MEDICAL PROGRESS

Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection

Writing Committee of the WHO Consultation on Clinical Aspects
of Pandemic (H1N1) 2009 Influenza*

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DURING THE SPRING OF 2009, A NOVEL INFLUENZA A (H1N1) VIRUS OF swine origin caused human infection and acute respiratory illness in Mexico.[1,2] After initially spreading among persons in the United States and Canada,[3,4] the virus spread globally, resulting in the first influenza pandemic since 1968 with circulation outside the usual influenza season in the Northern Hemisphere (see the Supplementary Appendix, available with the full text of this article at NEJM.org). As of March 2010, almost all countries had reported cases, and more than 17,700 deaths among laboratory-confirmed cases had been reported to the World Health Organization (WHO).[5] The number of laboratory-confirmed cases significantly underestimates the pandemic's impact. In the United States, an estimated 59 million illnesses, 265,000 hospitalizations, and 12,000 deaths had been caused by the 2009 H1N1 virus as of mid-February 2010.[6] This article reviews virologic, epidemiologic, and clinical data on 2009 H1N1 virus infections and summarizes key issues for clinicians worldwide.

VIRAL CHARACTERISTICS

Pandemic 2009 H1N1 virus derives six genes from triple-reassortant North American swine virus lineages and two genes (encoding neuraminidase and matrix proteins) from Eurasian swine virus lineages.[4] Although the 2009 H1N1 virus is antigenically distinct from other human and swine influenza A (H1N1) viruses,[4] strains of this virus have been antigenically homogeneous, and the A/California/7/2009 strain that was selected for pandemic influenza vaccines worldwide is antigenically similar to nearly all isolates that have been examined to date.[7] Multiple genetic groups have been recognized, including one recently predominant lineage,[8] but any possible clinical importance of different lineages remains uncertain. Reassortment has not occurred with human influenza viruses to date. The level of pulmonary replication of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses in experimentally infected animals,[9-11] but the 2009 pandemic strain generally lacks mutations that are associated with increased pathogenicity in other influenza viruses (Table 1 in the Supplementary Appendix).

EPIDEMIOLOGY

INFECTION, ILLNESS, AND DISEASE BURDEN

Most illnesses caused by the 2009 H1N1 virus have been acute and self-limited, with the highest attack rates reported among children and young adults. The relative sparing of adults older than 60 years of age[3,12,13] is presumably due to the exposure

of persons in this age group to antigenically related influenza viruses earlier in life, resulting in the development of cross-protective antibodies (Table 2 in the Supplementary Appendix).[10,14]

Rates of illness from 2009 H1N1 virus infection have varied, but during one outbreak in New Zealand, the attack rate of illness was estimated at 7.5%, and the attack rate of overall infection was estimated at 11%.[15] An estimated one third of infections in one boarding school were subclinical.[16] After the peak of a second wave of infection in Pittsburgh, the seroprevalence of hemagglutination-inhibition antibody suggested that about 21% of all persons and 45% of those between the ages of 10 and 19 years had become infected.[17]

The overall case fatality rate has been less than 0.5%, and the wide range of estimates (0.0004 to 1.47%) reflects uncertainty regarding case ascertainment and the number of infections.[18-20] The case fatality rate for symptomatic illness was estimated to be 0.048% in the United States[21] and 0.026% in the United Kingdom.[13] In contrast to seasonal influenza, most of the serious illnesses caused by the pandemic virus have occurred among children and nonelderly adults, and approximately 90% of deaths have occurred in those under 65 years of age.

Rates of hospitalization and death have varied widely according to country.[22] Hospitalization rates have been highest for children under the age of 5 years,[22] especially those under the age of 1 year, and lowest for persons 65 years of age or older.[23] In the United States, among patients who were hospitalized with pandemic influenza, 32 to 45% were under the age of 18 years.[23,24] Approximately 9 to 31% of hospitalized patients have been admitted to an intensive care unit (ICU), where 14 to 46% of patients have died.[23-27] The overall case fatality rate among hospitalized patients appears to have been highest among those 50 years of age or older and lowest among children.[1,13,23,27]

TRANSMISSION AND OUTBREAKS

The mechanisms of person-to-person transmission of the 2009 H1N1 virus appear to be similar to those of seasonal influenza, but the relative contributions of small-particle aerosols, large droplets, and fomites are uncertain. Rates of secondary outbreaks of illness vary according to the setting and the exposed population, but estimates range from 4 to 28%. Household transmission is highest among children and lowest among adults over 50 years of age.[28,29] In the United Kingdom and the United States, the rates of secondary outbreaks in households were 7% and 13%, respectively, with children at increased risk for infection by a factor of two to four.[16,28] Many outbreaks have occurred in schools, day-care facilities, camps, and hospitals.[16,30,31] Estimates of the basic reproduction number (the mean number of secondary cases of infection transmitted by a single primary case in a susceptible population) generally range from 1.3 to 1.7 according to the setting, which are similar to or slightly higher than the estimates for seasonal influenza,[20,32,33] but may be as high as 3.0 to 3.6 in outbreaks in crowded schools.[31]

RISK GROUPS AND RISK FACTORS FOR SEVERE DISEASE

Approximately one quarter to one half of patients with 2009 H1N1 virus infection who were hospitalized or died had no reported coexisting medical conditions.[13,23,26,27,34] Underlying conditions that are associated with complications from seasonal influenza also are risk factors for complications from 2009 H1N1 virus infection (Table 1). Pregnant women (especially those in the second or third trimester), women who are less than 2 weeks post partum, and patients with immunosuppression or neurologic disorders have also been overrepresented among those with severe 2009 H1N1 virus infection.[23,24,26,35] Although pregnant women represent only 1 to 2% of the population, among patients with 2009 H1N1 virus infection, they have accounted for up to 7 to 10% of hospitalized patients,[22-24] 6 to 9% of ICU patients,[26,27] and 6 to 10% of patients who died.[23,35] There appears to be a particularly increased risk of death among infected women during the third trimester,[36] especially among those who have coinfection with the human immunodeficiency virus (HIV).[37]

Among patients with severe or fatal cases of 2009 H1N1 virus infection, severe obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥35) or morbid obesity (body-mass index, ≥40) has been reported at rates that are higher by a factor of 5 to 15 than the rate in the general population.[23,26,27,38] In addition to obesity-associated risks, such as cardiovascular disease and diabetes, possible adverse immunologic effects and management problems related to obesity may be contributory.

In certain disadvantaged groups, including indigenous populations of North America and the

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Table 1. Risk Factors for Complications of or Severe Illness with 2009 H1N1 Virus Infection.*	
Risk Factor	Examples and Comments
Age <5 yr	Increased risk especially for children <2 yr of age; highest hospitalization rates among children <1 yr
Pregnancy	Risk of hospitalization increased by a factor of 4 to 7, as compared with age-matched nonpregnant women, with highest risk in third trimester
Chronic cardiovascular condition	Congestive heart failure or atherosclerotic disease; hypertension not shown to be an independent risk factor
Chronic lung disorder	Asthma or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Neurologic condition	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Associated with HIV infection, organ transplantation, receipt of chemotherapy or corticosteroids, or malnutrition
Morbid obesity†	Suggested but not yet proved to be an independent risk factor for complications requiring hospitalization or ICU admission and possibly for death
Hemoglobinopathy	Sickle cell anemia
Chronic renal disease	Renal dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Long history of smoking	Suggested but not yet proved to be an independent risk factor
Long-term aspirin therapy in children	Risk of Reye's syndrome; drugs containing salicylates should be avoided in children with influenza
Age ≥65 yr	Highest case fatality rate but lowest rate of infection

* COPD denotes chronic obstructive pulmonary disease, HIV human immunodeficiency virus, and ICU intensive care unit.
† Morbid obesity is defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40 or more.

Australasia–Pacific region, rates of severe 2009 H1N1 virus infection have been increased by a factor of five to seven.[23,26,27] Factors that may contribute to this trend include crowding; an increased prevalence of underlying medical disorders, alcoholism, and smoking[27]; delayed seeking of or access to care; and possibly unidentified genetic factors. Aboriginal status, the presence of coexisting conditions, and delayed receipt of antiviral therapy were independently associated with severe disease in one Canadian study.[39]

PATHOGENESIS

VIRAL REPLICATION

Studies of hemagglutinin-receptor binding indicate that the 2009 H1N1 virus is well adapted to mammalian hosts and binds to both α2,6-linked cellular receptors (as do seasonal influenza viruses) and α2,3-linked receptors,[40] which are present in the conjunctivae, distal airways, and alveolar pneumocytes. The 2009 H1N1 virus shows increased ex vivo replication in human bronchial epithelium at 33°C, as compared with a seasonal influenza virus,[41] and is also characterized by increased replication and pathological changes in the lungs of nonhuman primates and increased replication in ex vivo human lung tissues.[10] Such observations may help explain the ability of the virus to cause severe viral pneumonitis in humans.

In uncomplicated illness, nasopharyngeal viral RNA loads peak on the day of onset of symptoms and decline gradually afterward.[42] However, viral replication may be more prolonged than in seasonal influenza, and on day 8 of uncomplicated illness in adults and teenagers, nasopharyngeal swabs have yielded viral RNA in 74% of patients and infectious virus in 13% of patients.[30,43] Infectious virus has been recovered from children up to 6 days after the resolution of fever.

Nasopharyngeal viral loads are increased in patients with severe pneumonia and decline slowly in critically ill patients.[44] Among intubated patients, viral RNA has been detected at higher levels and for longer periods in the lower respiratory tract than in the upper respiratory tract.[45] Viral RNA may be detected in secretions from the lower respiratory tract up to 28 days after the onset of

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severe pneumonia[46] and longer in patients with immunosuppression. Viral RNA and (infrequently) infectious virus have been detected in the stool of patients, and viral RNA has been detected infrequently in blood or urine of patients,[44,45] although one small study reported the frequent detection of viral RNA in blood, regardless of the severity of the illness.[47]

IMMUNE RESPONSES

The patterns of innate and adaptive immune responses in patients with 2009 H1N1 virus infection are incompletely characterized. Seasonal and pandemic 2009 H1N1 viruses induce similar proinflammatory mediator responses in human cells in vitro[41] but do not activate effective innate antiviral responses in human dendritic cells and macrophages.[48] Increased plasma levels of interleukin-15, interleukin-12p70, interleukin-8, and especially interleukin-6 may be markers of critical illness.[45,47] High systemic levels of interferon-γ and mediators involved in the development of type 1 and type 17 helper T-cell responses have been reported in hospitalized patients.[47] As compared with patients with less severe illness, patients who died or who had the acute respiratory distress syndrome (ARDS) had increased plasma levels of interleukin-6, interleukin-10, and interleukin-15 throughout the illness and of granulocyte colony-stimulating factor, interleukin-1α, interleukin-8, interferon-inducible protein 10, and tumor necrosis factor α during the late phase of illness.[44] Levels of serum hemagglutination-inhibition and neutralizing antibodies rise promptly after infection in immunocompetent persons,[14] but symptomatic reinfections have been reported.[49]

PATHOLOGICAL FEATURES

In fatal cases of H1N1 virus infection, the most consistent histopathological findings are varying degrees of diffuse alveolar damage with hyaline membranes and septal edema, tracheitis, and necrotizing bronchiolitis[50-52] (Fig. 1). Other early changes include pulmonary vascular congestion and, in some cases, alveolar hemorrhage. In addition to infecting cells in upper respiratory and tracheobronchial epithelium and mucosal glands, the 2009 H1N1 virus targets alveolar lining cells (type I and II pneumocytes)[50] (Fig. 2). Viral antigens have been readily detectable in about two thirds of patients who died within 10 days after the onset of illness and may be detectable for

more than 10 days.[50] Other autopsy findings include hemophagocytosis, pulmonary thromboemboli and hemorrhage, and myocarditis.[44] Bronchopneumonia with evidence of bacterial coinfection has been found in 26 to 38% of fatal cases.[50-52]

CLINICAL FEATURES

INCUBATION PERIOD

The incubation period appears to be approximately 1.5 to 3 days, which is similar to that of seasonal influenza.[18,28,31,32,53] In a minority of patients, the period may extend to 7 days.

CLINICAL PRESENTATION

Infection with the 2009 H1N1 virus causes a broad spectrum of clinical syndromes, ranging from afebrile upper respiratory illness to fulminant viral pneumonia. Mild illness without fever has been reported in 8 to 32% of infected persons.[53] Most patients presenting for care have typical influenza-like illness with fever and cough, symptoms that are sometimes accompanied by sore throat and rhinorrhea (Table 2).[2,24,34,53-56] Systemic symptoms are frequent. Gastrointestinal symptoms (including nausea, vomiting, and diarrhea) occur more commonly than in seasonal influenza, especially in adults.[3,57] Dyspnea, tachypnea in children, chest pain, hemoptysis or purulent sputum, prolonged or recurrent fever, altered mental status, manifestations of dehydration, and reappearance of lower respiratory tract symptoms after improvement are signs of progression to more severe disease or complications.[2,25-27,58]

The principal clinical syndrome leading to hospitalization and intensive care is diffuse viral pneumonitis associated with severe hypoxemia, ARDS, and sometimes shock and renal failure.[26,27] This syndrome has accounted for approximately 49 to 72% of ICU admissions for 2009 H1N1 virus infection.[26,27] Rapid progression is common, typically starting on day 4 to 5 after the onset of illness, and intubation is often necessary within 24 hours after admission. Currently available prognostic algorithms for community-acquired pneumonia, such as CURB-65 (a measure of confusion, urea nitrogen, respiratory rate, and blood pressure and an age of 65 years or older), may not apply.[58] Radiographic findings commonly include diffuse mixed interstitial and alveolar infiltrates, although lobar and multilobar distributions occur, particularly in patients with bacterial
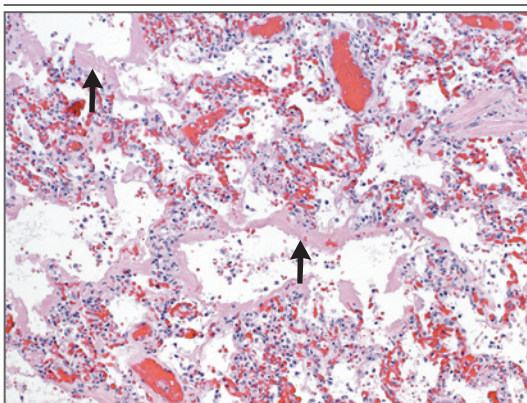
Figure 1. Lung-Tissue Specimen Obtained at Autopsy from a 13-Year-Old Boy after a 7-Day Clinical Course of 2009 H1N1 Virus Infection.

The specimen shows diffuse alveolar damage with hyaline membrane formation (arrows) and hemorrhage (hematoxylin and eosin). The patient, who had cerebral palsy, received oseltamivir for 2 days before he died. No evidence of bacterial coinfection was present. (Courtesy of Dr. Sherif R. Zaki, CDC.)
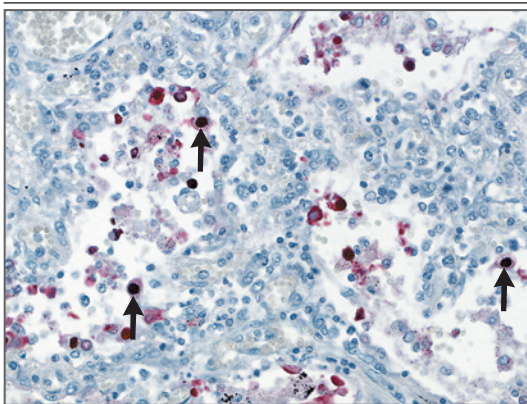

Figure 2. Immunostaining of Influenza Viral Antigens in Lung-Tissue Specimen Obtained at Autopsy from a 55-Year-Old Woman after a 7-Day Clinical Course of 2009 H1N1 Virus Infection.

The specimen shows viral antigens (red color) in the nuclei of alveolar-lining cells (arrows), including type I and type II pneumocytes. Many infected cells have detached and are seen in alveolar spaces. Evidence of *Streptococcus pneumoniae* coinfection was also present in the patient, who had Down's syndrome and hepatitis B infection (mouse anti-influenza nucleoprotein monoclonal antibody with naphthol fast-red substrate and hematoxylin counterstain). (Courtesy of Dr. Sherif R. Zaki, CDC.)

coinfection. Chest computed tomography has shown multiple areas of ground-glass opacities, air bronchograms, and alveolar consolidation, par-

ticularly in the lower lobes.[24] Small pleural effusions occur, but an increased volume suggests volume overload or possibly empyema. Pulmonary thromboemboli have occurred in some critically ill patients with ARDS.

Other important syndromes include severe, prolonged exacerbation of chronic obstructive pulmonary disease (COPD) or asthma (in about 14 to 15% of patients), bacterial coinfections, and decompensation of serious coexisting conditions (Table 1).[23,26,27] Among hospitalized patients with 2009 H1N1 infection, a history of asthma has been reported in 24 to 50% of children and adults, and COPD in 36% of adults.[23,24] Bacterial pneumonia, usually caused by *Staphylococcus aureus* (often methicillin-resistant), *Streptococcus pneumoniae*, *S. pyogenes*, and sometimes other bacteria, has been suspected or diagnosed in 20 to 24% of ICU patients and has been found in 26 to 38% of patients who died, often in association with a short clinical course.[26,27,50,52] Death from 2009 H1N1 virus and bacterial coinfection has occurred within 2 to 3 days in some cases. Sporadic cases of neurologic manifestations (confusion, seizures, unconsciousness, acute or postinfectious encephalopathy, quadriparesis, and encephalitis)[59] and myocarditis have been reported, including some fulminant cases.

Laboratory findings at presentation in patients with severe disease typically include normal or low-normal leukocyte counts with lymphocytopenia and elevations in levels of serum aminotransferases, lactate dehydrogenase, creatine kinase, and creatinine.[2,25,27] Myositis and rhabdomyolysis have occurred in severe cases. A poor prognosis is associated with increased levels of creatine kinase, creatinine, and perhaps lactate dehydrogenase, as well as with the presence of thrombocytopenia and metabolic acidosis (Table 3 in the Supplementary Appendix).[2]

SPECIAL POPULATIONS

Young children with 2009 H1N1 virus infection may have marked irritability, severe lethargy, poor oral intake, dehydration resulting in shock, and seizures.[56,60] Other complications include invasive bacterial coinfections, encephalopathy or encephalitis (sometimes necrotizing), and diabetic ketoacidosis.[59,61] Bronchiolitis in infants and croup in young children may require hospitalization but do not usually necessitate ICU care. Suspected transplacental transmission of the 2009 H1N1

Table 2. Symptom Profiles in Groups of Patients with Suspected or Confirmed Pandemic 2009 H1N1 Virus Infection Worldwide.*

Symptom	Mexico[54]		Japan[55]	United States[24]		Mexico[2]	China[53]	Argentina[34]	United Kingdom[56]
	All Inpatients and Outpatients (N=6376)†	Critically Ill Patients (N=255)	Laboratory-Confirmed Cases (N=217)	Hospitalized Patients <18 Yr Old (N=122)	Hospitalized Patients ≥18 Yr Old (N=150)	Critically Ill Patients (N=18)	Mildly Ill and Isolated Patients (N=426)	Hospitalized Patients <18 Yr Old (N=204)	Hospitalized Patients <17 Yr Old (N=78)
	number (percent)								
Temperature >38°C	2716 (43)	218 (85)	206 (95)	115 (94)	143 (95)	18 (100)	153 (36)	181 (89)	52 (81)
Myalgias	1900 (30)	80 (31)	41 (19)	22 (18)	76 (51)	8 (44)	43 (10)	6 (3)	20‡
Cough	2550 (40)	220 (86)	128 (59)	100 (82)	139 (93)	18 (100)	296 (70)	141 (69)	49 (73)
Headache	2480 (39)	75 (29)	28 (13)	24 (20)	68 (45)	4 (22)	83 (20)	6 (3)	19‡
Nasal congestion	1390 (22)	21 (8)	72 (33)	NA	NA	NA	68 (16)	NA	NA
Rhinorrhea	2104 (33)	63 (25)	72 (33)	55 (45)	48 (32)	5 (28)	101 (24)	63 (31)	45 (62)
Sore throat	1384 (22)	40 (16)	85 (39)	38 (31)	46 (31)	NA	156 (37)	8 (4)	26‡
Dyspnea	472 (7)	176 (69)	NA	52 (43)	110 (73)	18 (100)	NA	163 (80)§	30‡¶
Wheezing	NA	NA	NA	31 (25)	41 (27)	2 (11)	NA	24 (12)	20‡
Diarrhea	261 (4)	22 (9)	13 (6)	28 (23)	38 (25)	4 (22)	12 (3)	17 (8)	20‡
Abdominal pain or vomiting	625 (10)	26 (10)	5 (2)	39 (32)	39 (26)	NA	8 (2)	20 (10)	NA‖

* At the top of each column, the total number of study patients is indicated. However, many of the percentages were calculated with smaller denominators. NA denotes not available.
† Patients had either suspected or laboratory-confirmed cases of 2009 H1N1 virus infection.
‡ These numbers are percentages that were estimated from values in a figure in the published study.
§ These patients had hypoxemia.
¶ These patients had tachypnea.
‖ Of these patients, approximately 10% had abdominal pain, and 40% had vomiting.

virus has been reported,[62] and respiratory transmission from a symptomatic mother to a newborn can occur during the postpartum period. Newborn infants may also have apnea, tachypnea, cyanosis, and lethargy. Pregnant women are at increased risk for severe illness, spontaneous abortion, preterm labor and birth, and fetal distress.[35,36,57]

Afebrile or atypical presentations have occurred in pregnant women, patients with immunosuppression, those undergoing hemodialysis, and other risk groups (Table 1). Patients with severe immunosuppression are at increased risk for protracted viral replication and pneumonia.[63,64]

DIAGNOSIS

CLINICAL FACTORS

Clinical suspicion and the accuracy of diagnosis vary substantially, depending on whether the case occurs sporadically or during a recognized outbreak, when a typical presentation of influenza-like illness is likely to represent 2009 H1N1 virus infection. However, the wide clinical spectrum of 2009 H1N1 virus infection and its features that overlap with those of other common infections have sometimes led to the misdiagnosis of other potentially treatable infections (e.g., legionellosis, meningococcemia, leptospirosis, dengue, and malaria).[58] Coinfection with dengue or certain respiratory viruses (parainfluenza virus and respiratory syncytial virus) and detection of *S. pneumoniae* have been reported in some patients with severe 2009 H1N1 virus infection.[65] Coinfection with other respiratory viruses, including seasonal influenza virus, has also been reported.[34,65]

VIROLOGIC FACTORS

Viral RNA detection by conventional or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay remains the best method for the initial diagnosis of 2009 H1N1 virus infection.[58] Nasopharyngeal aspirates or swabs taken early after the onset of symptoms are suitable samples, but endotracheal or bronchoscopic aspirates have higher yields in patients with lower respiratory tract illness.[46,58,66] One study showed that among patients with detectable H1N1 viral RNA in bronchoscopic samples, 19% had negative upper respiratory tract samples.[66] Negative lower respiratory tract samples have been noted in 10% or more of patients with severe 2009 H1N1 virus infection. Consequently, negative results in single respira-

tory specimens do not rule out 2009 H1N1 virus infection, and repeated collection of multiple respiratory specimen types is recommended when clinical suspicion is high.

Commercially available rapid influenza antigen assays have poor clinical sensitivity (11 to 70%) for the detection of 2009 H1N1 virus in respiratory specimens and cannot differentiate among influenza A subtypes (Table 4 in the Supplementary Appendix). Consequently, negative test results should not be used to make decisions with respect to treatment or infection control. Direct or indirect immunofluorescence tests are less sensitive than RT-PCR.[66]

The 2009 H1N1 virus replicates in various cell types,[67] but isolation usually takes several days. Serologic assays (microneutralization and hemagglutination inhibition) that detect increases in antibody levels in paired serum samples provide a retrospective diagnosis; single high titers in serum samples from convalescent patients may be indicative of recent infection,[14] but routine testing of a single specimen to detect recent infection is not recommended.

CLINICAL MANAGEMENT

ANTIVIRAL THERAPY

The currently circulating 2009 H1N1 virus is susceptible to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) but is almost always resistant to amantadine and rimantadine.[3,10] Therapy with a neuraminidase inhibitor is especially important for patients with underlying risk factors, including pregnancy,[68] and those with severe or progressive clinical illness (Table 3).[69] Standard doses of oseltamivir or inhaled zanamivir can be used for the treatment of mild illness, unless viral resistance to oseltamivir has been documented or is suspected (e.g., because of chemoprophylaxis failure), in which case zanamivir is preferred.

Early therapy with oseltamivir in patients with 2009 H1N1 virus infection may reduce the duration of hospitalization[70] and the risk of progression to severe disease requiring ICU admission or resulting in death.[24,35,36] In one study involving 45 patients with 2009 H1N1 virus who had cancer or had undergone hematopoietic stem-cell transplantation, 18% had pneumonia and 37% were hospitalized; all patients received oseltamivir, and no deaths were reported.[71] Oseltamivir-

Table 3. Antiviral Therapy in Specific Subgroups of Patients.*

Subgroup of Patients	Antiviral Therapy	Comments
Patients at increased risk for severe or complicated illness	Start treatment with oseltamivir or inhaled zanamivir as soon as possible after the onset of illness if patient presents with uncomplicated illness.	Do not delay treatment pending laboratory diagnosis.
Patients with severe or progressive disease and hospitalized patients	Consider the use of an increased dose of oseltamivir (e.g., 150 mg twice daily) and an increased duration of treatment (e.g., 10 days). The use of intravenous peramivir or zanamivir (if available) provides reliable drug delivery, especially in critically ill patients.	Do not delay treatment pending laboratory diagnosis or stop treatment if initial test results are negative in suspected cases; treatment is warranted, even when delayed, whenever active viral replication is likely. Systemic corticosteroids are not recommended for routine treatment of lung injury.
Otherwise healthy patients with uncomplicated illness	Consider the use of oseltamivir or zanamivir, depending on clinical judgment and antiviral supply. Treatment is reasonable in patients presenting early (<48 hr) after the onset of febrile respiratory illness.	Instruct all patients to return for follow-up if signs or symptoms of progressive disease develop or if there is no improvement within 72 hours after symptom onset.
Neonates and young infants	Start weight-based oseltamivir (3.0 mg/kg/dose) once daily from birth to 13 days of age and twice daily from 14 days to 12 mo of age.	If an oral pediatric formulation of oseltamivir is not available, prepare a modified dose from hard capsules (www.tamiflu.com/hcp/dosing/extprep.aspx).
Pregnant women	Start oseltamivir or zanamivir as soon as possible after illness onset.	If antipyretic drugs are considered necessary, use acetaminophen (paracetamol); avoid the use of nonsteroidal antiinflammatory drugs, including aspirin, which have been associated with fetal risks and maternal bleeding.
Breast-feeding women	Start oseltamivir or zanamivir; breast-feeding can be continued.	Take appropriate infection-control precautions. Oseltamivir has been found in breast milk in laboratory animals.
Patients with immunosuppression	If oseltamivir is administered, consider an uninterrupted regimen of 10 days; inhaled zanamivir is an option for uncomplicated disease.	Monitor patients for the clearance of virus. If there is evidence of protracted replication, consider possible emergence of oseltamivir resistance.
Patients with suspected or proven oseltamivir-resistant virus	Start inhaled zanamivir in patients with uncomplicated illness; intravenous zanamivir (if available) should be used in patients with severe or progressive clinical illness.	The risk of oseltamivir resistance is increased among patients with prolonged illness, particularly those with severe immunosuppression receiving oseltamivir for an extended duration, and those in whom chemoprophylaxis has failed.

* Recommendations are based on the World Health Organization Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and Other Influenza Viruses.[69]

treated patients with HIV infection who were receiving highly active antiretroviral therapy had a clinical course similar to that in immunocompetent persons.[72] Deaths have occurred despite early therapy,[73] but the administration of oseltamivir even after an interval of more than 48 hours since the onset of illness has been associated with reduced rates of death among hospitalized patients infected with the 2009 H1N1 virus,[25] seasonal influenza virus, or H5N1 virus. Decisions regarding antiviral treatment should not await laboratory confirmation, and patients presenting with progressive illness more than 48 hours after the onset of illness should be treated empirically with oseltamivir as soon as possible. Patients with progressive or severe illness who have a negative initial test result for 2009 H1N1 virus should continue to receive therapy unless an alternative diagnosis is established.

In uncomplicated illness, the early use of oseltamivir is usually associated with prompt clearance of infectious 2009 H1N1 virus from the upper respiratory tract.[53] However, infectious virus has commonly been detected after the resolution of fever and has sometimes been detected after the completion of therapy,[30] and viral RNA of uncertain clinical significance may be detectable for up to 12 days after the onset of illness.[74] In one study, the independent risk factors for prolonged viral RNA detection were an age of less than 14 years, male sex, and an interval of more than 48 hours between the onset of illness and the start of oseltamivir treatment.[53]

In severely ill patients, viral RNA may be detectable in endotracheal aspirates for several weeks after the initiation of oseltamivir therapy.[45,46] An increased dose of the drug (e.g., 150 mg twice daily in adults) and particularly an increased duration of therapy (e.g., a total of 10 days) with avoidance of treatment interruptions are reasonable in patients with pneumonia or evidence of clinical progression.[69] Doses of up to 450 mg twice daily have been administered successfully in healthy adults, and controlled studies of higher-dose regimens are in progress. Higher weight-adjusted doses are also required in infants and young children to provide drug exposure similar to that in adults.[69,75] Bioavailability in critically ill patients receiving oseltamivir by nasogastric tube appears to be similar to that in patients with uncomplicated illness.[76] The tolerability and efficacy of inhaled zanamivir have not been ad-

equately studied in patients with severe influenza. However, the failure of inhaled zanamivir therapy to clear virus in patients with pneumonia has been reported.[63] Some seriously ill patients treated with inhaled zanamivir have had respiratory distress, and nebulized delivery of extemporaneously prepared solutions of zanamivir powder with its lactose carrier has been associated with lethal ventilator dysfunction.[77]

OSELTAMIVIR RESISTANCE

A His275Tyr mutation in viral neuraminidase confers high-level resistance to oseltamivir but not to zanamivir.[3,78] Most oseltamivir-resistant 2009 H1N1 viruses have been sporadic isolates from treated patients, particularly those with immunosuppression who received prolonged oseltamivir therapy[63,64] or those in whom postexposure oseltamivir chemoprophylaxis failed.[78] However, oseltamivir-resistant isolates have been found in patients without known exposure to oseltamivir and in limited clusters of cases associated with person-to-person transmission in otherwise healthy patients and those with immunosuppression.[78,79] Although in most cases oseltamivir-resistant variants have caused mild, self-limited illness, they have been associated with pneumonia in children and with severe, sometimes fatal illness in patients with immunosuppression.[64,78,80]

INTRAVENOUS NEURAMINIDASE INHIBITORS

Intravenous administration of zanamivir or peramivir provides rapid drug delivery at high levels (Table 5 in the Supplementary Appendix). The efficacy of intravenous peramivir appeared to be similar to that of oseltamivir in one study of adults hospitalized with seasonal influenza,[81] but peramivir is less active by a factor of at least 80 for oseltamivir-resistant viruses carrying the His275Tyr mutation than for oseltamivir-susceptible viruses. Intravenous zanamivir (if available) is the preferred option for hospitalized patients with suspected or documented oseltamivir-resistant 2009 H1N1 virus infection.[63,64,80] Both drugs are available on a compassionate-use basis for treating seriously ill patients, and peramivir was recently authorized for emergency use in hospitalized patients in the United States[81] and licensed for use in Japan.

General principles of clinical management and prevention are summarized in WHO[58] and country-specific guidelines and are reviewed in the Supplementary Appendix.

FUTURE DIRECTIONS

A large amount of information about the natural history and clinical management of 2009 H1N1 virus infection has been obtained in a remarkably short period of time, but considerable gaps remain. The uncertain evolution of this virus among humans and potentially other species highlights the need for continued virologic surveillance for antigenic changes, viral reassortment, antiviral resistance, and altered virulence. Improvements in the global capacity for detection of influenza viruses by molecular analysis, such as RT-PCR assay, and by viral isolation are needed. A simple, inexpensive, highly accurate rapid influenza diagnostic test that is easily deployable worldwide has yet to be developed. The burden and character of disease in low-resource settings are still incompletely understood,[82] especially with respect to disadvantaged populations, including marginalized, refugee, and aboriginal populations. Poverty, homelessness, illiteracy, recent immigration, language barriers, and cultural factors may impede access to care, with the potential for more serious outcomes of influenza. Thus, public health efforts reduce risk factors and to identify at-risk populations for the purpose of providing immunization and early care, including the use of antiviral drugs, should focus on social as well as clinical factors. Both experience with previous pandemics and recent modeling efforts indicate that the age bias observed for outbreaks of 2009 H1N1 virus infection may shift in coming months toward older persons, with implications for the allocation of public health resources.[83]

Major gaps exist in our understanding of viral transmission, pathogenesis of disease, genetic and other host factors related to susceptibility[84,85] or disease severity, and optimal management of severe illness. The development of new antiviral regimens with improved effectiveness, combinations with targeted adjunctive therapies (i.e., immunodulators and neutralizing antibodies or immunotherapy), and improved management of influenza-associated ARDS are priorities, along with better prevention, recognition, and treatment of invasive bacterial coinfections. Available findings highlight the importance of early use of antiviral drugs and antibiotics in the treatment of serious cases and of the potential value of influenza-specific and pneumococcal vaccines for prevention. Both the gaps in knowledge and the experience to date underline the urgent need for better international collaboration in clinical research, particularly in the case of diseases with pandemic potential, for which rapid detection, investigation, and characterization of clinical syndromes are prerequisites for improved mitigation of their public health consequences.

APPENDIX

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