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Antiviral therapy and vaccination are important strategies for controlling pandemic 2009 influenza A(H1N1) but efficacy depends on the timing of administration and is often limited by supply shortage. Patients with dyspnea, tachypnea, evidence of hypoxemia, and pulmonary infiltrates on chest radiograph should be hospitalized. Patients with severe illness or underlying medical conditions that increase the risk of more severe disease should be treated with oseltamivir or zanamivir as soon as possible, without waiting for the results of laboratory tests. Lung-protective ventilation strategy with a low tidal volume and adequate pressure, in addition to a conservative fluid management approach, is recommended when treating adult patients with ARDS. Extracorporeal membrane oxygenation has emerged as an important rescue therapy for critically ill patients. Use of systemic steroids was associated with delayed viral clearance in severe acute respiratory syndrome and H3N2 infection. Low-dose corticosteroids may be considered in the treatment of refractory septic shock. Passive immunotherapy in the form of convalescent plasma or hyperimmune globulin may be explored as rescue therapy. More data are needed to explore the potential role of IV gamma globulin and other drugs with immunomodulating properties, such as statins, gemfibrozil, and N-acetyl-cysteine. Health-care workers must apply strict standard and droplet precautions when dealing with suspected and confirmed case and upgrade to airborne precautions when performing aerosol-generating procedures. Nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, good community hygiene, and restrictions on travel are useful measures in controlling an influenza pandemic at its early phase.

**Clinical Management of Pandemic 2009 Influenza A(H1N1) Infection**

David S. Hui, MD, FCCP; Nelson Lee, MD; and Paul K. S. Chan, MD

Antiviral therapy and vaccination are important strategies for controlling pandemic 2009 influenza A(H1N1) but efficacy depends on the timing of administration and is often limited by supply shortage. Patients with dyspnea, tachypnea, evidence of hypoxemia, and pulmonary infiltrates on chest radiograph should be hospitalized. Patients with severe illness or underlying medical conditions that increase the risk of more severe disease should be treated with oseltamivir or zanamivir as soon as possible, without waiting for the results of laboratory tests. Lung-protective ventilation strategy with a low tidal volume and adequate pressure, in addition to a conservative fluid management approach, is recommended when treating adult patients with ARDS. Extracorporeal membrane oxygenation has emerged as an important rescue therapy for critically ill patients. Use of systemic steroids was associated with delayed viral clearance in severe acute respiratory syndrome and H3N2 infection. Low-dose corticosteroids may be considered in the treatment of refractory septic shock. Passive immunotherapy in the form of convalescent plasma or hyperimmune globulin may be explored as rescue therapy. More data are needed to explore the potential role of IV gamma globulin and other drugs with immunomodulating properties, such as statins, gemfibrozil, and N-acetyl-cysteine. Health-care workers must apply strict standard and droplet precautions when dealing with suspected and confirmed case and upgrade to airborne precautions when performing aerosol-generating procedures. Nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, good community hygiene, and restrictions on travel are useful measures in controlling an influenza pandemic at its early phase.
the global population became infected, of whom half suffered clinical illnesses. The A(H2N2) pandemic that occurred in 1957 to 1958 caused about 70,000 deaths in the United States. In 1968, another new type A(H3N2) emerged and remains in circulation today.1,2

Pandemic 2009 influenza A(H1N1) [A(H1N1)] is a new strain of influenza virus that was first identified in Mexico and the United States in March and April 2009, respectively. The pandemic A(H1N1) virus originated from the triple-reassortment swine influenza (H1) virus circulating in North American pigs.3,4 Complete genome sequencing has shown that the known molecular markers of pathogenicity (PB1-F2 and nonstructural-1 proteins) are not expressed in the pandemic A(H1N1) virus.5 Animal studies have shown that the novel influenza virus caused increased morbidity, replicated to higher titers in lung tissue, and was recovered from the intestinal tract of intranasally inoculated ferrets in contrast to seasonal influenza H1N1 virus.6,8 This may explain why the novel virus is relatively more pathogenic than seasonal influenza viruses in its capacity to invade the lower respiratory tract and cause rapidly progressive pneumonia in humans because of our lack of background immunity to the former. Within several weeks from onset, the novel virus has spread throughout the world through international air travel and resulted in an influenza pandemic.9 The World Health Organization (WHO) has raised the level of influenza pandemic alert from phase 5 to phase 6 since June 11, 2009.10

As of November 29, 2009, there have been >622,482 laboratory-confirmed cases of pandemic A(H1N1) and 8,768 deaths in 207 countries and territories reported to the WHO. As more and more countries have stopped counting individual cases, particularly of milder illness, the case count is significantly lower than the actual number of cases that have occurred.11

CLINICAL AND LABORATORY
FEATURES OF SEVERE CASES

The majority of patients with pandemic A(H1N1) infection develop mild upper respiratory tract symptoms similar to seasonal influenza, but gastrointestinal symptoms seem more common in the former. In a study of 642 confirmed cases during the early outbreak in the United States in April 2009, 60% of patients were 18 years of age. Among those with available data, 18% had history of recent travel to Mexico, whereas 16% were identified from school outbreaks. The most common presenting symptoms were fever (94%), cough (92%), and sore throat (66%); 25% of patients had diarrhea, and 25% had vomiting. Of the 399 patients for whom hospitalization status was known, 36 (9%) required hospitalization and two died.12 In a study of 863 confirmed cases in Ontario, Canada, cough, fever, sore throat, and gastrointestinal symptoms were reported in 92%, 91%, 41%, and 24% of patients, respectively, with a hospitalization rate of 3.6% and a case fatality ratio of 0.2%.13

Patients with more severe disease present with fever, cough, dyspnea or respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia (Figs 1A-C). Other common findings were an increased creatinine kinase level and lymphopenia.14 The WHO has outlined the warning signs for more severe disease as listed in Table 1.15 Although severe disease may occur in otherwise well and young subjects, there are often risk factors for developing more severe disease (Table 2).14,16-18

In contrast to seasonal influenza, most severe pandemic A(H1N1) disease and its related mortality have occurred among children and adults aged <60 years, whereas about 40% of patients who have required hospitalization or died were previously healthy.16-18 The number of ICU admissions due to pandemic A(H1N1) infection was 15 times the number due to viral pneumonia in recent years in Australia and New Zealand.17 The elderly (>65 years) are less frequently infected by the novel virus,16-19 probably because of some pre-existing cross-reacting immunity against the virus due to their past exposure to previous circulating seasonal influenza A(H1N1) strains similar to the current pandemic A(H1N1) viruses.20 However, it is controversial if the seasonal influenza vaccine antigen components confer any cross-immunity against the pandemic strain.20,21

Autopsy findings have shown three distinct pulmonary histologic patterns: diffuse alveolar damage, necrotizing bronchiolitis, and diffuse alveolar damage with intense alveolar hemorrhage. There is also evidence of ongoing pulmonary aberrant immune response.22 Pulmonary emboli were noted, whereas secondary bacterial or fungal pneumonia were reported in 7/50 (14%) fatal cases in California.23 A fatal case with coinfection with community-acquired methicillin-resistant Staphylococcus aureus (MRSA) occurred in a Filipino sailor who died in Hong Kong.24 In a study of 77 American patients with fatal cases of confirmed pandemic A(H1N1) infection,25 evidence of concurrent bacterial infection was found in 22 (29%) patients, including 10 with Streptococcus pneumoniae, six with Streptococcus pyogenes, seven with S aureus, two with Streptococcus mitis, and one with Haemophilus influenzae; four cases involved multiple pathogens. The median age of the 22 patients was 31 years and median duration of illness was 6 days. These findings confirm that bacterial lung infections are occurring among patients with fatal cases of pandemic A(H1N1) infection and underscore both the need for early recognition/treatment of bacterial pneumonia in patients with influenza and the
importance of pneumococcal vaccination for persons at increased risk for pneumococcal pneumonia. The indications for hospitalization are listed in Table 3.

**Diagnostic Tests**

Nasal swabs with nasal secretions (from the anterior turbinate area) or nasopharyngeal aspirates or swabs are appropriate specimens for detecting human influenza A and B. Although the rapid influenza diagnostic tests were capable of detecting novel A(H1N1) virus from respiratory specimens containing high levels of virus, the overall sensitivity was low (40%-69%) among all specimens tested and declined substantially as virus levels decreased. Patients with illnesses compatible with pandemic A(H1N1) virus infection but with negative rapid influenza diagnostic test results should be treated empirically based on the level of clinical suspicion, underlying medical conditions, severity of illness, and risk for complications. If a more definitive determination of infection with influenza virus is required, testing with real-time reverse transcription-polymerase chain reaction (RT-PCR) or virus isolation should be performed. In patients who require invasive mechanical ventilation (IMV), tracheal aspirates may offer higher diagnostic yield than nasopharyngeal flocked swab (Fig 2). Sequential sampling is important because it increases opportunities for positive diagnosis and facilitates understanding of viral load/clearance during illness course, in addition to monitoring development of antiviral resistance.

**Antiviral Therapy**

The pandemic virus is currently susceptible to the neuraminidase inhibitors, but resistant to the matrix protein-2 inhibitors. Most patients infected with the pandemic virus experience typical influenza symptoms and fully recover within a week, even without any form of medical treatment. Healthy patients with uncomplicated illness need not be treated with antivirals. For patients who initially present with severe illness or whose condition begins to deteriorate, treatment with oseltamivir should commence as soon as possible and antiviral treatment should be provided even if started later than 48 h. If oseltamivir is unavailable or cannot be used for any reason, zanamivir may be given. This recommendation applies to all patient groups, including pregnant women, and all age groups, including young children and infants. The Food and Drug Administration in the United States has approved emergency use of intravenous peramivir for treatment of severe cases, whereas zanamivir dry powder should not be administered by nebulization as the

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**Figure 1.** (A) Chest radiograph of an obese, 23-year-old woman (BMI 31 kg/m²). She had influenza symptom onset on July 8, 2009, and was treated by a general practitioner with antibiotics. A chest radiograph taken on July 15, 2009, showed bilateral mid and lower zone patchy infiltrates. Reverse transcription-polymerase chain reaction (RT-PCR) from the nasopharyngeal aspirate was positive for the pandemic A(H1N1) virus. Oseltamivir 150 mg bid was started on July 15, 2009. (B) Despite treatment with high-dose oseltamivir and supplemental oxygen, her condition deteriorated, and a chest radiograph taken on July 18, 2009, showed bilateral and extensive consolidation. She required invasive mechanical ventilation (IMV) on July 18, 2009, with lung-protective ventilation strategy and conservative fluid management. (C) Her condition improved following intensive care support and high-dose oseltamivir for 10 days. She was extubated on July 24, 2009. Chest radiograph taken on July 29, 2009, showed marked clearing of the lung consolidation.
The risk of resistance is considered higher in patients with severely compromised or suppressed immune systems who have prolonged illness, have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication. The risk of resistance is also considered higher in people who receive oseltamivir for postexposure prophylaxis following exposure to another person with influenza and who then develop illness despite taking oseltamivir. In general, it is not recommended to use antiviral drugs for prophylactic purposes. An alternative option is close monitoring for symptoms in people who have had exposure to an infected person and are at a higher risk of developing severe or complicated illness, followed by prompt early antiviral treatment should symptoms develop.  

### Respiratory Support for Critically Ill Patients

About 1% to 10% of patients with clinical illness due to the novel infection have required hospitalization and the overall case fatality ratio has been estimated as <0.5%. Rapidly progressive respiratory failure is relatively common and about 10% to 30% of hospitalized patients have required ICU admission. IMV, with a lung-protective ventilation strategy, is recommended as the initial approach for managing patients with pandemic A(H1N1) infection complicated by ARDS. The recommendation is based on the ARDSNet trial demonstrating a relative risk reduction of mortality by 22% in patients with ARDS ventilated with the lower tidal volume (eg, goal of maximum tidal volume 6 mL/kg of predicted body weight with plateau pressures up to maximum 30 cm H$_2$O). Furthermore, it is prudent to adopt a conservative fluid management approach for patients with ARDS/acute lung injury, as this has been shown to increase ventilator-free days and improve oxygenation when compared with a fluid liberal strategy. In ICUs where expertise and technology are available, extracorporeal membrane oxygenation (ECMO), high-frequency oscillation ventilation, prone positioning, and inhaled nitric oxide have been reported as useful rescue therapies for critically ill patients.
The median duration for IMV was 8 days; 12% of the ventilated patients with severe respiratory failure in Australia and New Zealand received ECMO support, with a survival rate of 70% in this subgroup. The overall ICU mortality rate for the critically ill cases was close to 17%. Factors that were independently associated with death in the hospital included requirement of IMV at ICU admission, any coexisting condition, and older age.

Noninvasive positive pressure ventilation (NPPV) was applied to a small number of critically ill patients with pandemic A(H1N1) infection complicated by respiratory failure, but most patients subsequently required IMV support. NPPV is generally not recommended for patients with the novel influenza infection complicated by pneumonia and ARDS. NPPV temporarily improves oxygenation and reduces the work of breathing, but does not necessarily alter the course of the disease. The need for NPPV is an indication of severe disease and the likelihood of IMV. In addition, hemodynamic instability and multiorgan failure are contraindications to application of NPPV. The WHO interim guidelines on prevention and control of acute respiratory diseases in health care have included NPPV among those aerosol-generating procedures in which there is possibly increased risk of respiratory pathogen transmission. Low-dose heparin should be started prophylactically for critically ill patients who require ICU treatment in view of the reports of pulmonary embolism, especially among the critically ill obese patients with pandemic A(H1N1) infection.

**Systemic Corticosteroids**

High-dose corticosteroids have not been shown to be beneficial in ARDS and septic shock unrelated to A(H1N1) virus infection in reducing mortality. However, stress-dose corticosteroids (hydrocortisone 200-300 mg/d) may be beneficial in improving hospital mortality and morbidity outcomes. Although low-dose corticosteroids may be considered in the management of refractory septic shock, the precise role of systemic steroids in the setting of ARDS and refractory shock due to severe influenza pneumonitis requires further investigation as metaanalyses to date have mainly derived from data related to bacterial-induced...
Passive Immunotherapy

A metaanalysis has suggested that early administration of convalescent blood products might have reduced the risk for death in patients with Spanish influenza pneumonia during the 1918 pandemic. Convalescent plasma was used as rescue therapy with seemingly favorable response in a 31-year-old male patient in severe A(H5N1) infection complicated by multiorgan failure despite treatment with oseltamivir, although it is difficult to judge the efficacy of convalescent plasma without any randomized controlled study. There is, however, experimental evidence in animal models that administration of anti-H5N1-specific antibodies in the form of neutralizing monoclonal antibodies or polyclonal sera (convalescent or postimmunization) is effective in treating influenza A(H5N1) disease. Thus passive immunotherapy, including in the form of hyperimmune globulin made from convalescent plasma, is a potential option for treatment of pandemic A(H1N1) infection.

Other Immunomodulating Agents

Statins

High viral load and the resulting intense inflammatory response have been hypothesized as causing the organ damage and severe morbidity/mortality of A(H5N1) disease. Cytokine dysregulation has also been invoked in the pathogenesis of sepsis and septic shock. Statins have antinflammatory and immunomodulatory effects (eg, by repressing induction of major histocompatibility complex-II by interferon-γ and subsequent T-lymphocyte activation). Statins have been proposed to play a potential role for treatment and prophylaxis of pandemic influenza based on observational studies showing the survival benefits in patients receiving statins who developed bacteremia, sepsis, or pneumonia.

In H5N1-, H3N2-, and H1N1-infected BALB/c mice, 50 μg statin/200 μg caffeine effectively ameliorated lung damage and inhibited viral replication and was at least as effective as oseltamivir and ribavirin. The statins/caffeine combination also appeared to be more effective when administered preventatively rather than as treatment. These findings provide justification for further research into this novel antiviral formulation.

IV Ig

IV Ig may be considered as a treatment option for its immunomodulating effects in influenza with active systemic inflammation. IV Ig was used for treatment of SARS, but there were thromboembolic events, such as sepsis, and data specific for pandemic A(H1N1) are limited.

It is important to use systemic corticosteroids with caution in the treatment of respiratory viral diseases. Early use of corticosteroids might prolong viral replication in severe acute respiratory syndrome (SARS) and H3N2 influenza. In addition, prolonged use of systemic corticosteroids in SARS led to severe adverse effects, including fatal disseminated Aspergillus infection and osteonecrosis. During the SARS period in the ICU, the use of systemic steroids was associated with an increase in the rate of isolation of MRSA, Stenotrophomonas and Candida species. The ventilator-associated pneumonia rate was high, at 36.5 episodes per 1,000 ventilator-days, and 47% of episodes were caused by MRSA. The MRSA acquisition rate also increased from 3.53% during the pre-SARS period to 25.30% during the SARS period. The use of systemic steroids for acute exacerbation of COPD due to pandemic A(H1N1) infection may potentially prolong viral shedding (Fig 3).

**Figure 3.** Virus-shedding profile of a 68-year-old man who was hospitalized with acute exacerbation of COPD on July 6, 2009, with a 2-day history of cough, fever, and increased dyspnea. His chest radiograph showed no consolidation. He was given prednisolone 30 mg daily for 10 days and amoxicillin-clavulanate 1 g bid for acute exacerbation of COPD. RT-PCR from his nasopharyngeal aspirate taken on July 6, 2009, was positive for the pandemic A(H1N1) virus. Oseltamivir 75 mg bid was started on July 7, 2009, for 5 days. He developed hypercapnic respiratory failure on July 8, 2009, and required noninvasive positive pressure ventilation (NPPV) support for 2 days in a negative pressure isolation room. His nasopharyngeal flocked swab was still positive by RT-PCR on July 16, 2009, although clinically he was well. The use of systemic steroid for COPD might have prolonged his viral shedding. He was discharged from hospital well on July 26, 2009. Viral copy numbers were determined by real-time RT-PCR targeting the matrix protein gene. Specimens with undetectable viral copy number (lower detection limit = 62.6 viral copies/μL) were plotted at zero. See Figure 1 legend for definition of abbreviation.
as pulmonary embolism and ischemic stroke, despite use of prophylactic low-molecular-weight heparin.\textsuperscript{36-58} Thus, it is important to monitor for the complications of IV Ig, especially vascular thrombotic events.

\textbf{N-acetyl-L-cysteine}

Production of reactive oxygen species (ROS) has been shown to contribute to pulmonary damage caused by influenza virus infection.\textsuperscript{39} Different sources of ROS have been suggested in influenza A virus-infected lungs. Leukocytes may be activated and primed by influenza virus infection and produce ROS.\textsuperscript{60} Moreover, increased xanthine oxidase levels were found in influenza A virus-infected lungs.\textsuperscript{60} Epithelial cells of the lungs may also be a source of ROS since influenza A virus infection induced oxidant stress response in cultured airway epithelial cells.\textsuperscript{61} The antioxidant \textit{N}-acetyl-L-cysteine (NAC) has been shown to inhibit replication of seasonal human influenza A viruses. NAC inhibits H5N1 replication and H5N1-induced production of proinflammatory molecules.\textsuperscript{62} Therefore, antioxidants like NAC represent a potential additional treatment option that could be considered in the case of severe influenza infection. Other compounds with immunomodulating properties, such as macrolides, gemfibrozil, glitazone,\textsuperscript{55} and nutritional supplements,\textsuperscript{63} have been proposed as adjunct treatments, but these would require further investigation with controlled clinical trials.

\section*{Prevention and Infection Control Aspects}

There are some infection control lessons from SARS that have important clinical implications for infection control against human influenza pandemic. A case-control study involving 124 medical wards in 26 hospitals in Guangzhou and Hong Kong has identified six independent risk factors of super-spreading nosocomial outbreaks of SARS: minimum distance between beds < 1 m, performance of resuscitation, staff working while experience symptoms, and SARS patients requiring oxygen therapy or NPPV, whereas availability of washing or changing facilities for staff was a protective factor.\textsuperscript{64} Good hand and respiratory hygiene in 2003 led to significant reduction of common respiratory viral infections in the community in Hong Kong.\textsuperscript{65}

Several measures are recommended by the WHO in the context of pandemic A(H1N1) and other epidemics. These include maintaining standard and droplet precautions among the health-care workers (HCWs) at all levels of health care, emphasizing respiratory etiquette and hand hygiene, cohorting, adequate room ventilation, and separating a minimum distance of ≥ 1 m between patients when providing routine care to patients infected with pandemic H1N1 influenza and those with influenza-like symptoms.\textsuperscript{30,66} Recent data suggest that surgical masks are as effective as N95 masks for respiratory protection of HCWs in the routine care of hospitalized patients during seasonal influenza.\textsuperscript{67,68} It is also important to limit the number of HCWs/family members/visitors exposed to the patient with pandemic A(H1N1), in addition to implementing triage, early recognition, and reporting of pandemic A(H1N1) infection. In addition, it is important to monitor health of HCWs exposed to patients with pandemic A(H1N1), whereas HCWs with symptoms should stay at home. Vulnerable groups at high risk for complications of pandemic A(H1N1) infection should carefully follow recommended infection-control measures. In addition, alternatives such as reassignment to other duties should be considered. Antiviral prophylaxis should follow local policy.\textsuperscript{66}

When performing aerosol-generating procedures (eg, aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy), HCWs should be aware that these procedures have been associated with increased risk of infection transmission and should upgrade to airborne infection control precautions, including the use of N95 mask (Table 4).\textsuperscript{66} It is important to note that substantial exposure to exhaled air occurs within 0.4-m and 1-m radius of patients receiving oxygen therapy via Hudson mask and during application of NPPV, respectively.\textsuperscript{66,71} Geographically targeted nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, and restrictions on travel, are useful measures in controlling an influenza pandemic at its early phase.\textsuperscript{72}

Pandemic vaccine is an important strategy for control of pandemic A(H1N1) disease but the efficacy of this modality is limited by shortage of supply due to limited production capacity. If vaccines were available soon enough, it has been estimated that vaccination of children, followed by adults, reaching 70% overall coverage, in addition to high-risk and essential workforce groups, could mitigate a severe epidemic.\textsuperscript{73}

\begin{table}[h]
\centering
\caption{Airborne Precautions To Be Followed When Performing Aerosol-Generating Procedures\textsuperscript{66}}
\begin{tabular}{l}
\hline
Wear a facial particulate respirator (eg, EU FFP2, US NIOSH-certified N95), eye protection (eg, goggles or a face shield); a clean, nonsterile, long-sleeved gown; and gloves (some of these procedures require sterile gloves).  
Perform procedures in an adequately ventilated room (> 12 air changes per h) 
Avoid permitting unnecessary individuals into the room 
Perform hand hygiene before and after patient contact and after removal of personal protective equipment \\
EU FFP2 = European Union Filtering Face-Piece Class 2; NIOSH = National Institute for Occupational Safety and Health. \\
\hline
\end{tabular}
\end{table}
The priority groups to receive the pandemic vaccine are listed in Table 5.74 Because the pandemic virus is new, both nonclinical and clinical trials are being conducted to gain essential information on immune response and safety. Outcomes of trials completed to date suggest that pandemic vaccines are as safe as seasonal influenza vaccines. The WHO advises all countries administering pandemic vaccines to conduct intensive monitoring for safety and to report adverse events.75

In summary, antiviral agents and pandemic vaccines are important modalities in the control of a pandemic, but their efficacy is limited by timing of administration and supply. Oxygen therapy and NPPV should be applied in health-care facilities with good ventilation and respiratory protection for the HCWs, but most patients with severe respiratory failure will require IMV. A lung-protective ventilation strategy and a conservative fluid management approach are recommended for patients with ARDS. Rescue therapies, including ECMO, may be considered only after application of standard ICU management practices. Low-dose systemic steroids may be considered for patients with refractory septic shock. The role of passive immunotherapy and immunomodulating agents, such as IV Ig, statins, gemfibrozil, and NAC, requires further investigations. Nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, good community hygiene, and restrictions on travel, are useful measures in controlling an influenza pandemic during the early phase.

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