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Severe Cases of Pandemic H1N1 Pneumonia and Respiratory Failure Requiring Intensive Care

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Abstract

Background: The objective of our study is to analyze the clinical data of patients with pandemic H1N1 2009 infection admitted to the intensive care unit (ICU) and to report key features observed among these patients. **Methods:** A total of 18 patients were admitted to our ICU between July and November 2009, with a primary diagnosis of influenza. Clinical data were analyzed to identify potential risk factors and characteristics thought to affect outcomes. **Results:** Our patients were between ages 23 and 62 (mean 41). In all, 10 were obese. Two had no other comorbid conditions and 6 had obesity as their only comorbid condition. The most common symptoms were fever, shortness of breath, and cough. Laboratory data were notable for elevated creatine kinase levels, transaminitis, and lack of leukocytosis. The rapid influenza detection test (RIDT) had a 76% false negative result. Patients with a negative RIDT had their infection confirmed with real-time reverse transcriptase polymerase chain reaction (rRT-PCR). A total of 12 patients required invasive mechanical ventilation, with over half of whom responded only to nonconventional modes of ventilation. Most patients received high-dose (150 mg twice daily) oseltamivir. In all, 3 patients died and 11 were discharged without any long-term sequalae. **Conclusions:** Unlike seasonal influenza, our patients were not in the extremes of age. Most were obese and presented with severe respiratory distress and hypoxia in the summer months. A negative RIDT did not exclude pandemic H1N1 2009. Using a higher dose of oseltamivir and nonconventional modes of ventilation may have improved the outcome in our subset of patients. Hence, patients with a high clinical suspicion of severe influenza infection should be treated early and aggressively, even before confirmatory results are available.

Keywords

pneumonia, pandemic H1N1, respiratory failure, oseltamivir

Introduction

The outbreak of a new strain of influenza A virus, H1N1, started in Mexico months before it was first recognized in April 2009.[1-4] This novel influenza A is also known as the "swine flu," because the virus is a novel reassortment that contains elements of swine, avian, and human influenza viruses.[5] This is an H1N1 strain that had not previously circulated in humans but appeared to be extremely contagious as it spread rapidly.[6-8] It is still unclear whether the transmission is only human-to-human or whether there are other means of transmission. By June, it spread worldwide; this led the World Health Organization to declare a pandemic and rename the virus to, "Pandemic H1N1 2009."[2] The range of illness for this new virus is uncertain, varying in severity among different patient populations and regions of the world.[1-4] Recommendations are constantly evolving as new information is obtained.[2-4]

Soon after the emergence of this virus, it was observed that younger people, those under age 25, were preferentially infected.[9] Severe and fatal infections also occurred in those between ages 30 and 50, a younger age group when compared to the epidemics of seasonal influenza.[9] Preliminary data also showed that those affected had other comorbid conditions, including respiratory disease: asthma, diabetes, cardiovascular disease, autoimmune diseases, and possibly obesity.[2,3] Pregnancy also placed individuals at high risk of fatal complications.[2,3,10]

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Table 1. Demographic Characteristics

Pt #	Age (years)	Gender	Ethnicity	Body Mass Index (kg/m^2)	Comorbid Conditions	Tobacco Use	Sick Contacts
1	56	Male	Latino	23.8	DMII, HTN, HL	−	+
2	52	Male	Latino	39.1	Obesity	+	+
3	34	Male	Latino	52.5	Obesity	+	+
4	23	Male	Latino	65.6	Asthma, obesity	+	+
5	52	Male	Korean	27	None	+	+
6	36	Male	Latino	22.8	DMII	+	+
7	29	Female	Latino	34.6	DMI, HTN, CKD, Obesity	−	−
8	50	Female	Latino	32.5	CKD (post-kidney transplant), HTN, asthma, obesity	−	+
9	62	Female	Latino	28.2	SLE, AD	−	−
10	39	Female	Latino	28.5	None	−	−
11	52	Male	African American	30.2	Asthma, ILD (NSIP), systemic scleroderma, HTN, pulm-HTN, cor pulmonale, obesity	+	−
12	24	Male	Pakistani	21.6	DM, hemachromatosis, beta thalessmia major, chronic leukocytosis	−	−
13	24	Female	Latino	41.8	Obesity	−	−
14	32	Male	Latino	40.4	Obesity	−	−
15	54	Female	Armenian	22.7	Sjögren syndrome	−	+
16	42	Female	Latino	48.1	Obesity	+	+
17	24	Male	Filipino	46.9	Obesity	−	+
18	59	Female	Latino	25.5	CHF, AF, hypothyroidism, rheumatic heart disease	−	−

Abbreviations: pt, patient; kg, kilograms; m, meters; DM, diabetes mellitus; HTN, hypertension; HL, hyperlipidemia; CKD, chronic kidney disease; SLE, systemic lupus erythematosis; AD, Addison disease; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; pulm, pulmonary; CHF, congestive heart failure; AF, atrial fibrillation.

Initial reports in developed nations had disease ranging from mild-to-moderate in severity.[2,3,11,12] An overwhelming amount of patients had mild symptoms and made rapid and full recovery, suggesting that this novel influenza may have mortality rates similar to that of seasonal influenza.[2,3,12] This was initially seen at Olive View-UCLA Medical Center, with many confirmed cases being mild-to-moderate in severity. However, beginning in July 2009, more severe cases were noted. In this study, we would like to focus on those patients who had severe illness requiring intensive care unit (ICU) admission.

Materials and Methods

Study Design

This was a retrospective observational analysis of 18 adult patients admitted to the ICU at Olive View-UCLA Medical Center between July and November 2009, with a primary diagnosis of pandemic H1N1 influenza. Data were collected in a systematic fashion to help define the clinical features of severe pandemic H1N1 infection and their potential effect on outcome. The Institutional Review Board at the Olive View-UCLA Medical Center approved the study and waived informed consent because of the retrospective, observational study design. Ethical standards were used in the research.

Study Population

All 18 patients were adults admitted through the emergency department at Olive View-UCLA Medical Center with a primary diagnosis of pandemic H1N1 infection, confirmed either via rapid influenza detection test (RIDT) or by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assay for H1N1. One patient who tested positive for pandemic H1N1 infection and was admitted to the ICU was excluded because the primary diagnosis was pancreatitis. In addition to the primary diagnosis of pandemic H1N1 infection, secondary bacterial coinfections complicated the hospital course for 3 (17%) of the patients.

Study Variables

The variables considered and analyzed in each patient included demographics, underlying comorbidities, clinical presentation, laboratory data, ventilator settings, treatments, and outcomes.

Results

A total of 18 patients were admitted to the ICU at Olive View-UCLA Medical Center between July and November 2009, with a diagnosis of pandemic H1N1 infection (Table 1). They were between the ages of 23 and 62 (mean 41). Initially, there seemed to be a predominance of men, but in the later months, more women (44% total) developed severe influenza. In all, 13 patients (72%) were Latino; 10 patients (56%) were obese or morbidly obese (mean body mass index [BMI] 35.1); and only 4 patients (22%) had a normal BMI (<25). Two patients (11%) had no comorbid conditions and 6 patients (33%) had obesity as their only comorbid condition.

Patients presented with fevers (94%), shortness of breath (94%), cough (100%), and infiltrates on chest X-ray (100%). They complained of headaches (53%), myalgias (72%), and gastrointestinal symptoms (67%). Seven patients reported or had pink frothy sputum observed during their admission. Most patients were hypoxic (78%) and tachycardic (72%) in triage. Patients were considered hypoxic if their room air oxygen saturation was $\leq$93%. We assessed the severity of illness in the first 24 hours, using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and found the mean to be 14.7 $\pm$ 5.2 (Table 2).

Laboratory data (Table 3) were significant for a low or normal leukocyte count in 83% of patients. Aspartate aminotransferase was elevated in 65% of patients. Of the 14 patients, 11 (79%) had an elevated creatine kinase level, including patients who did not complain of myalgias. Only 4 (24%) of 17 patients tested positive using the RIDT, while 15 (94%) of 16 tested positive for H1N1 using the rRT-PCR assay. Of the 18 patients, 16 (89%) had bilateral infiltrates, while the remaining 2 (11%) had left lower lobe infiltrates. The characteristics of the infiltrates ranged from dense alveolar to interstitial changes.

Early bronchoscopy was performed in 2 patients (11%) to rule out other causes for severe respiratory decompensation, including opportunistic infections (Table 4). Both patients had a complete negative infectious workup. A bronchoscopy was not routinely performed when patients did not have indications or risk factors for other severe infections. Patients were also too unstable (often due to severe hypoxia) or there was a concern with generating more aerosols of the still not fully understood pandemic virus.

Of the 18 patients admitted to the ICU, 12 (67%) required invasive mechanical ventilation (Table 4). Of those 12, the mean number of days on the ventilator was 14.75 (range: 1 day to 36 days; note: patient 16 was mechanically ventilated for 23 days, extubated for 10 days, and reintubated for 28 days). All 12 patients were initially tried on conventional assist-control (AC) modes of ventilation (pressure-cycled AC and/or volume-cycled AC), however, airway pressure release ventilation (APRV) was required in over half of these patients (64%) to maintain adequate oxygenation. High-flow oscillatory ventilation (HFOV) was attempted in 1 patient but was complicated by pneumothorax. The average static compliance during the first 48 hours of mechanical ventilation ranged from 20.72 to 47.59 (mean 36.1). All patients who required mechanical ventilation met clinical and radiographic criteria for acute respiratory distress syndrome (ARDS).

In all, 2 patients (11%) received the standard dose of 75 mg twice daily of oseltamivir, whereas 15 patients (83%) received an increased dose of 150 mg twice daily. Two patients (11%) received peramivir after an apparent failed response to oseltamivir. Patient 1 did not receive any antiviral therapy (Table 4).

In all, 3 patients (17%) expired, 1 of whom expired suddenly the day after discharge. A total of 11 patients (61%) were discharged home without any long-term sequelae from their hospitalization. Two patients (11%) were discharged home with supplemental oxygen, 1 (6%) was discharged home on anticoagulation for thromboembolic disease, and 1 (6%) was discharged to a chronic ventilator facility.

Discussion

We described our 18 patients in the order of their presentation to the hospital. Limited data on this novel influenza virus led to challenging initial diagnoses and evolving treatment plans.

Comparison of Pandemic H1N1 Pneumonia to Other Viral Pneumonias

The first characteristic we noted was that many of our patients began to present with H1N1 influenza during the summer months, between July and August 2009, which is an unusual time of the year for the start of seasonal influenza. This was consistent with what was being seen around the world in the summer of 2009.[1,4,12-18] The time of symptom onset to hospitalization ranged from 1 to 14 days, but this did not seem to correlate with outcome. Our patients were younger than expected when compared to patients with severe pneumonia from seasonal influenza. Obesity or morbid obesity was present in over half of these patients. Similar characteristics were also noted in other pandemic H1N1 cases in Australia, New Zealand, Spain, Canada, Mexico, and Michigan, and were not previously known risk factors for severe influenza pneumonia.[14-18]

Fever, cough, myalgia, and sore throat are all expected symptoms for influenza. However, in addition to these usual symptoms, our patients also had a high incidence of gastrointestinal symptoms, such as nausea, diarrhea, decreased appetite, and abdominal pain. These findings were consistent with reports from other studies as well.[14,18] The majority of our patients complained of shortness of breath and were hypoxic on admission.

Recognition and Management

This novel influenza virus presented some unexpected laboratory results, including low or normal leukocyte counts, transaminitis, and elevated creatine kinase levels. In addition, we learned that diagnosis of pandemic H1N1 infection should not rely solely on the RIDT, particularly if the clinical suspicion is high. Of our most critically ill patients, 76% (13 of 17) had a negative RIDT. We found that this screen may be useful in patients with mild-to-moderate illness, but this did not change our management.[19] Even when using the rRT-PCR (the sensitivity ranges from 86% to 100%), we may not be able to confirm the diagnosis in all patients. Clinical suspicion of pandemic H1N1 infection in severely ill patients requiring hospitalization should be enough to prompt empiric antiviral therapy.

All of our patients had infiltrates on chest X-ray, either patchy or homogenous in distribution. The infiltrates ranged from alveolar to interstitial to dense consolidations, which is consistent with other reports.[20] The 12 patients who required mechanical ventilation all met clinical criteria for ARDS, with bilateral

Table 2. Chronology and Clinical Presentation

Pt #	Sx Onset to Hospital-ization (days)	Sx Onset to ICU Adm (days)	Signs and Symptoms							Triage Vital Signs (T, P, R, BP, O_2 sat)	APACHE Score
			Fever	H/A	SOB	Cough	Myalgia	GI Sx[a]	Other Sx		
1	5	10	+	+	+	+	+	+	Pink sputum, sore throat, chest pain	39, 79, 24, 131/88, 93% RA	15
2	3	4	+	+	+	+	+	−	Pink sputum, sore throat, night sweats	38.7, 122, 32, 159/67, 88% RA	20
3	4	4	+	+	+	+	−	+	Fatigue	36.9, 68, 20, 104/50, 73% RA	10
4	3	5	+	+	+	+	+	+	Sore throat, decreased appetite	39.1, 118, 20, 137/73, 86% RA	10
5	10	10	+	−	+	+	+	+	Sore throat, decreased appetite	37.2, 102, 22, 100/72, 67% RA	15
6	3	3	+	−	+	+	+	+	Decreased appetite, chest pain	36.7, 139, 16, 176/108, 97% RA	17
7	7	7	+	−	+	+	−	+	Fatigue, also presented with DKA	36.4, 75, 18, 136/89, 98% RA	10
8	2	3	+	−	+	+	−	−		38.7, 117, 20, 210/107, 95% 3L	21
9	4	4	+	+	+	+	+	+	Rhinorrhea, chills, dizziness	39.5, 124, 30, 103/70, 91% RA	9
10	7	7	+	−	+	+	+	+	Sore throat	37, 119, 20, 71/55, 93%RA	21
11	7	7	−	−	+	+	−	−	Pink sputum, LE edema, orthopnea, PND	37.4, 122, 26, 138/104, 76%RA	14
12	2	3	+	+	−	+	−	+	Pink sputum, sore throat, decreased appetite, nasal congestion	37.2, 108, 20, 129/62, 100%RA	13
13	5	5	+	+	+	+	+	+	Sore throat, decreased appetite	39.9, 125, 18, 126/79, 93%RA	14
14	7	9	+	−	+	+	+	+	Pink sputum, decreased appetite, 16lb weight loss in 1 week	37.1, 79, 22, 127/72, 90%RA	10
15	1	1	+	ND	+	+	+	+	Pleuritic chest pain, dysuria, suprapubic pain	38.3, 108, 22, 65/45, 92%RA	10
16	4	5	+	+	+	+	+	−	Pink sputum, decreased appetite	37.6, 121, 28, 135/74, 57%RA	8
17	14	14	+	−	+	+	+	−	Pink sputum, lethargic	40.2, 147, 5, 212/132, 81%RA	25
18	7	8	+	+	+	+	+	−	Sore throat, decreased appetite, pleuritic chest pain	37.6, 72, 20, 119/62, 97%RA	22

Abbreviations: Pt, patient; Sx, symptoms; ICU, intensive care unit; adm, admission; H/A, headache; SOB, shortness of breath; GI, gastrointestinal; T, temperature, degree Celsius; P, pulse, beats per minute; R, respirations, breaths per minute; BP, blood pressure, mm Hg; O_2 sat, oxygen saturation; APACHE, acute physiology and chronic health evaluation; ND, unknown; DKA, diabetic ketoacidosis; LE, lower extremity; PND, paroxysmal nocturnal dyspnea; lb, pound; RA, room air.

[a] GI Sx include nausea, vomiting, diarrhea, decreased appetite, abdominal pain.

Table 3. Laboratory Data

Pt #	Leukocyte Count (cells $\times$ 10^9/L)[a]	Platelet Count (cells $\times$ 10^9/L)	AST Level (units/L)	ALT Level (units/L)	Creatine Kinase (units/L)	Rapid Influenza A and B Ag Screen	rRT-PCR for H1N1 2009
1	2.5	105	176	183	532	−	+
2	4.4	84	100	50	1249	−	+
3	2.9	152	79	55	335	−	+
4	6.8	234	155	58	6697	−	+
5	2.6	143	733	533	264	−	+
6	19.3	227	44	76	19	+ A/−B	+
7	6.3	320	24	22	ND	−	+
8	2.5	156	28	18	ND	+A/−B	ND
9	6.1	161	35	21	172	+A/−B	ND
10	4.7	135	43	22	ND	−	+
11	7	175	ND	ND	312	−	+
12	19.3	435	171	139	206	−	+
13	3.6	200	77	46	413	−	+
14	7.9	219	15	15	402	−	+
15	10.1	255	25	25	ND	+A/−B	−
16	4.2	141	59	37	483	ND	+
17	25.5	277	121	48	29 433	−	+
18	4.2	157	33	20	69	−	+

Abbreviations: Pt, patient; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rRT-PCR, real-time reverse transcription-polymerase chain reaction; ND, no data or not done.

[a] Normal range for leukocyte count, 3.8 to 10.9 cells $\times$ 10^9/L; for platelet count 141 to 401 cells $\times$ 10^9/L; for aspartate aminotransferase level 15 to 41 units/L; for alanine aminotransferase level 14 to 54 units/L; for creatine kinase 26 to 174 units/L.

infiltrates, partial pressure of oxygen in the alveoli/fraction of inspired oxygen (P_{AO_2}/F_{IO_2}) ratio <200, and no clinical evidence of heart failure.[21] An open lung ventilation mode, specifically APRV, was used in 7 patients (64%) due to a lack of response to conventional modes of ventilation (pressure and volume AC). Although no specific conclusions can be drawn from this experience, we noted that APRV was an effective mode of ventilation in our patients with hypoxemia that was refractory to more standard modes. This observation was also noted by the University of Michigan in their initial report.[14] Of the 12 patients who required mechanical ventilation, 3 patients (25%) developed prolonged respiratory failure (>14 days) requiring a tracheostomy. Of these patients, 1 (patient 16) developed critical care neuropathy/myopathy thought to be precipitated by use of paralytics and steroids. This specific case highlights the importance of weighing the risks and benefits of therapies while maintaining a high index of suspicion for pandemic H1N1 infection.

For patients who presented over 48 hours after the onset of symptoms, it was unclear whether oseltamivir should be administered. We questioned the recommended dose of 75 mg, especially in our obese patients. Our patients presented as late as 14 days after the onset of symptoms. Initially, our patients were treated with 75 mg of oseltamivir twice daily. However, due to the limited response observed, all subsequent hospitalized patients suspected of having the pandemic H1N1 were empirically treated with oseltamivir 150 mg twice daily. This higher dosing was also used for the highly pathogenic avian influenza H5N1 in Asia in 2003.[22,23] More favorable outcomes were noted when 150 mg oseltamivir was given on admission. The time of symptom onset to hospitalization did not appear to have a significant effect on outcome, however, the number of days from admission to oseltamivir use did. A total of 11 patients were discharged home without any long-term sequelae. Of the 3 who expired, 1 (patient 10) died less than 12 hours after admission due to severe respiratory failure and shock; 2 patients (patient 16 and 17) had a long and complicated hospital course and were both given peramivir. Peramivir is an experimental antiviral drug developed by BioCryst Pharmaceuticals, authorized by the Food and Drug Administration for emergency use for patients who did not respond to oseltamivir.[24-26]

Of our 18 patients, 11 (61%) received steroids for various reasons at various doses. Three (17%) received steroids for possible *Pneumocystis jirovecii* pneumonia, 1 (6%) for possible nonspecific interstitial pneumonitis (NSIP), 2 (11%) for asthma exacerbation, four (22%) received steroids for treatment of adrenal insufficiency; 1 patient (6%) received steroids for unclear reasons. Although no specific conclusions can be drawn from our retrospective analysis, all 3 patients who expired received steroids. Furthermore, the patients who received steroids had an average number of days on mechanical ventilation (14.875 days) similar to that of the patients who did not receive steroids (14.5). This contrasts data reported by Meduri at the *Chest* conference in 2009, in which he prospectively demonstrated in a small pilot study that 11 of 13 patients who received steroids and oseltamivir 150 mg twice daily had a marked improvement in lung injury scores by day 7. Additionally, the 15% in-hospital mortality rate was lower than expected for such a critically ill population. A larger, randomized controlled trial is soon to commence in France, and should provide us with further guidance on the role of steroids in severe respiratory failure due to pandemic H1N1 infection.[27]

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Table 4. Ventilation, Treatment, and Outcome

Pt #	Days on Mech Vent	Avg Compliance First 48 hours on Vent (mL/cm H_2O)	Vent Modes Used	PaO_2/FiO_2 Ratio <200	Osltvr use and Dosage[a] Peramivir use	Adm to Osltvr use (days)	Steroid Admin	Vasopressor Use	ICU Stay (days)	Length of Hospital (days)	Trach	Outcome
1	3	34.5	A/C	Yes	No	N/A	Yes	Yes	11	26	No	Survived, discharged home with 3 Liters nasal cannula
2	10[b]	38.8	A/C, APRV	Yes	Yes, 75 mg BID	6	Yes	Yes	11	11	No	Died, ESRD requiring HD
3	7	36.7	APRV, A/C	Yes	Yes, 150 mg BID	0	No	No	12	13	No	Survived, discharged home
4	36	29.5	PRVC, A/C, APRV, SIMV	Yes	Yes, 150 mg BID	2	Yes	Yes	42	64	Yes	Died, discharged home with oxygen but sudden death next morning
5	12	51.7	A/C	Yes	Yes, 150 mg BID	0	Yes	No	15	17	No	Survived, discharged home
6	2	36.9	A/C	Yes	Yes, 150 mg BID	0	Yes	No	8	9	No	Survived, discharged home
7	N/A	N/A	N/A	No	Yes, 150 mg BID	0	No	No	1	3	No	Survived, discharged home
8	N/A	N/A	N/A	No	Yes, 150 mg BID	0	Yes	No	1	12	No	Survived, discharged home
9	N/A	N/A	N/A	No	Yes, 150 mg BID	0	Yes	Yes	2	3	No	Survived, discharged home
10	<1[c]	ND	ND	Yes	Yes, 150 mg BID	0	Yes	Yes	1	1	No	Died, pulm hemorrhage, septic shock, GAS bacteremia, ptx, pneumomediastinum
11	N/A	N/A	N/A	No	Yes, 150 mg BID	0	No	No	7	11	No	Survived, discharged home with home oxygen
12	4	31.6	APRV, A/C	Yes	Yes, 75 mg BID	0	Yes	Yes	5	8	No	Survived, AKI, discharged home
13	11	20.72	A/C	Yes	Yes, 150 mg BID	0	No	No	13	21	No	Survived, discharged home
14	5	47.59	APRV	Yes	Yes, 150 mg BID	0	No	Yes	8	20	No	Survived, discharged home
15	N/A	N/A	N/A	No	Yes, 150 mg BID	0	Yes	Yes	2	5	No	Survived, discharged home
16	23 + 28[d]	30.2	Inverse ratio, A/C, APRV, APV	Yes	Yes, 150 mg BID[a] peramivir	0	Yes	Yes	59	69	Yes	Survived, AKI, MDR Acinetobacter PNA, CNS/VRE bacteremia, Serratia UTI/PNA, discharged to SNF
17	35[b]	38.75	HFOV, APRV, A/C	Yes	Yes, 150 mg BID[a] peramivir	0	No	Yes	43	51	Yes	Survived, AKI, rhabdo, HD, DVT bil LE, bil hemopneumothoacies, MDR Acinetobacter PNA, bleeding rectal ulcer, pseudomonas UTI, discharged home
18	N/A	N/A	N/A	No	Yes, 150 mg BID	0	No	No	3	8	No	Survived, AKI, discharged home

Abbreviations: Pt, patient; Mech Vent, mechanical ventilation; Avg, average; mL, milliliters; cm H_2O, centimeters of water; Vent, ventilator; Osltvr, oseltamavir; Adm, admission; Admin, administration; ICU, Intensive Care Unit; Trach, tracheostomy; N/A, not applicable; ND, no data, unknown; mg, milligram; BID, twice daily; A/C, assist control; APRV, airway pressure release ventilation; PRVC, pressure regulated + volume control; SIMV, synchronized intermittent mandatory ventilation; APV, adaptive pressure ventilation; HFOV, high-frequency oscillation ventilation; ESRD, end-stage renal disease; HD, hemodialysis; pulm, pulmonary; GAS, group A β-hemolytic streptococcus; ptx, pneumothorax; AKI, acute kidney injury; MDR, multidrug resistant; PNA, pneumonia; CNS, coagulase-negative staphylococcus; VRE, vancomycin-resistant Enterococci; UTI, urinary tract infection; SNF, skilled nursing facility; rhabdo, rhabdomyolysis; DVT, deep vein thrombosis; bil, bilateral; LE, lower extremity.

AQ3

[b] Patients who had a bronchoscopy.

[c] Patient expired <12 hours after admission.

[d] Patient was intubated for 23 days, extubated for 10 days, then reintubated again for 28 days.

Further Observations and Speculation

Our first 2 patients were not placed into isolation. Both of these patients had sick contacts and later had an acute onset of symptoms. An extensive infectious workup was negative and they remained without isolation for weeks. The diagnosis of pandemic H1N1 was not reported until patient 1 was transferred out of the ICU and patient 2 died. For the following patients, strict infection control procedures were instituted early. Despite debates regarding the mode of transmission, we chose to use airborne isolation as recommended by the *Center for Disease Control and Prevention*.[3] Although we did not have enough evidence to make conclusions about those who were exposed to the first 2 patients, we found that all hospital staff, including physicians and nurses directly caring for them, did not develop influenza-like illnesses. The family members of these patients were also asymptomatic or had mild illness with rapid recovery. Additional data and studies would be needed, but we questioned whether severe illness may be a result of an impaired host immune response. Some studies demonstrated that an impaired immune response might lead to worse outcomes.[28] However, the actual reasons for more severe disease in our patients remain unclear; it may be due to a more virulent virus, lack of previous exposure in younger patients, or genetic predisposition. With regard to the association with obesity, recent animal studies suggest that diet-induced obesity leads to less robust immune responses in infected mice.[29] As a result, it is not always easy to determine which patients have increased vulnerability to infection, further emphasizing the importance of early suspicion and isolation, especially in the ICU setting, where patients are already critically ill or acutely unstable.

Final Comments

As far as we know, this study is the first single-center report of pandemic H1N1 infection requiring intensive care. All authors were the primary or consulting physicians who managed these patients in the ICU and followed them up in clinic after discharge. Our discussion of these cases are not solely based on retrospective data review, but rather from personal experiences when caring for these patients. We had similar patient demographics and presentation when compared to other studies, but the mortality for our ICU subset (17%) is better than that of other ICU subset of patients.[14,16-18] In our patients, mortality also did not seem to affect the older age group as suggested in some studies.[17]

We learned to develop a high level of suspicion early on, despite negative initial tests (RIDT), so we could initiate early aggressive treatment. We were especially aware that these patients were younger, though not in the extremes of age, usually obese without other comorbid conditions, and mostly presented with respiratory distress, atypical symptoms, notable laboratory and radiographic findings, and rapid clinical deterioration in the summer months. We agree that obesity should be considered a risk factor for H1N1 pneumonia, even though it is not a clearly known risk factor for other pneumonias.[14-18] We recognized severe hypoxemia and difficulty with ventilation in these patients and found that many responded favorably to nonconventional modes of ventilation such as APRV. Early changes in our management, including the use of high-dose oseltamivir empirically may have improved the outcome for our patients. We suspect that a higher dose may be indicated in obese patients and potentially in those with ARDS and severe pneumonia.

Although the recommendations for management of these critically ill patients are constantly being modified, early recognition is crucial in preventing mortality and morbidity. We hope our report would help raise clinical suspicion in patients with severe respiratory impairment who require ICU admission, especially in patients who do not appear to have any classic risk factors for severe influenza, in order to initiate rapid aggressive treatment.

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Authors' Note

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Declaration of Conflicting Interests

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