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Concise Definitive Review: Influenza

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Introduction

Influenza is a major concern for intensivists in all communities in the United States. While there is considerable concern whether or not the country will be ready for a pandemic influenza, even seasonal influenza poses a major challenge to hospitals. This concise review summarizes current knowledge about influenza.

Seasonal Influenza

Seasonal influenza, the influenza disease that occurs on a yearly basis, causes more than 200,000 hospitalizations and 41,000 deaths in the U.S. every year and is the seventh leading cause of death in the United States.[1] Despite this, 38% of unimmunized individuals feel they are not at risk for influenza and its related complications.[2] While this may be easy to attribute to the perceptions of the lay public, physicians' attitudes are not much better; only 35–40% of health care workers are vaccinated annually; 40% of physicians believe that influenza is a benign disease that does not require treatment; and 29% believe that antiviral therapy decreases mortality, an efficacy that has never been shown in clinical trials.[3, 4] Intensivists need to recognize the importance of seasonal influenza as a cause of severe morbidity and mortality, and be well versed on diagnosis, complications, therapy, and infection control measures associated with this disease.

Virus

Influenza viruses are member of Orthomyxoviridae family of viruses, and are negative strand RNA viruses.[5] Influenza viruses can be classified as A, B or C. Influenza A is found in humans, other mammals, and birds, and is the only influenza virus, which has historically caused pandemics. Types B and C, while previously thought found only in humans, have been isolated from seals and pigs respectively. [6–8] Influenza A and B are more common than type C, and cause more severe disease. Influenza C is a significant cause of respiratory infections in children younger than 6 years of age.[9] The majority of humans acquire protective antibodies to influenza C early in life and do not subsequently develop clinical disease.[10]

Influenza A can be further classified based on surface glycoproteins: hemagglutinin and neuraminidase. The viral hemagglutinin (HA) binds to host cell sialic acid conjugated glycoproteins.[11] This attachment is necessary for viral entry into the cell. The configuration of the sialic acid conjugated glycoproteins varies from species to species, and

may serve to enhance transfer of viruses across species.[12] Neuraminidase (NA) is important for viral release and propagation.[13] The naming convention signifies which of these proteins is on a given virus. Thus, the standard nomenclature is Influenza A H_xN_x (*the x is the number corresponding to the specific type of hemagglutinin and neuraminidase*). The nomenclature is relevant to clinicians because changes in hemagglutinin antigens, and to a lesser extent neuraminidase antigens, signal viruses that that population may have little or no prior immunity to. When major antigenic shifts occur, patients unimmunized against the new strain may develop particularly severe disease.

Wild aquatic birds are the natural reservoir of influenza A viruses. There are 16 types of hemagglutinin (H1-H16) and nine types of neuraminidase (N1-N9) and all have been found circulating in wild and domestic birds.[14] Three types of HA (H1-3) and two neuraminidase (N1-2) are known to have caused widespread disease in humans (H1N1, H2N2, H3N2). Only two of these viruses (H1N1 and H3N2) are currently circulating as seasonal influenza. H2N2 has not circulated in humans since 1968.

Avian Influenza

It has been recognized in the last decade that other influenza A viruses that circulate in birds are able to infect humans. Currently Avian influenza is an episodic zoonotic disease. Most human cases have been associated with concurrent outbreaks of influenza in domestic and wild birds.[15] While individual cases and small clusters have occurred, widespread circulation of the virus in any human population has not occurred yet.

Sporadic human cases of H5N1 have occurred over the last several years, as have outbreaks of H7N3, H7N7, H9N2, and H10N7. These later viruses have caused relatively few human cases. Gene reassortment of these viruses with other animal or human influenza viruses could produce more virulent and transmissible viruses. Most experts predict that a major reassortment will eventually occur that will include avian and human genes that will produce a transmissible, virulent virus against which humans have little or no preexisting immunity. When this will occur is impossible to predict, but most scientists think that this will occur within several decades of the last major antigenic shift, (1977). Thus, since such an outbreak has not occurred in 30 years, there is great concern that a global pandemic could be imminent.

Epidemiology

The epidemiology of influenza varies depending on locale. In North America and other northern climates, influenza activity is noted is seasonal: activity increases during the cooler months and peaks from December to March. There is large variation in this activity, however, and peaks may occur as early as October and as late as May.[16]

For locations that are more proximate to the equator, the influenza season becomes prolonged to the point of multi-phasic or year round disease.[17–19] In the United States, influenza rarely occurs between May and September, unless the virus was acquired outside the U.S.

Transmission

Human influenza attaches and invades the epithelial cells of the upper respiratory tract. Viral replication in these epithelial cells lead to pro-inflammatory cytokines, and necrosis of ciliated epithelial cells.[20, 21] This combination of events may cause coughing.

When humans exhale or talk, small respiratory droplets are generated on a routine basis, but these are generally less than 1 micron.[22] With a cough, larger droplets (> 5 microns) are

generated. The size of the droplet dictates the distance that the droplet can be carried by air currents (airborne vs. droplet spread): smaller droplets remain airborne longer, and thus spread further.

Though rigorous data are lacking, influenza is thought primarily transmitted from person to person by large droplets (> 5 microns) that are generated when infected persons cough or sneeze.[23] These large droplets settle on the mucosal surfaces of the upper respiratory tracts of susceptible persons. Given the size and weight of these droplets, transmission primarily occurs in those who are near the infected person (within 3 feet).

Coughs also generate smaller droplet nuclei, which theoretically can be spread longer distances by air currents (airborne). Several epidemiologic investigations have invoked airborne transmission of influenza, but such transmission patterns have seldom been documented.[24] Lastly, contact transmission may play a role. Infected individuals will often touch mucous membranes prior to direct interpersonal contact (e.g. hand shaking) or indirect contact such as touching common surfaces. Influenza virus has been detected on over 50% of the fomites tested in homes and day care centers during influenza season.[25] Uninfected individuals touch these surfaces on engage in interpersonal contact, then touch their mucous membranes, thereby depositing infectious virus on their mucous membranes. Whether the route of exposure or infectious dose influences the incubation period or clinical manifestations is not well documented.

Infection Control

If patients with influenza are admitted to the hospital, especially early in the clinical course while they are actively shedding virus, they should be isolated with “droplet precautions”. The Center for Disease Control and Prevention defines this as placing the patients in private rooms (or cohorting patients with influenza) and having personnel entering the room or within 3 feet of a person use a surgical or procedure mask and standard precautions (i.e., hand washing, gloving, and gowning when soiling with the patient’s respiratory secretions is likely).[26] If the patient needs to be transported from the room, the patient should wear a surgical mask, if possible, to minimize the dispersal of droplets. Certain droplet generating procedures such as intubation have been shown increase the risk of transmission to the health care workers in other viral respiratory infections such as SARS.[27] There is no demonstrated added value of placing patients with influenza in rooms for airborne infection isolation (i.e., negative-pressure rooms), using N95 respirators, or personal air powered respirators (PAPR).[26] If a highly virulent form of influenza were to circulate widely, however, such added precautions might well be prudent if the magnitude of the outbreak made such measures feasible.

Clinical Features

The incubation period for influenza is usually 1–2 days, but can be up to 4 days. The classic clinical symptoms of influenza are fever, myalgia, sore throat, and nonproductive cough. However, only about 50% of infected persons present with these classic symptoms. The fever is usually 101°–102°F, and often occurs with an abrupt onset. Additional symptoms may include rhinorrhea, headache, nausea, and diarrhea. In most patients, these symptoms and fever last 2 to 3 days.

While most influenza is associated with a mild acute self-limited illness, more severe manifestations can occur. Influenza infections can present as a typical community acquired pneumonia with fever, cough, bilateral interstitial infiltrates, hypoxemia, and leucopenia. In several series, influenza is the etiology of 5–10% of community acquired pneumonias[28–30]. The incidence is slightly higher in pediatric series (12%) and immunosuppressed

populations (11%).[31, 32] More severe disease is generally seen in young children, persons aged >65 years, and persons of any age with underlying health conditions.[33] In one series comparing influenza upper respiratory infection and pneumonia, those with pneumonia were older (63 vs. 51 years old), and more likely to have chronic respiratory disease (41% vs. 6%).[34] Bilateral diffuse interstitial/alveolar infiltrates were seen as the most common radiographic abnormality (52%), followed by right lower lobe consolidation (35%).

Primary influenza pneumonias are difficult to distinguish from other viral, bacterial or atypical pneumonias based on clinical radiologic, or laboratory alone. In one series, 9% of people hospitalized with CAP had a dual infection with both a respiratory virus and bacterial pathogen, and an additional 9% had only a respiratory virus isolated, with influenza the most common.[33]

There are no clinical criteria that can differentiate influenza or other viral pneumonias from bacterial pneumonias. Cough and expectoration occur less common in viral pneumonias, but productive cough is still present in more than 50% of cases.[33] Patients with more severe disease shed virus longer than uncomplicated influenza, with a median duration of viral shedding of 4 days compared to 1–2 days in less severe disease.[35] Immunosuppressed patients can shed influenza for months.[36] This clearly has implications for infection control.

Diagnosis

In the community, the triad of fever, respiratory symptoms (cough, sore throat, or nasal symptoms), and constitutional symptoms (headache, malaise, myalgia, sweats/chills or fatigue) had a sensitivity of 60% if influenza is known to be present in the community.[37] However, in order to guide isolation policy and therapy, definitive diagnosis of influenza as the causative organism is often warranted.

Virus replication begins within 6 hours of infection, and at least 24 hours before the onset of symptoms.[38] The duration of shedding depends on the severity of illness and age [35, 37, 39], but generally virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. In adults, viral shedding continues for 1–3 days after onset of symptoms. Children can shed virus for 10 days or more.[39]

There are several modalities to document influenza infection. These include direct viral detection (antigen tests, PCR, immunofluorescence, and culture), or serologies. The choice among these tests is dependant on the use and answers sought.

Rapid tests of respiratory secretions: Direct testing of sputum and nasal washes for influenza antigen permits a rapid diagnosis in a variety of settings. There are commercially available rapid antigen testing kits. These vary by their complexity, storage conditions, and reporting metrics, but the tests characteristics (sensitivity and specificity) are largely similar. Generally, these tests are very specific (95–100%), but sensitivity is modest, especially in adults (50–70%).[40–42]. Higher sensitivity is reported in children compared to adults.[43]

Immunofluorescence microscopy of respiratory specimens to detect influenza antigens increases the sensitivity (80%) compared to rapid antigen kits with similar specificity.[40] Immunofluorescence microscopy involves deposition of respiratory epithelial cells from a pelleted sample onto a slide, followed by staining with specific antibodies directly conjugated to a fluorescent dye (direct fluorescent antibody or DFA) or staining with an antibody to the viruses and a second conjugated antibody directed at the first (immunofluorescent antibody or IFA).[44] Because of time and expense, few laboratories do this type of test.

Culture is the gold standard for diagnosis. It is performed by inoculation of cell cultures that support viral replication, and takes a minimum of 48 hours to demonstrate viral growth, with additional time for specific viral identification. Cultures are helpful in defining the etiology of local outbreaks, and may demonstrate other pathogens. Clinicians need to be cognizant, however, that the presence of influenza clearly does not preclude the concurrence of another pathogen, especially pneumococcus or staphylococcus. In research settings drug susceptibility testing of influenza isolates can be done.

Nucleic acid testing (PCR) is gaining widespread use due to the versatility while maintaining high sensitivity and specificity. PCR has a sensitivity and specificity approaching 100%, and sometimes the sensitivity may exceed cultures.[45] These tests will not only establish a diagnosis of influenza, but will provide strain specific information that may be useful for epidemiologic and therapeutic purposes. Multiplex PCR platforms allow simultaneous testing for multiple pathogens.[46, 47] Some of these platforms allow simultaneous testing of multiple viral, bacterial, mycobacterial, and fungal agents. Newer techniques such as PCR with electrospray ionization mass spectrometry may have future clinical applications but currently are still for research purposes.[48]

Serologic testing for IgM or IgG antibodies can be performed to confirm a diagnosis, but such testing is rarely helpful in the ICU setting since 7–21 days are required to document seroconversion or rising titers.

Complications

Influenza deaths can result from pneumonia (either primary or secondary bacterial pneumonia), or from exacerbations of cardiopulmonary conditions. When overall influenza attributable mortality is examined by comparing deaths above seasonal baseline in years of high influenza versus low influenza activity, influenza and influenza pneumonia account for only 15% of the attributable excess mortality, while COPD has been the cause of death in 14% and ischemic heart disease has been the cause in a staggering 23%. [49]

There are several well-described extra pulmonary complications of influenza. While many of these complications occur in subjects known to have influenza, others will present for medical care due in patients not recognizing or seeking medical care for primary influenza infection. The most frequent complication of influenza is secondary bacterial pneumonia. Causative agents are classically *Staphylococcus aureus*, but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and other Gram-negative bacilli.

Recent reports have signified the emergence of oxacillin resistant staph aureus (ORSA) in secondary bacterial pneumonias.[50, 51] While relatively uncommon, so far, the increasing association of this organism and significant morbidity/mortality if not treated appropriately suggest that empiric coverage of ORSA for secondary bacterial pneumonias is warranted in many communities. Linezolid and vancomycin would be the appropriate antibiotics in these cases (daptomycin would not be an appropriate choice due to poor lung penetration). Some community-acquired oxacillin-resistant *Staphylococcus aureus* are positive for Pantone-Valentine leukocidin (PVL). PVL creates lytic pores in the membranes of neutrophils and induces release of neutrophil chemotactic factors. For PVL positive ORSA, there may be an advantage to antimicrobial therapy that inhibits toxin production such as linezolid [52], though supportive clinical trials are lacking.

Viral myocarditis is a rare complication of influenza.[53, 54] Older studies have shown up to 9% of patients with serologically proven acute influenza infections have myocarditis on the basis of electrocardiographic ST segment and/or T wave changes, and echocardiography documented regional myocardial dysfunction. [53] Newer studies showing no increase in

troponin I or T, or CPK-MB percentage in 152 subjects with acute influenza have suggested that these electrocardiographic changes may not be specific for true myocarditis. [55] Refractory and lethal dilated cardiomyopathy can occur. While originally thought to be immunologically mediated,, viral transcripts of influenza have been found in the myocardium suggesting the mechanism may be direct viral damage.[56] No therapy has been proven to be beneficial for viral myocarditis, and care is primarily supportive measures. Fatal and refractory cardiomyopathies requiring assist devices have been described.[57, 58]

Reye syndrome is a complication that occurs almost exclusively in children who take/are given aspirin after being infected with influenza. It presents with severe vomiting and confusion, which may progress to coma. Rarely, adults have also been reported to develop Reye Syndrome after aspirin administration.[59, 60] Aspirin should not be used in the treatment of influenza

Encephalitis has rarely been associated with influenza infections. Some series have reported incidences of roughly 1 in 1 million total population in a given influenza season. [61] Some cases are fulminate with extensive gray and white matter necrosis, referred to as acute necrotizing encephalopathy. Mild cases have also been described. It has been debated if encephalitis is due to direct viral invasion or immune response. Recently, PCR has detected influenza RNA in the CSF in some patients with influenza associated encephalitis.[62]

Acute coronary syndromes increase during influenza season. Vaccination for influenza has been shown to decrease death from cardiac causes by over half.[63] Influenza viruses can directly infect vascular endothelial cells in culture and thus, may damage endothelial cells in vivo.[63] Such damage can cause an increase in pro-inflammatory cytokine production.[64] Influenza has also been shown capable of inducing procoagulant activity in cultured endothelial cells through expression of tissue factor.[65] A recent retrospective study showed that those patients on statins prior to infection had a 40% reduction in death from influenza.[59] The utility of adding statins at the time of infection is unknown.

Exacerbation of chronic bronchitis and other chronic pulmonary diseases can also result from influenza. From vaccination studies, influenza frequently causes COPD exacerbations (28 per 100 person-years).[66] Vaccination prevents over 80% of the influenza related events in this population.

Antiviral Treatment

For intensivists, treatment options are limited since no parenteral drug is available and no drug has been proven to be effective once life threatening disease occurs. Currently four antiviral drugs are available for the treatment of influenza. These are available only for oral administration while one is available as an inhalation agent. These drugs include amantadine, rimantadine, oseltamivir, and zanamivir. (Table 2)

Amantadine and rimantadine should no longer be used for the treatment of influenza due to the high incidence of resistance. Resistance was uncommon (below 2% in 1995–2002) in community isolates until recently. In 2005–6 the resistance frequency in A (H3N2) 92 % in the United States.[67]

The neuraminidase inhibitors currently available include zanamivir (Relenza) and oseltamivir (Tamiflu). Both are sialic acid analogues that inhibit the viral neuraminidases by competitively binding with the active enzyme site of influenza A and B viruses. The neuraminidase is critical for viral release from infected cells after replication.

Oseltamivir is administered enterally as a prodrug (oseltamivir phosphate). Esterases in the liver, gastrointestinal tract, and blood cleave this to the active oseltamivir carboxylate. The bioavailability is estimated to be 80%, and the time to maximum plasma concentrations is 3 to 4 hours. Administration with food may delay absorption slightly but does not decrease overall bioavailability. Following oral administration of oseltamivir, the plasma half-life is 7 to 9 hours, and is eliminated primarily unchanged through the kidney.

Oral oseltamivir can be associated with nausea and emesis. Gastrointestinal complaints are usually mild in intensity and ameliorated by administration with food.

Zanamivir is currently available only as a powder for inhalation (Rotadisk). About 4% to 17% of inhaled zanamivir is systemically absorbed. Zanamivir has a half-life of 2.5–5.1 hours. Zanamivir is very well tolerated but bronchospasm has been reported and is of special concern in the ICU.[68]

Prospective data supporting the use of oseltamivir in the treatment of human influenza comes from four adult studies. Two of these studies evaluated experimentally induced influenza and the other two evaluated community acquired influenza.[37, 68–70] For zanamivir, there have been four adult studies. One of these studies evaluated experimentally induced influenza and three evaluated community acquired influenza.[71–74]

The adult acute treatment trials for oseltamivir and zanamivir studied those who presented within 36 hours of developing fever, respiratory symptoms and constitutional symptoms. Treatment with oseltamivir was associated with decreased duration and severity of illness. [37, 75] Duration decreased by about one day when a dose of 75 mg bid was given. There was no greater clinical benefit from the higher dose of oseltamivir. Oseltamivir treatment resulted in decreased nasal viral titers in both studies compared to placebo, but in only one study was this suggested to be dose dependent. The mortality was nil in all treatment groups including placebo.

Treatment with zanamivir also reduced the symptoms of influenza. Inhaled zanamivir improved symptoms 1.5–1.9 days faster than placebo.[71, 73] There was no benefit to intranasal topical zanamivir in addition to inhaled zanamivir [73]

The earlier the administration of both of these agents and the shorter the duration of fever, the greater the benefit of drug intervention.[76, 77] Oseltamivir has also been shown to reduce lower respiratory tract complications such as bronchitis and pneumonia.[78]

The studies above were performed in a healthy ambulatory population. No subjects with community acquired influenza died in these studies despite more than 30,000 people dying each year from influenza in the US. The optimal antiviral therapy for lower respiratory tract manifestations is not clear. In one study 41 hospitalized patients with influenza pneumonia were treated with rimantadine +/- nebulized zanamivir: the mortality was 8% but there was no comparison group.[35] Oseltamivir has not been studied prospectively in patients hospitalized with severe lower respiratory tract disease due to influenza. Clinical studies to address this question are underway. Thus, there is no clear evidence that oseltamivir improves outcomes in this population, but most clinicians would use oral oseltamivir if patients had any severe manifestations of influenza.

Currently no parenteral agent is available for the treatment of influenza. However, new injectable neuraminidase inhibitors (peramivir and zanamivir), and novel agents such as polymerase inhibitors (T-705) are in human clinical trials.

Treatment of Pandemic Influenza

Treatment of pandemic influenza will need to be guided by sensitivities of the circulating strain. Treatment recommendations of sporadic cases of avian influenza in humans are to use oseltamivir at currently licensed doses.[79] Zanamivir is efficacious in animal models but there is no experience with this agent in the treatment of humans with avian influenza. Amantidine and rimantidine should be avoided due to high prevalence of resistance in some clades.[79] ICU management during a pandemic would need to emphasize strict epidemiologic control to avoid nosocomial spread, prompt initiation of antibacterial therapy when appropriate, and well thought out triage.

Special Populations

In spite of the profound impact of HIV on cell mediated immunity, HIV does not appear to be a risk factor for more frequent or more severe disease with influenza.[80–82] In one population series, an excess mortality due to influenza was been reported in the HIV population in the pre-HAART era compared to the general population.[83] It has not been shown that those with HIV have any different spectrum of disease with influenza.

Patients with leukemia, organ transplantation, and hematopoietic stem cell transplantation (HSCT) do appear to have a more severe disease with influenza. Influenza virus infection in the immunocompromised is associated with a higher rate of viral pneumonia and higher attributable mortality.[84] Viral shedding is also prolonged to an average of 11 days[85], which is associated with the development of resistance.[86] For this reason, standard dose and duration of antivirals may not be adequate in this population. Some authors have advocated higher use of oseltamivir (150mg bid) in the immunocompromised host.[84]

Antiviral Impact on Complications

Additional analysis of the controlled studies have shown that oseltamivir treatment was associated with significant reductions in bronchitis and pneumonia, antibiotic use, and all-cause hospitalizations in the month after influenza diagnosis.[78] Zanamivir as also been shown to reduce complications and secondary antibiotic use, particularly in the high risk patients (immunocompromised, or having underlying respiratory, cardiovascular, or endocrine disorders).[73]

Conclusion

Intensivists need to be prepared to manage both seasonal influenza and pandemic influenza. Parenteral antiviral agents are needed, and studies need to be performed to determine if these agents provide benefit to severely ill patients.

Intensivists can diminish the impact of influenza on their patients and their staff. Immunization for health care workers ought to be considered as a mandatory condition of employment for those without a medical or ethical contraindication, and immunizations should be completed by early Fall. Strict adherence to isolation procedures should be emphasized regularly. Recognition of treatment complications of influenza such as bacterial pneumonia should be prompt.

Intensivists also have an obligation to participate in hospital, regional and national programs to coordinate and develop services for a pandemic, which will eventually occur. The media and some health care organizations seem to have developed “flu fatigue” i.e., they are less engaged in pandemic preparation since no large outbreak has occurred. A pandemic will occur. Intensivists and the global society must be prepared.

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Table 1

Diagnostic Tests

	Time to Result	Advantages	Disadvantages
Rapid Antigen	<30 min	Fast, not technically difficult, POC testing	Marginal sensitivity especially in adults, Does not distinguish subtypes of influenza
Immunofluorescence	1–4 hours	Fast and versatile.	Not widely available, requires technical expertise.
Nucleic acid Testing	4–24 hours	Very sensitive, subtypes virus, detects other respiratory pathogens	Requires technical expertise
Culture	24 hours – 5 days	Very sensitive, detects other respiratory viruses	Slow results
Antibody testing	several weeks	Highly specific and sensitive	Labor intensive, slow results.

Table 2

Antivirals

	Drug	Route	Usual Adult Dosage	Threshold for Adjustment in Renal Insufficiency/Failure	Adjustment for Hepatic Failure
Influenza A and B viruses	Oseltamivir	PO	75 mg bid for 5 days	CrCl 50 mL/min/1.73 m ²	No Adjustment
	Zanamivir	Inhalation	10 mg bid by inhaler for 5 days	CrCl 10 mL/min/1.73 m ²	No Adjustment
Influenza A	Amantadine	PO	100 mg bid for 5 days	CrCl 30 mL/min/1.73 m ²	No Adjustment
	Rimantadine	PO	100 mg bid for 5 days	No Adjustment	100mg daily