MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

MMWR Dispatch
Vol. 58 / July 10, 2009

Intensive-Care Patients With Severe Novel Influenza A (H1N1) Virus Infection — Michigan, June 2009

In April 2009, CDC reported the first two cases in the United States of human infection with a novel influenza A (H1N1) virus (*1*). As of July 6, a total of 122 countries had reported 94,512 cases of novel influenza A (H1N1) virus infection, 429 of which were fatal; in the United States, a total of 33,902 cases were reported, 170 of which were fatal.* Cases of novel influenza A (H1N1) virus infection have included rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of acute respiratory distress syndrome (ARDS), and prolonged intensive care unit (ICU) admission (*2*). Since April 26, communitywide transmission of novel influenza A (H1N1) virus has occurred in Michigan, with 655 probable and confirmed cases reported as of June 18 (Michigan Department of Community Health [MDCH], unpublished data, 2009). This report summarizes the clinical characteristics of a series of 10 patients with novel influenza A (H1N1) virus infection and ARDS at a tertiary-care ICU in Michigan. Of the 10 patients, nine were obese (body mass index [BMI] ≥30), including seven who were extremely obese (BMI ≥40); five had pulmonary emboli; and nine had multiorgan dysfunction syndrome (MODS). Three patients died. Clinicians should be aware of the potential for severe complications of novel influenza A (H1N1) virus infection, particularly in extremely obese patients.

The surgical intensive care unit (SICU) at the University of Michigan Health System (UMHS) specializes in the evaluation of adult patients with severe ARDS for advanced mechanical ventilation and possible extracorporeal membrane oxygenation (ECMO). During May 26–June 18, the unit received 13 patients for evaluation from outlying hospitals, 10 of whom were confirmed to have novel influenza A (H1N1) virus infection by testing of respiratory specimens with real-time reverse transcription–polymerase chain reaction (rRT-PCR) at MDCH and CDC. Direct immunofluorescent antibody staining at UMHS was negative for influenza A in all 10 patients. Viral culture at UMHS was positive for influenza A in two patients. All 10 patients were referred to the SICU because of severe hypoxemia, ARDS, and an inability to achieve adequate oxygenation with conventional ventilation modalities. Medical records of all 10 patients were reviewed for demographics, case characteristics, clinical findings, and clinical course.

Illness onset of the 10 patients occurred during May 22–June 13. The median age was 46 years (range: 21–53 years); nine patients were obese, including seven who were extremely obese (Table). In the three fatal cases, the time from illness onset to death ranged from 17 to 30 days. Four patients received steroids during their illness before transfer to the SICU; two with asthma received oral steroids as outpatients during the initial evaluation and treatment of their acute respiratory illness (one was on chronic oral steroids for underlying lung disease, and one without chronic pulmonary disease was prescribed oral steroids and oral antimicrobials). Five patients received intravenous corticosteroids during their SICU hospitalization: four for treatment of severe vasopressor-dependent refractory septic shock, and one for continuation of therapy for chronic pulmonary disease.

All 10 patients required initial advanced mechanical ventilation (high-frequency oscillatory or bilevel ventilation with high mean airway pressures [32–55 cm H_20]). Two patients required veno-venous ECMO support. Six required continuous renal replacement therapy (CRRT) for acute renal failure. Upon transfer to the SICU, five had elevated white blood cell counts, and one had a decreased white blood cell count. The median white blood cell count (WBC) was 9,500 cells/mm^3 (range: 3,700–19,700 cells/mm^3; normal: 4,000–10,000 cells/mm^3). All ten patients had elevated aspartate transaminase (AST) levels. The median AST level was 83.5 IU/L (range: 41–109 IU/L; normal: 8–30 IU/L). Six of the nine patients who were tested had elevated creatine phosphokinase (CPK) levels. The median CPK level was 999 IU/L (range: 51– 6,572 IU/L; normal: 38–240 IU/L). Nine patients were admitted to the

* Information on the number of cases of novel influenza A (H1N1) virus infection worldwide is available from the World Health Organization at http://www.who.int/csr/don/2009_07_06/en/index.html. Information on the number of cases of novel influenza A (H1N1) virus infection in the United States is available from CDC at http://www.cdc.gov/h1n1flu/update.htm.

TABLE. Selected characteristics of intensive-care patients with severe novel influenza A (H1N1) virus infection — Michigan, June 2009

Patient	Age (yrs)	Sex	Underlying conditions	Initial signs or symptoms	BMI*	No. days between onset and first hospitalization	No. days between illness onset and SICU† admission	Advanced mechanical ventilation	Diagnosis		Vaso-pressors	Outcome**
									PE§	MODS¶		
1	28	M	Asthma	High fever, cough, sore throat that progressed to blood-tinged sputum, decreasing mental status	34.2	7	8	HFOV††	Yes	Yes	Yes	Death
2	21	M	None	Fever, sore throat, dry cough, sneezing; progressed to tachypnea and dyspnea	50.5	7	8	Bilevel	Yes	Yes	Yes	Improved, transferred
3	48	F	Asthma, smoker	Shortness of breath, rhinorrhea, non-productive cough	58.9	5	9	HFOV	No	Yes	Yes	Improved, transferred
4	35	M	None	Upper respiratory tract illness symptoms	51.7	6	8	HFOV	Yes	No	No	Improved, transferred
5	43	M	None	Fever, cough, malaise, chills, sweats	48.7	4	5	HFOV to ECMO§§	Yes	Yes	Yes	Death
6	52	M	None	Sinus drainage, cough with clear sputum production, decreased appetite	NA¶¶	6	13	HFOV	Yes	Yes	Yes	Improved, transferred
7	44	M	None	Fever, productive cough with black/red sputum, nausea, vomiting, diarrhea	50.2	5	7	HFOV	No	Yes	Yes	Death
8	51	M	Granulomatous chronic lung disease	Fever, worsening dyspnea, rigors, nausea, vomiting, malaise	39.7	1	9	HFOV to ECMO	No	Yes	Yes	ECMO plus ventilator
9	53	M	None	Fever, chills, cough, shortness of breath	38.5	7	16	HFOV	No	Yes	Yes	Improved, transferred
10	53	M	None	Fever, cough	47.8	6	6	HFOV	No	Yes	Yes	HFOV

* Body mass index. Based on admitting weight at University of Michigan Health System surgical intensive care unit.
† Surgical intensive care unit.
§ Pulmonary emboli.
¶ Multiorgan dysfunction syndrome.
** As of July 8, 2009.
†† High-frequency oscillatory ventilation.
§§ Extracorporeal membrane oxygenation.
¶¶ Not available. Height unknown; weight = 72 kg.

SICU with MODS, and nine manifested septic shock requiring vasopressor support. All 10 patients required tracheostomy.

Chest radiograph findings in all 10 patients were abnormal, with bilateral infiltrates consistent with severe multilobar pneumonia or ARDS. Computed tomography (CT) of the chest confirmed pulmonary emboli in four patients at admission to the SICU and in one additional patient who deteriorated 6 days after admission to the SICU. A hypercoagulable state was evident in two additional patients. One of these patients had frequent clotting of the CRRT circuit despite regional citrate anticoagulation. Another patient had bilateral iliofemoral deep venous thromboses, necessitating systemic heparin anticoagulation. None of the 10 patients had evidence of concomitant disseminated intravascular coagulation by laboratory studies.

As of July 8, none of the 10 patients had evidence of bacterial infection after admission to the SICU or in subsequent blood, bronchoalveolar lavage, or urine cultures. All patients received antibiotic therapy upon admission to the initial hospitals, and broad spectrum antibiotics were continued upon transfer to the SICU.

The timing of antiviral treatment initiation was difficult to determine because patients were transferred from other hospitals; however, the estimated median number of days from illness onset to initiation of antiviral treatment was 8 days (range: 5–12 days). During their care at the SICU, all 10 patients were administered oseltamivir and amantadine beyond the standard 5-day course, including higher-dose oseltamivir (up to 150 mg orally twice a day), with dose adjustment for decreased renal function.

As of July 8, one patient remained in the SICU requiring ECMO, one remained on advanced mechanical ventilation, five were transferred back to the referring facility in stable condition, and three had died. Autopsies were performed on two patients; results in both patients confirmed bilateral severe hemorrhagic viral pneumonitis with interstitial inflammation and diffuse alveolar damage and concurrent bilateral pulmonary emboli.

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Editorial Note: This report describes the clinical findings of a limited series of patients with novel influenza A (H1N1) virus infection and refractory ARDS admitted to a tertiary-care ICU for advanced mechanical ventilation. This patient group represents the most severely ill subset of persons with novel influenza A (H1N1) virus infection and is notable for the predominance of males, the high prevalence of obesity (especially extreme obesity), and the frequency of clinically significant pulmonary emboli and MODS. All required advanced mechanical ventilator support, reflecting severe pulmonary damage. The pulmonary compromise described in this report suggests that severe pulmonary damage occurred as a result of primary viral pneumonia. Although data are not available, this damage also might be attributable to secondary host immune responses (e.g., through cytokine dysregulation triggered by high viral replication). However, bacterial coinfection in the lung not identified by blood culture or bronchoalveolar lavage cannot be excluded.

Only three of the patients in this series had underlying conditions associated with a higher risk for seasonal influenza complications. Conditions associated with an increased risk for complications from seasonal influenza include extremes of age, pregnancy, chronic underlying medical conditions (e.g., pulmonary, cardiovascular, hepatic, hematologic, neurologic, and neuromuscular conditions and metabolic disorders or immunosuppression), long-term aspirin therapy in persons aged ≤18 years, and being a resident of a nursing home or other chronic-care facility (*3*). However, fatal disease associated with novel influenza A (H1N1) virus infection has occurred among persons without these conditions who previously were healthy (*2*).

The high prevalence of obesity in this case series is striking. Whether obesity is an independent risk factor for severe complications of novel influenza A (H1N1) virus infection is unknown. Obesity has not been identified previously as a risk factor for severe complications of seasonal influenza. In a mouse model, diet-induced obese mice had significantly higher mortality when infected with seasonal influenza virus compared with their leaner counterparts (*4*). In addition, extremely obese patients have a higher prevalence of comorbid conditions that confer higher risk for influenza complications, including chronic heart, lung, liver, and metabolic diseases.

One study of patients admitted to critical-care units indicated that obesity was an independent risk factor for mortality (*5*). A meta-analysis concluded that prolonged duration of mechanical ventilation and longer SICU length of stay, but not mortality, are associated with obesity (*6*). Another study reported that extremely obese ICU patients had higher rates of mortality, nursing home admission, and ICU complications compared with moderately obese patients (BMI 30–39) (*7*). Further investigations of the role of extreme obesity and accompanying comorbidities in severely ill patients with novel influenza A (H1N1) virus infection are needed.

Pulmonary emboli are not known to be a common complication of ARDS or of sepsis syndrome, but both ARDS and sepsis represent hypercoagulable states (*8*). Pulmonary emboli were not noted in patients hospitalized with novel influenza A (H1N1) virus infection in Mexico (*3*). One clinical study did not identify any increased risk for pulmonary embolism with seasonal influenza virus infection (*9*). However, a report of two patients with rapidly progressive hypoxemia associated with influenza A (H3N2) virus infection noted that they received a diagnosis of acute pulmonary embolism (*10*). Clinicians providing care to patients with novel influenza A (H1N1) virus infection should be aware of the potential for patients with ARDS to develop a hypercoagulable state and for pulmonary emboli to cause severe complications, including fatal outcomes.

Two observational studies have demonstrated a reduction in mortality with oseltamivir treatment among hospitalized patients with seasonal influenza compared with untreated patients (*11,12*). Although early antiviral treatment (<48 hours from illness onset) is optimal to reduce illness among outpatients with seasonal influenza (*13*), a reduction in mortality of hospitalized persons with seasonal influenza or avian influenza A (H5N1) virus infection was reported even when oseltamivir treatment was initiated later (*11,14*). Early antiviral treatment of hospitalized patients with suspected influenza is recommended, including for patients admitted ≥48 hours after illness onset (*13*).

The patients in this series received higher oseltamivir dosing and longer duration of treatment than standard therapy. Data to inform clinical guidance are needed on viral shedding, pharmacokinetics, and clinical effectiveness of standard versus higher-dose oseltamivir treatment and on optimal duration of therapy for patients, including obese persons, with severe or progressive novel influenza A (H1N1) virus infection. Limited data for seasonal influenza treatment suggest that doubling the oseltamivir dose is well-tolerated with a comparable adverse event profile as the standard adult dose (75 mg orally twice a day) (*15*). Higher oseltamivir dosing and longer duration of treatment has been suggested for H5N1 (avian influenza) patients with severe pulmonary disease (*14*). Until additional data are available, higher oseltamivir dosage (e.g., 150 mg orally

twice a day for adults) or extending the duration of treatment can be considered for severely ill hospitalized patients with novel influenza A (H1N1) virus infection.

Further characterization of severe cases of novel influenza A (H1N1) virus infection in the United States and worldwide is needed to determine the frequency of the findings from this limited case-series. Clinicians caring for patients with suspected novel influenza A (H1N1) virus infection should monitor them closely for rapid clinical deterioration, especially with regard to increasing oxygenation requirements and potential for development of complications (e.g., respiratory failure, ARDS, multiorgan failure, septic shock, and pulmonary emboli). Empiric antiviral treatment is recommended for all hospitalized patients at admission with suspected novel influenza A (H1N1) virus infection,[†] including persons who have received a diagnosis of community-acquired pneumonia. Empiric antibiotic agents also should be used as appropriate for suspected bacterial infection. Depending on the antiviral susceptibilities of circulating influenza A virus strains, either zanamivir monotherapy or combination therapy with oseltamivir (for treatment of novel influenza A [H1N1] virus infection) and rimantadine (for treatment of oseltamivir-resistant seasonal influenza A [H1N1]) might be indicated in hospitalized patients until final virus identification is available. In communities in which novel influenza A (H1N1) virus is the predominant circulating influenza virus, oseltamivir or zanamivir should be administered as early as possible to hospitalized patients with suspected novel influenza A (H1N1) virus infection, even before diagnostic testing results are available. Clinicians should be aware that negative results of rapid influenza diagnostic tests, immunoflouresence, or viral culture do not exclude the possibility of novel influenza A (H1N1) virus infection. Although five patients in this case-series received corticosteroids, their role in the management of severely ill patients with novel influenza A (H1N1) virus infection is unclear, and routine corticosteroid use is not recommended.[§]

Many hospitalized patients with novel influenza A (H1N1) virus infection have had underlying comorbidities recognized to be high-risk conditions for complications of seasonal influenza. However, clinicians should be aware that severe illness and fatal outcomes also can occur in patients without known risk factors for complications of seasonal influenza, including persons with extreme obesity.

[†] Interim guidance on antiviral recommendations for patients with novel influenza A (H1N1) virus infection and their close contacts is available from CDC at http://www.cdc.gov/h1n1flu/recommendations.htm.

[§] Initial guidance on the clinical management of patients with novel influenza A (H1N1) virus infection is available from the World Heallth Organization at http://www.who.int/csr/resources/publications/swineflu/clinical_management H1N1_21_May_2009.pdf.

Acknowledgment

This report is based, in part, on contributions from C Miller, PhD, Michigan Department of Community Health.

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