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INFLUENZA VIRUS

Manisha Hanmante*, Hariom Raut, Manish Wahul, Deep Jawalkar

India.

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***Corresponding Author**
Manisha Hanmante
India.

ABSTRACT

1. Influenza is a highly contagious respiratory illness caused by the influenza A or B virus. It frequently manifests in outbreaks and epidemics across the globe, particularly during the winter months. Infected individuals excrete substantial quantities of influenza virus particles in their respiratory secretions, facilitating transmission through sneezing and coughing, which release large droplets. In immunocompetent adult patients, the average duration of influenza virus shedding is approximately five days, although it may extend to ten days or longer, especially in children, the elderly, individuals with chronic health conditions, and those with compromised immune systems. The onset of influenza is typically marked by a sudden high fever, muscle aches, headaches, and general malaise. These symptoms are often accompanied by respiratory issues, including a dry cough, sore throat, and nasal congestion. Following the initial phase, influenza can lead to complications affecting other organs such as the lungs, brain, and heart, potentially resulting in hospitalization. The most effective preventive measure against influenza is the administration of annual vaccinations. For severely ill patients, initiating antiviral treatment within two days of symptom onset is linked to decreased morbidity and mortality, with the most significant benefits observed when treatment begins earlier. Given the considerable impact of this disease, we have reviewed the most recent developments in the diagnosis and management of influenza.

KEYWORDS: Influenza, Human, Respiratory system, Vaccination.

INTRODUCTION

1. Influenza, commonly known as "flu," is a contagious viral infection primarily caused by the influenza virus types A and B. This illness predominantly impacts the upper respiratory system, including the nose, throat, and bronchi, and may occasionally affect the lungs as well

as other organs such as the heart, brain, and muscles. It is a global health concern, leading to significant rates of illness and death, manifesting in pandemic, epidemic, or seasonal forms. Seasonal flu epidemics typically occur each year during the autumn and winter months in temperate regions, resulting in considerable morbidity and mortality annually. The virus spreads through respiratory droplets released when an infected individual coughs or sneezes, with close contact (less than 1 meter) often necessary for transmission. While most individuals recover within a few days, influenza can lead to serious complications and even fatalities, particularly among high-risk populations, including pregnant women and those with compromised immune systems. Symptoms of influenza encompass high fever, body aches, headaches, extreme fatigue, dry cough, sore throat, and a runny nose. It is essential to distinguish influenza from the common cold based on clinical symptoms. Unique characteristics of influenza include its epidemic nature, driven by ongoing antigenic variations, and the associated mortality, which is partly attributed to pulmonary complications.

ETIOLOGY

1. Influenza viruses are classified within the family known as "Orthomyxoviridae," which encompasses RNA viruses exhibiting a range of antigenic properties. These viruses are categorized into three primary types: A, B, and C. The majority of influenza epidemics and outbreaks are attributed to types A and B, while type C is typically associated with isolated instances of mild upper respiratory symptoms.

The viruses exhibit either spherical or filamentous forms, enveloped by a membrane that contains glycoproteins and a single-stranded RNA genome. The two principal glycoproteins present on the surface of the influenza virus are hemagglutinin (H, or HA) and neuraminidase (N, or NA), both of which play crucial roles in the disease's pathogenesis.

For influenza type A, researchers have identified at least 16 highly variable hemagglutinins (H1 to H16) and 9 distinct neuraminidases (N1 to N9). Utilizing these diverse antigens, the influenza type A virus is further categorized into subtypes based on the unique combinations of their specific H or N proteins (for instance, H1N1 or H3N2). Additionally, the nomenclature of these viruses incorporates other factors, such as the location of initial isolation and the year of discovery.

The structure of the influenza B virus is comparable to that of type A; however, due to the stable antigenic characteristics of its HA and NA proteins, this virus does not possess subtypes. Nevertheless, minor antigenic variations have been observed since 1970, leading to the emergence of two antigenically distinct lineages of the virus.

Epidemiology

1. In 1933, researchers successfully isolated Influenza A, followed by the isolation of Influenza B seven years later. Influenza viruses are classified as an epidemic in specific geographic areas of the northern and southern hemispheres, occurring annually during the winter months. The severity, duration of the influenza season, the age groups most affected, and the rates of complications, including hospitalizations and fatalities, vary considerably from one influenza season to another. The predominance of H3N2 viruses is associated with more severe seasons, particularly impacting children and the elderly. The World Health Organization (WHO) carries out global surveillance of influenza virology, revealing that influenza viruses are isolated from humans in various geographic regions on a monthly basis. In temperate climates, influenza activity typically peaks during the winter season. In the Northern Hemisphere, outbreaks and epidemics generally take place from October to March, while in the Southern Hemisphere, influenza activity is most prevalent from April to August. In tropical regions, influenza viruses circulate continuously throughout the year.

Pathophysiology

1. Influenza is an acute illness that primarily affects the upper respiratory system, leading to inflammation of the upper respiratory tract and trachea. The acute symptoms typically last between seven to ten days, and the condition is generally self- limiting in most healthy individuals. The immune response to the viral infection, along with the interferon response, contributes to the viral syndrome characterized by high fever, nasal congestion, and body aches. Individuals in high-risk categories, such as those with chronic lung conditions, heart disease, or those who are pregnant, are at an increased risk for severe complications,

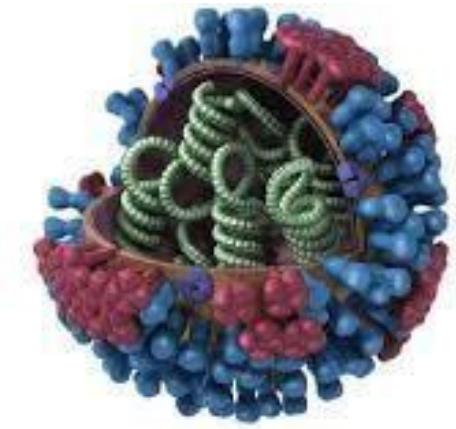
including primary viral pneumonia, secondary bacterial pneumonia, hemorrhagic bronchitis, and even death. These serious complications can arise within as little as 48 hours after the onset of symptoms. The virus begins to replicate in both the upper and lower respiratory tracts from the moment of exposure, with replication peaking approximately 48 hours later.

In terms of virulence, both neuraminidase and hemagglutinin play crucial roles, as they are the primary targets for neutralizing antibodies. Hemagglutinin facilitates the attachment of the virus to epithelial cells in the respiratory tract, thereby promoting the infection's progression. Neuraminidase is responsible for cleaving the bonds that hold the virus together, aiding in its dissemination. The H and N proteins are essential for the identification of influenza viruses.

Histopathology

1. Influenza viruses proliferate within the epithelial cells that line both the upper and lower respiratory tracts. The pathological manifestations remain consistent regardless of whether the infection is natural or experimentally induced. A definitive diagnosis of influenza requires serological, immunological, and molecular assessments, particularly through RT-PCR analysis of specimens from the upper or lower respiratory tracts. In mild cases, there are observable pathological alterations in the respiratory tracts; however, severe cases present distinct evidence of pneumonia-related pathological changes. The tracheobronchial alterations resulting from influenza infection can be characterized macroscopically by redness and inflammation accompanied by mucous and purulent discharge, while microscopically, there is desquamation and damage to the pseudostratified epithelium of the trachea and bronchi, with only the basal layer remaining viable yet inflamed.

Complication of influenza



Pneumonia

1. Pneumonia stands out as the most significant and prevalent complication associated with influenza, particularly among high-risk populations. This condition can manifest as a direct progression of the acute influenza syndrome when it is induced by the influenza virus (primary pneumonia) or may develop as a combination of viral and bacterial infections following a brief interval (secondary pneumonia).

Primary Influenza Viral Pneumonia

1. The condition manifests following the usual progression of influenza, characterized by a swift escalation of fever, dyspnea, cough, cyanosis, and respiratory distress. It predominantly affects individuals with pre- existing cardiovascular or pulmonary conditions, such as asthma. Clinical examination typically indicates bilateral lung involvement, while imaging studies reveal reticular or reticulonodular opacities, which may or may not be accompanied by additional consolidation. Distinguishing the radiological features of primary influenza pneumonia from pulmonary edema can be challenging due to the presence of perihilar congestion and hazy opacification, particularly in the lower lobes. In rarer instances, radiographs may display localized areas of infiltration. Established pneumonia severity assessment tools, such as CURB65 or the Pneumonia Severity Index, are not effective in guiding hospitalization decisions for primary influenza pneumonia, as these instruments were not designed or validated for use during an influenza pandemic. Therefore, meticulous history taking, physical examination, assessment of pregnancy or hypotension, and prompt identification of younger patients exhibiting low oxygen saturation, a respiratory rate exceeding 25 breaths per minute, and concurrent diarrhea are essential for making admission decisions. The characteristic radiographic features of primary influenza pneumonia include bilateral reticular or reticulonodular opacities, occasionally with superimposed consolidation. In less common cases, radiographs may reveal focal areas of consolidation absent of reticular opacities.

High-resolution computed tomography frequently demonstrates multifocal peribronchovascular or subpleural consolidation, with or without ground-glass opacities. The most severe instances can rapidly progress to acute respiratory distress syndrome and multilobar alveolar infiltrations. Patients in these severe cases typically exhibit worsening dyspnea and significant hypoxemia within 2 to 5 days following the onset of standard influenza symptoms. The rapid escalation of hypoxemia can lead to respiratory failure,

necessitating intubation and mechanical ventilation.

Secondary Bacterial Pneumonia

1. The occurrence of secondary bacterial pneumonia during the influenza pandemic of 1957–58 varied between 2% and 18%. A notable threefold rise in the incidence of secondary Staphylococcus aureus pneumonia was recorded during the 1968–69 influenza pandemic when compared to a non-epidemic period characterized by various pneumonia etiologies. Recently, cases of community- acquired methicillin-resistant Staphylococcus aureus have been identified following seasonal influenza; however, Streptococcus pneumonia remains another prevalent etiological bacterium. Patients typically present with classic influenza symptoms, followed by a maximum two-week period of improvement. Subsequently, a recurrence of symptoms such as fever, productive cough, and dyspnea, along with new consolidations observed in chest imaging, may occur in affected individuals.

Therefore, a biphasic pattern of signs and symptoms in patients diagnosed with influenza should raise suspicion for secondary superimposed bacterial pneumonia.

Non-Pulmonary Complications

1. Beyond its impact on the respiratory system, the virus can influence various other bodily systems, including the musculoskeletal, cardiac, and neurological systems. Myocarditis and pericarditis are uncommon yet significant complications associated with both seasonal and pandemic influenza. A prospective study revealed that 50% of adult patients with influenza, who did not report any cardiac issues, exhibited abnormal ECG results upon initial evaluation. Typically, myocarditis resolves within 28 days, with patients demonstrating normal heart muscle function and no decrease in ejection fraction. Although significant cases of myositis and rhabdomyolysis are rarely documented in seasonal influenza, varying levels of creatine phosphokinase elevation have been observed in numerous studies following seasonal or pandemic influenza infections. Mild myositis and myoglobinuria, often accompanied by tenderness in the legs or back, are primarily observed in children, though adults may also experience these symptoms, which can include discomfort while walking or standing.

Additionally, other rare complications such as Guillain–Barré syndrome, encephalitis, acute liver failure, and Reye syndrome may occur following an influenza A infection.

Diagnosis

1. Most influenza cases are identified based on their clinical symptoms, eliminating the necessity for laboratory testing. However, in certain situations, laboratory confirmation of influenza is required, which can be achieved through various tests, including nucleic acid tests (such as polymerase chain reaction [PCR]), rapid diagnostic kits, or, in rare instances, virus isolation through culture methods.

Rapid Diagnosis Influenza Tests

1. Rapid influenza diagnostic tests are designed to identify influenza viral antigens and facilitate timely screening of patients suspected of having influenza, offering advantages over other diagnostic methods. The predominant technique employed involves the detection of viral antigens present in the respiratory secretions of patients through immunological approaches. These rapid tests are user-friendly and can yield results in as little as 30 minutes. The capability of each test to differentiate between influenza A and B varies. However, these tests have not yet been able to identify specific subtypes of influenza A, such as H1N1 and H3N2. The specificity rates achieved by these tests are generally high and consistent across different manufacturers. In contrast, the sensitivity of these tests has demonstrated significant variability across various studies, influenced by the type of samples and patient demographics, with sensitivity rates ranging from 4.4% to 80% when compared to cell culture, which is considered the gold standard. Generally, sensitivity tends to be lower in adults compared to younger patients, and it may be higher during the initial stages of the illness when viral load is elevated. Economic evaluations comparing rapid testing to clinical diagnosis of influenza have yielded inconclusive results. Some research indicates that clinical judgment combined with antiviral treatment is often the most cost-effective approach, while other studies propose that testing may be the more economical strategy. These studies have shown that initiating oseltamivir treatment based on point-of-care (POC) testing is a superior option compared to traditional methods that do not utilize screening tests, with cost-effectiveness observed in 80% of scenarios according to the cost-effectiveness acceptability curve. Additionally, antiviral treatment for influenza based on POC testing could be economically viable under certain conditions related to performance, pricing, and disease prevalence.

Molecular Tests

1. Given the limitations of other diagnostic techniques for influenza detection, molecular

assays have increasingly been recognized as the gold standard in hospital diagnostic laboratories for identifying the influenza virus. While various amplification methods have been developed, the predominant assays currently employed in clinical settings primarily utilize the PCR amplification technique. These tests are capable of simultaneously assessing multiple targets, thus providing detailed type and subtype information for each virus. Furthermore, they can be swiftly adapted to detect new targets, a capability that proved essential during the 2009 influenza pandemic. PCR is generally more sensitive than cell culture methods and can identify nonviable viruses in samples. The sensitivity of these tests is influenced by the patient's sample site and is comparable to that of rapid tests. Enhanced sensitivity is achievable with nasopharyngeal swab samples. PCR-based molecular assays have demonstrated significant clinical utility for the detection and identification of influenza viruses at the point of care, with numerous FDA-cleared commercial devices now available.

Role of the Laboratory Diagnosis of Flu in Clinical Case Management

1. Due to the self-limiting characteristics of the disease in otherwise healthy individuals, it is unnecessary to perform diagnostic tests for every case that presents. Such tests should only be carried out if their outcomes are expected to affect subsequent clinical management and if they are considered significant in determining the initiation of specific antiviral therapies, influencing other diagnostic assessments, guiding antibiotic treatment decisions, and shaping infection control measures. Furthermore, during influenza seasons, hospitalized patients of any age exhibiting fever and severe respiratory symptoms, including those diagnosed with community-acquired pneumonia, require laboratory testing regardless of the duration since the onset of illness.

Treatment and management

1. Influenza infections are generally mild and self-limiting in most healthy individuals without additional comorbidities. In such cases, antiviral treatment is typically unnecessary.

However, antiviral medications may be utilized to treat or prevent influenza, particularly during outbreaks in healthcare environments like hospitals and long-term care facilities. Oseltamivir, zanamivir, and peramivir are classified as neuraminidase inhibitors and are effective against both influenza A and B. The adamantanes antiviral class includes amantadine and rimantadine, which are effective solely against influenza A. Recent influenza seasons have shown a significant prevalence of resistance to adamantanes in influenza A, leading to their non- recommendation for treatment or prophylaxis. While resistance to

neuraminidase inhibitors has remained low, the potential for viral mutation and resistance development exists, particularly in immunocompromised patients. Oseltamivir is an option for chemoprophylaxis in individuals aged one year and older during outbreaks and for those in high-risk categories. Notable side effects of oseltamivir include severe skin reactions and occasional transient neuropsychiatric events, which may limit its use among the elderly and those at increased risk. Zanamivir is contraindicated only in individuals with an egg allergy.

Vaccination is strongly advised at the onset of the winter season, with the following recommendations for the flu vaccine

- All individuals aged six months and older should be vaccinated.
- Individuals with an egg allergy who experience only hives are encouraged to receive the vaccine.
- Resuscitation equipment must be available in all settings, and patients should be monitored for 10-15 minutes post- vaccination.
- The nasal flu vaccine has demonstrated limited effectiveness in recent years, making the injectable form preferable.

CONCLUSION

1. Influenza epidemics and pandemics create significant socioeconomic challenges for societies worldwide. Hospitalization, treatment, and intensive care unit (ICU) services are frequently required for high- risk populations, including the elderly and pregnant women. Nevertheless, the repercussions of influenza should not be overlooked in young adults, primarily due to the associated loss of productivity. Given the characteristics of the virus and the rising trends in antiviral drug resistance, the most effective approach is to vaccinate high-risk groups at suitable intervals. Inactivated influenza vaccines are generally well-tolerated, with the most prevalent side effect being localized pain at the injection site. Clinical trials indicate that serious adverse events occur in less than 1% of vaccinated individuals. Therefore, prioritizing vaccination for high-risk groups is essential in combating influenza.

With the growing concern regarding resistance to both adamantanes and neuraminidase inhibitors (NAIs), the potential for antiviral drug resistance must be taken into account when considering treatment for all patients diagnosed with influenza. Patients exhibiting severe symptoms, such as those with lower respiratory tract infections (e.g., dyspnea, tachypnea, and low oxygen saturation), those showing rapid clinical decline, or those at elevated risk for

complications should receive antiviral treatment. Antiviral medications should be initiated within 48 hours of symptom onset. For pregnant patients, who face higher mortality rates, it is recommended that all individuals with suspected or confirmed influenza— regardless of whether they present more than 48 hours after symptom onset—be treated if they are not showing improvement. Furthermore, a reevaluation of antiviral chemoprophylaxis and its judicious application may lead to a decrease in morbidity and mortality associated with influenza in high-risk populations.

Conflict of Interest: None declared.

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