eligible cases presenting to our pandemic ICU between July to September 2009 were included in this case series. These cases conformed to the American-European Consensus ARDS definition[5] and had a diagnosis of primary viral pneumonitis.

Primary viral pneumonitis was defined in patients with preceding influenza-like illness (ILI) who presented with ARDS, alveolar consolidation in two or more lobes with negative respiratory and blood bacterial cultures. Bronchoscopy with bronchoalveolar lavage was not routinely performed in our ICU, mainly because most of our patients were on high ventilatory settings as well as due to concerns of generating aerosolised particles during the procedure. Respiratory cultures were based on tracheal aspirates that were obtained following intubation.

The patients' charts were reviewed for baseline characteristics, presenting complaints, therapeutics, clinical course and outcomes. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were recorded within 24 hours of ICU admission. Extra pulmonary organ dysfunction was noted. Acute renal failure was staged in accordance with the Acute Kidney Injury Network (AKIN) classification.[6] Hepatic dysfunction was defined as an elevated transaminitis that is three times the upper limit of normal.

RESULTS

A total of 18 H1N1 patients were admitted to the pandemic ICU during the study period. Of these, 12 patients fulfilled the inclusion criteria and were included in the case series. Of the six patients who were excluded, two had unilateral alveolar consolidation on chest radiographs (CXR). One patient with acute lung

Table II. Ventilatory requirements and adjunct therapy.

Patient no.	Mode of mechanical ventilation	Highest PEEP^ (cm H_2O)	PaO_2/FiO_2 ratio (mmHg)	LIS (Day 1)	Adjunct therapy
1	AC/PC	18	51	4.0	No
2	AC/VC	16	101	3.3	No
3	AC/PC	24	41	3.7	Prone position, iNO
4	AC/PC	14	100	2.7	No
5	APRV	24 (42*)	45	3.7	iNO
6	APRV	30 (45*)	45	3.7	Nebulised, prostacyclin
7	AC/PC	12	108	3.0	No
8	AC/VC	10	92	3.3	No
9	AC/VC	20	92	3.7	No
10	AC/VC	7	87	2.3	No
11	AC/VC	10	132	2.7	No
12	AC/VC	8	161	2.0	No

^ Highest PEEP recorded on conventional mechanical ventilation. *Highest Phigh recorded on APRV.
PEEP: positive end expiratory pressure; APACHE II: Acute Physiologic and Chronic Health Evaluation II; LIS: lung injury score; AC: assist control; PC: pressure cycle; VC: volume cycle; APRV: airway pressure release ventilation; iNO: inhaled nitric oxide.

injury was admitted for shock requiring vasopressor therapy, while another required non-invasive ventilation (NIV) for underlying obstructive sleep apnoea. Two patients with end stage renal failure were admitted for fluid overload that was resolved following dialysis.

The baseline characteristics and clinical presentation are summarised in Table I. Seven of the 12 patients were female, none of whom were pregnant. The median age was 46 (range 27–66) years. While the majority of the patients had underlying chronic illnesses, three patients did not.

The predominant presenting symptoms were cough (100%), fever (92%) and dyspnoea (64%). One patient had an out-of-hospital pulseless electrical activity (PEA) arrest, following a week of ILI symptoms. The median times from symptom onset to both hospitalisation and ICU admission were five (range 2–9) days. 75% (9/12) of the patients had three or more quadrant opacification on CXR upon presentation.

Oseltamivir (Tamiflu®, F Hoffmann-LA Roche Ltd, Basel, Switzerland) was prescribed to all the patients at presentation based on clinical suspicion. The diagnosis of H1N1 was subsequently confirmed by the RT-PCR results. While the first two patients were administered oseltamivir 75 mg twice daily for five days, high-dose oseltamivir (150 mg twice daily) was administered to the remaining patients for an intended duration of ten days. The median time from the onset of symptoms to the first dose of oseltamivir was five (range 2–8) days.

It should be noted that Patient 11 was initiated on a standard dose of oseltamivir by his family physician one day prior to his presentation at our institution. Following his hospitalisation, a second neuraminidase inhibitor, aerosolised zanamivir (Relenza®, GlaxoSmithKline Australia Pty Ltd, Boronia, Australia) was concurrently administered.

All patients received empirical broad-spectrum antibiotics that are considered appropriate for severe community-acquired pneumonia in accordance with the consensus guidelines.[7] Both serum C reactive protein (CRP) and procalcitonin were measured on the day of admission. While the mean CRP and procalcitonin levels were elevated at 126.3 ± 91.0 mg/L and 0.59 ± 0.47 μg/L, respectively, no secondary bacterial co-infection was documented from the specimens obtained from these patients. These specimens included tracheal aspirates for Gram stain/cultures, blood cultures, mycoplasma serology, meloidosis serology, urine for legionella and pneumococcal antigens.

Ten (83%) patients required intubation and invasive mechanical ventilatory support within 24 hours of presentation. Two patients (Patients 10 and 11) were intubated for worsening hypoxaemia with increasing respiratory distress following an unsuccessful trial of NIV. The ventilatory requirements and adjunct therapies in the patients are summarised in Table II.

Oxygenation targets and titration were performed using ARDSnet positive end expiratory pressure (PEEP)-FiO_2 titration table.[8] An exception was Patient 6, who had 30 cm H_2O of PEEP at FiO_2 of 1.0 and morbid obesity, which limited her chest wall compliance. This patient's true transpulmonary pressure gradient could possibly be lower than the applied PEEP. The mean PaO_2/FiO_2 ratio was 87.9 ± 37.3 mmHg. Overall, the mean PEEP required was 16.1 ± 7.3 cm H_2O. None of the patients developed any clinical evidence of barotrauma.

Table III. Clinical course and outcomes.

Patient no.	Extrapulmonary organ dysfunction	Vasopressors	Low-dose systemic corticosteroids	Renal replacement therapy	Outcome
1	No	No	No	No	Discharged
2	No	Yes	Yes	No	Died
3	Renal	Yes	Yes	No	Died
4	No	Yes	No	No	Discharged
5	Renal, hepatic	Yes	Yes	Yes	Died
6	Renal	Yes	Yes	Yes	Died
7	No	No	No	Yes*	Discharged
8	Cardiac, renal, hepatic	Yes	Yes	No	Died
9	No	Yes	No	No	Discharged
10	No	Yes	Yes	No	Discharged
11	No	Yes	No	No	Died
12	No	No	No	No	Discharged

*Dialysis for end-stage renal failure required.

The mean lung injury score[9] was 3.18 ± 0.64.

Despite the high PEEP settings and attempts at lung recruitment, refractory hypoxaemic respiratory failure remained the predominant issue in our patients. Patients 3, 5 and 6 were placed on adjunct therapies, which included prone positioning (Patient 3) and iNO (Patients 3 and 5) (INOvent, Datex-Ohmeda Inc, Madison, WI, USA). With data suggesting equivalent physiologic effects as iNO,[10,11] nebulised prostacyclin (Ventavis®, Berlimed SA, Madrid, Spain) was used for Patient 6 in the face of resource constraints. Patients 5 and 6 had an unconventional mechanical ventilation (MV), airway pressure release ventilation (APRV), as rescue therapy.

The clinical course and outcomes of the patients are summarised in Table III. Four patients developed acute kidney injury, with AKIN stages ranging from 2 to 3. Two patients required continuous renal replacement therapy (CRRT). Another patient, with end stage renal failure, required dialysis while in the ICU. Liver dysfunction manifested as elevated transaminases without significant coagulopathy. One patient, who had no prior history of cardiac disease, had cardiomyopathy (left ventricular ejection fraction of 10%) on echocardiography. Overall, four (33%) patients had extrapulmonary organ dysfunction. Vasopressors were required for eight patients. The mean APACHE II score in the first 24 hours was 12.7 ± 9.1.

There were six fatalities in our case series. Two of the deaths could be attributed to severe hypoxaemia and acidosis. One patient developed acute ST elevation myocardial infarction and three patients had PEA. Among the survivors, the median number of ventilator days was 7.5 (range 5–11), while the median length of ICU stay was ten (range 6–14) days. The median length of hospitalisation was 13.5 (range 9–31) days.

DISCUSSION

Our study was limited by its retrospective nature and small patient number. However, it has provided some useful insights on local patients with H1N1 ARDS/viral pneumonitis, which are not dissimilar to reports emerging elsewhere.[12-16]

The patients in our case series tended to be younger. Although most of our patients had identifiable risk factors, 25% did not have any comorbidities. In a subgroup analysis of 574 H1N1-related deaths,[12] approximately 20% had no underlying risk factors. While this study may have a variable quality of data collection, it appears that youth and prior good health may not necessarily be good discriminators against the development of severe disease. This is unlike seasonal influenza.

We also note that the durations between symptom onset to both hospitalisation and first dose of oseltamivir were five days. It is generally believed that early initiation of anti-viral therapy (within the first 48 hours of illness onset) is more likely to be beneficial. Whether the delay in presentation at our institution had an impact on their adverse outcomes is not yet clear. Perhaps such considerations should be highlighted when drafting medical advisories to the public.

Another point of interest was that despite the elevated serum CRP and procalcitonin levels, no secondary bacterial co-infection was isolated. Previous studies have established elevated procalcitonin as a useful biomarker for bacterial infections.[17,18] Thus, all our patients received empirical broad-spectrum

antibiotics. Intuitively, such an approach is prudent until a clearer disease pattern emerges.

Refractory hypoxaemic respiratory failure featured prominently among our patients. NIV did not appear to alter the need for intubation and invasive mechanical ventilatory support. Kauffman et al reported a similar experience in their case series.[13] As such, we caution against the use of NIV in such individuals. If deemed appropriate, NIV should only be considered as an interim measure, with clear clinical endpoints. Physicians should be prepared to proceed to elective intubation once it is clear that these endpoints are unlikely to be achieved.

High PEEP levels have minimal effects on improving oxygenation. Experimental data of H1N1 influenza supports more severe pathologic lesions in the lungs of animal models.[19] Adjunct/rescue therapies improve oxygenation, albeit transiently.

Napolitano et al reported initial success by combining unconventional MV (high frequency oscillatory ventilation/APRV) with extracorporeal membrane oxygenation (ECMO) in a group of H1N1 patients with refractory hypoxaemia.[14] While this approach appears promising and warrants further evaluation, it is limited by the need for specialised expertise and resources. Our experience inadvertently tested available adjunct therapies without resorting to early rescue ECMO. The high ICU mortality rate may indicate that ECMO might be an early consideration in many cases.

Out of the six fatalities reported, three patients had PEA. While Patient 8 had an out-of-hospital PEA, the other two patients were in the convalescent stage of their illness, with improving physiologic parameters and decreasing ventilator requirements prior to their arrests. There were no immediately identifiable causes for PEA in these patients. Due to local cultural sensitivities, academic post mortems were declined by the patients' families.

While all our patients received deep vein thrombosis (DVT) prophylaxis, pulmonary embolism remains a distinct possibility. In their case series, Napolitano et al documented pulmonary emboli in 50% (5/10) of their patients, with another patient developing bilateral DVT.[14] Conceivably, severe H1N1 patients may have a higher incidence of venous thromboembolic events due to a hypercoaguable state. Such an argument appears to be supported by observations that both our patients who received CRRT experienced frequent clotting of their circuits, despite adequate systemic anti-coagulation using unfractionated heparin.

A mortality risk of 40%–45% from conventional ARDS has been noted in observational studies.[20] The mortality rate in our case series was 50%. While our study was purely observational, with a small number of patients, it appears that the patients' APACHE II scores (first 24 hours) were not consistent with their outcomes. This, perhaps, is due to a significantly lower incidence of multiple organ dysfunction syndrome in these patients compared to conventional ARDS. We postulate that the APACHE II scores for the first 24 hours may not necessarily be accurate reflections of disease severity in H1N1 patients with ARDS.

As we enhance and fortify pandemic response plans to cater to an anticipated surge, we hope that data such as ours can provide a better understanding of severe H1N1 infections and aid decisions on prioritisation and resource allocation.

REFERENCES

1. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009; 361:680-9.
2. World Health Organization. Pandemic (H1N1) 2009 - update 69 [online]. Available at: http://www.who.int/csr/don/2009_10_09/en/index.html. Accessed October 9, 2009.
3. Ministry of Health, Singapore. First confirmed case of Influenze A (H1N1-2009) in Singapore [online]. In: Ministry of Health Singapore, Press Releases, May 27, 2009. Available at: www.moh.gov.sg/mohcorp/pressreleases.aspx?id=21914. Accessed October 9, 2009.
4. Ministry of Health, Singapore. 26 confirmed new cases of Influenze A (H1N1-2009) [online]. In: Ministry of Health Singapore, Press Releases, 19 Jun 2009. Available at: www.moh.gov.sg/mohcorp/pressreleases.aspx?id=22202. Accessed October 9, 2009.
5. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818-24.
6. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11:R31.
7. Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44:S27-72.
8. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327-36.
9. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720-3.
10. Zwissler B, Kemming G, Habler O, et al. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 1996; 154:1671-7.
11. Lowson SM. Inhaled alternatives to nitric oxide. Crit Care Med 2005; 33:S188-95.
12. Vaillant L, La Ruche G, Tarantola A, Barboza P; epidemic intelligence team at InVS. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill 2009;

14:pii:19309.
13. Kaufman MA, Duke GJ, McGain F, et al. Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza). Med J Aust 2009; 191:154-6.
14. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection-Michigan, June 2009. Morb Mortal Wkly Rep 2009; 58:749-52.
15. Centers for Disease Control and Prevention (CDC). Hospitalized patients with novel influenza A (H1N1) virus infection- California, April-May, 2009. Morb Mortal Wkly Rep 2009; 58:536-41.
16. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care 2009; 13:R148. Epub 2009 Sep 11.
17. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systemic review and meta-analysis. Clin Infect Dis 2004; 39:206-17.
18. Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J 2007; 30:556-73.
19. Itoh Y, Shinya K, Kiso, M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature 2009; 460:1021-5.
20. Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systemic review. Am J Respir Crit Care Med 2009; 179:220-7.