REVIEW ARTICLE

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Update on 2009 Pandemic Influenza A (H1N1) Virus

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ABSTRACT

The pandemic influenza A (H1N1/2009) virus as a new challenge for health care providers has caused significant morbidity and mortality worldwide. Although many aspects of this virus are similar to other human influenza viruses, there are some disparities. This article reviews different aspects of influenza H1N1/2009 virus with focus on clinical features and management of patients. ***(Tanaffos2010; 9(1): 8-14)***

INTRODUCTION

Influenza A viruses belong to the family Orthomyxovirus with 16 varieties of haemagglutinin (HA) and 9 varieties of neuraminidase (NA) proteins used for subtyping (1).

Hippocrates explained the disease 2,400 years ago but the word "influenza" originated from Italy, meaning "influence", because it was considered to be caused by unfavorable astrological conditions (2).

Influenza A pandemics have occurred three times in the 20th century: H1N1 in 1918 which killed up to 40 million people, H2N2 in 1957, and H3N2 in 1968 (3, 4, 5). H1N1 reemerged in 1977 to periodically cocirculate with A (H3N2) subtypes as seasonal flu (6).

A new influenza pandemic arrived on April 2009. Mexico was the first country in which a significant increase was observed in reports of patients requiring hospitalization for pneumonia (4). This novel H1N1 virus was initially termed "swine origin influenza virus" (S-OIV) but further studies revealed that it represents quadruple reassortment of one human, one avian, and two swine strains (7). Retrospective studies showed a strain similar to S-OIV appeared in Thailand in 2000 (8).

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Epidemiology

As of December 27, 2009, more than 208 countries and communities have reported laboratory confirmed cases of pandemic influenza H1N1, including at least 12,220 deaths (9). In Iran, as of January 2, 2010, 3672 confirmed cases and 140 deaths have been reported (10).

Children and young adults are most susceptible to this infection and it seems that a substantial proportion of persons over 60 years of age have cross-reacting antibodies, although the mortality rate is higher in the latter (1, 11).

The incubation period appears to be approximately 2-3 days, but it may take up to 7 days (12).

Routes of transmission include respiratory droplets (they are produced when an infected patient talks, coughs, or sneezes), contact exposure of mucosal surfaces, and small particle aerosols in special situations (13).

Patients may excrete the virus from 24 hours before the initiation of symptoms up to 7 days thereafter or until complete resolution of the symptoms (14).

High risk groups for complications are pregnant women, adults older than 65 years, children younger than 5 years, patients with underlying conditions (chronic pulmonary, cardiovascular or neurologic disease, immunosuppression, hematologic disorders, chronic liver disease or renal failure, metabolic disorders (especially diabetes mellitus) and morbid obesity (15, 17).

Patients with multi-drug resistant tuberculosis (MDR-TB) are generally more likely to die or suffer from advanced lung disease; therefore, they may have a poorer prognosis after influenza (18).

Although patients with conditions that confer some degree of immunosuppression, e.g., asplenia, may not have increased risk for influenza-associated complications, they may be at high risk for secondary invasive infection with encapsulated bacteria (e.g., pneumococcal disease) (19).

Clinical aspects

The signs and symptoms are similar to those of seasonal flu, except for the fact that about 25% of patients with pandemic flu develop gastrointestinal symptoms (11, 20, 21).

As Mexicans experienced, the major symptoms are cough (86%), fever (85%), dyspnea (74%), expectoration and malaise (52% and 48%, respectively), followed by myalgia (27%), headache (25%) rhinorrhea and cyanosis (23% each), hemoptysis (19%), odynophagia (18%) chest pain (14%), vomiting, nasal obstruction, conjunctival hyperemia and diarrhea in less than 10% of cases (3).

In some reports, fever was absent in 50% of outpatients and 15 to 30% of hospitalized patients (17,13).

Atypical presentations may occur in those with significant immunosuppression (22). Therefore, clinicians should suspect influenza in any severely immunosuppressed patient with acute respiratory symptoms (19).

Approximately, 10-30% of hospitalized patients have required admission to intensive care units (12).

Diagnosis

The radiographic appearance is similar to that of severe pneumonia with multifocal infiltrates and nodular alveolar or basal changes (20).

Nonspecific laboratory features include: raised lactate dehydrogenase levels, some degree of renal impairment, lymphopenia, leukopenia or leukocytosis and raised creatinine phosphokinase levels (20, 23).

The respiratory secretion samples should be collected by the third day after the onset of symptoms. If necessary, this period can be extended to a maximum of 7 days after symptoms' onset (14). Samples must be collected preferably through nasopharyngeal aspirate; alternatives are the nasopharyngeal or pharyngeal swab. Specimens from the lower respiratory tract are more sensitive than samples from the upper part (24).

Rapid antigen tests have lower sensitivity (10% to 51%) and will not differentiate novel H1N1 from other strains of influenza A. Consequently, negative rapid tests cannot exclude the diagnosis (22).

The preferred test is RT-PCR. It has a sensitivity of 98%, a positive predictive value of 100%, and a negative predictive value of 98% (11).

Treatment

Antiviral drugs are recommended only for high risk groups: pregnant women, adults 65 years of age

and older, children younger than 5 years old, patients with underlying conditions at any age and those suffering from morbid obesity. (15, 25) Recent experience strongly indicates that earlier treatment is associated with better outcomes, but it may also be effective at any stage of active disease when ongoing viral replication is anticipated. Therefore, when antiviral treatment is indicated, it should be initiated immediately and without waiting for laboratory confirmation of diagnosis (12, 19).

The recommended dosage for Oseltamivir and zanamivir is demonstrated in Table 1 (22, 26). Some experts recommend the dosage of oseltamivir to be doubled (e.g. increased to 150 mg bid.) in critically ill adult patients.

Table 1. Recommended dosage for oseltamivir and zanamivir

Age	Treatment (Duration = 5 days)	Chemoprophylaxis (Duration = 10 days)
Oseltamivir		
Children <3 months	12 mg twice daily	Not recommended
Children 3–5 months	20 mg twice daily	20 mg once daily
Children 6–11 months	25 mg twice daily	25 mg once daily
Children ≤15 kg	30 mg twice daily	30 mg once daily
Children 15–23 kg	45 mg twice daily	45 mg once daily
Children 24–40 kg	60 mg twice daily	60 mg once daily
Children>40kg, adults	75 mg twice daily	75 mg once daily
Zanamivir*		
Adults and children	Two 5-mg inhalations twice daily	Two 5-mg inhalations once daily

** Zanamivir use is impractical below 7 years of age.*

In patients who have persistent severe illness despite oseltamivir treatment, intravenous administration of alternative antiviral medications such as zanamivir, peramivir or ribavirin is recommended but ribavirin should not be administered as monotherapy or for pregnant women; and inhalation form of zanamivir should not be delivered via nebulizer due to the presence of lactose, which may compromise the ventilator function (12).

Previously healthy adults with acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics. Patients with secondary infection should be considered for antibiotics. Most of them can be adequately treated with oral antibiotics. Antibiotic chemoprophylaxis should not be used (16).When secondary bacterial pneumonia is suspected, treatment with antibiotics should follow guidelines for community-acquired pneumonia (15). In outpatients, the preferred choices of medication include co-amoxiclav, tetracyclines, macrolides or respiratory fluoroquinolones (16).

Viral replication beyond 7–10 days despite active antiviral therapy or progression of symptoms despite therapy should raise the concern for drug resistance (22). Ninety six cases of oseltamivir resistance have been reported by December, 2, 2009. One-third of these cases were immunosuppressed patients and they were all susceptible to zanamivir (27).

Other treatment measures include supportive care, antipyretics (not Aspirin for patients younger than 18 years old), and ventilation support in case of respiratory failure.

Furthermore, corticosteroids should not be routinely used, (15) although dramatic response with steroid use has been observed in severe pneumonia due to H1N1. (Mansouri et al, Personal communication)

Complications

The most important complications are lower respiratory tract involvement, respiratory failure, and acute respiratory distress syndrome (ARDS) with refractory hypoxemia. Other severe complications include secondary invasive bacterial infection, septic shock, renal failure, multiple organ dysfunction, myocarditis, and worsening of underlying chronic disease conditions such as asthma, chronic obstructive pulmonary disease (COPD) or congestive

heart failure (12,19). Neurologic complications, including seizures, encephalitis, and encephalopathy have also been reported (28).

The most common bacteria causing secondary pulmonary infections are *S. pneumoniae*, other Streptococci, *H. influenzae* and *S. aureus* particularly methicilin resistant Staph. aureus (MRSA) (16).

Autopsies have shown that major pathological changes are localized to the lungs, with three distinct histological patterns: extensive diffuse alveolar damage, pulmonary hemorrhage and necrotizing bronchiolitis (29).

Special Considerations

Dose of Oseltamivir for patients with glomerular filtration rate (GFR) less than 30 ml/min is 75 mg daily, and in patients who need hemodialysis, 30 mg after alternate dialysis sessions is preferred. For inhaling zanamivir, no dosage adjustment is required (30).

In immunosuppressed patients it seems prudent to withdraw or diminish immunomodulator drugs temporarily (22, 31). There is not yet any documented information on clinical interactions between HIV and influenza A (H1N1) infection (32).

Hospitalization was necessary in nearly one-third of the pregnant women with confirmed novel H1N1 virus infection. The likelihood of sequel increases with advancing gestational age and ten percent of the women who died were pregnant (11).

Both medications are pregnancy category C drugs and safe during lactation. Because of its systemic activity, the drug of choice for treatment is oseltamivir and zanamivir is preferred for chemoprophylaxis because of its limited systemic absorption. Infected mothers may breast feed while wearing a face mask (7).

Regardless of the duration of symptoms, treatment of all transplant patients is recommended (22). Oseltamivir has no interactions with cyclosporine, tacrolimus, mycophenolate mofetil, and Steroids, and it can be safely used (30). Lung transplant recipients with impaired lung function may need longer treatment than other organ transplant cases (22).

In immunosuppressed patients, some experts recommend continuing antiviral therapy until viral replication has ceased (e.g. check PCR once a week and treat until negative result) (22).

Infection control

Influenza A virus remains viable on hard nonporous surfaces for 24-48 h and on porous materials for less than 8-12 h (22).

In direct contact with patients, standard and droplet precautions should always be applied (33). Surgical and N95 masks were equally effective in preventing the transmission of influenza (34, 35) but healthcare personnel conducting aerosol-generating procedures such as intubation or bronchoscopy should wear fit-tested N-95 respirators (36). When procedures include a risk of splash to the face and/or body, facial protection by means of either a medical mask and goggles, or a face shield and a gown and clean gloves are necessary (33).

All patients should remain on droplet precautions for a minimum of 7 days following symptoms' onset or until 24 hours following resolution of acute influenza symptoms, particularly fever, whichever is longer (33).

For immunosuppressed patients, some experts have recommended that isolation should be continued until symptoms have resolved and RT-PCR test becomes negative (19).

Prophylaxis

Post-exposure chemoprophylaxis is not recommended for healthy children or adults, or for cases in which more than 48 hours have elapsed since the last contact with an infectious person (15).

Prophylaxis with oseltamivir can be considered for those who are at a higher risk for complications of influenza and are in close contact with a person with confirmed or probable pandemic virus infection during that person's infectious period. Chemoprophylaxis of infants younger than 3 months old is not typically recommended (7).

Prophylaxis is necessary for health care personnel with unprotected close contact exposure to a person with confirmed disease (15) but it is not indicated for personnel wearing facemasks during the care of patients (13, 36).

Doses and duration of prophylaxis are shown in Table 1 (22).

More than 30 pandemic (H1N1) 2009 vaccines have been developed and licensed including live attenuated vaccines and inactivated unadjuvanted and adjuvanted vaccines. Since September 2009, more than 50 countries have implemented immunization programs (37).

Based on the information received by the WHO from 65 million people who have been vaccinated, common side effects have been swelling, redness, and pain at the site of injection and fever, headache, fatigue, and muscle aches, occurring shortly after vaccine administration which resolve usually within 48 hours. In addition, allergic reactions have been observed. Few cases of Guillain-Barre syndrome and deaths have been reported, but a direct link with the vaccine has not yet been established (38). The overall rates reported for anaphylaxis range from 0.1 to 1.0 per 100,000 injected doses (37).

In one study on 216 healthy adults, vaccination was effective in 95% of them (39). Another study showed that lung recipients are not at significantly increased risk of vaccine failure (40).

The CDC recommends vaccination for persons aged 6 months to 24 years, pregnant women, health care workers, people who have certain health conditions (e.g. diabetes, heart disease, and lung disease) and people who live with or care for children younger than 6 months of age (11).

Unlike the inactivated vaccine, the live attenuated novel H1N1 nasal vaccine is contraindicated during pregnancy (7). Also, the inhaled vaccine should not be given to children under 2 years old. Neither vaccine should be given to people allergic to hen eggs, from which the vaccine is produced (11).

If resources or vaccine supplies are limited, the findings suggest a rationale for focusing prevention efforts on younger populations (6).

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