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Novel H1N1 Influenza

Introduction/Overview

The novel H1N1 influenza pandemic differs in significant ways from typical seasonal influenza in demographics and epidemiology.¹ Its morbidity and mortality are most significant in the pediatric and younger adult population due to the novelty of the virus and resultant lack of immunity in this previously unexposed population. This review summarizes information current through November 1, 2009. Since the first cases in the United States were confirmed only six months ago, in mid-April 2009, additional scientific information has become available on an almost daily basis and further shapes our understanding of and approach to this disease.

Widespread media attention to the novel H1N1 influenza impact on the southern hemisphere, on U.S. preparedness efforts, and on the pandemic itself has resulted in high levels of public awareness and increased visits to the emergency department for evaluation.² Because severe disease and death are occurring in a significant number of individuals without predisposing factors, thorough understanding of this disease is essential to the emergency physician's ability to recognize, appropriately manage, and counsel affected patients.³ Even more important is the ability to differentiate those with severe illness from the less critically ill.

Epidemiology

The 2009 novel H1N1 influenza virus is characterized as “novel” because it is significantly different from seasonal influenza in its epidemiology.^{4,5} Ninety-four 2009 influenza A (H1N1) viruses have been antigenically described by the Centers for Disease Control and Prevention (CDC). All of these are related to World Health Organization (WHO) designated 2009 H1N1 vaccine virus, A/California/07/2009 (H1N1).⁶ The match between the novel H1N1 influenza vaccine virus and those characterized by the CDC during the US outbreak to date suggests that available vaccine will be protective for novel H1N1 influenza circulating in the United States. A study assessing pre-existing immunity showed only 4% of individuals younger than age 30 had cross-reactive circulating antibodies to H1N1, supporting the idea that there is virtually no immunity in the younger population. However, one-third of those older than age 60 had cross-reactive H1N1 antibodies due to prior exposure.⁷ As a result, illness is much more common in the unvaccinated pediatric and young adult population than in older age groups.

Worldwide, the WHO reports nearly 400,000 cases of laboratory-confirmed H1N1 as of October 11, 2009, with 4735 deaths. These numbers and the figures that follow throughout this article underestimate cases because many countries discontinued confirmatory laboratory testing as the disease became widespread.⁸ Current surveillance reports indicate rates well above baseline seasonal influenza rates. Surveillance has followed both influenza-like illness (ILI), defined as a combination of fever with either cough and/or sore throat, as well as acute respiratory illness (ARI), defined as two or more of fever, cough, sore throat, and rhinorrhea.⁹ The CDC recently updated its methodology to more accurately delineate H1N1-related morbidity and mortality by linking surveillance through

Executive Summary

- Younger patients have no cross-reactive antibodies and are more susceptible to H1N1.
- Hospitalization rate is highest in 0- to 17-year-old age group. Of those hospitalized, 25% require ICU, with a majority of these having underlying medical conditions.
- The contagious period is 2 days on average.
- Early antiviral treatment decreases complications and shortens duration of illness.

the Influenza-like Illness Network (ILINet) with Emerging Infections Program (EIP) data and correcting for local hospitalization levels and underreporting.¹⁰

Age. Experience from the southern hemisphere during the spring of 2009, showed the young to be the most affected by novel H1N1 influenza.^{8,11-13} Median patient age has been in the early 20s, with a preponderance in the 10- to 29-year-old age group.^{13,14}

Transmission Method. Infection control guidance is based on three transmission methods: droplet, contact with surfaces and bodily fluids, and aerosols in the immediate vicinity of the patient.^{15,16} Avoiding close contact (less than six feet) with infected individuals and meticulous attention to respiratory and hand hygiene are the best strategies for avoiding transmission.

Transmissibility. For ARI and ILI, the secondary attack rates within a household are approximately 18% and 10%, respectively, which is slightly less than is typical for seasonal influenza, though higher transmissibility was noted in Mexico.^{9,17} One study found a household secondary attack rate for H1N1 as high as 27.3%.¹⁸ Of individuals exposed on an airline flight, the secondary attack rate was highest (41%) in those 18–39 years old in closest physical proximity, with a much lower rate (21%) in those older than age 40.¹⁹

Contagious Period. The doubling time for cases is 2.4-3.1 days for novel H1N1 ILI, and 2.0-3.1 for ARI.⁹ The contagious period averages two days, ranging from one to four. Viral shedding (or infectiousness) begins a day prior to symptom onset, and may persist for 7 days, but is greatest in the first few days and when fever is high-

est. Immunocompromised individuals and young children may be infectious for longer periods.¹⁵

Outpatient Demand. There is concern for significantly increased demand for emergency department and ICU resources as a second pandemic wave threatens the world population.²⁰ U.S. surveillance through ILINet shows 43 states with widespread influenza activity as of November 14, 2009. Outpatient visits for ILI for that week were down to 5.5% (regional range 2.6%-7.9%). This figure is decreased from the high of 7.8% four weeks prior, but continues to be well above the national baseline rate of 2.3%.²¹

Hospitalized Patients. U.S. experience with hospitalization rates is just beginning to be published. As a result, experience in southern hemisphere countries provides the only guide to what may happen in the United States. Hospitalization rates in these countries have varied widely, with prevalence of testing likely part of the reason for the disparity. Rates ranged between a low of 2 to a high of 31.8.²² In Germany, overall hospitalization rate was 7%. Half of these patients had comorbid conditions, but only a fraction of patients presented with pneumonia.²³ In New Zealand, 31% of cases were hospitalized, with 12% of those to the ICU, and an average national hospitalization rate of 22.8 per 100,000 population. Rates were highest in infants younger than 1 year old (218.5 per 100,000), and lowest in those older than 70 years (15.3 per 100,000).²²

To date in the United States, cumulative hospitalization rate has been highest in the 0- to 17-year-old age group, with the latest figures showing the highest laboratory-confirmed H1N1 hospitalization rates in the 0-

to 4-year-old subgroup.^{22,24} A review of hospitalized patients in the United States showed a 25% ICU admission rate and 7% death rate in this group. Forty-five percent of admissions were pediatric (< 18 years old), and only 5% were 65 or older, with a median age of 29 years for ICU-admitted patients. Because of this, there has been an overall greater demand for ICU beds.^{1,23} Seventy-three percent of ICU patients had underlying conditions as noted in the risk factor discussion below.²³

Early evidence showed a significant majority of deaths (87%) and severe pneumonia (71%) in patients aged 5-59 years, compared to a much smaller number of each (17% and 32%) in prior influenza seasons.²⁵ Severe respiratory failure is seen in a number of cases, requiring early and sometimes prolonged mechanical ventilation, high levels of positive end-expiratory pressure (PEEP), and even extracorporeal membrane oxygenation (ECMO).^{26,27} Noninvasive ventilation has not been found to be a useful option in most cases.²⁶ An early series of pediatric ICU cases with H1N1 in the United Kingdom showed that most patients had comorbidities and a fulminant course unlike seasonal influenza. Half of the patients in shock were catecholamine- and steroid-resistant.²⁸

All deaths in the cohort had been ICU admissions and had been ventilated, with a median of 15 days from onset to death. Sixty-two percent of ICU patients required mechanical ventilation, of whom more than half had acute respiratory distress syndrome (ARDS).²³ Only 23% of ICU patients received antivirals within 48 hours, with a median time to antiviral therapy of six days. Two-thirds of the deaths had underlying medical condi-

tions, most notably neurologic disease (21%), asthma or chronic obstructive pulmonary disease (COPD) (16%), and pregnancy (16%). There were higher than expected hospitalizations in pregnant patients (7% vs. 1% expected); 9% of ICU admissions were pregnant patients in Australia and New Zealand.^{1,23}

Risk Factors and Unique

Features. Patient groups at risk for poor outcomes with novel H1N1 influenza include:

- children younger than age 2;
- adults older than age 65;
- pregnant women and those up to 2 weeks postpartum (including pregnancy loss);
- those with chronic medical, neurologic, and metabolic diseases, especially those that compromise respiratory function;
- immunosuppressed patients; and
- those younger than age 19 on long-term aspirin therapy.^{9,29}

Although morbid obesity has been noted in a population-disproportionately high number of severely affected patients, it is yet uncertain whether this in itself is a risk for severe disease or whether the higher rate of comorbid conditions is to blame.¹⁹ Patients at greatest risk for complications are third-trimester pregnant women, children younger than age 2, and individuals with chronic lung diseases, including asthma.³⁰ Two-thirds of patients admitted to the ICU had underlying medical conditions. In adults, the most common underlying conditions were asthma, diabetes, chronic cardiovascular disease, and immunosuppression. In children younger than 18, asthma was by far the most common underlying condition, with neurocognitive, neuromuscular, and seizure disorders the next most common.²³

A small minority of patients are severely affected with rapidly progressive respiratory failure.²⁶ The patients who experience fulminant, resource-intensive disease rapidly deteriorate 3-5 days following onset of symptoms, often requiring mechanical ventilation and frequently progressing to multi-system organ failure.³¹ Approximately half of such cases are due to primary

viral pneumonia, but streptococcal and staphylococcal bacterial superinfection are common as well.¹

Mortality. The most common cause of death due to novel H1N1 influenza is respiratory failure and shock.³² Severe disease in South Africa was characterized by an older median age in fatal cases compared to nonfatal cases (33.5 years vs. 15 years, $p < 0.01$). The overall epidemiology in that country is likely significantly different than in the United States due to its large prevalence of pregnancy, HIV and related infectious diseases, and obesity, with all of these identified as significant risks for death.¹¹

Southern hemisphere experience confirmed that the lowest morbidity and mortality rate was in patients older than age 60, and that comorbidities nearly double the risk of death.¹² Median age for admitted patients was 23 years, for ICU admissions 38 years, and for deaths 50 years. Twenty-six percent of evaluated admissions went to the ICU, and 6% died.³² The highest number of U.S. deaths was noted in 25- to 49-year-old age group, followed by 50-64, then 5-24 year olds, as opposed to seasonal flu, in which the overwhelming majority of deaths are in the over-65-year-old group.⁹

Independently associated risk factors for death included requirement for mechanical ventilation (OR 5.51, CI 3.05-9.94), pre-existing conditions (OR 2.56, CI 1.52-4.30), and older age (OR 1.02 per year of age, CI 1.01-1.04). Notably, one-third of patients who died did not have any pre-existing condition.¹

A review of the 36 U.S. pediatric deaths with laboratory-confirmed H1N1 showed a median age of 9 years, with 19% younger than age 5. Forty-two percent were non-Hispanic white, 33% were Hispanic. Two-thirds of these had high-risk medical conditions, the vast majority neurodevelopmental. More than half had more than one neurodevelopmental diagnosis, and 41% had associated chronic pulmonary conditions. The percentage of deaths in pediatric patients with high-risk conditions is higher than has been seen in recent seasonal

influenza. It is important to note that 22% of deaths in the 5- to 18-year-old age group did not have any known high-risk conditions.³⁰

In Mexico, the case fatality rate was 0.4%,³³ and in New Zealand was 0.005%, which is comparable to seasonal influenza.³⁴ Because the U.S. outbreak continues to evolve, a reliable U.S.-specific case fatality rate has not been calculated.³⁵

Clinical Features

Although early reports indicated that clinical features of novel H1N1 influenza were identical to seasonal influenza, additional experience has modified this thinking.³⁶ In sharp contrast to seasonal influenza patterns, hospitalization and death rates with novel H1N1 influenza have been highest in the young and lowest in those 65 and older.³⁷ Younger patients have shown a significantly greater prevalence of associated vomiting and diarrhea.³⁸ Patients without fever or a history of fever represent a significant number of those with laboratory-confirmed novel H1N1 influenza, with 10-50% of cases being afebrile.³⁸

Hospitalized patients most commonly presented with fever (93%), cough (83%), shortness of breath (54%), fatigue or weakness (40%), followed by chills, myalgias, rhinorrhea, sore throat, headache, vomiting, and diarrhea.⁹ A review of 272 patients hospitalized in the United States also found hematologic abnormalities, with leukopenia in 20%, anemia in 37%, and thrombocytopenia in 14% of cases. Positive blood cultures were found in only 3 of 182 patients. The majority of patients had a chest radiograph on admission, and of these, 40% showed pneumonia.²³ Nearly half of ICU patients had ARDS or viral pneumonitis, and 20% had superimposed bacterial pneumonia. The median time for mechanical ventilation in this group was 8 days, with 11.6% of patients requiring ECMO.

Management and Recommendations for Patients

Novel H1N1 influenza and seasonal influenza should both be part of the differential diagnosis for patients pre-

senting with fever and cough. The vast majority of novel H1N1 influenza patients will require only supportive care, with progressively smaller percentages needing antiviral therapy, hospitalization, mechanical ventilation, or other critical care interventions. Some patients will appear to have an ILI but in fact have other pathology. Because a small number of patients rapidly develop respiratory insufficiency, failure, and shock, rapid assessment and early empiric antiviral therapy are crucial to successful management. (*See Rapid Reference Card for a unified approach to assessment and management consistent with current recommendations.*)

Social Distancing and Hygiene.

Soap and water have been found to be better than alcohol hand sanitizer, but both are effective in limiting transmission.²⁹ Social distancing measures in combination with vaccination are vital in containing disease. The CDC recommends that patients remain at home until afebrile for 24 hours without antipyretics.³⁹ Household mask use, although theoretically useful, was rendered ineffective by high levels of noncompliance.⁴⁰ Early implementation of nonpharmaceutical interventions may have utility in future pandemics.⁴¹

Testing. Current CDC guidance suggests testing be considered only for specific groups: those hospitalized with suspected novel H1N1 influenza, those for whom testing will impact clinical decision-making for the patient and/or his or her close contacts, and in those who have died of suspected novel H1N1 influenza.⁴² Rapid influenza diagnostic tests (RIDTs) provide results within 30 minutes and, based on their type, either: detect influenza viral antigen but not identify type, distinguish between type A and B influenza, or detect only influenza A.⁴³ RIDTs for novel H1N1 influenza showed a sensitivity of 10-70%, while direct immunofluorescence assays (DFAs) have a sensitivity of 47-93%. Both RIDTs and DFAs have high specificity, so a positive result is clinically helpful. However, a negative test does

not reliably rule out H1N1 infection.⁴³⁻⁴⁷ As a result, patients should be treated empirically based on their clinical picture, even in the face of a negative test. Tests are most likely to be positive with high viral titers early in the course of illness.⁴⁶ In patients for whom H1N1 type identification is needed, real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) tests should be used, as they are the most sensitive and specific.⁴³

Antiviral Therapy. Antivirals reduce respiratory complications and symptom duration and are more effective the earlier in the patient's course they are started.⁴⁸ At recommended doses, there was a 1.3-1.5-day median decrease in the time to improvement of symptoms when compared to placebo if started within 40 hours of symptom onset.⁴⁹ Treatment should be offered to those in high-risk categories and given to those who require hospitalization.⁴⁸ Because of influenza A resistance to adamantanes (rimantidine and amantadine) in the United States, they should not be used. Neuraminidase inhibitors (oseltamivir or zanamivir) are the antivirals of choice.^{37,50,51} While oseltamivir and zanamivir are both currently available commercially, the CDC continues to release antiviral therapy courses from the Strategic National Stockpile to supplement state stockpiles.⁵²

The U.S. Food and Drug Administration (FDA) has approved an emergency use authorization (EUA) to allow use of oseltamivir and zanamivir outside their previous FDA-approved indications in seriously ill influenza patients.⁴⁸ Current EUAs allow for the use of oseltamivir in manufactured suspension formulation for children younger than 1 year of age, and compounding of oseltamivir suspension from 75-mg capsules due to shortage of suspension, and extension of expiration dates on some stockpiled antivirals.⁵³ See Table 1 for antiviral dosing recommendations for both treatment and prophylaxis.

Sporadic resistance to oseltamivir has been documented and is being closely monitored, but no changes in first-line management are recom-

mended at this time.⁵⁴⁻⁵⁶ History of resistant virus development has been widely variable in other countries.⁵⁷ To date, oseltamivir-resistant virus has remained sensitive to zanamivir.^{58,59} Development of resistance to H1N1 in Europe in 2007-8 was associated with inconsistent compliance with therapy but was not statistically related to prescription rates.^{60,61} Resistance is also likely higher in the immunocompromised and in those who develop disease while on oseltamivir postexposure prophylaxis.⁶²

Both oseltamivir and zanamivir are FDA pregnancy category C, and both are recommended for therapy or prophylaxis in pregnant or lactating women.^{50,63} For postexposure close contact prophylaxis, zanamivir can be used in pregnant women without underlying respiratory problems.⁵⁰ More information is available on oseltamivir use in pregnancy, so it may be preferable in this patient group.

In a review of adult cases in the United States, 97% of the hospitalized patients received antibiotics; only 73% received antivirals (mostly oseltamivir). Slightly more than a third were treated with antivirals within 2 days of symptom onset, and there was a median of 3 days from symptom onset to antiviral treatment. In patients who died, there was an eight-day median time from symptom onset to antivirals. None of the patients who died received antiviral treatment within 48 hours of onset.²³ In the review of pediatric deaths, just more than 10% received antivirals within 2 days of onset, and only 61% ever received antivirals.³⁰ As a result, early treatment with antivirals is recommended by the WHO and the CDC, even prior to confirmed H1N1.⁶⁴ There is some evidence of effectiveness of antiviral therapy even when started more than 48 hours post-onset.⁶⁵

Neuraminidase inhibitors provide coverage for both influenza A and B. Oseltamivir is available in capsules and as a powder for suspension.⁴⁹ Although it is converted to the active metabolite by the liver, it does not affect cytochrome P450. No dosage

adjustment is recommended for mild to moderate hepatic impairment. Excretion is largely through the kidney, and dosage should be adjusted in those with creatinine clearance < 30 mL/min as shown in Table 1.⁴⁹ Shortages of oseltamivir suspension have been resolved by providing specific instructions on how to reconstitute 75-mg capsules into suspension; however, the resultant suspension concentration (15 mg/mL) differs from the manufactured (12 mg/mL) suspension. Because of this, special emphasis is needed on proper dosing of oseltamivir suspension, as noted in Table 1.

Zanamivir is an inhaled powder. Because of its lactose powder vehicle, zanamivir can induce bronchospasm and is therefore not recommended for those with underlying pulmonary pathology.⁶⁶ Zanamivir should not be nebulized, but only inhaled using the provided device. Similar to oseltamivir, no dosage adjustment is needed with hepatic or renal impairment. Zanamivir has no approved indication for influenza in children younger than age 5.⁶⁶

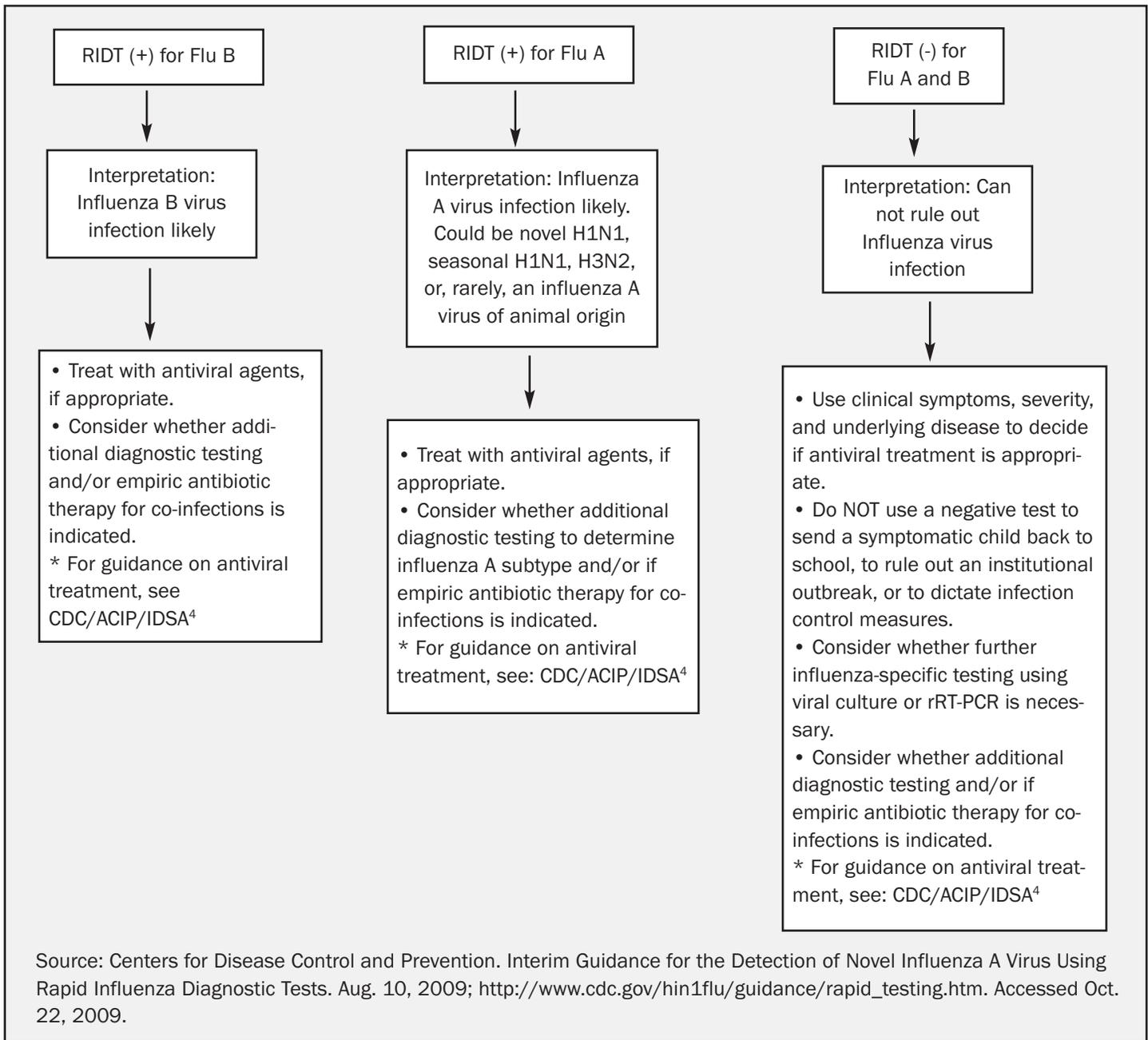
Both neuraminidase inhibitors are generally well tolerated compared to placebo, with principally gastrointestinal adverse effects.⁴⁹ Some neuropsychiatric events have been reported, which may be attributable either to neuraminidase inhibitors or to influenza itself.^{49,66} Rare occurrence of allergic and serious skin reactions, including Stevens-Johnson and toxic epidermal necrolysis, have been noted with both oseltamivir and zanamivir and demand cessation of therapy.^{49,66}

Although peramivir is unlikely to be used in the emergency department, physicians should be aware of this therapeutic option in patients whose illness is refractory to other therapies. Peramivir is an investigational intravenous neuroaminidase inhibitor authorized under an EUA for hospitalized patients suspected to have novel H1N1 influenza who are not responding to oral or inhaled neuroaminidase-inhibitor therapy, for whom other medication routes are not dependable, or if the clinician feels IV therapy is appropriate.

Table 1: Neuraminidase Dosing

For both oseltamivir and zanamivir:		
<u>Treatment:</u> Indicated dose given TWICE daily for FIVE days		
<u>Prophylaxis:</u> Indicated dose given ONCE daily for TEN days		
Oseltamivir Dosing^{1,2}		
Age	Dose (mg)	
Infants less than 12 months of age	< 3 months	12 mg
	3-5 months	20 mg
	6-11 months	25 mg
Children 12 months and older	≤ 15 kg OR ≤ 33 lbs	30 mg
	> 15 kg to 23 kg	45 mg
	OR > 33 lbs to 51 lbs	
	> 23 kg to 40 kg	60 mg
	OR > 51 lbs to 88 lbs	
	> 40 kg OR > 88 lbs	75 mg
Adults	75 mg	
Dosing less than 1 year of age from US FDA, does not include premature infants. ² Recommendations for 12 months and older taken from CDC recommendations. ¹		
Renal impairment dosing for creatinine clearance < 30 mL/min: ³		
For patients with creatinine clearance < 10 mL/min:		
• CAPD: 30 mg weekly		
• Hemodialysis: 30 mg alternate dialysis cycle		
For patients with creatinine clearance > 10 and < 30 mL/min:		
• 30 mg daily or 75 mg alternate days		
Pediatric dosing should be written as milligrams, as there may be different concentrations of oseltamivir suspension (12 mg/mL in commercial oral suspension; 15 mg/mL if made by emergency compounding from capsules).⁴		
Zanamivir Dosing^{1,4}		
Age	Dose (mg)	
Children	≥ 5 years old for chemoprophylaxis	10 mg (two 5 mg inhalations)
	≥ 7 years old for treatment	10 mg (two 5 mg inhalations)
Adults	10 mg (two 5 mg inhalations)	
Note: Zanamivir is not recommended for children younger than 5 years of age.		
1. CDC. Novel H1N1 Flu: Facts and Figures. Aug. 4, 2009. www.cdc.gov/h1n1flu/surveillanceqa.htm#5 . Accessed 10/19/09.		
2. U.S. Food and Drug Administration. Emergency use of Tamiflu in infants less than 1 year of age. Sept. 25, 2009. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm183870.htm . Accessed 11/1/09.		
3. Tamiflu capsules. www.gene.com/gene/products/information/tamiflu/pdf/pi.pdf . Accessed 11/10/09.		
4. CDC. Emergency Use Authorization of Relenza (zanamivir). Nov. 5, 2009. www.cdc.gov/h1n1flu/eua/pdf/Relenza_FDA_Letter_110509.pdf . Accessed 12/9/09.		

Figure 1: Testing and Antiviral Therapy in Influenza



Additional specific information regarding clinical indications, use, patient information, conditions of the EUA, and method of requesting peramivir are available through the referenced link.⁶⁷ Delivery of peramivir following online request may take up to 24 hours.

Chemoprophylaxis.

Chemoprophylaxis is not recommended for healthy individuals based on potential exposures, exposures outside the index case’s infectious period, or if presenting greater than 48 hours post-exposure. Because

severe disease has been associated with postexposure oseltamivir prophylaxis, the individuals’ risk for complicated disease should be a part of the decision to provide chemoprophylaxis. Starting oseltamivir household postexposure prophylaxis within two days of index case symptom onset decreased incidence from 12% to 1% in adults and 17% to 3% in children.⁴⁹ Prompt treatment of ILI or ARI once symptoms develop is preferred to chemoprophylaxis, even in high-risk patients.⁹

Antibiotic Therapy. Empiric

antibiotics that cover streptococcus and staphylococcus (and methicillin-resistant *S. aureus* [MRSA]) are indicated in rapidly progressive disease with respiratory failure and with patients with lung infiltrates.^{23,64,68,69} For pediatric deaths with culture results, 43% had bacterial co-infections, all were streptococcus or staphylococcus species (including MRSA in 3 of the 23).³⁰

Countermeasures. *Vaccine.* Vaccine is now available, with more than 35 million doses shipped to providers by November 13, 2009. Clearly, pre-pan-

demic vaccination is ideal, but even at this point it is likely to limit morbidity, mortality, and healthcare costs.^{70,71} Younger individuals (< 30 years of age) apparently have little or no immunity to this novel virus, so vaccination is an important preventive strategy.⁷ A single dose of vaccine was shown in clinical trials to be immunogenic in adults, with adequate antibody titers in more than 96% after 14 days for adjuvanted vaccine.⁷²⁻⁷⁵ Seasonal influenza vaccine is ineffective in providing protection against 2009 novel H1N1 influenza virus.^{51,76}

The Vaccine Adverse Event Reporting System on the novel H1N1 influenza vaccine experience has confirmed the expected good safety profile, consistent with seasonal flu vaccines.⁷⁷ Ninety-five percent of the 2365 reported adverse events to date were not serious.⁷⁷ Side effects are expected to be rare, mild, and short-lived.^{78,79} They potentially include local swelling, low-grade fever, and myalgias with the trivalent influenza vaccine (TIV), as well as upper respiratory symptoms with the live-attenuated influenza vaccine (LAIV).⁸⁰ With the exception of the 1976 swine influenza vaccine, studies have failed to show statistically significant correlation between vaccine and Guillian-Barre syndrome (GBS).³⁷ However, in those with a history of GBS, there is a greater risk of recurrence, so a judgment should be made about the risk/benefit.³⁷

Primary groups targeted for early vaccination include pregnant women, healthcare workers, six-month to 24-year-old individuals, individuals who care for children under six months old, and 25- to 64-year-olds with risks for influenza-related complications.^{81,82} Targeted vaccination of children in schools is a valuable strategy in not only limiting cases in the population as a whole, but also morbidity and mortality in this vulnerable age group.^{83,84}

The effect vaccination will have on overall outcomes and ICU utilization in the United States has yet to be determined.

TIV may be given simultaneously with antivirals. LAIV should not be

given until antiviral therapy has been completed for at least 48 hours.³⁷ LAIV should not be given to those with hypersensitivity to eggs, individuals younger than 2 or older than 49 years of age, those with history of GBS, or anyone in high-risk groups for novel H1N1 influenza, as previously noted.³⁷ (*See Rapid Reference Card.*)

Additional Healthcare Worker Precautions. Ideally, all healthcare workers should be vaccinated to prevent not only illness in themselves, but also to prevent transmission to patients. Strategies to encourage healthcare worker compliance with vaccination should be implemented to increase compliance levels.⁸⁵ Other proactive measures to prevent transmission in health care settings include exposure elimination, engineering controls, and prevention of exposures through administrative measures such as cohorting.¹⁵

The final rung in the preventive ladder is use of personal protective equipment to manage what should only be unavoidable close contact exposures (< 6 feet). Fit-tested N95 masks are recommended for healthcare workers exposed to patients with novel H1N1 influenza.⁸⁶ This differs from recommendations for seasonal influenza. Should fit-tested respirators be in limited supply, they should be prioritized for personnel exposed to aerosol and droplet-generating invasive procedures with infected patients. High-risk procedures include bronchoscopy, sputum induction, endotracheal intubation and extubation, open airway suctioning, cardiopulmonary resuscitation, and autopsy. High-flow oxygen therapy and nasopharyngeal swabbing are not included as high-risk procedures.⁸⁶

Disposition

Recommendations for disposition are summarized on the enclosed Rapid Reference Card. For high-risk patients with suspected novel H1N1 influenza, empiric antiviral therapy should be initiated as soon as possible.²⁹ Patients who present with respiratory impairment, new hypoxia, or lower respiratory tract infection should be considered for hospital admission.⁶⁵ If

the patient's respiratory symptoms are rapidly progressive, consider ICU admission, as these patients often require mechanical ventilation within the first day of admission.²³

Systems Effects. Emergency departments are overwhelmed by increased patient demand, isolation that decreases inpatient bed supply, and need for pediatric and ICU beds. Emergency medical services (EMS) demand has increased significantly as well. Altered dispatch or transport standards may be implemented by EMS agencies based on their specific community's experience.⁸⁷ Ideally, communities should be involved in what steps are taken to address excess demand.

Disaster Mode. Specific strategies, checklists, and resources for emergency department planning and management of novel H1N1 influenza are provided in the American College of Emergency Physicians National Strategic Plan for Emergency Department Management of Outbreaks of Novel H1N1 Influenza.⁸⁸ Innovative options include self-triage and patient-focused decision support tools that allow patients to assess their risk and encourage them to seek care as needed in an appropriate setting.⁸⁹

Hospitals should have disaster plans in place that include working cooperatively with community resources to manage patient surge related to this pandemic or other disasters. Numerous strategies exist that are consistent with existing laws and regulations that allow hospitals to deal with significantly increased patient demand while complying with Emergency Medical Treatment and Labor Act (EMTALA) and Health Insurance Portability and Accountability Act (HIPAA) requirements, and are specifically described in the reference.⁹⁰ EMTALA compliance can be particularly challenging for emergency departments in disaster situations. For example, it is acceptable to set up alternate sites either on or off the hospital campus for medical screening. Regardless, hospitals may not divert patients who have already presented to an emergency department.

ment before providing an appropriate medical screening exam. Additional specifics are available through the Centers for Medicare & Medicaid Services (CMS) link.⁹¹ For communities that wish to reinforce their existing pandemic response capabilities going forward, cited resources provide additional insight.^{87,92,93}

The Secretary of Health and Human Services (HHS) has authority under section 1135 of the Social Security Act to waive certain Federal requirements for healthcare facilities that could otherwise limit the ability of our nation's healthcare system to respond to the surge of patients during an emergency.⁹⁴ Section 1135 permits the Secretary of HHS to waive or modify certain Medicare, Medicaid, Children's Health Insurance Program (CHIP) and HIPAA requirements, but the Secretary of HHS may only authorize such waivers or modifications after certain events occur. More specifically, there must be both a presidential declaration of emergency or disaster under the National Emergencies Act or Stafford Act and a public health emergency declaration under the Public Health Service Act by the Secretary of HHS in order for the Secretary to issue 1135 waivers. At that point, the Secretary has the discretion to issue certain waivers or modifications that may have specific implications for emergency department practice.⁹⁵ Waivers or modifications under section 1135 generally can last for up to the duration of the public health emergency.⁹⁶

On October 23, 2009, President Obama issued a proclamation declaring the 2009 novel H1N1 influenza pandemic a National Emergency pursuant to the National Emergencies Act and the HHS Secretary's prior public health emergency declaration for H1N1. Following that declaration, the HHS Secretary formally invoked section 1135 on October 29, 2009, retroactive to October 23, 2009.⁹⁵ The Secretary may now issue waivers or modifications under section 1135 for specific requirements to match the specific situational needs.⁹⁴ Such waivers may support healthcare facilities' ability to respond to the surge of

patients with the 2009 novel H1N1 influenza virus.

Summary

Novel H1N1 influenza is significantly different from seasonal influenza in epidemiology, medical management, and complications. Although there are identifiable high-risk patient groups, emergency physicians must be aware that there is significant prevalence and severity of this disease in otherwise healthy individuals. One in three adults and one in five 5- to 18-year-olds who died had no pre-existing or high-risk condition.^{1,30}

Although severe illness is uncommon, 25% of hospitalized patients with novel H1N1 influenza require intensive care, and a similar proportion require mechanical ventilation.²³ Cornerstones of management include vaccination, clinical diagnosis, early antiviral therapy, and concurrent antibiotic therapy when indicated. Careful assessment and ongoing vigilance for development of severe disease and respiratory insufficiency is vital in both the high-risk population and those without known risk factors.

The daily evolution of information and experience with novel H1N1 influenza has helped mature management of this disease entity and narrow the practice gap. Diligent monitoring of reputable resources is essential to remain current on this topic. Numerous resources and links are available in the reference list. One particularly helpful bookmark is www.flu.gov, which provides both patient and administrative guidance, current information and recommendations, and acts as a clearinghouse for federal information and resources for novel H1N1, seasonal, and other influenza strains.

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Physician CME Questions

1. Early empiric treatment with a neuraminidase inhibitor should be started for which of the following patients with suspected novel H1N1 influenza?
 - A. a 3-year-old female with asthma
 - B. a 17-year-old on chronic aspirin therapy
 - C. a 26-year-old female in second trimester of uncomplicated pregnancy
 - D. all of the above
2. Recommended management strategies include:
 - A. early antiviral therapy for high-risk patients with suspected novel H1N1 influenza
 - B. influenza A/B testing for all suspected novel H1N1 influenza cases
 - C. empiric antibiotic therapy for hospitalized patients with novel H1N1 influenza
 - D. confirm novel H1N1 influenza type before initiating therapy
3. Novel H1N1 influenza is most likely to be transmitted by which method?
 - A. fecal-oral transmission
 - B. medication nebulization
 - C. droplet exposure of mucosal surfaces
 - D. aerosolization over longer distances
4. What is the primary recommended respiratory protection method against novel H1N1 for healthcare workers?
 - A. surgical facemask
 - B. fit-tested N95 respirator
 - C. duckbill mask
 - D. environmental HEPA filtration
5. Chemoprophylaxis is indicated for:
 - A. healthcare workers during the pandemic
 - B. household contacts of confirmed cases
 - C. a patient exposed 72 hours ago
 - D. all pregnant women
6. The recommended antiviral therapy for a pregnant H1N1 patient is:
 - A. rimantidine
 - B. ceftriaxone
 - C. amantadine
 - D. oseltamivir
7. Mortality related to novel H1N1 influenza A is primarily due to:
 - A. pulmonary edema and hypoxia
 - B. bacterial superinfection and sepsis
 - C. respiratory failure and shock
 - D. bacterial pneumonia
8. In the absence of the HHS Secretary invoking section 1135 of the Social Security Act, which of the following applies?
 - A. Patients who present to the ED can be

- directed to flu clinics.
- B. EMTALA requirements are automatically waived.
- C. Alternate care sites can be established.
- D. Medical screening exams are no longer required.

9. Which of the following statements regarding novel H1N1 influenza antiviral therapy is correct?
- A. Amantadine is first line for influenza A treatment.
 - B. zanamivir dosing should be adjusted with hepatic impairment.
 - C. No dose adjustment is needed for oseltamivir in renal insufficiency.
 - D. Zanamivir is indicated for treatment in children age 7 and older.
10. For patients with H1N1 influenza, which of the following is true?
- A. Gastrointestinal symptoms are unusual.
 - B. Viral titers are highest early in the disease course.
 - C. Those older than age 60 are the most affected age group.
 - D. Oseltamivir may be used only in patients older than 1 year.

CME Answer Key

1. D; 2. A; 3. C; 4. B; 5. B; 6. D; 7. C; 8. C; 9. D; 10. B

In Future Issues

Dental Emergencies

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications which may be associated with the particular medical problems discussed in the publication.

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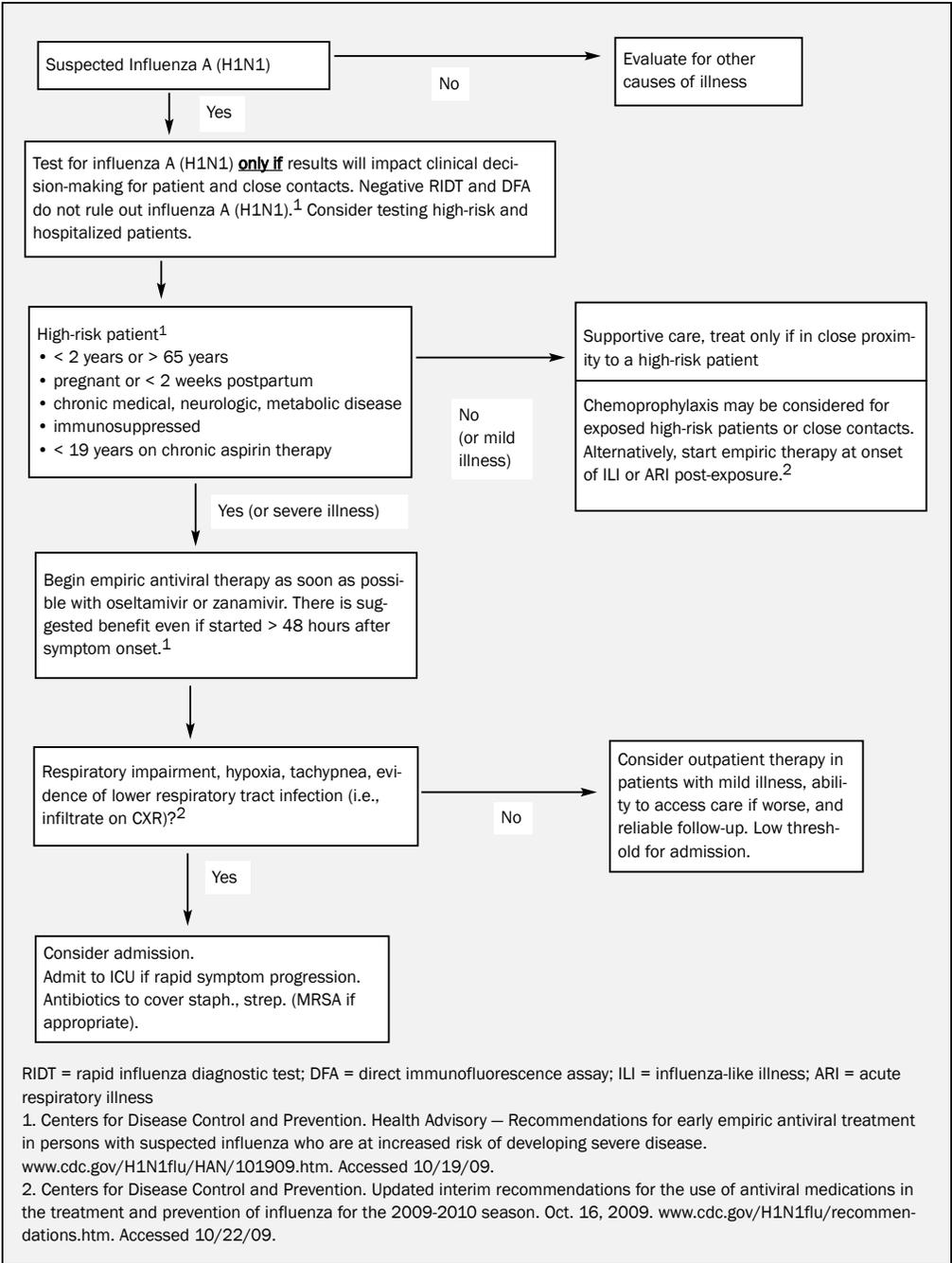
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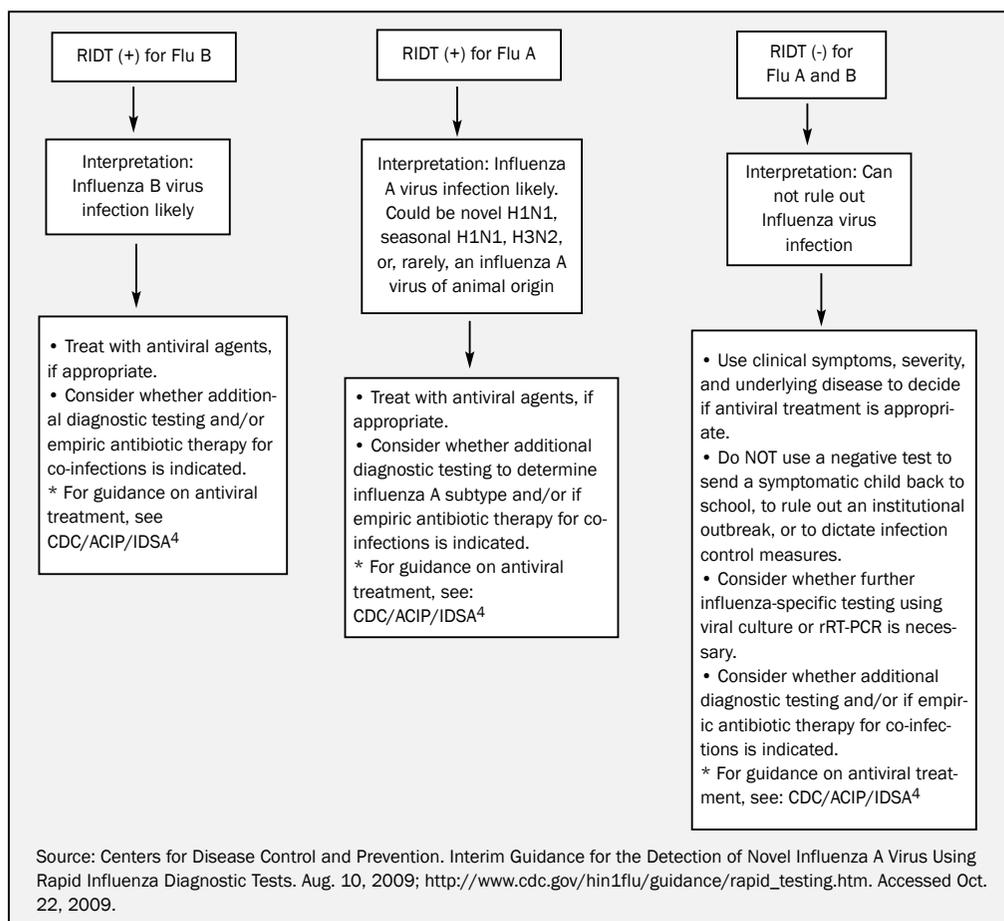
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Emergency Department Assessment and Management of H1N1 Influenza



Testing and Antiviral Therapy in Influenza



Neuraminidase Dosing

For both oseltamivir and zanamivir:
Treatment: Indicated dose given TWICE daily for FIVE days
Prophylaxis: Indicated dose given ONCE daily for TEN days

Oseltamivir Dosing ^{1,2}		
Age		Dose (mg)
Infants less than 12 months of age	< 3 months	12 mg
	3-5 months	20 mg
	6-11 months	25 mg
Children 12 months and older	≤ 15 kg OR ≤ 33 lbs	30 mg
	> 15 kg to 23 kg OR > 33 lbs to 51 lbs	45 mg
	> 23 kg to 40 kg OR > 51 lbs to 88 lbs	60 mg
	> 40 kg OR > 88 lbs	75 mg
	Adults	

Dosing less than 1 year of age from US FDA, does not include premature infants.² Recommendations for 12 months and older taken from CDC recommendations.¹

Renal impairment dosing for creatinine clearance < 30 mL/min:³
 For patients with creatinine clearance < 10 mL/min:
 • CAPD: 30 mg weekly
 • Hemodialysis: 30 mg alternate dialysis cycle
 For patients with creatinine clearance > 10 and < 30 mL/min:
 • 30 mg daily or 75 mg alternate days

Pediatric dosing should be written as milligrams, as there may be different concentrations of oseltamivir suspension (12 mg/mL in commercial oral suspension; 15 mg/mL if made by emergency compounding from capsules).¹

Zanamivir Dosing ^{1,4}		
Age	Dose (mg)	
Children	≥ 5 years old for chemoprophylaxis	10 mg (two 5 mg inhalations)
	≥ 7 years old for treatment	10 mg (two 5 mg inhalations)
Adults		10 mg (two 5 mg inhalations)

Note: Zanamivir is not recommended for children younger than 5 years of age.

1. CDC. Novel H1N1 Flu: Facts and Figures. Aug. 4, 2009. www.cdc.gov/h1n1flu/surveillanceqa.htm#5. Accessed 10/19/09.
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 3. Tamiflu capsules. www.gene.com/gene/products/information/tamiflu/pdf/pi.pdf. Accessed 11/10/09.
 4. CDC. Emergency Use Authorization of Relenza (zanamivir). Nov. 5, 2009. www.cdc.gov/h1n1flu/eua/pdf/Relenza_FDA_Letter_110509.pdf. Accessed 12/9/09.

Supplement to *Emergency Medicine Reports*, January 1, 2010: “Novel H1N1 Influenza.” Authors: **Sabina Braithwaite, MD, MPH, FACEP**, ACEP/ASPR Policy Fellow, Emergency Care Coordination Center, Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services, Washington, DC; and **Michael T. Handrigan, MD, FACEP**, Director, Emergency Care Coordination Center, Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services, Washington, DC. *Emergency Medicine Reports’ “Rapid Access Guidelines.”* Copyright © 2010 AHC Media LLC, Atlanta, GA. **Editors:** Sandra M. Schneider, MD, FACEP, and J. Stephan Stapczynski, MD. **Associate Publisher:** Russ Underwood. **Specialty Editor:** Shelly Morrow Mark. For customer service, call: **1-800-688-2421**. This is an educational publication designed to present scientific information and opinion to health care professionals. It does not provide advice regarding medical diagnosis or treatment for any individual case. Not intended for use by the layman.

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Emergency Medicine Reports, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours - the best possible patient care.

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both likely and rare complications that may be associated with the particular medical problems discussed in the publication.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers against the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of each semester you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form we will mail you a letter of credit. This activity is valid 24 months from the date of publication. The target audience for this activity includes primary care and family physicians.

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On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

A handwritten signature in black ink that reads "Cynthia E. Molnar". The signature is written in a cursive style with a large, looped initial "C".

Cynthia Molnar
Director of Continuing Education
AHC Media LLC

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Donald R. Johnston
Senior Vice President/Group Publisher
AHC Media LLC

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