A NARRATIVE REVIEW OF INFLUENZA: A SEASONAL AND PANDEMIC DISEASE

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Abstract: Influenza virus is an acute respiratory disease caused by the influenza A or influenza B virus. These virus show effect mainly during winter season it often occurs in outbreaks and epidemics worldwide. Influenza virus is respiratory viral disease. Significant numbers of influenza virus particles are present in the respiratory secretion of infected persons , so infection can be transmitted through sneezing and coughing via large particle of droplets. The duration of influenza virus shedding in immune competent adult patients is around 5 to 10 day or more and it can be show particularly in children, elderly adults, patient with chronic illnesses, and immune compromised hosts. If any person infected with influenza they show many symptoms such as high-grade fever, mayalgia, headache, and malaise. Some symptoms are found such as nonproductive cough, sore throat and nasal discharge. After that influenza can attack other organs like that the lungs, brain, heart but mainly it affect respiratory tract and patient can be admitted in hospital. We can prevent the influenza by using proper annual vaccination. If sever patient- we can early treatment by antiviral drugs. So, due to disease burden, we reviewed the currently finding in diagnosis and treatment of influenza.

Introduction

 Influenza (also known as "flu") is a viral infection caused by the influenza A or influenza B. it affects mostly the upper respiratory organs (the nose, throat, bronchi and lungs) but some cases they also affect the other organs like heart, brain and muscles. It spread worldwide and cause pandemic, epidemic or seasonal pattern the epidemical flu happen annually during winter and autumn in temperate areas and produce significant mortality and morbidity each year.[1] The influenza virus is transmitted from person to person with respiratory droplets produced when the patient sneezes or coughs with close contact (<1 m) is most probably to infected. Individuals usually recover after a few days, but influenza can give rise to complications and even can be death. The higher risk group like pregnant women and those who Compromised with immunodeficiency. The symptoms shown in infected person may high fever, body ache,

headache, sever malaise dry cough, sore throat, and runny nose. it should be differ from Common cold according to the clinical presentation. There are some unique feature of influenza such as the epidemic nature of the disease due to its persistent antigenic changes and mortality, caused in part by pulmonary complications.[2] Our aim to review different aspects of the influenza infection for the annually incidence, significant mortality, and burden.

History

The Influenza virus has caused current epidemic of acute febrile syndrome every 1 to 4 year for at least the recent centuries. The first epidemic report of an influenza like illness was noted in 1173-74,[3] but the first definite epidemic was reported in 1694.[4] The greatest pandemic in recorded history occurred between 1918 and 1919, when approx. 21 million deaths were recorded worldwide.[5] I was very deadliest events reported in human history. After that three other pandemics occurred in the 20th century and now in 21st century we suffer from another pandemic named as covid-19. In the 1957 H2N2 pandemic, the 1968 H3N2 pandemic, and the 2009 influenza A (H1N1) virus (pH1N1) pandemic. Recently an influenza strain with a combination of gene segments other than previously reported in the swine flu or human influenza virus strains was identified firstly in mexico and then in the USA(United State of America).[6] After they spread in many countries, the Pandemic was declared in August 2010 by WHO.[7]

Etiology

Influenza viruses are belonging to the family of "***Orthomyxovirdae"***, an RNA type virus with diverse antigenic characteristics. They are divided into three main types: A,B & C. mostly epidemic and outbreaks are caused by the types A and B, with type C being only responsible for sporadic mild upper respiratory symptoms.[8,9]

 Virus have spherical shape with an envelop,   it contain glycoproteins and a single stranded RNA gene. There are two most important glycoproteins present in outer layer of the flu virus are hemagglutinin(H, or HA) and nuraminidase (N or NA). both are play most important roles in the pathogenesis of the disease.

 For influenza type A mainly it show at least 16 highly variable hemagglutinins (H, or HA) and 9 distinct NAs (N1- N9) have been recognized so far. With the aid of these different antigens , type A influenza virus is further subdivided into subtype on the basis of their variable combination patterns of their own specific H or N proteins for ex. H1N1 or H3N2. In the nomenclature of the viruses, other variables such as the place of initial isolation are included.[10]

 The influenza B virus has a similar viral structure to type A; however, due to the fixed antigenic characters of HA and NA, they not show any subtype in this virus. Still, some small antigenic variabilities reported since 1970 in this virus , with the virus having started to diverge into 2 antigenically distengushable lineages.[11]

Epidemiology

Flu occurs in distinct outbreaks of varying extension and intensity every year. This epidemic pattern of influenza is based on multiple factors such as the changing nature of the antigenic properties of the virus, transmissibility power of the virus, and the susceptibility of the population. The susceptibility of community is one of the most important factors in the strength of epidemics and its mortality or morbidity effects in specific. For example, in a recent pandemic due to the presence of baseline partial immunity in the Iranian community, the country did not have a high mortality rate.[12]

The influenza A virus, in particular, has a specific ability to undergo periodic changes in the antigenic characteristics of its surface glycoproteins, hemagglutinin, and neuraminidase. Major changes in these proteins are termed "antigenic shifts", and minor changes are termed "antigenic drifts". Antigenic shifts are associated with the epidemics and pandemics of influenza A, whereas antigenic drifts are responsible for more localized outbreaks of varying extent.

Due to the segmented pattern of the influenza virus gene and the high rates of reassorment on its genome, the emergence of pandemic strains usually has been caused by animal- and human-type reassorment and the resultant antigenic shifts.

Between the years of antigenic shifts, antigenic drifts have happened almost annually and have resulted in outbreaks of variable extent and severity. The outbreaks of antigenic drifts are usually less extensive and severe than the epidemics or pandemics associated with antigenic shifts. Antigenic drifts are resulted from point mutations in the RNA gene segments that are responsible for hemagglutinin or neuraminidase; accordingly, they occur sequentially as the virus spreads through susceptible populations.[13]

Influenza usually has the highest attack rates among young people, while high mortality rates are reported among older adults. In addition to the elderly, mortality and morbidity are specifically high in those with definite high-risk medical conditions—including extreme of ages, cardiovascular diseases, and metabolic diseases such as diabetes mellitus. Specifically, the increased risk of influenza morbidity and mortality during pregnancy were observed during the 2009 pandemic.[14] Also, the data from previous pandemics and seasonal influenza outbreaks suggest that the risk of influenza complications may be higher in the 2nd and 3rd trimesters of pregnancy in comparison to the 1st trimester.[15]

Transmission

In the respiratory secretion of the patients suffering from influenza, large amounts of virus load are often present and, as a result, each infected person can be transmitting infection to other individuals by sneezing and coughing. It has been posited that the disease is transmitted primarily via large particle droplets (>5 μ).[16]

Owing to the large size of infectious droplets, close contact is needed for the acquisition of the disease. These large particles usually do not remain suspended in the air for a long time and they travel only short distances. Airborne transmission is, therefore, not often considered for disease spread.[17] However, limited data show that small particle respiratory droplets, which become aerosolized and can stay suspended in the air for a long time, also contain the influenza virus and can potentially cause disease spread.[18] In a recent study, aerosol transmission accounted for around half of all the transmission events. This suggests that activities to reduce transmission by contact or large droplets may not be enough to control the transmission of the influenza A virus in households or communities.[19] Thus, the prevention strategies that are drawn upon routinely in hospitals require further re-evaluation.

Moreover, contact with contaminated surfaces containing respiratory droplets is another potential source of disease transmission. In adults without other underlying diseases, the shedding of virus starts from 24 to 48 hours before disease manifestation and the shedding stops after 6 or 7 days according to most studies and after 10 days according to some other investigations.[20] It should be considered that longer periods of shedding and infectiousness can occur in children, elderly adults, immunocompromised hosts, and patients with chronic illnesses.[21,22]

Clinical Manifestations

Uncomplicated Influenza

Influenza typically begins with the abrupt onset of symptoms following an incubation period of 1 to 2 days. Primarily, these symptoms are systemic and consist of fever sensation, true chills, headache, severe myalgia, malaise, and anorexia. Mostly headache, myalgia, and fever determine the severity of the disease insofar as they are more prominent.[23] Myalgia is prominent in the calf muscle (especially in children) and the paravertebral and back muscles, but all striated muscles may become involved such as the extraocular muscle, which causes painful eye movement. These symptoms are mostly accompanied by the manifestations of respiratory tract illnesses such as dry cough, nasal discharge, and sore throat. Often, so abrupt is the onset that the patient can remember the precise onset of the disease. However, the manifestations of influenza infections can range from afebrile respiratory illnesses similar to the common cold, to diseases in which systemic signs and symptoms predominate with relatively little respiratory tract infection symptoms.[24,25] In the early days, the patient has high-grade fever and on the 2nd and 3rd days, the fever decreases and diminishes gradually. It may, nonetheless, last for 4 to 8 days. Early in the course of the disease, the patient's face is plethoric with watery and red eyes. A convalescent period of some weeks may ensue, during which dry cough and malaise are the most salient complaints of the patient.

Complicated Influenza

Pneumonia

The most important and common complication of influenza is pneumonia, not least in high-risk individuals. Pneumonia may happen as a continuum of the acute influenza syndrome when caused by the influenza virus (primary pneumonia) or as a mixed viral and bacterial infection after a gap of a few days (secondary pneumonia).

Primary Influenza Viral Pneumonia

The illness occurs after the typical course of flu with a rapid progression of fever, dyspnea, cough, cyanosis, and difficult breathing. It happens predominantly among individuals with cardiovascular or underlying pulmonary diseases such as asthma. Physical examination is in favor of bilateral lung involvement, and imaging findings in the lungs constitute reticular or reticulonodular opacities with or without superimposed consolidation. Sometimes the radiological appearance of primary influenza pneumonia can be difficult to distinguish from pulmonary edema because of the presence of perihilar congestion and hazy opacification, at least in the lower lobes. Less frequently, radiographs show focal areas of infiltration. Commonly used pneumonia severity assessment tools such as the CURB65 or the Pneumonia Severity Index are not useful in determining which patients to hospitalize due to primary influenza pneumonia since these tools have not been developed and validated during an influenza pandemic.[26] Thus, careful history taking and examination, determination of pregnancy or hypotension, and early identification of young patients with decreased oxygen saturation, respiratory rate >25 per minute, and concomitant diarrhea are crucial for admission decision-making. The typical radiographic findings of primary influenza pneumonia are bilateral reticular or reticulonodular opacities, sometimes accompanied by superimposed consolidation. Less frequently, radiographs show focal areas of consolidation without reticular opacities. High-resolution computed tomography often shows multifocal peribronchovascular or subpleural consolidation with or without ground-glass opacities.[27] The most severe cases progress rapidly to acute respiratory distress syndrome and multipolar alveolar infiltrations. These patients usually present with progressive dyspnea and severe hypoxemia 2 to 5 days after the onset of typical influenza symptoms. Hypoxemia increases rapidly and causes respiratory failure, requiring intubation and mechanical ventilation, maybe after only 1 day of hospitalization.[28]

Secondary Bacterial Pneumonia

The incidence of secondary bacterial pneumonia ranged from 2% to 18% during the influenza pandemic in 1957–58.[29] A threefold increase in the incidence of secondary Staphylococcus aureus pneumonia during the influenza pandemic of 1968–9 compared to a non-epidemic period of pneumonia etiologies was observed.[30] Recently, community–acquired methicillin-resistant Staphylococcus aurous was determined after seasonal influenza,[31] but

another very common etiologic bacterium is Streptococcus pneumonia. The patient has a classic influenza disease, followed by an improvement period lasting maximally 2 weeks. The recurrence of the symptoms such as fever, productive cough, and dyspnea and findings of new consolidations in chest imaging can be found in involved patients. Accordingly, a biphasic pattern of signs and symptoms in influenza-labeled patients should be considered as secondary superimposed bacterial pneumonia.

Non-Pulmonary Complications

In addition to its respiratory effects, the virus can exert effects on other body systems such as the musculoskeletal, cardiac, and neurologic systems. Myocarditis and pericarditis constitute unusual but significant complications of seasonal or pandemic flu. In a prospective study, half of adult flu patients without cardiac complaints had abnormal ECG findings at presentation.[32] Myocarditismostly resolves by 28 days, and the patients has a good heart-muscle function without a reduced ejection fraction. Significant myositis and rhabdomyolysis have rarely been reported with seasonal influenza,25 but different amounts of creatine phosphokinase elevation have been reported in many studies after seasonal or pandemic flues.[33-35] Mild myositis and myoglobinuria with tender leg or back muscles can mainly be seen in children, although they can occur in adults and be accompanied by symptoms of painful walking or standing. Other rare complications such as the Guillain–Barré syndrome, encephalitis, acute liver failure, and the Reye syndrome may happen after influenza A infection.

Diagnosis

The majority of influenza cases are diagnosed by their clinical manifestations and there is no need for laboratory tests. Be that as it may, in special circumstances, the diagnosis of flu necessitates laboratory confirmation using available tests such as nucleic acid tests (e.g., polymerase chain reaction [PCR]) or rapid diagnosis kits or rarely virus isolation by culture methods.

Rapid Diagnosis Influenza Tests

Rapid influenza diagnostic tests detect influenza viral antigens and screen patients with suspected influenza in a timely manner in comparison to other diagnostic modalities. The most widely used technique is based on the detection of viral antigens in the respiratory secretions of patients by immunologic methods. All rapid tests are performed with ease and can provide results within 30 minutes. Each test varies with regard to whether it can distinguish between influenza A and B. Nevertheless, these tests have thus far been unable to specify types of influenza A such as H1N1 and H3N2. The overall specificities achieved by these tests are high and comparable between the manufacturers. However, their sensitivities have shown great heterogeneity across studies depending on the nature of the samples tested and the patients, ranging from 4.4% to 80% in comparison to cell culture as a gold standard test.[36-38] As a general

concept, sensitivity in adults is less than that reported in younger patients. Also, the sensitivity may be higher at the onset of the disease, when a higher load of the virus exists.   Economic studies comparing rapid testing to the clinical diagnosis of influenza remain inconclusive. Indeed, some studies have suggested that, in most cases, clinical judgment combined with antiviral treatment is the most cost-effective strategy,[39] while new studies have suggested that testing may be the most cost-effective strategy and shown that oseltamivir treatment based on the point-of-care (POC) test is a dominant option compared to conventional approaches without screening tests in the baseline scenario and that they could be cost-effective in 80% of cases according to the cost-effectiveness acceptability curve.39 Furthermore, influenza antiviral treatment based on POC could be cost-effective in specific conditions of performance, price, and disease prevalence.[40]

Molecular Tests

Due to the limitation in other diagnostic modalities in influenza detection, molecular assays have increasingly been considered the gold standard diagnostic method for the detection of the influenza virus in hospital-based diagnostic laboratories. Although several amplification methods have been developed, the majority of the current assays—particularly those used in clinical laboratories—are based on the PCR amplification method. These tests have the ability to check several targets concurrently and thereby provide type and subtype information for each virus. Additionally, they have the ability to be adapted rapidly for the detection of novel targets; these features[41] played a critical role during the influenza pandemic of 2009. PCR is potentially more sensitive than cell culture, and it can detect the nonviable virus in samples. The sensitivity of these tests is dependent on the sample site of the patient and is similar to that of the rapid tests. Higher sensitivity can be obtained by swab samples of a nasopharyngeal origin. PCR-based molecular assays have yielded excellent clinical utility for the detection and identification of influenza viruses at bedside as POC, and numerous Food and Drug Administration (FDA)-cleared commercial devices are now available.[42-44]

Role of the Laboratory Diagnosis of Flu in Clinical Case Management

Given the self-limiting nature of the disease in otherwise healthy individuals, there is no need for diagnostic tests in all presenting cases. Diagnostic tests should be conducted if the results of the test are thought to be able to influence subsequent clinical management and if the results of the test are deemed influential in decisions on the initiation of specific antiviral treatment, impact on other diagnostic tests, antibiotic treatment decision-making, and infection control practices.[45] In addition, duringinfluenzaseasons, hospitalized individuals of any age with fever and severe respiratory symptoms—including those with a diagnosis of community-acquired pneumonia—need laboratory testing irrespective of time from illness onset.

Therapy

Currently, at least 4 antiviral drugs are available for the treatment and prevention of influenza. It is deserving of note that in healthy immunocompetent individuals with intact immunity, there is a rapid limitation in the ability of the influenza virus; therefore, the anti-replication power of antiviral drugs is limited and has no theoretical effect. Also, no study to date has demonstrated a beneficial effect for antiviral agents starting beyond 48 hours of symptom onset. The greatest effect is classically seen when therapy is started in the first 24 hours. Treatment is recommended for both adults and children with the influenza virus infection with the following criteria:[46]

1) Persons with laboratory-confirmed or highly suspected influenza virus infection in high-risk groups, within 48 hours after symptom onset

2) Patients requiring hospitalization for laboratory-confirmed or highly suspected influenza disease, regardless of underlying illnesses, if treatment can be initiated within 48 hours after symptom onset

3) Outpatients at high risk of complications with an illness that is not improving and outpatients with a positive influenza test result from a specimen obtained >48 hours after symptom onset.

Individuals whose onset of symptoms is >48 hours before presentation with persisting moderate-to-severe illness.

During the last pandemic wave, neuraminidase inhibitors (NAIs)—primarily oseltamivir and zanamivir—were widely prescribed for patients with confirmed or suspected A H1N1pdm09 infection.[47,48] However, before the 2009–10 pandemic, evidence of their effectiveness in seasonal influenza, while strong for modest symptom reduction, was less strong for decreases in pneumonia incidence or pneumonia outcome improvment.[49-52] Recent data demonstrated that patients with influenza-related pneumonia treated early (≤48 h after illness onset) with an NAI experienced around one-third lower likelihood of dying or requiring ventilator assistance compared to those treated at later hours.[53] Influenza viruses and their susceptibilities to available antiviral medications are changing rapidly. Clinicians should be aware of the local patterns of influenza circulations and susceptibilities. For instance, a meta-analysis showed that NAIs were able to lessen mortality in patients admitted to the hospital with A H1N1pdm09 infection.30Sporadic oseltamivir-resistant infections have been identified, together with rare episodes of limited transmission.[54] Given the currently circulating influenza A (H3N2) and 2009 H1N1 virus resistance to adamantanes, these medications are not recommended for use against influenza A virus-induced infections. However, most influenza A and B virus strains are still susceptible to neuraminidases such as oseltamivir and zanamivir, with these drugs being selected for treatment in indicated persons (table 2). In addition, it should be considered that the

development of resistance to oseltamivir during treatment was more common among seasonal influenza A (H1N1) virus infections (27%) than among seasonal influenza A (H3N2) (3%) or B (0%) virus infections in a recent study.[55]

Due to the limitations in the current therapeutic options for the treatment of influenza virus infections, additional treatment options with a different mechanism of action have been investigated as treatment for individuals with severe influenza virus disease. For example, a handful of mAbs against influenza virus proteins are currently in the early phases of evaluation for human infection control.[56] These mAbs target the external portions (i.e. ectodomain) of the M2 protein (M2e). The M2e is an attractive target for influenza vaccines and therapeutic antibodies because of the extremely conserved nature of the amino acid sequences of its domains among isolates from different subtypes of influenza A viruses.[57]

The mechanisms of anti-M2e Ab–mediated protection are not completely determined. Anti-M2 Abs do not have hemagglutination inhibition ability or in vitro virus neutralization properties.[58] It is supposed that the main target for the anti-M2e antibody is virus-infected human cells, which heavily express M2e on their surface.[59]

Most studies have reported that corticosteroid therapy adversely influences influenza-related outcomes. During the 2009 influenza pandemic, 37% to 55% of the patients admitted to ICUs in Europe received corticosteroids as part of their treatment.[60-62] Nonetheless, in a recentmeta-analysis report, evidence from observational studies—albeit with important limitations—suggested that corticosteroid therapy for presumed influenza-associated complications was associated with increased mortality.[63]

Prevention

Vaccination

The most important strategy for the prevention of influenza and its severe outcomes is annual vaccination against seasonal influenza. The influenza virus is characterized for its high rate of mutation, beating the immune system's function against new variants,[64] which is why new vaccines are produced annually to match circulating viruses.[65] The selection of influenza antigens to include in the vaccines is based upon the global surveillance of influenza viruses in circulation and the spread of new strains of the influenza virus around the world. [66] For the following influenza season in the southern hemisphere, recommendations are made in September and for the influenza season in the northern hemisphere in February because around 6 to 8 months are needed to manufacture and approve new vaccines. Recently, the World Health Organization (WHO) recommended that trivalent influenza vaccines for use in the 2016 southern hemisphere influenza season contain the following virus antigens:[67]

An A/California/7/2009 (H1N1) pdm09-like virus

An A/Hong Kong/4801/2014 (H3N2)-like virus

A B/Brisbane/60/2008-like virus.

The WHO stresses that vaccination is especially important for individuals at higher risk of serious influenza complications, with the highest priority afforded to pregnant ladies—followed by children aged between 6 and 59 months, elderly and individuals with specific chronic medical conditions (e.g., renal failure and diabetes mellitus), and finally individuals at high risk (e.g., health staff).[68] In contrast in 2010, the United States' Advisory Committee on Immunization Practices (ACIP) extended the recommendation for annual influenza vaccination to encompass all individuals 6 months of age and older individuals who did not have contraindications without any priority.[69]

Schedule

The outbreaks of influenza generally occur during the last autumn and whole winter months. A single dose (0.5 cc) of an influenza vaccine should be injected to adults annually, preferably by October in the northern hemisphere and May in the southern hemisphere. Children aged between 6 months and 8 years require 2 doses of influenza vaccine (with at least 4 weeks apart) during their 1st season of vaccination foroptimal response.[69]

Efficacy

The vaccine effectiveness of influenza vaccines is a determinant of how much the seasonal influenza vaccine can prevent influenza virus infections in the given population during an influenza season.[70] Recently, the documentation of the antigenic drift from the vaccine strain in a majority of considered isolates raised concern that vaccine effectiveness might be suboptimal, especially in older ages or specific high-risk groups. TheCenters for Disease Control and Prevention (CDC) in the United Statesof America had an estimation of 23% of vaccine effectiveness for the northern hemisphere 2014–15 seasonal influenza vaccine due to a mismatch in the circulating viruses and vaccine contained viruses.[71] What should be taken into consideration is that even if a vaccine is not completely related to the predominant circulating virus, it can protect several different influenza viruses and can, as such, confer good protection and prevent influenza-related illnesses. It is also a fact that influenza vaccines are safe and are especially important for reducing severe disease in some high-risk populations. Accordingly, the WHO recommends seasonal influenza vaccines even if they are not closely related to the predominant circulating influenza viruses each year for the above-mentioned groups.[72]

Chemoprophylaxis Strategy

Available antiviral drugs play an important role for patients who have not been immunized or who are nonresponsive to vaccines. Oseltamivir and zanamivir are the recommended drugs for the prevention of influenza based on their established efficacy and low rates of resistance in

comparison to adamantanes.[73] Theseagentsare effective for the prevention of influenza in healthy individuals, persons at high risk of influenza complications, and those residing in long-term care facilities. The efficacy of oseltamivir and zanamivir has yet to be compared with each other.[74] It should be emphasized that when choosing a strategy of antiviral chemoprophylaxis, some parameters such as preventing complications in patients at high risk and reducing the risk of promoting antiviral drug resistance should be considered. There are, therefore, some indications for this approach.

1) Influenza prophylaxis during influenza outbreaks in long-term care centers in the elderly regardless of prior influenza vaccinations

2) In unvaccinated individuals at high risk of influenza complications who have been exposed to an individual with influenza infections within the previous 48 hours

3) Antiviral prophylaxis for vaccinated persons at high risk of influenza complications who have had close contact with an individual with influenza within the previous 48 hours when there is a poor match between the vaccine and circulating viruses in a given year

4) The United States' ACIP recommends that antiviral chemoprophylaxis be considered in pregnant women and in women up to 2 weeks postpartum who have close contact with suspected or confirmed influenza A-infected individuals. Zanamivir may be the drug of choice for prophylaxis due to its limited systemic absorption.[75]

Conclusion

Influenza epidemics and pandemics impose a heavy socioeconomic burden on all societies. Hospital admission and treatment and ICU care are more often necessary in high-risk individuals such as the elderly and pregnant ladies. However, the impact of influenza cannot be neglected even in young adults, mainly because of the loss of productivity.

Given the nature of the virus and the increasing patterns of the available antiviral drugs against the influenza virus, the best strategy is the vaccination of high-risk groups at appropriate times. Inactivated influenza vaccines are always well-tolerated, with the most common side effect being burning pain at the injection site. In clinical trials, serious adverse events have been reported in <1% of the individuals vaccinated. Consequently, the vaccination policy in high-risk groups should be the priority in the battle against flu.

With concerns over increasing resistance against both adamantanes and NAIs, the risk of the development of antiviral drug resistance should be considered if we opt to treat all patients who are labeled as suffering from flu. Individuals with suspected flue with severe disease such as those with signs and symptoms of lower respiratory tract infections (e.g., dyspnea, tachypnea, and low oxygen saturation) and those who have signs of rapid clinical deterioration or those at high risk of complications should receive antiviral therapy. In all cases, antivirals should be

started <48 hours after symptom onset. In pregnant patients due to higher mortality, there is a suggestion that all patients with suspected or confirmed influenza—even those who present >48 hours after symptom onset—be treated provided that they are not improving. In addition, a new look at antiviral chemoprophylaxis and its appropriate use may effect a reduction in morbidity and mortality allied to flu in high-risk groups.

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