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REVIEW ARTICLE

Influenza in Children

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Abstract In children, influenza is one among the commonest causes of acute respiratory illness and loss of school days. Influenza A, B, and C are 3 types of viruses responsible for illness. Type A virus has many subtypes based on antigens but Type B and Type C viruses have no known subtypes. Currently, influenza A/H1N1, A/H3N2, and influenza type B viruses are circulating in humans. Transmission of influenza occurs through droplets from infected person or through direct contact with person or fomites. Clinically, influenza is characterized by acute onset fever, chills, running nose, cough, sore throat, headache and myalgia. Mostly, febrile illness lasts for 3–4 d with resolution of disease in 7–10 d. Confirmation of influenza can be done either by virus culture, RT-PCR or specific neutralizing antibodies in blood. Basic principles of management include prompt institution of infection control measures, early identification of children at higher risk, supportive care and antiviral drugs. Vaccine and chemoprophylaxis are two commonly used methods for prevention of influenza. Currently, inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are available for use with good efficacy. Cough etiquette, use of face masks and hand hygiene are the most important measures to reduce the risk of infection transmission from person to person.

Keywords Influenza · H1N1 · Oseltamivir · Influenza vaccine

Learning objectives: After reading this article readers should be able to
- understand pathogenesis and epidemiology of influenza
- identify the common features and complications of influenza
- manage influenza in children
- decide when children should be referred to the specialist

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Introduction

Acute respiratory illnesses are the most common problems of childhood and influenza viruses are among the common viruses responsible for them. Influenza infection rate is higher in preschool children. It is generally considered as a mild disease, however, it may contribute to significant mortality, especially in children with underlying chronic medical conditions. Influenza viruses are known to cause seasonal outbreaks, epidemics and pandemics. The first pandemic of influenza H1N1 virus was reported in 1918, infecting 500 million people across the world and killed 50–100 million people, 3–5 % of the world's population [1]. The last pandemic with influenza virus (swine-origin H1N1 strain) was reported in 2009 and accounted for the loss of about 17,000 people across the globe [2]. In India also, pandemic H1N1 strains are circulating and more than 2500 deaths have been reported till date [3].

Etiology

Influenza viruses are RNA viruses belonging to the Orthomyxoviridae family. There are three types of influenza viruses (Type A, B and C). Segmented viral genome is encased in a lipid containing surface envelope having Hemagglutinin (H) and Neuraminidase (N), two major surface antigens. Subtype of influenza virus is determined by these H and N antigens. Type A virus has many subtypes with a different combination of 17

H and 10 N antigens (*e.g.*, H1N1, H3N2, H5N1). Type B and Type C viruses have no known subtypes [4].

Type A viruses are capable of infecting multiple species (Human, Avian, Swine, Equine). They are antigenically unstable, and known to undergo mutations within the viral genome (antigenic shift) causing sporadic cases, seasonal outbreaks and epidemics. Whereas reassortment of genetic material among the subtypes results in a new virus strain (antigenic shift) for which the population has no immunity. This new strain may become easily transmissible from person to person, posing a potential risk of epidemics or pandemics in humans.

Type B viruses infect humans only and have no known animal reservoir. They have less frequent antigenic variations in genome, limiting themselves to cases of seasonal influenza or rarely, epidemics. Type C viruses infect humans and pigs and cause mild upper respiratory disease only. They are antigenically stable and do not cause epidemics [4].

Epidemiology

Currently three strains of influenza virus are mainly circulating in humans, two of type A (H1N1 and H3N2) and one of type B. Each year's strain is new to infants, as they lack their own protective antibodies. Antibodies transferred from the mother protect only for first few months of life. The attack rate of primary influenza infection is highest in young children and they shed virus for longer than adults [5].

Though sporadic cases are reported round the year, outbreaks in temperate zones occur in winter and in tropic and sub tropics in rainy season. Report of Influenza Surveillance Network in India shows an increase in influenza cases in the month of June to September, coinciding with the monsoon in India [2, 6]. Overcrowding helps in rapid transmission of infection, mostly affecting urban and sub urban areas. Higher attack rate is also observed in army barracks, schools, colleges and public transport system.

Disease transmission occurs through droplets from infected person or through direct contact with the person or fomites. Incubation period of influenza is short; 1–2 d only. Peak viral shedding occurs on first day of illness but communicable period may last up to 7–10 d in young children. Children on immunosuppressive drugs or immunodeficiency state shed virus for longer period. Antibodies appear in first week and reach maximum level in two weeks. Cross immunity between different strains does not occur and immunity drops down to pre infection level by about 12 mo period [5, 7].

Influenza Virus Infections in Humans

Seasonal Influenza

Seasonal disease caused by circulating influenza viruses occurs in humans every year. All three types (A, B, and C) of influenza viruses can cause seasonal disease.

Pandemic Influenza

Type A influenza virus is mainly responsible for pandemics. As a result of major antigenic change in circulating influenza viruses, a new strain may emerge for which population has no immunity. This may result in rapid spread of influenza from person to person and the pandemic. In 2009, a strain of influenza A (H1N1) emerged and caused pandemic. This pandemic A (H1N1) virus is now established as a seasonal influenza virus in humans.

Zoonotic or Variant Influenza

When animal influenza viruses infect their natural animal host, they are named for that host, such as avian influenza, swine influenza, or equine influenza. Rarely, humans can also get infected with these animal influenza viruses, resulting in mild to severe respiratory illness [8].

Clinical Features

Like any other viral respiratory illness, clinically, influenza is characterized by acute onset fever, chills, running nose, cough, sore throat, headache and myalgia. Diarrhea, vomiting and abdominal pain may be seen. In uncomplicated cases, the disease mostly presents as mild upper respiratory illness and the febrile illness lasts for 3–4 d with resolution of disease in 7–10 d. Dry cough however, may last longer in some cases [6, 9, 10]. The infants and young children may look very sick and toxic and present with illness resembling sepsis, pneumonia, croup or bronchiolitis. Though overall prognosis for recovery from influenza is good, deaths are reported even in children without risk factors. Probability of death is higher in first 3 d of illness [9].

Complications

Acute otitis media, sinusitis, pneumonia and bronchitis are common complications of influenza. Secondary bacterial invasion of damaged respiratory epithelium with *Streptococcus pneumoniae* or *Staphylococcus* is mainly responsible for these complications. Children with underlying bronchopulmonary dysplasia, asthma, cystic fibrosis, heart disease and

neuromuscular diseases are at higher risk for severe disease and complications [5].

Diagnosis

Diagnosis of influenza is usually made on the basis of clinical features of flu like symptoms without localization, especially if linked epidemiologically to influenza cases. Routine investigations may show nonspecific hematological and radiological changes, including leucopenia or infiltrates/atelectasis in some cases. Laboratory confirmation is not required in all cases. However, it should be done in all children with severe disease requiring hospitalization or in children who are at a higher risk for complications [11].

Confirmation of influenza can be done by:

(1) Virus culture
(2) Real time polymerase chain reaction (RT-PCR)
(3) Four-fold rise in virus specific neutralizing antibodies.

Respiratory specimen for virus culture and RT-PCR may be obtained from nasopharyngeal/throat swab or tracheal aspirates in intubated patients, preferably within 4–5 d of illness. Among all these tests, Real-time polymerase chain reaction (RT-PCR) test remains the mainstay of diagnosis. The sample collection and transportation should be done as per the guidelines [11].

Case Definition

Suspected Case

Acute febrile respiratory illness with onset within 7 d of close contact with a confirmed case of influenza or within 7 d of travel to an area where confirmed case has been reported, or resides in an area where there are one or more confirmed influenza cases [12].

Probable Case

Any suspected case of influenza with a positive test for influenza viral infection or a person with clinically compatible illness who died of an unexplained respiratory illness and epidemiologically linked to a probable or confirmed case [12].

Confirmed Case

Any person with acute respiratory illness with confirmed influenza infection from WHO certified laboratory, with either RT-PCR or culture or four fold rise in virus specific antibodies [12].

Treatment

The basic principles of management are

- Prompt institution of infection control policy to minimize healthcare or household spread of disease.
- Early initiation of antiviral drugs if indicated and other supportive care to prevent severe disease and complications.
- Early identification of children at higher risk for disease prevention and surveillance.

Categorization of Influenza A H1N1 cases during screening for home isolation, testing treatment, and hospitalization is shown Table 1 [3, 7].

All clinical or confirmed cases of influenza requiring hospitalization should be managed in isolation room. If it is not possible, these cases can be managed in well ventilated isolation ward with a bed to bed distance of at least one meter and provision of separate material and supplies and waste disposal.

Treatment options primarily depend on the disease severity. Children with mild disease can be managed at home with supportive care including rest, adequate fluid intake, paracetamol for fever and myalgia. Aspirin should always be avoided due to risk of Reye's syndrome. Hospitalization and antiviral drugs are not indicated in mild disease.

Children with risk factor or moderate to severe disease or requiring hospitalization are managed with maintenance of hydration, oxygenation, antipyretics, and antiviral drugs. Secondary bacterial infection should be suspected if deterioration in general condition, prolonged fever or recurrence of fever is observed. In such cases, appropriate antibiotics should be used as per the hospital policy. The author prefers using a combination of Ceftriaxone (50 mg/kg/dose, twice a day) and Vancomycin (15 mg/kg/dose, three times a day). Most of the children with uncomplicated influenza feel better by second or third day of illness [5].

Antiviral drugs used for the treatment of influenza are Oseltamivir, Zanamivir, Amantadine and Rimantadine. However, Oseltamivir is the one which is widely available and easy to administer. It can be used for treatment and prophylaxis both. Though Oseltamivir is generally well tolerated in children, nausea, vomiting, abdominal pain, epistaxis and rash may be observed.

When to Refer to Specialist/Higher Centre

Most of the children can be managed at home or primary health center, however, children with following conditions should be considered for early referral.

Table 1 Categorization of influenza A H1N1 cases during screening for home isolation, testing, treatment, and hospitalization

Categories	Clinical features	Investigations	Treatment
Category-A	Mild fever plus cough / sore throat with or without body ache, headache, diarrhea and vomiting	No testing for H1N1 is required Reassessed at 24 h to 48 h by the doctor	• No need for Oseltamivir; • Symptomatic treatment; • Avoid mixing up with public and high risk members in the family
Category-B (i)	In addition to Category-A: high grade fever and severe sore throat	No testing for H1N1 is required	• May require home isolation and Oseltamivir
Category-B (ii)	Children with mild illness but with predisposing risk factors; lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer, HIV/AIDS and on immunosuppression	No testing for H1N1 is required	• Requires home isolation and Oseltamivir • Consider broad spectrum antibiotics
Category-C	In addition to the above signs/ symptoms, if the patient has one or more of the following: somnolence, high/ persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, worsening of underlying chronic conditions	Testing for H1N1 is required but should not delay the treatment	• Immediate hospitalization • Oseltamivir • Supportive treatment • Broad spectrum antibiotics

– Children with mild disease having risk factors for severe disease or complications.
– Children with high fever and sore throat interfering with feeding.
– Children with persistent vomiting.
– Children not able to feed.
– Children on long term corticosteroid therapy.
– Children with severe respiratory distress (cyanosis, RR > 60/min, severe chest indrawing, $SpO_2 < 92$ %).
– Children with circulatory failure (cold hands, weak and fast pulse, capillary refill time > 3 s).
– Children with CNS symptoms (drowsiness, seizures).

Prevention

Vaccine and chemoprophylaxis are two commonly used methods for prevention of influenza, in addition to reduction of exposure to influenza cases. Currently, inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are available for use with good efficacy. LAIV is for intranasal administration while IIV is given by intramuscular route. American Academy of Pediatrics recommends annual seasonal influenza immunization for all children above 6 mo of age. Children with following conditions should receive the vaccine on priority:

– Children who are at higher risk for severe disease or complications of influenza, such as asthma and other chronic respiratory diseases, diabetes, immunosuppression, significant heart disease or progressive neurological diseases.
– Household contact and out of home care provider of children less than 6 mo of age.
– Pregnant and lactating mothers.

Children between 6 mo to 8 y of age who have received influenza vaccine in the preceding season should be given one dose, otherwise give two doses of IIV at 4 wk interval (age 6–36 mo – 0.25 ml, IM; > 3 y – 0.5 ml, IM). Children 9 y and above should be given only one dose of IIV (0.5 ml, IM) annually. It takes about two weeks after vaccination to develop protective levels of antibodies against influenza.

LAIV is given by intranasal route and recommended for use in children more than 2 y of age. Children between 2 and 4 y who have asthma or had wheezing in last one year, LAIV should be avoided. It is contraindicated in children receiving aspirin, antiviral medications, egg allergy, pregnancy and immunecompromised state. Other live vaccines should also be avoided within 4 wk of LAIV [13].

Chemoprophylaxis

Oral Oseltamivir and inhaled Zanamivir are approved for chemoprophylaxis; however Oseltamivir is the first choice. Prophylaxis should be given till 10 d after the last exposure, for a maximum period of 6 wk. Prophylaxis is not indicated for infants <3 mo of age. They should be referred to specialist for critical evaluation in this regard [5].

Infection Control Measures

At the level of community/individual [12].

1. Hand hygiene is the most important measure to reduce the risk of infection transmission from person to person. Hands should be washed with non-medicated soap and water/alcohol based hand rub after contact with respiratory secretions or contaminated surfaces.
2. Cough etiquette must be practiced by all the persons having flu like symptoms.
    - This includes covering nose and mouth with a clean cloth/ tissue paper while coughing.
    - Use tissue paper to clear respiratory secretions and dispose them in nearest available waste disposal bin.
    - Clean hands after contact with respiratory secretions or contaminated surfaces.
    - Stay at least one meter away from a person having cough or sneeze.
3. Use of mask is not routinely advised unless there is epidemic situation. As a matter of extreme precaution, family contacts may be advised to use surgical three layer mask.
4. While transporting the patient to a health care facility, patient and contacts both should wear three layered surgical masks.
5. The waste generated from influenza cases should be considered as clinical infectious waste.

Compliance with Ethical Standards

Conflict of Interest None.

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