H1N1-Associated Acute Respiratory Distress Syndrome

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Abstract: The worldwide 2009–2010 pandemic of novel H1N1 influenza reminds us that influenza can still be a lethal disease. Acute lung injury and acute respiratory distress syndrome (ARDS) have been the most devastating complications of this pathogen. We present a case of a previously healthy 40-year-old obese man who succumbed to H1N1-associated ARDS. In this focused review, we discuss the pathophysiologic peculiarities and management of acute lung injury/ARDS related to H1N1 infection.

Key Indexing Terms: Influenza; H1N1; Acute lung injury; Acute respiratory distress syndrome; Mechanical ventilation; Fluid therapy; Glucocorticoids; Prone positioning. **[Am J Med Sci 2010;340(6):499–504.]**

CASE

A 40-year-old man with no significant medical history was hospitalized with complaints of shortness of breath, fever, nausea, and body aches of 2 days duration. His symptoms were preceded by an episode of sore throat and cough beginning approximately 5 days before his current presentation for which he received a course of azithromycin and antitussives from an urgent care facility. Of note, the patient's spouse had had fever and a cough 1 week before the onset of his symptoms. Vitals signs at presentation revealed a temperature of 100.4°F, pulse rate of 122 per minute, blood pressure of 142/72 mm Hg, respiratory rate of 19/min, and oxygen saturation of 93% at room air. His body mass index was 39 kg/m^2. Respiratory examination was significant for bilateral rhonchi and occasional expiratory wheezes. Pertinent laboratory abnormalities included a serum creatine kinase of 4985 units (normal <230). The remainder of his initial laboratory work was within normal limits. Rapid human immunodeficiency and influenza screens

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were negative. Chest x-ray at presentation revealed diffuse bilateral alveolar opacities (Figure 1). Initial antibiotic coverage included vancomycin, moxifloxacin, piperacillin, and oseltamivir. Weight-based enoxaparin was used for thromboprophylaxis. His respiratory status deteriorated within a few hours of hospitalization requiring intubation and mechanical ventilation. Novel H1N1 influenza was confirmed based on a positive polymerase chain reaction (PCR). He was initially managed with lung-protective mechanical ventilation and fluid restriction. Because of worsening hypoxemia, he was started on intravenous peramivir. Although a computed tomography angiogram of the thorax did not show evidence of pulmonary embolism (Figure 2), he was fully anticoagulated. On day 8, inhaled nitric oxide (NO) therapy was started because of refractory hypoxemia (Sao$_2$ <80%). His condition continued to deteriorate, and he died 12 days after admission. Lung histopathology on postmortem examination revealed diffuse alveolar damage (DAD), alveolar hemorrhage, necrotizing bronchiolitis, and small thromboemboli (Figure 3).

Recent History of Novel H1N1 Influenza

Within months of an initial outbreak of novel H1N1 influenza in Mexico in late March 2009, the World Health Organization declared that a global pandemic of influenza was underway. In the summer and fall of 2009, H1N1 influenza sickened approximately 50 million Americans, hospitalized another 213,000, and killed >10,000, 90% of whom were younger than 60 years. These mortality data contrasted significantly with those typical of seasonal influenza in which the overwhelming majority of deaths had occurred in the elderly.

In direct terms, 1 of every 6 Americans has been affected by 2009 H1N1 influenza infection.[1] Most have suffered typical flu-like symptoms—fever, headache, cough, and myalgias—and have had a self-limited course. However, a small proportion of patients infected with H1N1 have presented with rapidly progressive lower respiratory tract involvement resulting in respiratory failure, development of acute lung injury (ALI), and acute respiratory distress syndrome (ARDS).[2] Case reports of such patients have described a high morbidity and mortality when ALI/ARDS is present.[3] In this review, we discuss the
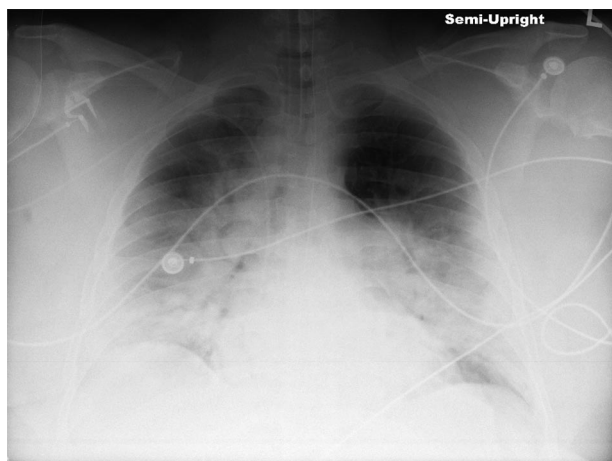
FIGURE 1. Postintubation anterior-posterior portable chest radiograph of a 40-year-old man with acute respiratory distress syndrome (ARDS) caused by proven novel 2009 H1N1 influenza. Sputum cultures were negative for bacterial pathogens.

pathophysiology and management of ALI/ARDS related to H1N1 infection.

Definition and Epidemiology of ALI/ARDS

ARDS is the most severe manifestation of ALI and affects approximately 150,000 Americans each year. Although there are many causes of ARDS, far and away the most common is pneumonia. Most afflicted individuals require intubation and mechanical ventilation, often for weeks. The syndrome is associated with significant morbidity and resource utilization. Mortality rates vary from 25% to 40% depending on patient demographics and the number of extrapulmonary organ failures. In an attempt to standardize the diagnosis of ARDS, an American European Consensus Conference has proposed the following definition[4]:
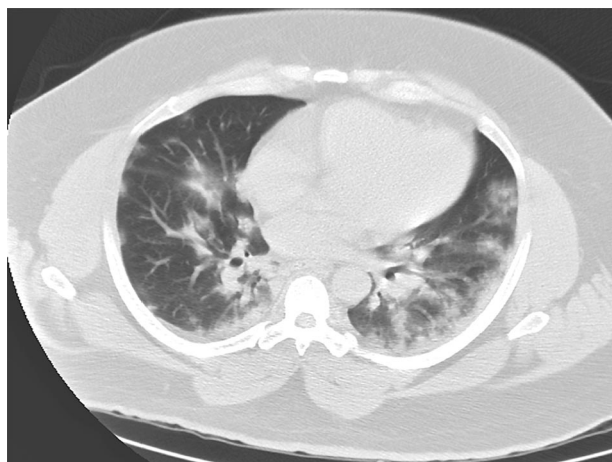

FIGURE 2. Contrasted computed tomography (CT) angiogram of the thorax of the above patient was performed to look for evidence of pulmonary embolism. Lung windows demonstrate the parenchymal abnormalities. No pulmonary emboli were identified on this examination, although small segmental pulmonary emboli were found at autopsy.

1. The acute onset of bilateral alveolar infiltrates on chest radiograph consistent with pulmonary edema
2. PaO_2/FiO_2 ratio <200 mm Hg for ARDS or <300 mm Hg for ALI
3. Pulmonary artery occlusion pressure <18 mm Hg or no clinical evidence of left atrial hypertension

Although, on first consideration, the American European Consensus Conference definition of ALI/ARDS may seem overly simplistic, it seems to define a reasonably homogenous type of lung injury. Of the patients meeting this consensus definition, 88% have had DAD at autopsy, whereas 83% of patients with DAD at autopsy have met the consensus definition.[5,6]

The incidences of ALI and ARDS have been estimated to be approximately 80 cases per 100,000 person-years and 60 cases per 100,000 person-years. The incidence of each was found to be higher with advancing age.[7] Recent experience with novel H1N1 influenza has estimated that 6% of patients who have clinical influenza will require hospitalization and 12% of those will develop respiratory failure.[8] Reports of ARDS occurring in association with novel 2009 H1N1 influenza identified a younger median patient age than has historically been associated with ARDS with other respiratory infections, including seasonal influenza.[9] For reasons that remain unclear, the incidence of H1N1-related ALI seems to be highest in patients who are obese or pregnant.[10–12]

Histopathogenesis of H1N1 ALI

The H1N1 virus has shown tropism not only for tracheal and bronchial cells but also for type 1 and type 2 pneumocytes, resulting in widespread denudation of epithelial layers.[13] As a consequence, a range of pathologic changes has been described in H1N1-related ARDS, including tracheobronchial injury, alveolar hemorrhage, and DAD (Figure 3). Exuberant expression of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1, interleukin-6, and interferon-γ and disruption of the alveolar epithelial barrier can lead to a robust systemic inflammatory response associated with multiple organ dysfunction.[14] The ALI pattern of DAD, characterized by hyaline membrane formation within alveolar spaces, may resolve with relatively minor residual pulmonary impairment in surviving patients or may initiate a fibroproliferative response in the lung with protracted respiratory failure.[13] Autopsy evidence of acute bacterial pneumonia has been seen in >50% of fatal cases.[13,15] Gram-positive cocci, both streptococcal and staphylococcal species, predominate.[16]

Clinical Presentation

In general, the initial symptoms of novel 2009 H1N1 influenza are similar to those of seasonal influenza. Presenting symptoms usually include 1 or more of the following: fever and chills, cough, sore throat, myalgias, headache, and fatigue. A higher prevalence of diarrhea and vomiting has been reported with the 2009 outbreak than is typically seen with seasonal influenza. Dyspnea, chest discomfort, confusion, or severe vomiting may be signs of severe influenza requiring hospitalization.[17] Early reports of experience from Mexico observed a median of 6 days between the onset of symptoms and admission to a hospital. Progression to respiratory failure, when it occurred, usually occurred rapidly with the majority of such patients requiring intubation within 24 hours of hospitalization.[8]

Diagnosis

In the absence of significant influenza activity in a community, influenza-like symptoms have low specificity for
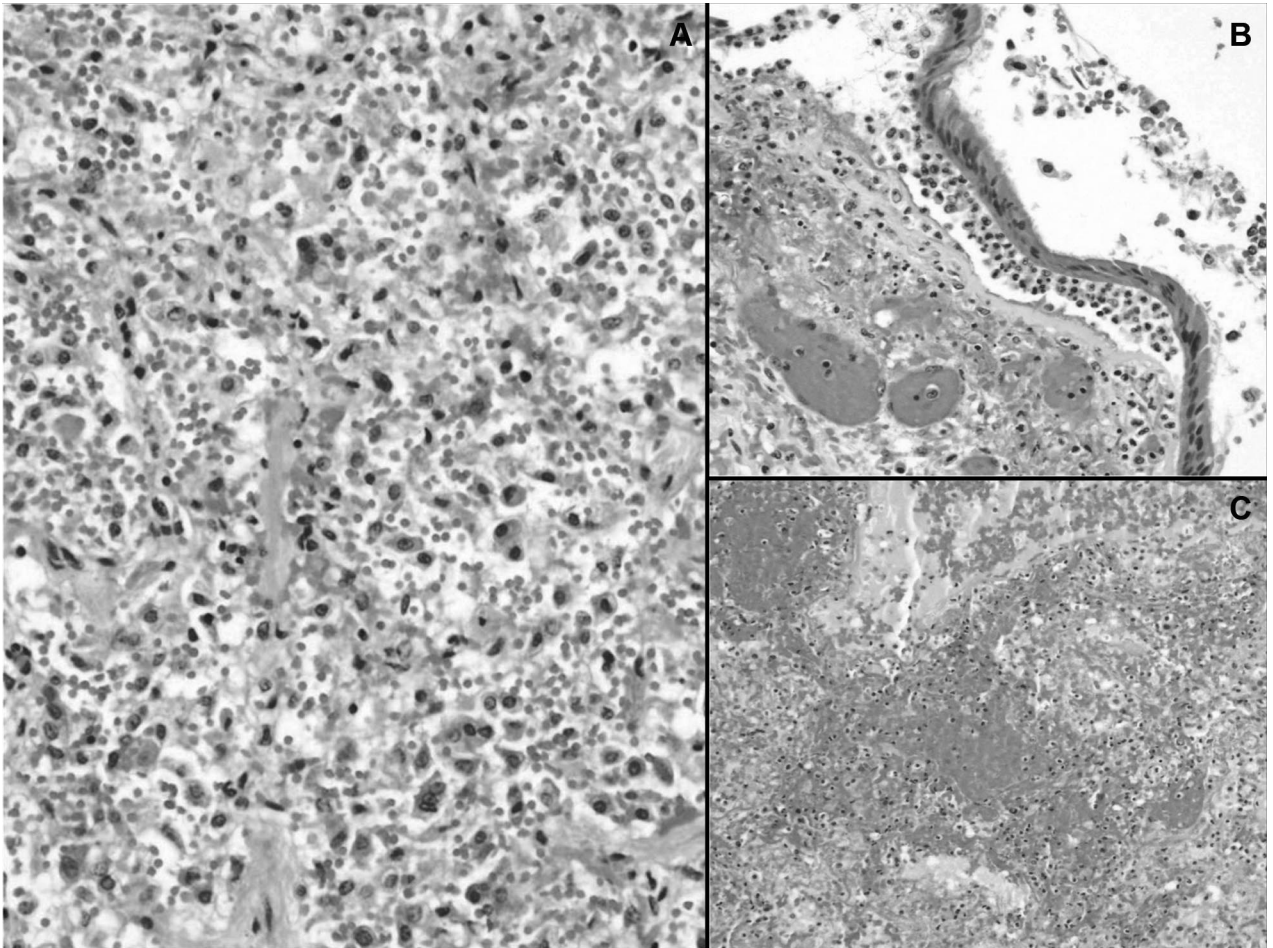
FIGURE 3. Postmortem histopathology of the above patient. (A) Diffuse alveolar damage characterized by hyaline membrane formation and intraalveolar collections of denuded and reactive appearing pneumocytes. (B) Marked necrotizing bronchiolitis characterized by bronchial epithelial sloughing and necrosis with extensive subepithelial neutrophilic infiltrate. (C) Diffuse intraalveolar distention by recent hemorrhage.

influenza. In contrast, during an influenza epidemic, up to 80% to 90% of patients who present with the above symptoms will actually have influenza. It is important to remember that a patient with a comorbid illness may present only with an exacerbations of the underlying disease state as the primary manifestation of influenza. For example, exacerbation of asthma, congestive heart failure, and acute myocardial infarction have all been associated with acute influenza infection.[18] For these reasons, the threshold for suspecting influenza should be low in the setting of an epidemic. Rapid influenza screening based on lateral flow immunodiagnostic testing ("rapid flu test") has been reported to have a wide range of sensitivity between 10% and 70% for the 2009 H1N1 strain, limiting the utility of this test.[19,20] Reported sensitivity and specificity for reverse transcriptase PCR (RT-PCR) approaches 100%.[21] However, because of the long turnaround times for RT-PCR results, treatment must be initiated based on clinical suspicion only. For intubated patients, initial testing for pandemic H1N1 infection should consist of paired nasopharyngeal and tracheal aspirate specimens for RT-PCR.[17]

In severe H1N1 influenza, hematologic and biochemical testing may reveal leukopenia and increases of serum lactate dehydrogenase and creatine kinase. Uncommonly, thrombocy-

topenia may occur.[8] Chest radiography may be normal or may reveal ill-defined patchy airspace disease or large areas of consolidation (Figure 1).[22] Hypoxemia is an ominous sign.

Infection Control

Standard contact and droplet precautions should be practiced at all levels of health care, emphasizing respiratory etiquette and hand hygiene, distancing, cohorting, adequate room ventilation, and use of surgical masks for those in close contact with patients with respiratory illness.[17]

Antiviral Therapy

For patients with significant comorbid illnesses and for those requiring hospitalization for H1N1 influenza, oseltamivir is recommended as the first-line therapy. Higher doses and longer duration of therapy may be appropriate in this setting. Experience to date suggests that treatment in critically ill patients should be continued for at least 10 days, unless there is conclusive evidence that viral replication has ceased.[17] Resistance of novel 2009 H1N1 influenza to oseltamivir has been reported, especially in immunocompromised patients. This has been attributed to the H275Y mutation that confers resistance to oseltamivir. Resistant H1N1 isolates have so far been sus-

ceptible to zanamivir.[23] Peramivir is an experimental neuraminidase inhibitor that received emergency use authorization by the US Food and Drug Administration for hospitalized patients in whom other available methods of treatment are ineffective or unavailable. Peramivir is currently the only intravenous antiviral for treating the novel H1N1 influenza. However, it is not recommended in cases of oseltamivir resistance.[24]

Role of Antibiotics

Because 50% of patients dying of influenza have microbiological or pathologic evidence of secondary pneumonia and because there is no convincing way to exclude bacterial pneumonia in patients presenting with pulmonary infiltrates and flu-like symptoms, empiric antibiotics are justified. Empiric antibiotics should be based on evidence-based guidelines for community-acquired pneumonia with the caveat that community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia occurs with increased frequency in the postinfluenza period. Whenever possible, the results of microbiological studies should be used to guide antibiotic usage. Healthcare-associated respiratory infections, including those associated with invasive ventilation, may be of particular significance in patients with H1N1-related ARDS and appropriate measures to prevent them should be applied. Empiric antibiotic therapy in this setting should be based on local epidemiology.[17]

Conventional Mechanical Ventilation

Although there is no specific treatment for ALI/ARDS, much research has been devoted to optimizing ventilatory management of these patients. A large study conducted by the National Institutes of Health Network for Acute Respiratory Distress Syndrome (ARDSnet) showed conclusively that a lung-protective mechanical ventilation strategy using low-tidal volume ventilation (6 mL/kg predicted body weight and plateau pressure <30 cm H_2O) significantly reduced patient morbidity and mortality.[25] A recent meta-analysis reiterated the beneficial effects of a low-tidal volume strategy in managing these patients.[26] The use of lower-tidal volume ventilation is now considered the standard of care for patients with ALI/ARDS.[27] Use of an explicit standardized written protocol improves physician compliance with lung-protective mechanical ventilation.[28]

Positive end-expiratory pressure (PEEP) reduces intrapulmonary shunt and improves oxygenation in ALI.[29] The optimal level of PEEP in ALI/ARDS remains controversial. Some have advocated the use of PEEP levels above the lower inflection point on the lung pressure-volume curve as a method of avoiding repetitive recruitment and derecruitment of alveoli and resultant "atelectrauma."[30–32] Others have suggested titration of PEEP and FiO_2 to the lowest levels compatible with acceptable oxygenation.[33] Several randomized controlled clinical trials have failed to demonstrate a benefit of higher levels of PEEP on clinical outcomes.[34–36] Therefore, in unselected patients with ALI/ARDS, we currently recommend titration of PEEP and FiO_2 to target levels of oxyhemoglobin saturation until further evidence becomes available.

Recruitment maneuvers involve intentional, short-term use of high transpulmonary pressures in an effort to open derecruited lung units and increase end-expiratory lung volume.[37] Various maneuvers, such as sustained inflation and sighs, have been investigated. Although these maneuvers may improve oxygenation, they have not translated into survival benefits.[34–36] On the basis of available evidence, recruitment maneuvers should be considered for use only on an individualized basis in patients with ALI/ARDS who have life-threatening hypoxemia.

The ARDSnet low tidal volume ventilation trial was performed using volume-preset mechanical ventilation at a tidal volume of 6 mL/kg predicted body weight.[25] Recently, there has been a significant interest in various modes of pressure-preset ventilation because it may permit better patient ventilator synchrony. Airway pressure release ventilation is a pressure-limited, time-cycled mode of partial ventilatory support that allows unrestricted spontaneous breathing during the entire ventilatory cycle. Because it permits diaphragmatic contraction, some have suggested that it might reduce dependent atelectasis.[38,39] However, there is significant evidence to demonstrate that lung overdistention can occur with pressure-preset modalities even when plateau airway pressure remained below 30 cm H_2O.[40] If a pressure-preset mode of ventilation is chosen, it is imperative to ensure that exhaled tidal volumes do not exceed current guidelines.

Fluid Management

Critical illness is often a water-avid state. In retrospective studies, positive fluid balance has been associated with adverse clinical outcomes.[41] A prospective, randomized, controlled clinical trial by the ARDSnet Investigators showed that use of a restrictive fluid management strategy improved lung function and increased number of ventilator- and intensive care unit (ICU)-free days. Furthermore, conservative fluid management did not increase the incidence of shock or the need for dialysis.[42] On the basis of this large, well-conducted study, a restrictive fluid strategy is recommended for hemodynamically stable patients with ALI/ARDS.

Salvage Therapies

Salvage therapies are techniques that may be considered in patients with ARDS with critical refractory hypoxemia. Mechanical ventilation in the prone position can lead to improved gas exchange in such patients. Prone ventilation is believed to benefit patients with ARDS by eliminating dependent atelectasis perhaps by reducing mechanical compression of lungs by the heart. Other potential mechanisms of action include redistribution of blood flow to high ventilation-perfusion areas, improvement in the homogeneity of transpulmonary pressure administration, improvements in respiratory mechanics, and enhanced secretion clearance.[37,43,44] Although the technique can improve oxygenation, there does not seem to be any survival benefit.[45] In addition, it is a labor-intensive technique that is particularly difficult to implement in obese patients who are more prone to developing severe ARDS caused by H1N1.

High-frequency oscillatory ventilation provides alveolar ventilation with very small tidal volumes (1–5 mL) and thus theoretically may provide optimum lung protection against ventilator-induced lung injury.[46] Animal studies have indeed shown that high-frequency oscillatory ventilation may attenuate ventilator-induced lung injury.[47,48] However, available human data have not demonstrated a survival benefit in ARDS.[49,50] Because the technique requires special expertise, we cannot advocate its routine use at this time.

Nitric oxide is a potent endogenous vasodilator. Exogenously administered, inhaled NO reduces intrapulmonary shunt and physiologic dead space by vasodilating pulmonary arterioles in well-ventilated units.[51] Although inhaled NO may result in a transient improvement in oxygenation, these improvements have not translated into survival benefits.[52,53] In addition, patients receiving NO may be at an increased risk for renal insufficiency.[54]

Extracorporeal membrane oxygenation (ECMO) is a widely accepted rescue modality in neonatology and pediatrics,

but its role in adults with ARDS remains controversial. Several case series have documented good clinical outcomes associated with the use of ECMO. Most recently, the Australia and New Zealand ECMO Influenza Investigators reported excellent outcomes in a series of patients with H1N1-associated ARDS.[9] However, to date, only 2 prospective, randomized clinical trials have been reported. The first by Zapol et al[55] did not demonstrate survival benefit in a cohort of patients with various causes of acute respiratory failure. More recently, Peek et al[56] reported the results of the United Kingdom National Health Services Trial (CESAR trial). This study randomized 180 adults with severe ARDS to receive either conventional mechanical ventilation in a community hospital or ECMO in a tertiary referral center. An intent-to-treat analysis demonstrated better clinical outcomes in the group referred for ECMO. Among patients referred for ECMO, who actually received ECMO, mortality was only 37%. However, among patients referred for ECMO but who received lung-protective mechanical ventilation instead, mortality was even lower at 18%. In summary, available data do not provide a compelling rationale for the use of ECMO in severe ARDS at this time.

The rationale for the use of glucocorticoids in ARDS is founded on the fact that they have broad antiinflammatory and antifibrotic effects. A prospective randomized crossover trial of 91 patients with severe, early ARDS suggested that methylprednisolone infusion (1 mg/kg/d) reduced lung injury scores, multiple organ dysfunction syndrome scores, duration of mechanical ventilation, and ICU mortality.[57] Furthermore, treated patients had a lower rate of secondary bacterial infections. Unfortunately, this study was limited by its crossover design. Use of steroids as a rescue therapy late in the course of ARDS was investigated in 180 patients in another randomized controlled trial called the Late Steroid Rescue Study. Steroids did not show any survival benefit when treatment was initiated 7 or more days after the onset of ARDS.[58] Although observational studies of patients with ALI caused by H1N1 have reported good clinical outcomes with a combination of oseltamivir with methylprednisolone, controlled data are lacking.[2] On the basis of the failure of steroids to benefit patients with ARDS caused by other viral etiologies, such as severe acute respiratory syndrome, H5N1, Hantavirus, and respiratory syncytial virus, the above data fail to produce a convincing argument for their use in H1N1-associated ARDS.[59]

In summary, increased clinical suspicion of influenza, early initiation of appropriate antimicrobial therapy, and knowledge of optimal ICU support modalities are necessary skill sets for all physicians who care for patients with potential H1N1-associated ALI/ARDS.

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