Severe H1N1-Associated Acute Respiratory Distress Syndrome: A Case Series

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ABSTRACT

BACKGROUND: Acute respiratory distress syndrome resulting from novel influenza A virus (H1N1) infection remains uncommon.

METHODS: We describe the clinical profiles of adult patients with acute respiratory distress syndrome due to microbiologically confirmed H1N1 admitted to a medical intensive care unit in San Francisco, California over a 2-month period.

RESULTS: Between June 1 and July 31, 2009, 7 patients (age range: 25-66 years; 4 patients under the age of 40 years; 6 male; 1 pregnant) were diagnosed with H1N1, with 5 of 6 (83%) having initial false-negative rapid testing. All developed respiratory failure complicated by acute respiratory distress syndrome, with 4 additionally developing multiorgan dysfunction. All were managed with a lung protective ventilator strategy (average number of days on the ventilator: 16), and 4 patients also required additional rescue therapies for refractory hypoxemia, including very high positive end-expiratory pressure, inhaled epoprostenol, recruitment maneuvers, and prone positioning. Despite these measures, 3 patients (43%) ultimately died.

CONCLUSIONS: Clinicians should be vigilant for the potential of H1N1 infection to progress to severe acute respiratory distress syndrome in a variety of patient demographics, including younger patients without baseline cardiopulmonary disease. A high degree of suspicion is critical, especially with the relative insensitivity of rapid testing, and should prompt empiric antiviral therapy.

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KEYWORDS: Acute respiratory distress syndrome; ARDS; H1N1 influenza

The pandemic novel influenza A virus (H1N1) was first documented in April 2009 and has since been associated with significant morbidity and mortality. Early investigations described an epidemiology and clinical course similar to previous influenza trends, including an initial skew toward younger and sicker patients, but the full extent of its impact is not yet known.

There have been few published studies of severe pulmonary disease, particularly acute respiratory distress syndrome, in adults, although more data are emerging. This report describes the clinical profiles of adult patients with documented H1N1 and consequent development of acute respiratory distress syndrome who were admitted to our medical Intensive Care Unit (ICU) over a 2-month period.

METHODS

San Francisco General Hospital is a 300-bed county hospital with 14 medical intensive care beds, affiliated with the University of California, San Francisco. Through chart review, adult patients aged 18 years or older admitted to the medical ICU with the diagnosis of acute respiratory distress syndrome from June 1 through July 30, 2009. Polymerase
chain reaction (PCR)-confirmed H1N1 were included in this series. Acute respiratory distress syndrome and multigorgan dysfunction syndrome were defined as per standard accepted definitions. This study was approved by the Institutional Review Board at the University of California, San Francisco.

RESULTS
Between June 1 and July 30, 2009, 66 inpatients were tested for influenza; 8 were positive for influenza A, and 1 was positive for influenza B. Of these, 7 adult patients with PCR-confirmed H1N1 infection developed acute respiratory distress syndrome (Table). The age range was 25-66 years, with 4 patients under the age of 40 years. Six were male, and the 1 female patient was pregnant. Most presented with fever, cough, dyspnea, or hemoptysis. The number of days from symptom onset to hospitalization ranged from 1-10. Five of 6 patients (83%) initially evaluated with rapid antigen testing for influenza on nasal wash samples tested negative. Three (43%) were bacteremic on presentation with Staphylococcus or Streptococcus.

All 7 patients required intubation and mechanical ventilation and were managed with a conventional low volume, low pressure lung protective ventilation strategy, with an average of 16 days on the ventilator. Four of 7 patients (57%) rapidly developed severe hypoxemia refractory to the conventional approach and were managed with rescue therapies. These included the administration of very high levels of positive end-expiratory pressure, recruitment maneuvers, inhaled epoprostenol, or prone positioning. One of these patients, without underlying lung disease, developed marked pneumomediastinum and diffuse subcutaneous emphysema (Figure 1) that resolved with tube thoracostomy drainage.

Four patients were evaluated for pulmonary embolism. One with echocardiographic findings highly suggestive of pulmonary embolism, resulting in empiric lysis, and 1 confirmed by computed tomography angiogram. Four required vaspressors for septic shock and also developed multigorgan dysfunction. All had been immediately treated upon admission to the medical ICU with oseltamivir at standard doses for at least a 5-day course.

Three of the 4 patients (ages 38, 52, and 66 years) managed with rescue therapies ultimately died. One of these was the pregnant woman, and her 32-week-old fetus ultimately survived. The other 2 were patients with chronic medical conditions. The survivor was an obese 25-year-old man who spent 24 days on the mechanical ventilator.

Autopsy of 1 patient revealed histopathology characteristic of the fibroproliferative, later phase of acute respiratory distress syndrome (Figure 2).

Of the other 3 patients not requiring additional rescue therapies, 1 was discharged home in good condition; 1 was transferred to another medical facility for further management; and 1 was transferred to the Neurology service with a poor neurologic prognosis.

Detailed profiles of 3 of our patients are provided in the Appendix (available online), highlighting the severity of H1N1 infection in the young and healthy, pregnant, and those with underlying co-morbidities.

DISCUSSION
Over a 2-month period, our medical ICU managed 7 patients with severe H1N1 infection complicated by acute respiratory distress syndrome, with 3 deaths. These cases are notable for their relatively young age and lack of significant underlying co-morbidities, as has been reported in prior reports.

The majority of our patients had initial falsely negative rapid antigen tests, highlighting the limitations of this technique. At our institution, the rapid test has a sensitivity of 51%-80% and a specificity of 93%-100%, which are comparable with reported test characteristics from other institutions. Thus, a high index of clinical suspicion remains paramount, and the use of PCR testing may assist in confirming the diagnosis but should not delay empiric treatment.

In 4 of the 7 patients, the rapid development of severe hypoxemia refractory to a conventional lung-protective ventilation strategy led to the implementation of rescue therapies. Of these 4, 3 died. One of the deaths was a pregnant woman, supporting prior data that pregnant individuals represent a population that is more vulnerable to severe H1N1-associated complications than the general population. The severity of hypoxemia may reflect a novel virologic effect, as well as a possible lack of pre-existing immunity in this patient population. Clinicians should be prepared to manage severe hypoxemia that may be refractory to a conventional lung-protective ventilation strategy with the use of rescue therapies.

The expected high rate of incident infection for this influenza season, and its potentially critical morbidity, may portend a significant resource burden on health care institutions. Clinicians should be vigilant for the potential severity of H1N1-associated complications in all affected patients admitted to the hospital setting, implement prompt isolation, and administer immediate antiviral therapy.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Comorbid Conditions</th>
<th>Symptoms</th>
<th>BMI (kg/m²)</th>
<th>Rapid Influenza Antigen Test</th>
<th>Blood Cultures on Admission</th>
<th>MODS and Vasopressor Use</th>
<th>Rescue Therapies</th>
<th>Days of MV</th>
<th>Days in ICU</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>ESRD, CHF, DM, HTN</td>
<td>Fever, chills, dyspnea, cough, hemoptysis, orthopnea, myalgias</td>
<td>21.9</td>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>NMBA day 9; prone day 9; epoprostenol day 9</td>
<td>15</td>
<td>16</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>HIV (CD4 = 673), DM, HTN, epilepsy, dementia, polyneuropathy Smoker, obesity, remote methamphetamine</td>
<td>Confusion, dyspnea, diarrhea</td>
<td>27.9</td>
<td>Initially negative, then repeat positive</td>
<td>MSSA</td>
<td>Yes</td>
<td>None</td>
<td>28</td>
<td>30</td>
<td>Discharged with poor neurologic prognosis</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>M</td>
<td>Smoker, obesity, remote methamphetamine</td>
<td>Fever, chills, dyspnea, cough</td>
<td>37.1</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>NMBA day 1; RM day 1; PEEP &gt; 20 day 1; prone day 8</td>
<td>24</td>
<td>30</td>
<td>Improved, discharged</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>32 weeks pregnant, smoker</td>
<td>Fever, dyspnea, cough, hemoptysis, myalgias</td>
<td>41.7</td>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>NMBA day 2; epoprostenol day 2; prone day 3; PEEP &gt; 20 day 3; RM day 4</td>
<td>19</td>
<td>19</td>
<td>Death, fetus survived</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>COPD, chronic pleural effusion, HCV, PSA, bipolar</td>
<td>Dyspnea, hemoptysis</td>
<td>23.9</td>
<td>Not done</td>
<td>S. pneumoniae</td>
<td>No</td>
<td>None</td>
<td>7</td>
<td>9</td>
<td>Improved, transferred</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>M</td>
<td>Smoker, LVH/HTN diagnosed on admission DM, HTN</td>
<td>Fever, chills, dyspnea, hemoptysis, diarrhea</td>
<td>30.0</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>None</td>
<td>10</td>
<td>12</td>
<td>Improved, discharged</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td></td>
<td>Fever, dyspnea, cough</td>
<td>23.6</td>
<td>Positive</td>
<td>MRSA</td>
<td>Yes</td>
<td>NMBA day 2; prone day 2; PEEP &gt; 20 day 2; epoprostenol day 2</td>
<td>6</td>
<td>6</td>
<td>Death</td>
</tr>
</tbody>
</table>

BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTN = hypertension; ICU = intensive care unit; LVH = left ventricular hypertrophy; MODS = multi-organ dysfunction syndrome; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; MV = mechanical ventilation; NMBA = neuromuscular blocking agent; PEEP = positive end-expiratory pressure; PSA = polysubstance abuse; RM = recruitment maneuver.
ACKNOWLEDGMENT

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References

APPENDIX

Clinical Profiles

Below we describe 3 of the 7 unique cases of novel influenza A virus (H1N1) admitted to our medical intensive care unit (ICU), highlighting the severe presentation of H1N1 and acute respiratory distress syndrome in patients who were: young, pregnant, and with multiple co-morbidities.

Case 1: A 25-year-old Obese Male Smoker Who Survived

A 25-year-old Filipino man with a history of smoking, methamphetamine use, obesity, sleep apnea, and treated latent tuberculosis infection was admitted with a 3-day history of fevers, chills, dry cough, dyspnea, and weakness.

On admission, he was febrile to 40°C, tachycardic to 120 beats per minute and had an initial room air oxygen saturation of 75%, which improved with 4 L of oxygen therapy by nasal cannula. Examination was remarkable for tachypnea with accessory muscle use, poor air movement, and scattered wheezes. Rapid antigen test for influenza was negative. Initial chest radiograph revealed a left lower lobe pneumonia and a pleural effusion. In the Emergency Department he received vancomycin, ceftriaxone, and doxycycline, and was admitted to the stepdown unit.

Within 24 hours, he quickly developed severe hypoxemia, and a trial of noninvasive ventilation was attempted but failed. He was transferred to the medical ICU for invasive mechanical ventilation and was diagnosed with acute respiratory distress syndrome. He then developed shock and was treated with aggressive intravenous fluid resuscitation (12 L) and vasopressors. His antimicrobial coverage was expanded to include oseltamivir.

Within hours, his hypoxemia became refractory to 100% FiO₂, and a positive end-expiratory pressure of 18 cm H₂O, so he was paralyzed to reduce ventilator dysynchrony and underwent a recruitment maneuver. The recruitment maneuver consisted of a brief period of positioning (day #3), and a recruitment maneuver (day #4).

Over the following days, her hypoxia worsened, and she was treated with inhaled epoprostenol (day #2), prone positioning (day #3), and a recruitment maneuver (day #4). This recruitment maneuver consisted of a brief period of ventilation in a pressure-controlled mode with the inspiratory plateau pressure set at 55 cm H₂O and positive end-expiratory pressure of 36 cm H₂O. She also was treated with packed red blood cell transfusions, stress dose steroids, and a fluid conservative management strategy after shock was resolved.

On hospital day #13, she developed a new fever and worsened hypoxia. On examination, new diastolic and systolic murmurs and gallop were noted. Duplex Doppler ultrasonography of her lower extremities revealed a deep vein thrombosis in the right common femoral vein, and transthoracic echocardiogram demonstrated new right ventricular enlargement, tricuspid regurgitation, and pulmonary hypertension. Because she was too tenuous to transport to the computed tomography scanner to confirm pulmonary embolus, empiric thrombolytic therapy was initiated. Subsequently, she developed acute renal failure due to acute tubular necrosis and was treated with a continuous infusion of bumetanide. Continuous renal replacement therapy was not possible because of her inability to lie supine to obtain vascular access. On hospital day #19, she suffered an asystolic cardiac arrest. Cardiopulmonary resuscitation was not performed given her do-not-resuscitate status. The H1N1 diagnosis was confirmed by polymerase chain reaction. Notably, her 32-weeks infant survived.

Case 2: A 39-year-old Pregnant Woman with Presumed Pulmonary Embolus

A 39-year-old Caucasian G4P1 woman with a history of polysubstance abuse presented at 32 weeks’ gestation to Obstetrics triage with a 3-day history of fevers, dyspnea, productive cough with hemoptysis, nausea, vomiting, and myalgias. She had an initial oxygen saturation of 74% on room air, respiratory rate of 40 breaths per minute, and a PaO₂ of 50 mm Hg while receiving 10 L of oxygen therapy via a nonrebreathing mask. She was immediately intubated, diagnosed with acute respiratory distress syndrome, and underwent an emergent caesarean section in the medical ICU. She was empirically treated with vancomycin, ceftriaxone, azithromycin, and oseltamivir. Immediately after the delivery, she developed severe hypoxemia, refractory to 100% FiO₂, and high levels of positive end-expiratory pressure, which prompted paralysis. Shock was treated with aggressive fluid resuscitation (14 L) and vasopressors. Initial rapid antigen testing for influenza was negative.

She was transferred to the medical ICU. She was empirically treated with vancomycin, ceftriaxone, azithromycin, and oseltamivir. Initially, she developed severe hypoxemia, refractory to 100% FiO₂, and high levels of positive end-expiratory pressure, which prompted paralysis. Shock was treated with aggressive fluid resuscitation (14 L) and vasopressors. Initial rapid antigen testing for influenza was negative.

Over the following days, her hypoxia worsened, and she was treated with inhaled epoprostenol (day #2), prone positioning (day #3), and a recruitment maneuver (day #4). This recruitment maneuver consisted of a brief period of ventilation in a pressure-controlled mode with the inspiratory plateau pressure set at 55 cm H₂O and positive end-expiratory pressure of 36 cm H₂O. She also was treated with packed red blood cell transfusions, stress dose steroids, and a fluid conservative management strategy after shock was resolved.

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Case 3: A 66-year-old Salvadoran Man with Multiple Comorbidities

A 66-year-old Salvadoran man with a history of end-stage renal disease, congestive heart failure, hypertension, diabetes mellitus, and remote tobacco and alcohol use presented with a 1-day history of left-sided pleuritic chest pain and dyspnea. He also reported a 1-month history of a productive cough and 1 week of fevers, chills, night sweats, worsening cough, and hemoptysis. Initial temperature was 38.5°C, blood pressure was 219/108 mm Hg, and room air oxygen saturation was 92%. Examination was significant for left basilar crackles and an elevated jugular venous pressure. Laboratory values were significant for a B-type natriuretic peptide >5000 pg/mL and a creatinine of 4.9 mg/dL. Chest
radiograph revealed mild pulmonary edema and bilateral lower lobe opacifications. Rapid viral antigen testing was negative. The patient was diagnosed with community-acquired pneumonia and acute heart failure. He was treated with ceftriaxone, doxycycline, diuretic therapy, and subsequent hemodialysis for worsening renal failure.

By hospital day #5, he continued to spike high fevers and developed worsened hypoxemia, thrombocytopenia, and sepsis. The patient was transferred to the medical ICU and treated with high-flow oxygen therapy (40 L, 100% FiO₂). Antibiotics were broadened to vancomycin, meropenem, fluconazole, and oseltamivir. The patient was intubated on ICU day #6 to undergo bronchoscopy and was subsequently diagnosed with acute respiratory distress syndrome and treated with a lung-protective ventilation strategy. The culture of the bronchoalveolar lavage fluid grew H1N1 after 1 week.

On day #4 of mechanical ventilation (hospital day #8), he developed dysynchrony with the ventilator and acute worsening of his hypoxia. Chest radiograph revealed pneumomediastinum, extensive subcutaneous emphysema, and a small pneumothorax, which was treated with tube thoracostomy drainage. On day #9 of mechanical ventilation, his hypoxemia became refractory to 100% FiO₂ and moderate levels of positive end-expiratory pressure, so he was paralyzed and treated with inhaled epoprostenol, with temporary PaO₂ improvement. However, by day #15 of mechanical ventilation, the patient required the prone position for refractory hypoxemia. Subsequently, he developed atrial fibrillation requiring amiodarone and then pulseless ventricular tachycardia treated successfully with defibrillation. Because continuous renal replacement therapy could not be carried out in the prone position due to malfunction of the central venous catheter, the patient was made supine. On day #16 of mechanical ventilation (hospital day #20), the patient developed shock refractory to high dose vasopressors and died.