H1N1 Influenza-A : The Pandemic Resurgence and Emerging Strategies in Management

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ABSTRACT

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'Influenza' is the respiratory infection resulting from an infection of the respiratory system by a virus specific for the system. H1N1 Influenza is a novel virus introduced to the word for the first time in April 2009. H1N1 spread to many parts of the world and is a pandemic now. It is different from the seasonal flu occurring every year in many parts of the world during winter and early spring seasons. It is the same in terms of the signs, symptoms and the clinical course. But it is different in terms of the infectivity. Because of the fact that the virus is new, the general population at large has no resistance against the virus.

The clinical spectrum of the disease is explained.

The World Health organization published the new recommendations for the treatment of H1N1 based on the prevailing drug sensitivity and drug resistance across the world, in February 2010.

Keywords: Influenza, Pandemic, Pigs, Oseltamivir, WHO Recommendations

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WHAT IS H1N1 INFLUENZA?

'Flu' is the abbreviation of the word Influenza. 'Influenza' is the respiratory infection resulting from an infection of the respiratory system by a virus specific for the system. H1N1 Influenza is a novel virus introduced to the word for the first time in April 2009. It probably originated in the pig farms in Mexico. Pigs turned out to be the mixing vessel for the newly assorted virus. Once the virus was transmitted to human beings from pigs, it became a human infection. Pigs were no longer involved in the transmission of the virus to the human beings. Therefore it would be incorrect to call this infection as 'swine flu' anymore.

The Pandemic of 2009

H1N1 spread to many parts of the world and is a pandemic now. It is different from the seasonal flu occurring every year in many parts of the world during winter and early spring seasons. It is the same in terms of the signs, symptoms and the clinical course. But it is different in terms of the infectivity. Because of the fact that the virus is new, the general population at large has no resistance against the virus. Since it involves the majority of subjects, the morbidity and to some extend the mortality is higher than the seasonal flu. Even though the overall mortality is 0.1-0.3%, because of the shear increase in the number of population affected the death rate became high.

The Virus

Genetic analyses of this virus have shown that it originated from animal influenza viruses and is unrelated to the human seasonal H1N1 viruses that have been in general circulation among people since 1977. The virus is named as H1N1 based on the same principle applied for the international nomenclature of Influenza viruses. H1 – indicating the type of Hemagglutinin enzyme on the virus surface, N1 – indicating the type of Neuraminidase enzyme, Influenza –A – the type of influenza which is more lethal to human beings and 2009 –indicating the year of origin of the virus. The Human Influenza virus and the Avian Influenza virus prevalent in foul probably infected the swine. Inside the swine a re- assortment of the virus occurred resulting in a major antigenic shift. This was responsible for the emergence of the new strain of Influenza virus.

Current Epidemiology

The impact of pandemic H1N1 2009 Influenza - A virus has been highest in the pediatric and young adult population, when measured by the attack rates and the hospitalization rates. There is enough reason to

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believe that H1N1 influenza A virus may displace other circulating influenza A viruses, at the same time a novel influenza virus like H5N1 remain a pandemic threat.

Situation in Kerala

During the last year Kerala state was hit like any other state in India with the H1N1 pandemic infection. According to the Heath Services Department Data obtained from the H1N1 Cell in Trivandrum, 2560 cases of swab positive reports occurred of which 80 patients died. Among them 22 were associated with pregnancy or post partum period. During the second wave of infection starting from May 1st this year the number of cases reported till July 7, 2010 is 946, among these 43 died and 14 were related to pregnancy. This time around, Kerala and Maharashtra were the two states predominantly hit by the pandemic resurgence

H1N1 infection in humans

Human infection with influenza virus can vary from asymptomatic infection to uncomplicated upper respiratory tract disease and to serious complicated illness that may include exacerbation of other underlying conditions and severe viral pneumonia with multi organ failure. Since a wide range of pathogens can cause influenza like illness (ILI), a clinical diagnosis of influenza should be guided by clinical and epidemiologic data and can be confirmed by laboratory tests. However, on an individual patient basis, initial treatment decisions should be based on clinical presentation and epidemiological data and should not be delayed pending laboratory confirmation.

Clinical Features of Uncomplicated Influenza

Symptoms start as fever, cough, sore throat, nasal congestion, rhinorroea, headache, muscle pain and malaise, but not as shortness of breath / dyspnoea. Patients may present with some or all of these symptoms. Gastrointestinal illness may also be present, especially in children but without evidence of dehydration.[1] Some patients with uncomplicated illness may not have fever, especially those who are immunocompromised and elderly.

Complicated or severe Influenza

Patient presents with breathlessness, tachypnoea, dyspnoea, hypoxia and cyanosis with or without radiological signs of lower respiratory tract infection. Viral bronchopneumonia is suggested by bilateral fluffy non-homogenous opacities of both lung fields. Central nervous system involvement may manifest in the form of encephalitis or encephalopathy. Gastrointestinal symptoms may be complicated with severe dehydration in children. Few patents develop secondary complications like renal failure, multi organ failure and septic shock. Other complications can include rhabdomyolysis and viral Myocarditis.[1] The illness may be complicated by viral pneumonia requiring hospital admission

Patients with underlying chronic conditions present with signs and symptoms of exacerbation of these conditions. These include bronchial asthma, chronic obstructive pulmonary disease, chronic liver diseases, congestive heart failure or chronic renal failure.

Progressive disease

Patients who present initially with mild illness may progress to have more severe disease. Rapid and unexpected deterioration may occur within 24 hours in certain patients. Close observation of the patient is mandatory to identify these signs of deterioration. These symptoms and signs include shortness of breath at rest or during exertion, dyspnoea, tachypnoea, presence of cyanosis, hemoptysis, chest pain and fall in blood pressure. In children the only evidence for the same may be fast or labored breathing. Hypoxia as indicated by pulse oximeter or arterial blood gas analysis is highly suggestive of catastrophic course of illness. CNS signs like altered level of consciousness or convulsions are suggestive. Severe weakness, lethargy, paralysis and signs of dehydration develop in some patients.

High risk groups

Even though certain patients with H1N1 virus infection are recognized to be in the high risk group, the fact remains that up to 1/3rd of patients admitted to the intensive care units are previously healthy patients not belonging to any known high risk groups.

The following risk groups are identified for H1N1 Influenza A virus infection:

1. Infants and young children, in particular <2 years
2. Pregnant women
3. Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
4. Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure).
5. Persons with metabolic disorders (e.g. diabetes)
6. Persons with chronic renal disease, chronic hepatic disease, certain neurological conditions (including neuromuscular, neurocognitive and seizure

disorders, but not including autism spectrum disorders),

7. Hemoglobinopathies, or immunosuppression, whether due to primary immunosuppressive conditions, such as HIV infection, or secondary conditions, such as immunosuppressive medication or malignancy.
8. Children receiving chronic aspirin therapy
9. Persons aged 65 years and older.

The higher risk during pregnancy should be applied to a two week post partum period.

There are limited data from the pandemic on the extent to which HIV infected patients are at higher risk of complicated or severe illness, though there are some data from seasonal influenza indicating a higher risk and limited data relating to mortality from pandemic influenza.

Pharmacological management of H1N1 Influenza A virus infection

The World Health organization published the new recommendations for the treatment of H1N1 based on the prevailing drug sensitivity and drug resistance across the world, in February 2010.

The major recommendations are as follows:

1. Patients who have severe or progressive illness should be treated with Oseltamivir as soon as possible. The dose of treatment in adults is 75mg BID for 5 days.
    a. This recommendation applies to all patient groups including pregnant and post partum women up to two weeks after delivery and breast feeding women. Treatment should be started as soon as possible. Laboratory confirmation of Influenza virus infection is not necessary for the initiation of treatment.
    b. A negative laboratory test for H1N1 does not exclude the diagnosis in all patients. Therefore early empiric treatment is strongly recommended. The evidence from clinical trials from uncomplicated influenza suggests that most patients benefit from antiviral treatment started within 48 hours of onset of symptoms.
    c. Anti-viral treatment should be maintained without break until viral infection is resolved or satisfactory clinical improvement occurs. Patients who have severe or progressive clinical illness, but who are unable to take oral medications may be given Oseltamivir through nasogastric tube or orogastric tube (mechanically ventilated patient).
2. In situations where oseltamivir is not available or not possible to use Oseltamivir (eg: drug allergy) and patients who have severe or progressive clinical illness should be treated with inhaled Zanamivir, where feasible.
3. Consideration should be given to the use of higher doses such as 150mg twice daily (for adults), and for longer duration of treatment depending upon the clinical response.
    a. This recommendation takes account of the impaired host immune response, such that standard anti-viral regimens may not be as effective in clearing the virus.
    b. The higher probability of emergence of oseltamivir resistant virus in these patients.
4. When a patient with Influenza Virus A infection present in the immediate setting of severely immunosupressed patients, the later may be offered chemoprophylaxis with oseltamivir or zanamivir
    a. Oseltamivir 75mg OD for 10 days is the recommended dose of oseltamivir in these situations.
    b. This recommendation takes account of the importance of prevention of infection in this vulnerable group of patients.
    c. Infection control procedures should be rigorously applied in this context including vaccination against seasonal and pandemic influenza, when ever feasible.
    d. In severely immuno compromized patients, chemoprophylaxis should be continued till there is no evidence of ongoing viral replication in any patient in the same room.
    e. Other infection control procedures include hand hygiene, gowns, gloves and masks to be used by all health care personal caring for these group of patients.
5. Patients who have uncomplicated illness due to confirmed or strongly suspected viral infection and are in a group known to be at higher risk of developing severe or complicated illness, should be treated with oseltamivir or zanamivir as soon as possible.
    a. This recommendation applies to all patient

groups, including pregnant and postpartum women, up to 2 weeks following delivery, and breastfeeding women.

b. Patients who have uncomplicated illness, and are not in a group known to be at higher risk of developing severe or complicated illness, may not need treatment with antivirals.

c. Patients who present for medical attention, but do not receive anti-viral treatment should be counseled for signs of progression or deterioration of illness and advised to seek medical attention immediately, should their condition deteriorate or persist.

6. Children who have severe or progressive clinical illness should be treated with oseltamivir as soon as possible.

   a. This recommendation applies to all children, including neonates and young children (in particular those less than 2 years of age).

   b. Oseltamivir treatment doses for children from 14 days up to 1 year of age should be 3 mg/kg/dose, twice daily.

   c. Powder for oseltamivir oral suspension, where available, is the preferred formulation for children unable to take the capsules.

7. Patients who have severe or progressive clinical illness with virus resistant to oseltamivir but known or likely to be susceptible to zanamivir, should be treated with zanamivir.

   a. Intravenous zanamivir is likely to be the preferred formulation in this setting.

   b. This recommendation takes into account the practical difficulties in administering inhaled zanamivir to severely ill patients in its current dosage form as inhalation.

8. Pregnant women and children aged less than 1 year with uncomplicated illness due to seasonal influenza A (H1N1) virus infection should not be treated with amantidine or rimantidine.

9. If higher risk individuals have been exposed to a patient with influenza, consider presumptive treatment with oseltamivir or zanamivir.

   a. This recommendation takes account of reports of oseltamivir resistance following the use of post-exposure prophylaxis failure.

10. Patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless otherwise indicated or as part of approved research protocol.

    a. A lack of evidence of benefit in these patients.

    b. Risk of harm, including opportunistic infection and prolongation of virus replication.

    c. The need for corticosteroid treatment for other conditions such as asthma, COPD, ongoing anti inflammatory treatment, and adrenal insufficiency.

Use of antivirals when drug resistance is known or suspected.

In general, when it is known that the infection is highly resistant to the antiviral drug, the antiviral medication should not be use. The use of combination treatment or alternative drugs may be appropriate in this circumstance. Of current concern is the mutation H275Y in the neuraminidase that confers resistance to oseltamivir, not zanamivir. When Intravenous Zanamivir is not available, the next choice would be intravenous peramivir, where ever available

Vaccination for Human H1N1 Influenza Virus

Regulatory authorities have approved pandemic vaccine in a number of countries including India. Most of these vaccines are being produced using chicken eggs, while a few manufacturers are using cell culture technology for vaccine production. Production of the pandemic influenza vaccines continued, but in some countries including India, demand for vaccination is greater than the supply. This gap will narrow as more vaccines become available over time.

WHO continues to recommend that health care workers be given first priority for early vaccination to protect themselves and their patients, and help keep health systems functioning as the pandemic evolves. Other groups at higher risk for severe illness, based on clinical studies, should also be considered as priorities. These other groups include pregnant women; those aged above 6 months with one of several chronic medical conditions.

CONCLUSIONS

1. H1N1 Influenza A 2009 remains a major threat to human lives in the second half of 2010, throughout the world.
2. Kerala is one of the worst hit states in India, most probably due the population density and the over-crowding in cities.
3. The infection in relation to pregnancy or immediate post partum period remains the major cause of mortality due to hitherto unidentified reasons.
4. Dyspnoea and hypotension at presentation can be considered as the major indicator of mortality in the young population.
5. Early treatment with Oseltamivir, can effectively reduce the morbidity and mortality as well as the viral load, thereby helping in prevention of spread of infection in the community.
6. Oseltamivir resistance has not been reported in any part of India so far, and therefore remains the drug of choice in patients with Influenza A infection.
7. Continued surveillance of new cases and their isolation from community at large, as well as the possibility of emergence of drug resistance are the major concerns at present.

END NOTE

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