Influenza A H1N1 (2009): clinical spectrum of disease among adult patients admitted to a regional hospital in Singapore

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ABSTRACT

Introduction: The worldwide spread of Influenza A H1N1 (2009) has proceeded at an unprecedented rate, with the World Health Organization rapidly raising its influenza pandemic alert to phase six. We describe the disease spectrum of H1N1 (2009) to aid the triaging and identification of patients at risk.

Methods: This is a retrospective chart review of all confirmed H1N1 (2009) cases admitted to our institution between June and September 2009.

Results: The disease severity of the 153 patients studied was classified as mild (n is 75), moderate (n is 55) and severe (n is 23). 81 patients were female. The median age was 26 years. While comorbidities were more prevalent among patients with moderate–severe illness, 47.4 percent reported no pre-existing illness. Presenting complaints of breathlessness, tachycardia, low-pulse oximetry, higher leukocyte counts and C-reactive protein with low albumin levels were more commonly noted in moderate–severe illness (p-value less than 0.001). All patients received oseltamivir at a median of four days from illness onset. 18 required intensive care unit admission, with the majority (94.4 percent) within the first 24 hours of hospitalisation. The overall mortality rate was 4.6 percent. Median lengths of hospitalisation were four and nine days for moderate and severe cases, respectively.

Conclusion: While the majority of H1N1 (2009) patients have mild illness, a subgroup can become critically ill. Prior good health is not necessarily a good discriminator against severe illness. The presence of dyspnoea, tachycardia and desaturation at triage should heighten the index of suspicion for H1N1 (2009)-related complications.

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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 (2009) virus in Mexico.[1] In the following months, the worldwide spread of H1N1 (2009) proceeded at an unprecedented rate, aided in part by the convenience of global air travel.[2] In response to the threat of an influenza pandemic, the World Health Organization (WHO) raised its influenza pandemic alert to phase 6. Since then, more than 213 countries and overseas territories have reported laboratory-confirmed cases of H1N1 (2009), including at least 16,813 fatalities.[3]

Singapore first reported its case of H1N1 (2009) on May 27, 2009,[4] with evidence of community transmission emerging by June 19, 2009.[5] National healthcare policies had to be adapted to the evolving disease epidemiology. The Health Ministry's pandemic preparedness plan targeted containment during the initial phase of the outbreak. When it became apparent that community transmission was inevitable, measures were adopted to mitigate the extent of the outbreak in the local community. As such, hospital admission criteria for suspected/confirmed H1N1 (2009) cases were amended accordingly between the months of May and September 2009.

While some may argue that certain containment measures adopted during this outbreak were too draconian, we believe that it provided a unique opportunity to study the disease spectrum of H1N1 (2009) infection. We feel that this information would allow us to better triage patients at the primary healthcare level and identify patients who are at risk of developing H1N1 (2009)-related complications. In addition, while the concerns of a second wave of H1N1 (2009) cases may seem to have abated in the recent months,[6] we hope that our experience may be beneficial in the planning of expedient healthcare delivery

Table I. Discharge criteria of H1N1 (2009) patients from the emergency department during the mitigation phase of the outbreak in Singapore.*

Patient criteria	Clinically stable No other acute diagnosis at the point of review No significant comorbid conditions For female patients of child-bearing age, ascertain that the patient is not pregnant
Physical criteria	Available local accommodation Patient must be able to distance himself from household members
Social criteria	The patient must not have any vulnerable individuals at home. These individuals include: • Children aged < 5 years • Adults aged > 65 years • Family members with chronic metabolic disease (e.g. diabetes mellitus) and chronic pulmonary or heart disease • Family members with a diagnosis of cancer on active treatment, undergoing organ transplant or dialysis, or immunosuppressed individuals • Children or teenagers aged < 18 years who are receiving long-term aspirin therapy • Pregnant family members

*The discharge criteria were derived from the recommendations and guidelines on the management of H1N1 patients from Circulars 79, 81, 87/2009, Ministry of Health, Singapore.

and appropriate resource utilisation in the event that Singapore is faced with the prospect of another influenza pandemic. We describe the demographics, presentation, clinical course and outcomes of all patients admitted to our institution between June and September 2009.

METHODS

Our institution is a 790-bed regional hospital in the eastern region of Singapore. It does not provide in-patient neonatal/paediatrics or obstetrics services. As part of the hospital influenza pandemic response plan, an independent pandemic intensive care unit (ICU)/high dependency (HD) care area, as well as an isolation ward equipped with negative pressure rooms and *en suite* bathrooms, were set up in anticipation of an expected surge of cases. These care areas, however, did not have on-site radio imaging facilities. The study period was defined as three months following the admission of the first H1N1 (2009) case to our institution. All H1N1 (2009)-positive patients admitted during this period, regardless of concomitant diagnoses, were included in our case series.

The decision to admit patients diagnosed with H1N1 (2009) depended on the interplay between clinical and public health considerations, as coordinated by the Ministry of Health, Singapore. During the containment phase of the outbreak, all patients at the Emergency Department (ED) who were diagnosed with H1N1 (2009) were admitted to our institution for treatment and isolation. Following transition to the mitigation phase, patients who could be treated at home were given standard doses of oseltamivir (Tamiflu®, F Hoffmann-LA Roche Ltd, Basel, Switzerland) and discharged from the ED. Such patients were also issued home quarantine orders (HQO) for seven days. Table I shows the ED discharge criteria of H1N1 (2009) patients during the mitigation phase of the outbreak in Singapore.

The diagnosis of H1N1 (2009) was confirmed on reverse transcriptase polymerase chain reaction (RT-PCR) testing of specimens from nasal and/or throat swabs. For intubated patients, tracheal aspirates were obtained instead. Management decisions, including admission to ICU or HD, the use of antiviral agents, prescription of antibiotics and the need for escalation of level of care, were determined by the attending physician. Investigations for bacterial co-infection or secondary infection were performed when deemed necessary. Specimens sent for investigations included tracheal aspirates or sputum for Gram stain or cultures, blood cultures, urine cultures, mycoplasma serology, meloidosis serology, urine for *Legionella* and pneumococcal antigens.

The patients' charts were reviewed for the following information: demographic data, comorbidities, presenting symptoms, triage parameters, clinical findings of the ED physician, clinical course during hospitalisation, laboratory results, therapeutics and outcomes. Based on the clinical assessment at triage, the disease severity of each patient was classified as mild, moderate or severe. Mild illness referred to patients who, in the absence of public health measures, could have been treated at home. They were prescribed antiviral therapy and symptomatic treatment. Patients with moderate illness required certain medical interventions beyond what could be provided at a primary care setting. These patients had stable parameters and were thus treated in a general ward setting. Severe

Table II. Clinical features and laboratory results.

	No. (%)¶			p-value*
	Mild (n = 75)	Moderate (n = 55)	Severe (n = 23)	
Median age; IQR	20.5; 18.0–27.5	40; 19.5–55.5	51; 40.0–54.0	< 0.001
Female gender	41 (54.7)	24 (43.6)	16 (69.6)	0.104
Comorbidities present	14 (18.7)	26 (47.3)	15 (65.2)	
Symptoms				
Nasal congestion	45 (60.0)	24 (43.6)	6 (26.1)	0.011
Sore throat	51 (68.0)	28 (50.9)	9 (39.1)	0.024
Cough	70 (93.3)	50 (90.9)	22 (95.6)	0.740
Sputum production	33 (44.0)	32 (58.2)	16 (69.5)	0.063
Breathlessness	14 (18.7)	29 (52.7)	17 (73.9)	< 0.001
Triage parameters†				
Temperature (deg C)	38.4 ± 1.0	38.5 ± 1.2	39.0 ± 1.1	0.353
Mean arterial pressure (mmHg)	90.9 ± 2.1	91.6 ± 16.3	94.4 ± 13.5	0.945
Heart rate (beats per min)	89.9 ± 15.6	98.7 ± 23.3	104.2 ± 28.4	0.045
Pulse oximetry (%)	97.4 ± 1.4	95.8 ± 3.5	89.0 ± 10.5	< 0.001
Normal chest auscultation	70 (90.9)	28 (50.9)	3 (13.0)	< 0.001
Laboratory findings†				
Leukocytes (10^3/μL)	5.6 ± 2.9	8.6 ± 5.0	9.4 ± 6.1	< 0.001
Haemoglobin (g/dL)	14.0 ± 1.6	14.0 ± 1.9	11.7 ± 2.5	< 0.001
Platelets (10^3/μL)	238.9 ± 65.4	260 ± 87.9	228.8 ± 88.9	0.160
CRP (mg/L)	27.3 ± 30.2	62.7 ± 71.8	87.5 ± 82.7	0.003
Procalcitonin (μg/L)	0.23 ± 0.20	2.02 ± 4.38	3.14 ± 9.21	0.340
Albumin (g/L)	39.5 ± 3.7	36.0 ± 6.6	29.7 ± 4.8	< 0.001
ALP (U/L)	34.8 ± 30.8	48.5 ± 25.1	83.1 ± 68.3	< 0.001
ALT (U/L)	53.2 ± 28.1	44.3 ± 37.7	66.4 ± 75.0	0.132
AST (U/L)	27.6 ± 17.2	36.2 ± 24.1	122.0 ± 234.1	0.001
Abnormal CXR findings	0 (0)	10 (18.2)	20 (87.0)	< 0.001

*Comparison of trend by ANOVA (continuous variable) or Kruskal-Wallis test (categorical).
¶Values are expressed as number (percentage), unless otherwise specified.
†Values are expressed as mean ± standard deviation.
IQR: interquartile range; CRP: C-reactive protein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CXR: chest radiograph

cases referred to patients who were either hypoxaemic, needed ≥ 4 L/min of oxygen and/or critically ill patients who required HD or ICU level of care. Clinical and laboratory findings of patients in these three categories were compared. Data was analysed using the Statistical Package for the Social Sciences for Windows version 12.0 (SPSS Inc, Chicago, IL, USA). Comparisons were made with ANOVA test and Kruskal-Wallis test for continuous and categorical data, respectively. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

During our study period, 10,081 patients with influenza-like symptoms attended the ED at our institution. Of these, 345 cases were confirmed to be H1N1 (2009) on RT-PCR. A total of 153 patients were admitted to our institution; 75 were classified as mild, 55 as moderate and 23 as severe illness. Of these 153 patients, 54 (mild: 44; moderate: 8; severe: 2) were admitted during the containment phase of the outbreak. Out of the 23 patients with severe illness, 18 were admitted to the pandemic ICU, while the remaining five required HD level of care. The clinical features and laboratory results are summarised in Table II.

Among the 153 hospitalised patients, 148 were residents of Singapore. The majority of patients (n = 113) resided in the eastern region of Singapore, which has a land area of 110 km^2. There was clustering of cases, predominantly around the residential districts of the region. Of note, one of these districts (District A), with an estimated area of 5 km^2, accounted for 32.7% (n = 37) of the H1N1 (2009) patients admitted to our institution. In addition, a higher proportion of patients (67.6%) within

this district had moderate–severe illness as compared with the proportion of moderate–severe patients in both the overall study population (50.9%) and in the cohort of patients from the eastern region (54.8%) (Table III).

A total of 81 of the 153 patients (53%) were females. None of the female patients (of child-bearing age) were pregnant. The median age was 26 (interquartile range [IQR] 19–49) years. Hypertension (22.9%), diabetes mellitus (10.5%) and bronchial asthma (10.5%) were the three most common comorbidities present in our patients. Although pre-existing diseases were more common in individuals with moderate–severe illness as compared to those with mild illness, 47.4% of patients with moderate–severe illness reported prior good health.

The most common presenting symptom was cough (92.8%). While upper respiratory tract symptoms predominated in patients with mild illness (nasal congestion 60%, sore throat 68%), breathlessness ($p < 0.001$) and sputum production were more commonly reported by patients with moderate–severe illness. Two patients (aged 15 and 18 years, respectively) with no prior history of epilepsy presented to the ED with seizures. There was no evidence of viral encephalitis on magnetic resonance imaging of the brain and lumbar puncture in one of the patients. The other patient declined further investigations. Both patients had an uncomplicated hospital stay and were discharged well. Another patient had an out-of-hospital pulseless electrical activity collapse after one week of influenza-like illness (ILI). This patient was transferred to the ICU but passed away the following day.

The mean temperature at triage was 38.5°C ± 1.1°C. Shock (one out of 153) was an unusual presenting feature. Unsurprisingly, increasing tachycardia ($p < 0.045$) with decreased pulse oximetry ($p < 0.001$) appeared to be associated with increased disease severity. Even among patients with severe illness, the mean pulse oximetry readings at presentation were lower in the subgroup who were subsequently admitted to the ICU (87.6% ± 11.4%) than in those who were not admitted (93.4% ± 4.5%). The mean leukocyte count was 7.2 ± 4.6 × 10^3/μL, with mean neutrophil and lymphocyte counts at 5.9 ± 4.4 × 10^3/μL and 1.4 ± 1.0 × 10^3/μL, respectively. The mean platelet count was 245 ± 78 × 10^3/μL. Leukopenia (< 5 × 10^3/μL) was noted in 47 (30.7%) patients who mainly had mild illness. Thrombocytopenia (< 150 × 10^3/μL) was present in seven (4.6%) patients. Transaminitis was noted predominantly in the severe illness group. The mean serum aspartate aminotransferase (AST) was 44.8 ± 104.4 U/L, with alanine aminotransferase levels at 52.3 ± 43.4 U/L.

Table III. Comparison of disease severity among the study population, the eastern region cohort and District A cohort.

	No. (%)		
	Study population	Eastern region cohort	District A cohort
Total no. of patients	153 (100.0)	113 (100.0)	37 (100.0)
Severity of illness			
Mild	75 (49.0)	51 (45.1)	12 (32.4)
Moderate	55 (35.9)	44 (38.9)	20 (54.1)
Severe	23 (15.0)	18 (15.9)	5 (13.5)

Mean serum C-reactive protein (56.0 ± 66.9 mg/L) and procalcitonin (1.91 ± 6.03 μg/L) levels were elevated. These were seen more frequently in patients with moderate–severe illness. Of the 105 patients whose specimens were sent for isolation of bacterial infection within 48 hours of hospitalisation, only four (3.8%) had a positive result. Among the positive isolates, *Haemophilus influenzae* was found in two patients (from tracheal aspirate and sputum, respectively), *methicillin-sensitive Staphylococcus aureus* bacteraemia in one patient and *Citrobacter* in the urine culture of another patient. There appeared to be a trend toward increased disease severity with elevated leukocyte counts ($p < 0.001$), CRP ($p < 0.003$) and AST levels ($p = 0.001$), as well as low haemoglobin ($p < 0.001$) and albumin ($p < 0.001$) levels.

None of the patients with mild illness had an abnormal chest radiograph (CXR) finding. In all, 30 patients (moderate = 10, severe = 20) had radiological abnormalities present on their CXR. These abnormalities included unilateral air bronchogram (n = 10), bilateral air bronchogram (n = 4), atelectasis (n = 2), pulmonary congestion (n = 2) and changes consistent with acute respiratory distress syndrome (n = 12). None of our patients had any radiologically significant pleural effusion.

All the patients received oseltamivir regardless of their duration of illness. While most patients were prescribed a standard dose of oseltamivir at 75 mg bd for five days, high-dose oseltamivir (150 mg bd) was administered to critically ill patients for an intended duration of ten days.[7] One patient received a second neuraminidase inhibitor, aerosolised Zanamivir (Relenza®, GlaxoSmithKline, Australia Pty Ltd, Boronia, Australia), as standard dose oseltamivir was initiated by the family physician one day prior to hospitalisation. The median duration of illness onset to first dose of antiviral therapy was four (IQR 3–5) days. Empirical antibiotics were prescribed when deemed necessary by the attending physician.

All the patients who were assessed to have mild or moderate illnesses had an uncomplicated hospital stay. 18 (11.8%) patients, all from the severe illness group, required ICU care, primarily for hypoxaemic respiratory failure. The majority of these patients (94.4%) were admitted to the ICU within 24 hours of hospitalisation. The median days from illness onset to ICU admission was five (IQR 3–6) days. 16 patients were intubated and required invasive mechanical ventilation. Detailed descriptions of the first 12 patients admitted to the pandemic ICU can be found in another study.[8]

There were seven in-patient fatalities in our case series. Of these, one patient (with terminal-stage motor neuron disease) had a do-not-resuscitate order. The overall in-patient mortality rate was 4.6%. Due to local cultural sensitivities, academic post mortems were declined by the families. There were no recorded H1N1 (2009)-related mortalities at the ED. The median lengths of hospital stay among patients with moderate and severe illnesses were four (IQR 3–5) days and nine (IQR 5–13.5) days, respectively. Among patients who were monitored for viral shedding with serial nasal and/or throat RT-PCR swabs (54 out of 153), the median duration for viral shedding from onset of symptoms was 8.5 (IQR 7–10) days. Of note, the RT-PCR tests remained positive for H1N1 (2009) in 70% of the patients, eight days after developing ILI symptoms.

DISCUSSION

We report a case series of 153 hospitalised patients with H1N1 (2009) infection of varying degrees of severity. Unique to our study, we were able to compare a group of patients (mild illness) who were hospitalised solely as a public health measure with patients who had clinical indications for hospitalisation (moderate–severe illness).

Consistent to experiences elsewhere,[9-11] our patients were from a younger age group. Only 12 (7.8%) patients were aged 65 years and above. Not unexpectedly, however, patients with moderate–severe illness were older (median age 44.5 years, IQR 22–55 years) as compared to those with mild illness (median age 20.5 years, IQR 18–27.5 years). While comorbidities were also more common with increased severity of illness, 47.4% of patients with moderate–severe illness reported no pre-existing medical conditions or risk factors, suggesting that prior good health is not necessarily a good discriminator against severe disease. Using a simple classification based on the clinical assessment at triage, we were able to categorise the patients according to their disease severity. Of note, all the patients in our case series remained in the same disease severity category throughout their hospitalisation stay.

The data from our study suggests that the symptom of dyspnoea at presentation warrants caution, and may help to predict the severity of illness as well as the need for in-patient care at triage. In a cohort of 272 hospitalised patients, Jain et al found that the proportion of patients with shortness of breath who needed ICU care or who died were higher (87%) compared to that of patients who were not admitted to an ICU and survived (51%).[11] Thus, bedside findings of tachycardia, low pulse oximetry readings and abnormal chest auscultations should also alert the triage physician to the potential of severe disease. Patients with moderate–severe illness were noted to have higher leukocyte counts, CRP levels and incidence of transaminitis. Lower serum albumin and haemoglobin levels were also seen in this group of patients.

In Singapore, infected patients were initially required to be hospitalised for isolation (containment phase). By early mitigation phase, stable H1N1 (2009) patients were discharged from ED for home treatment while serving a seven-day HQO. Intuitively, such a measure appeared to be appropriate for containment of the outbreak. Different countries had adopted a variety of containment and mitigation strategies.[12,13] Our study showed that up to 70% of patients had persistent viral shedding beyond eight days after the onset of ILI symptoms, despite antiviral treatment with oseltamivir. Prolonged viral shedding had also been reported elsewhere.[14,15] While the amount of viral shedding required to transmit disease remains unclear, emerging data suggests that persistent viral shedding may render quarantine policies counterproductive. In addition to its psychosocial and economic impacts, further stress may be placed on our already strained healthcare systems. Therefore, the benefits of public health interventions need to be evaluated together with available scientific data and the assessed risk of the outbreak.[16]

Our data suggested that an area within our institution's catchment area had a higher incidence of patients with more severe illness. The possible hypotheses include a more virulent influenza strain, higher viral loads, late presentation and secondary or co-infections. We postulate, however, that there may be an underestimation of mild cases, possibly because many patients with self-limiting ILI symptoms were being managed at primary healthcare level or were not seeking medical consultation at all. Even so, it remains unclear as to why an area would experience a higher prevalence of H1N1 (2009) compared to the surrounding region. Future studies on the epidemiology and infectivity of the H1N1 (2009) virus as well as on viral genomics may clarify this, and thus

result in improvements to pandemic response plans and their implementation.

Our study has several limitations. The case series did not include neonatal, paediatric and pregnant H1N1 (2009) patients. These subgroups have previously been identified as specific patient populations with a high risk of developing influenza-related complications.[17,18] Admittedly, our case series was not designed for epidemiological analysis. However, our national healthcare policies enabled us to be in a unique position to examine the clinical spectrum of disease and to monitor any trends that may help in the design of future studies. During the course of our study, the admission criteria for H1N1 (2009) patients was modified in line with changes in the national pandemic response policies. This resulted in a change in the demographics of patients admitted to our institution, with a significantly lower proportion of hospitalised patients with mild illness in the later part of the study. Finally, the management decisions, including the use of antimicrobial therapy and diagnostic tests, were not standardised but determined by the attending physician. These differences may have influenced the clinical course of illness and outcomes in our case series.

Since the onset of the pandemic in Singapore, a significant number of local residents would have acquired natural immunity from the H1N1 (2009) infection. Vaccinations against H1N1 (2009) infection began in early November 2009, with more than 420,000 recorded vaccinations since then.[6] Nevertheless, we hope that data from case series such as ours will help us to better triage and identify patients at risk of developing H1N1 (2009)-related complications. This will also allow us to adapt our pandemic response plan accordingly, accord appropriate resource allocation and utilisation, as well as formulate the pandemic influenza vaccination policy.

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