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Critically Ill Patients With Influenza A(H1N1)pdm09 Virus Infection in 2014

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The 2009 pandemic caused by influenza A(H1N1) pdm09 virus resulted in more than 18 500 deaths reported worldwide and global estimates that were 15-fold higher.[1] In contrast to seasonal influenza epidemics, during which elderly persons have the highest risk for hospitalization and death, many critically ill patients during the 2009 H1N1 pandemic were young or middle-aged adults.[2] Other notable riskfactors were morbid obesity and pregnancy, including the early postpartum period.[2] The dominant feature of critical illness during the 2009 H1N1 pandemic was severe acute respiratory distress syndrome (ARDS)that often developed very quicklyfollowing presentation to the hospital and frequently was associated with a long and protracted course and high mortality.[2]

Since 2009, H1N1pdm09 virus has continued to circulate and cause critical illness worldwide, but it has not predominated in the United States until this season, with a corresponding resurgence of influenza-related hospitalizations, critical illness, severe ARDS, and deaths. This year more than 60% of laboratory-confirmed influenza-associated hospitalizations and deaths reported in adults younger than 65 years to date have been attributed to H1N1.[3,4] No significant antigenic changes in circulating H1N1pdm09 virus strains compared with vaccine strains have been detected since 2009. The relative effect on young and middle-aged adults might be partially due to their low influenza vaccine coverage and cross-reactive immunity to H1N1pdm09 virus that elderly individuals have acquired

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from past exposure to antigenically related viruses. Based on lessons learned from the 2009 H1N1 pandemic, we offer suggestions for the care and management of H1N1pdm09 patients at risk for critical illness during this influenza season.

Clinical Features

Although most persons with H1N1pdm09 virus infection will not develop critical illness, those who do often deteriorate rapidly. The typical presentation is influenza-like illness with sudden onset of fever, cough, rhinorrhea, and myalgia. Deterioration occurs after approximately 4 to 5 days and is characterized by hypoxemia, shock, and multiorgan dysfunction.[2] Hemodynamic and oxygenation monitoring is recommended so that intubation and resuscitation can be instituted promptly. Of note, 60% of those requiring noninvasive ventilation progressed to endotracheal intubation.[5]

Patients with H1N1pdm09 who require intubation are at high risk of a rapidly progressive viral pneumonia and severe ARDS (Pao_2/Fio_2 <100). The pathogenesis of H1N1pdm09 virus infection resultingin critical illness is primarily driven by an intense inflammatory (and sometimes hemorrhagic) host response in the lung to the virus (eFigure in the Supplement). The severity of ARDS is likely influenced by multiple factors, including H1N1pdm09 virus infection of the respiratory tract as the initiator, the host inflammatory response (which can be extremely variable), and possible secondary bacterial pneumonia. Although corticosteroids could theoretically ameliorate inflammation-induced injury, they are associated with prolonged viral replication and secondary gram-negative bacterial and fungal pneumonia and higher mortality; thus, corticosteroids should be avoided for specific treatment of influenza and associated ARDS.[6] Concomitant bacterial community-acquired pneumonia, especially with *Staphylococcus aureus* (including methicillin-resistant *S aureus*), *Streptococcus pneumoniae,* or *Streptococcus pyogenes,* has been reported. Empirical broad-spectrum antimicrobial therapy should be initiated to cover these pathogens, with appropriate de-escalation of antibiotics when lower respiratory tract bacterial cultures return with definitive results.

ARDS and Nonrespiratory Organ Dysfunction

The cornerstone of modern ARDS care is low tidal volume lung protective ventilation and an open-lung approach with increased positive end-expiratory pressure/mean airway pressure. Despite standard ARDS management including conservative fluid strategy, H1N1pdm09-associated ARDS can be associated with severe hypoxemia and markedly abnormal lung compliance, with failure of routine ARDS management strategies in some patients. Thus, it is important for clinicians to consider early transfer of intubated patients with presumed H1N1pdm09 virus infection, especially if severe hypoxemia develops, to a regional referral center with experience providing more advanced “rescue” care, such as extracorporeal membrane oxygenation (ECMO).

Rescue strategies are approaches reserved for very critically ill patients to attempt to alleviate hypoxia and improve cardiopulmonary dynamics, although their effect on mortality is less clear. Examples include prone positioning, ECMO, neuromuscular blockade, inhaled

nitric oxide, and lung recruitment maneuvers. Prone positioning and ECMO appear to be associated with lower mortality in severe ARDS, although results are inconsistent.[7] These strategies require considerable experience and resources, and the reported benefits are largely restricted to trials at referral centers.

Septic shock and refractory hypotension occur in approximately 30% of patients with H1N1pdm09-associated critical illness despite adequate fluid resuscitation, and high-dose vasopressors may be required.[8] Acute kidney injury can occur and may require treatment with continuous renal replacement therapy due to concomitant hypotension from septic shock. Other less common severe complications, such as influenza-associated encephalopathy, encephalitis, myocarditis, and pericarditis, may be secondary to tissue injury from inflammation triggered by H1N1pdm09 virus infection of the respiratory tract. Additional complications include myositis and rhabdomyolysis with creatine phosphokinase elevations. In some severe ARDS cases, thromboembolic events (some fatal) have been documented, including primary pulmonary thrombi/emboli and deep venous thrombosis, and empirical systemic anticoagulation may be considered in high-risk patients. For patients with H1N1pdm09-associated ARDS and critical illness, prolonged ICU length of stay is common, clinical improvement is very slow, and some patients require weeks to months of mechanical ventilation and critical care support.

Influenza Testing and Antiviral Therapy

During influenza season, patients with respiratory failure or ARDS without an etiology should have lower respiratory tract specimens (endotracheal aspirate, bronchoalveolar lavage fluid) tested by reverse transcription-polymerase chain reaction (RT-PCR) for influenza viral RNA because upper respiratory tract specimens may be negative. Antigen detection tests (rapid influenza diagnostic tests, immunofluorescence assays) can produce false-negative results compared with RT-PCR.

There is no robust evidence from randomized clinical trials to guide antiviral therapy in critically ill patients with influenza. However, antiviral treatment, by reducing viral load, may ameliorate the inflammatory response and observational studies in critically ill influenza patients suggest some clinical benefit, especially if started early.[9] To date, detection of oseltamivir-resistant H1N1pdm09 viruses has been uncommon.[4] Therefore, empirical oseltamivir treatment is recommended as soon as possible before testing results are available.[10] Standard-dose oseltamivir administered enterally in critically ill adults can be adequately absorbed. Higher oseltamivir dosing has been administered in hospitalized patients without benefit over standard dosing, but optimal dosing and duration of oseltamivir treatment in critically ill influenza patients are unknown. Because influenza viral replication may be prolonged, testing of serially collected lower respiratory tract specimens by RT-PCR may help inform length of therapy and duration of infection control measures. Severely immunosuppressed patients (eg, hemopoietic stem cell transplant recipients) are more likely to develop oseltamivir-resistant H1N1pdm09 virus infection due to prolonged viral replication.

Patients for whom enteric administration is contraindicated or those with oseltamivir-resistant virus infection may benefit from a parenteral neuraminidase inhibitor such as the investigational drug intravenous zanamivir. Antiviral dosing may need to be adjusted for patients requiring renal replacement therapy or ECMO. Failure to improve or clinical deterioration during oseltamivir treatment may be due to the progression of acute lung injury or other influenza-associated ARDS complications and is less likely due to emergence of oseltamivir resistance.

Strict adherence to influenza prevention and control measures can prevent health care-associated influenza. All health care workers should receive influenza vaccination annually. Suspected and confirmed influenza patients should be isolated, and standard and droplet precautions should be implemented. For aerosol-generating procedures, fit-tested N95 respirator or higher level of respiratory protection is indicated.

Future Directions

Key topics for clinical management of critically ill influenza patients include (1) how to better identify which patients will deteriorate; (2) what are optimal antiviral treatment strategies and end points; (3) what is the role of immunomodulators and other adjunctive therapies; and (4) what are the efficacy and effectiveness of ARDS rescue strategies? A better understanding of risk factors may be gleaned from ongoing observational studies and electronic health record data. However, optimal understanding requires prospective collection of high-quality clinical data and biologic specimens, including from randomized clinical trials conducted across ICU networks where care is standardized during epidemics and linked to public health surveillance data. National and international clinical research networks—including ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium), InFACT (International Forum for Acute Care Trialists), USCIITG (US Critical Illness and Injury Trials Group), and PREPARE (Platform for European Preparedness Against Reemerging Epidemics)—are exploring a novel approach using an adaptive design that would permit testing of multiple therapies, including novel agents, enrollment across different regions and countries, random allocation rules that favor therapies that appear most efficacious, and recruitment during interpandemic periods. Such efforts can also inform clinical management of critically ill patients with infection caused by novel influenza A viruses (H5N1, H7N9) or other emerging viruses (eg, MERS-CoV) of global public health concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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