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Swine Flu (H1N1 Influenza A): A concise review

Gautam Rawal[1,*], Sankalp Yadav[2], Raj Kumar[3], Sujana R[4]

[1]Associate Consultant, [3]Senior Consultant & Incharge, Respiratory Intensive Care, Max Super Specialty Hospital, Saket, New Delhi, [2]General Duty Medical Officer- II, Dept. of Medicine & TB, Chest Clinic Moti Nagar, North Delhi Municipal Corporation, New Delhi, [4]Infection Control Unit, Max Super Specialty Hospital, Saket, New Delhi

***Corresponding Author:**
Email: drgautamrawal@hotmail.com

Abstract

The H1N1 influenza A, also known as swine flu, has caused widespread panic not only in India, but across the world. It emerged as pandemic in 2009 and made the whole world realize its dreadful presence. Early diagnosis, identification of the risk factors and prompt antiviral treatment along with preventive measure, including vaccination and chemoprophylaxis are the mainstay of management and can help in containment of this deadly disease. The authors give a concise review of the H1N1 influenza A.

Keywords: H1N1 influenza; Influenza A virus; Oseltamivir, Swine-flu; Zanamivir

Introduction

Swine flu or the H1N1 influenza has emerged as one the deadliest infectious disease in the past decade, occurring as pandemic or epidemic throughout the world [1,2]. It is now recognized as a global health burden and has been baffling the health authorities worldwide to prevent its spread, especially from human to human. The World Health Organization (WHO) declared the swine flu a pandemic in 2009 and since then it has been on every physician's mind, knowing its lethal nature. Swine flu was named so as the virus was first isolated in pigs (swine) in 1930 in the United States of America (USA) [1-4]. The swine flu pandemic of 2009, originated in Mexico [1-4].

Swine flu is a respiratory disease caused by influenza virus affecting the pigs, which, when infected show the symptoms like decreased appetite, increased nasal secretions, cough, and listlessness [1,4]. Thus the pigs are the reservoirs the virus. The causative virus of the swine influenza is the Influenza A with five subtypes namely: H1N1, H1N2, H2N3, H3N1, and H3N2. Out of these subtypes, the H1N1 Influenza A strain was isolated in the infected humans and the rest of the four subtypes were only exclusive in pigs [4]. The H1N1 virus is an enveloped RNA virus belonging to the family orthomyxoviridae, and name comes from the two surface antigens: H1 (Hemagglutinin type 1) and N1 (Neuraminidase type 1).

Transmission: People who work in close proximity with pigs, like farmers and pork processors, are at increased risk of catching swine flu from pigs through aerosol transmission [1-5]. The modes of transmission of H1N1 influenza virus in humans, from person to person, includes: inhalation of infected droplets (during sneezing, or cough), direct contact with the infected patient and contact with fomites that are contaminated with respiratory or gastrointestinal secretions as the virus can survive over the hard surfaces for about 24-48 hours and porous surface like cloth, tissue, paper for about 8-12 hours [3,5,6]. Various researches have shown that the H1N1 swine influenza is a contagious disease and can spread among the household members of the infected person (8% to 19% of contacts likely to get infected) [4]. The infected person may be infective to others from one day before the onset of symptoms and up to 7 or more days after becoming symptomatic [7]. The 2009 H1N1 pandemic was not a zoonotic disease, but spread from human to human. Also, the virus does not spread by eating cooked pork. The incubation period of swine flu ranges from 1-7 days (likely 1-4 days) [1,4].

Clinical manifestations: The clinical manifestations of the H1N1 influenza are similar to any other flu. The symptoms include: fever, chills, upper respiratory tract symptoms (rhinorrhea, cough, sore throat, watery eyes, redness of eyes and oropharyngeal mucosa), malaise, myalgia, arthralgia, headache, dyspnea, tachypnea, vomiting and diarrhea [1]. The immuno-compromised patients and the patients in extremes of age (infants and elderly) may show atypical presentations like altered mental status and respiratory distress [1].

Persons at high risk of getting a severe infection with swine flu [7]:

- Children younger than 5 years old
- Elderly persons (65 years of age and older)
- People with disease conditions like diabetes mellitus, chronic pulmonary condition (including asthma), congestive cardiac failure, renal failure, hepatic failure, hematological abnormalities (including sickle cell disease), neurologic or neuromuscular disorders
- Immuno-compromised patients (caused by medications or by HIV)
- Pregnant women;

- Residents of nursing homes and other chronic-care facilities;
- Obesity.

Severe cases of swine flu may present with the following clinical syndromes [8]:

- diffuse pneumonitis/pneumonia with rapid progression associated with severe, refractory hypoxemia (acute respiratory distress syndrome), in relatively healthy teens or adults requiring extracorporeal oxygenation support;
- decompensation of the chronic underlying diseases like congestive heart failure, chronic renal failure, chronic liver disease or end-stage liver disease, poorly controlled diabetes, or immune-compromised patients ;
- acute exacerbation of chronic obstructive pulmonary disease and asthma in those with pre-existing disease;
- secondary bacterial pneumonia (often with gram positive pathogens including *S. pneumoniae, S. aureus* and Group A Streptococci) on a background of mild or severe H1N1 influenza infection;
- bronchiolitis and croup in infants and young children requiring hospitalization

Case definition for swine flu:[4] **A suspected case** - a person with acute febrile viral like illness, having flu like respiratory symptoms and either of the following: resides in a state with confirmed cases of swine flu OR has traveled to a state/country within last 7 days where there are one or more confirmed cases OR has been in close contact with a suspected/confirmed case of swine flu with last 7 days.

A probable case- a person with flu like symptoms who is positive for influenza A, but the subtype (H1 or H3) cannot be determined by the tests.

A confirmed case- a person having flu like symptoms with laboratory-confirmed novel influenza A (H1N1) virus infection by real-time polymerase chain reaction (RT-PCR) or viral culture or fourfold rise in new influenza A(H1N1) virus-specific neutralizing antibodies.

Diagnosis: In a patient with suspicion of swine flu, diagnosis of H1N1 influenza virus requires collection of respiratory specimen (nasopharyngeal swab, throat swab, nasal aspirate or nasal washing) within the first 4 to 5 days of onset of illness (when an infected person is most likely to be shedding virus). The sample is then tested by using reverse transcriptase polymerase chain reaction (RT-PCR), virus culture or isolation, and assays to detect a 4-fold rise of influenza virus antigens [7, 9,10]. The other Rapid Antigen Tests available have low sensitivity and specificity so not recommended for diagnosis [4,7,10]. RT-PCR is considered the gold standard for diagnosis with high sensitivity and specificity [10].

Management: The management of the H1N1 influenza infected person consists of isolation precautions to curtail its spread to the contacts of the patient, treatment with antiviral medicines, supportive care and treatment of the complications. The contacts of the patient who are at risk of getting infected are also followed up.

General measures: Isolation or quarantine of the infected patient, supportive care consisting of bed rest, increased fluid consumption (oral or intravenous), cough suppressants, and antipyretics and analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs for fever and myalgias/arthralgias.

Antiviral Therapy: The antiviral drugs that are available and approved for the prevention and treatment of influenza can be divided into two classes: Adamantanes (Amantadine and Rimantadine) and neuraminidase inhibitors (NAIs) (Oseltamivir, Zanamivir, Peramivir, Laninamivir) [3,4]. The strain of the pandemic H1N1Influenza A (swine flu), has been found to be resistant to adamantanes, so the only choice of treatment are the NAIs [3,4]. The NAIs act by inhibiting the escape of the virus from the infected cell and therefore controlling the spread of infection [4]. The antiviral must be started as soon as possible as the studies have shown their effectiveness to be maximized, if initiated within 48 hours of developing clinical symptoms [1,4,10,11]. In severe cases or high risk cases the medicine can be started later also [4,10,11].

Oseltamivir and Zanamivir are the two drugs which are approved and widely used. Oseltamivir is available in the form of oral capsules and can be used in patients above one year of age, for both treatment and chemo prophylaxis. Oseltamivir is the drug of choice recommended by the Indian government. It is usually well tolerated with some gastrointestinal side effects (nausea, vomiting) with high doses and less common side effects includes anaphylaxis, rashes, insomnia, vertigo and bronchitis [11]. Zanamivir is available in the form of dry powder, to be administered by inhalational route. Zanamivir is recommended as treatment for patients above seven years of age and as chemo prophylaxis in patients above five years of age [11].

The resistance to the antiviral drugs has been reported in quite a few numbers of cases worldwide [11]. Various studies have shown the H1N1 resistant to the Oseltamivir, requiring the use of Zanamivir as the drug of choice in these patients [4,12,13]. Resistance to Oseltamivir is commonly seen in patients who were exposed to the drug previously and also in immune-compromised patients (hematological malignancies, chronic renal or liver failure).

WHO guidelines for H1N1 influenza treatment [4]**:** These guidelines by WHO includes patients in all the age groups and pregnant patients too. The patients who present with uncomplicated illness and are not in the high risk group of developing severe illness may not be treated with antiviral therapy. The confirmed or the highly suspected patients with uncomplicated illness, but in the high risk group of developing severe illness

should be treated with antiviral therapy with NAI as soon as possible, preferably within 48 hours of onset of symptoms.

The patients who present with severe or progressive clinical symptoms (including children and adolescents), Oseltamivir should be initiated as soon as possible. It is not recommended to wait for the confirmatory lab report of influenza virus infection as a negative laboratory test does not necessarily exclude the diagnosis of swine flu. Therefore the empirical therapy with antiviral should be started immediately.

Patients suffering from severe and complicated H1N1 influenza pneumonia (mostly seen in immune-compromised patients like post transplant patients, hematological malignancies), the recommended dose of Oseltamivir is twice the standard dosing, that is 150mg twice daily and that too for longer duration of 10 days (standard therapy is for 5 days) [4,10-14]. This longer and higher dose treatment is required taking into consideration the decreased enteral absorption of Oseltamavir in critically ill patients and also the prolonged duration of viral replication and shedding seen in these patients [14].

Government of India guidelines for H1N1 patients [4, 15]**:** These guidelines were issued to contain the spread of swine flu considering the highly contagious nature of H1N1 influenza.

Category A patients: These are the patients presenting with mild fever, cough, sore throat with or without myalgia, headache, diarrhea, or vomiting. They do not require treatment with Oseltamivir, symptomatic treatment may be offered and must be re-assessed after 24-48 hours. They can be managed at home while taking precautions not to be in close contact with high risk contacts. No H1N1 test is required, unless the symptoms progressively get worse.

Category B patients: The patients with signs and symptoms of Category A but having high grade pyrexia associated with severe sore throat maybe started on Oseltamivir with home isolation. This category also includes patients of category A with high risk of severe infection (infants and young children, pregnant women, elderly over 65 years of age, patients with chronic diseases of lung, liver, renal and heart, blood disorders, uncontrolled diabetes mellitus, malignancy, patients on long term steroids). The category B patients also do not require test for H1N1 but need home isolation and treatment with broad spectrum antibiotics for community acquired pneumonia.

Category C patients: This category includes the patients having signs and symptoms of category A and B along with worsening of their chronic underlying disease condition, or signs of severe pneumonia (cyanosis, respiratory distress, hypotension, altered sensorium, hemoptysis, chest pain) or children with inability to feed properly, breathing difficult, persistent pyrexia, increased sleepiness). All the patients in this category require testing for H1N1 influenza along with hospitalization and immediate treatment.

Adamantanes (Amantadine and Rimantadine) are contraindicated to be used in pregnant women and children aged <1 year having H1N1 influenza infection considering the risk of adverse effects. The treatment dosage and duration for Oseltamivir is given in Table 1.

Table 1: Oseltamivir dosing

By Weight	For Infants (By Age)
For weight <15 kg: 30 mg for 5d	<3 months: 12mg bid for 5d
15 to 23 kg: 45 mg bid for 5d	3 to 5 months: 20 mg bid for 5d
24 to <40kg: 60mg bid for 5d	6 to 11 months: 25 mg bid for 5d
>40kg: 75mg bid for 5d	

Supportive care: This includes bed rest, administration of oral (intravenous in severe cases) fluids, broad spectrum antibiotics to treat or prevent secondary bacterial pneumonia (mostly gram positive), nutrition (enteral or parenteral as tolerated), electrolyte balance, oxygen therapy or in severe persistent hypoxia use of ventilator support or extracorporeal oxygenation in cases of severe refractory acute respiratory distress syndrome, and vasopressors for shock.

Salicylates (aspirin) are contraindicated during infection with influenza due to their potential to cause Reye's syndrome. The use of high dose corticosteroids has been shown to have no benefit, rather it causes more harm (low dose of 200mg/day can be used in cases of refractory septic shock) [10,11].

Discharge policy [11]**:** In various studies an observation was made that few cases after the treatment with Oseltamivir, continued to be positive for the RT-PCR test for H1N1, despite being asymptomatic. These patients carry minimal chances of infectivity for other contacts. The following recommendations were made:

a. Patients who have responded well to treatment with Oseltamivir after 48-72 hours and have become totally asymptomatic post treatment should be discharged after 5 days of complete treatment. A repeat test is not required.
b. Patients who are symptomatic (fever, sore throat, cough, mild respiratory distress, hypoxia) after 5 days of treatment with Osletamivir, should be continued with the antiviral for another 5 days. A repeat test is not recommended if these patients recover and become asymptomatic.
c. Patients who are symptomatic or in severe respiratory distress (where secondary bacterial infection is not the cause) and continue to be positive for H1N1 RT-PCR test, even after 10 days of treatment with Oseltamivir, then the resistance to this antiviral must be considered.

Prevention [4,16]**:**

Quarantine: The close contacts of the suspected, probable and confirmed swine cases are advised to remain at home and avoid travelling for at least 7 days after the last contact with the case and monitored for any symptoms. If any symptoms are reported the contacts should undergo prompt test for H1N1 influenza and consult physician.

If admitted in a health care facility, the patient should be managed in a single-patient room with the door kept closed, air condition ducts with high particulate air filter and with negative-pressure [1,4].

Cough and Hand hygiene: Highly recommended and most important for all the patients and their contacts. Hands must be frequently washed with soap and water/alcohol based hand rubs/ antiseptic hand wash and then thoroughly dried. The infected persons should cover their nose and mouth with a single use tissue while coughing or sneezing, and the tissue must be disposed off immediately.

The health care workers who are involved in the direct care of the patients with confirmed or suspected swine flu infection should observe strict contact and droplet precautions (use of gowns, eye protection, gloves, disposable N95 respirators) [1,4].

Chemo-prophylaxis: Antiviral medicines can be used for prophylaxis in contacts of the patient with high risk for complications and the healthcare personal (treating physician, nurses, and paramedical staff). The drug of choice is Oseltamivir, given to adults in the dose of 75 mg once a day until 10 days after the individual's last contact with the patient, and can be given for maximum period of 6 weeks [16].

Vaccination [16]**:** WHO recommends vaccination of all the healthcare staff coming in contact with the suspected or confirmed cases of swine flu (physicians, nurses, paramedical, ambulance staff). The injectable vaccine against influenza A/H1N1 is available and has to be taken yearly. The immune response of the body takes about 2-3 weeks to develop after vaccination and till then chemo-prophylaxis can be used.

There is a need to regularly update the guidelines for management of such a deadly disease by the government agencies also its imperative to disseminate such healthcare information to all [17].

Conclusions

The swine flu has emerged as a dreadful infectious disease all over the world. The preventive measures, chemoprophylaxis and vaccination have played a major role to curtail its spread. The mutations in the virus resulting in resistance to the antiviral treatment have become a cause of concern and being researched upon. In India, with the new cases coming every year this disease has resulted in a panicky situation. More research is needed to understand and control the spread of this disease.

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