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INFLUENZA VIRUS INFECTION: A REVIEW OF HUMAN MODEL

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ABSTRACT

Seasonal and pandemic influenza are the two faces of respiratory infections caused by influenza viruses in humans. As seasonal influenza occurs on an annual basis, the circulating virus strains are closely monitored and a yearly updated vaccination is provided, especially to identified risk populations. Nonetheless, influenza virus infection may result in pneumonia and acute respiratory failure, frequently complicated by bacterial co-infection. Accordingly, particular efforts are made to advance our knowledge on the disease biology and pathology and recent studies have brought new insights into IAV (Influenza A Virus) adaptation mechanisms to the human host, as well as into the key players in disease pathogenesis on the host side. Current antiviral strategies are only efficient at the early stages of the disease and are challenged by the genomic instability of the virus, highlighting the need for novel antiviral therapies targeting the pulmonary host response to improve viral clearance, reduce the risk of bacterial co-infection, and prevent or attenuate acute lung injury. This review article summarizes our current knowledge on the molecular basis of influenza infection and disease progression, the key players in pathogenesis driving severe disease and progression to lung failure, as well as available and envisioned prevention and treatment strategies against influenza virus infection.

Keywords: - IAV, pandemic, pneumonia, influenza viruses in humans.

INTRODUCTION

- **What is human influenza?**

Influenza, commonly known as "the **flu**", is an infectious disease caused by an influenza virus.[1]Symptoms can be mild to severe.[2]The most common symptoms include: a high fever, runny nose, sore throat, muscle pains, headache, coughing, and feeling tired. These symptoms typically begin two days after exposure to the virus and most last less than a week. The cough, however, may last for more

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than two weeks.[1]In children, there may be nausea and vomiting, but these are not common in adults. Nausea and vomiting occur more commonly in the unrelated infection gastroenteritis, which is sometimes inaccurately referred to as "stomach flu" or "24-hour flu".[3]Complications of influenza may include viral pneumonia, secondary bacterial pneumonia, sinus infections, and worsening of previous health problems such as asthma or heart failure.[2,4]

Three types of influenza viruses affect people, called Type A, Type B, and Type C.[4] Usually, the virus is spread through the air from coughs or sneezes.[1]This is believed to occur mostly over relatively short distances.[5]It can also be spread by touching surfaces contaminated by the virus and then touching the mouth or eyes.[2,5]A person may be infectious to others both before and during the time they are showing symptoms.[2]The infection may be confirmed by testing the throat, sputum, or nose for the virus. A number of rapid are available; however, people may still have the infection if the results are negative. A type of polymerase chain reactionthat detects the virus's RNA is more accurate.[4]

Influenza virus structure:

Influenza viruses are roughly spherical, although somewhat pleomorphic, particles, ranging from 80 to 120 nm in diameter[6,7]presents a model of the overall structure of the influenza virus. A characteristic feature of influenza virus particles is their external layer ofapproximately 500 spike-like projections. These spikes represent the envelope glycoproteins HA (which has a rod-like shape) and NA (which is mushroom-shaped). The HA spike is a trimer, consisting of three individual HA monomers,[8]while the NA spike is a tetramer.[9,10]HA is about four times more abundant than NA.

The viral envelope proteins

The major envelope glycoprotein HA is synthesized in the infected cell as a single polypeptide chain (HA0) with a length of approximately 560 amino acid residues, which is subsequently cleaved into two subunits, HA1 and HA2.[6,8]

The second envelope glycoprotein NA has enzymatic activity, cleaving sialic acid residues from glycoproteins or glycolipids.[9] Since sialic acid functions as a receptor for attachment of influenza virions, the neuraminidase activity of NA, cleaving such receptors,[11] mediates the release of newly formed virus particles from the surface of infected cells.[12]NA is the target for the antiviral drugs oseltamivir (Tamiflu®) and zanamivir (Relenza®). The influenza A virus envelope contains a small number of copies of a third integral membrane protein, M2 is involved in the infection process by modulating the pH within virions, weakening the interaction between

the viral ribonucleoproteins (RNPs) and the M1 protein.

The viral core

The influenza A or B virus genome consists of eight segments of negative-sense single-stranded RNA.[6]Each RNA segment 1–6 of influenza A viruses encode a single protein and it is associated with multiple copies of NP and with the viral transcriptase consisting of RNA polymerase components PB1, PB2 and PA, thus forming the RNP complex.[20]The RNPs are surrounded by a layer of the matrix protein, M1. With approximately 3000 copies per virion, M1 is the most abundant structural protein of influenza virus.

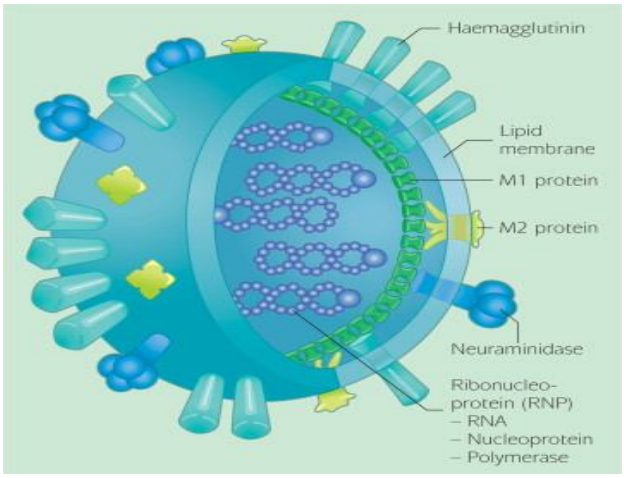

Fig1: Model of influenza virus.

In this figure, the three-dimensional structure of the influenza haemagglutinin (HA). The HA monomer (left) and trimer (right) are shown. In the monomer, the globular HA1 subunit is shown in dark blue, the HA2 subunit in light blue, with the "fusion peptide" in red. The receptor-binding site of HA1 is located at the tip of the molecule.

Influenza Sign and Symptoms

Influenza is a contagious respiratory illness caused by flu viruses. It can cause mild to severe illness, and at times can lead to death. The flu is different from a cold. The flu usually comes on suddenly. People who have the flu often feel some or all of these symptoms:

- Fever* or feeling feverish/chills
- Cough
- Sore throat
- Runny or stuffy nose
- Muscle or body aches
- Headaches
- Fatigue (tiredness)
- Some people may have vomiting and diarrhea, though this is more common in children than adults.

Influenza viruses are spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only a short distance (less than or equal to 1 meter) through the air. Contact with respiratory-droplet contaminated surfaces is another possible source of transmission. Airborne

transmission (via small-particle residue (less than or equal to 5μm) of evaporated droplets that might remain suspended in the air for long periods of time) also is thought to be possible, although data supporting airborne transmission are limited. The typical incubation period for influenza is 1—4 days (average: 2 days). Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days **after** becoming sick.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, non-productive cough, sore throat, and rhinitis). Among children, otitis media, nausea, and vomiting also are commonly reported with influenza illness. Uncomplicated influenza illness typically resolves after 3—7 days for the majority of persons, although cough and malaise can persist for >2 weeks.

Laboratory Diagnostic Procedures

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, reverse transcription polymerase chain reaction (RT-PCR), immunofluorescence assays, and rapid molecular assays. Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test, the type of test used, the time from illness onset to specimen collection, and the type of specimen tested. Among respiratory specimens for viral isolation or rapid detection of human influenza viruses, nasopharyngeal specimens typically have higher yield than nasal or throat swab specimens.

Rapid Influenza Diagnostic Tests

Rapid influenza diagnostic tests (RIDTs) are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and display the result in a qualitative way (positive vs. negative). Commercial rapid influenza diagnostic tests (RIDTs) are antigen detection assays that can detect influenza viruses within 15 minutes with low to moderate sensitivity and high specificity. Some tests are CLIA-waived(Clinical Laboratory Improvement Amendments)and approved for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid influenza diagnostic tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza virus types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types.None of the rapid influenza diagnostic tests provide any information about influenza A virus subtypes. The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal aspirates, swabs, or washes) also vary by test. The

specificity and, in particular, the sensitivity of rapid influenza diagnostic tests are lower than for viral culture and RT-PCR and vary by test.

Immunofluorescence

Immunofluorescence assays are antigen detection assays that generally require use of a fluorescent microscope to produce results in approximately 2-4 hours with moderate sensitivity and high specificity. Both direct (DFA) and indirect fluorescent antibody (IFA) staining assays are available to detect influenza A and B viral antigens in respiratory tract specimens. Subtyping or further identification of influenza A viruses is not possible by immunofluorescent assays. One rapid immunofluorescence assay is an RIDT and utilizes an analyzer device to produce results in approximately 15 minutes.

Rapid Molecular Assays

Rapid molecular assays are a new kind of molecular influenza diagnostic test for upper respiratory tract specimens with high sensitivity and specificity. One platform uses isothermal nucleic acid amplification and has high sensitivity and yields results in 15 minutes or less. Another platform uses RT-PCR and has high sensitivity and produces results in approximately 20 minutes.Two FDA-cleared rapid molecular assays are available in the United States. Rapid molecular assays can provide results in approximately 20 minutes. Alerei Influenza A&B was FDA cleared for use with both nasal swabs (direct) and NP or nasal swabs in VTM. It was CLIA-waived for use with nasal swabs (direct) only. Roche Cobas Influenza A/B was cleared and CLIA-waived by FDA for use with nasopharyngeal swabs only.

Other Molecular Assays

Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and other molecular assays can identify the presence of influenza viral RNA in respiratory specimens with very high sensitivity and specificity. Some molecular assays are able to detect and discriminate between infections with influenza A and B viruses; other tests can identify specific seasonal influenza A virus subtypes [A(H1N1)pdm09, or A(H3N2)]. These assays can yield results in approximately 1-8 hours depending upon the assay. It is important to note that not all assays have been cleared by the FDA for diagnostic use.

Influenza treatment

Treatments for influenza include a range of medications and therapies that are used in response to disease influenza. Treatments may either directly target the influenza virus itself; or instead they may just offer relief to symptoms of the disease, while the body's own immune system works to recover from infection.

The two main classes of antiviral drugs used against influenza are neuraminidase inhibitors, such as zanamivir and oseltamivir, or inhibitors of the viral M2 protein, such

as amantadine and rimantadine .These drugs can reduce the severity of symptoms if taken soon after infection and can also be taken to decrease the risk of infection. However, virus strains have emerged that show drug resistance to both classes of drug.

Antiviral drugs

Antiviral drugs directly target the viruses responsible for influenza infections. Generally, anti-viral drugs work optimally when taken within a few days of the onset of symptoms. Certain drugs are used prophylactically, that is they are used in uninfected individuals to guard against infection.Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir.[21]They are available through prescription only.

In Russia and China a drug called arbidol is also used as a treatment. Testing of the drug has predominantly occurred in these countries and, although no clinical trials have been published demonstrating this is an effective drug, some data suggest that this could be a useful treatment for influenza.[22,23]

Interferons

Interferons are cellular signalling factors produced in response to viral infection. Although interferon therapies became widespread in the Soviet Union, the method was doubted in the United States after high doses of interferon proved ineffective in trials. Though the 1969 study used 256 units of interferon, subsequent studies used up to 8.4 million units. It has since been proposed that activity of interferon is highest at low concentrations.[24]Phase III trials in Australia are planned for 2010, and initial trials are planned in the U.S. for late 2009.[25]

Viferon is a suppository of (non-pegylated[26]) interferon alpha-2b, ascorbic acid (vitamin C), and tocopherol (vitamin E) which was reported in two small studies to be as effective as arbidol.[27,28]It is sold in Russia for $4–$9 per suppository depending on dose.Another interferon alfa-2b medicine, "Grippferon", nasal drops, is used for treatment and emergency prevention of Influenza and cold.[29]

Influenza vaccine

Influenza vaccines, also known as **flu shots** or **jabs**, are vaccines that protect against influenza.[30] A new version of the vaccine is developed twice a year as the influenza virus rapidly changes.[31] While their effectiveness varies from year to year, most provide modest to high protection against influenza.[32,33]They decrease the number of missed days of work by a half day on average.[34]Vaccinating children may protect

those around them.[32] The effectiveness in those under two years old and over 65 years old is unknown due to the low quality of the research[33,34,35]. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommends yearly vaccination for nearly all people over the age of six months, especially those at high risk.[32,36]The European Centre for Disease Prevention and Control also recommends yearly vaccination of high risk groups.[39]These groups include pregnant women, the elderly, children between six months and five years of age, those with other health problems, and those who work in healthcare.[32]

The vaccines are generally safe. In children, fever occurs in five to ten per cent, as may muscle pains or feeling tired. In certain years, the vaccine causes Guillain–Barré syndrome in older people in about one per million doses. It should not be given to those withsevereallergies to eggs or to previous versions of the vaccine. The vaccines come in both inactive and weakened viral forms. The inactive version should be used for those who are pregnant. They come in forms that are injected into a muscle, sprayed into the nose, or injected into the middle layer of the skin.[32]

Vaccination against influenza began in the 1930s with large scale availability in the United States beginning in 1945.[38,39]It is on theWorld Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[40]The wholesale price in the developing world is about $5.25 USD per dose as of 2014.[41]In the United States, it costs less than $25 USD.[42]

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