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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Wise (editor) reports he is involved with sales for CNS Vital Signs and Clean Sweep. Dr. Sugalski (author), Dr. Ullo (author), Dr. Marco (peer reviewer), Ms. Coplin (executive editor), Ms. Mark (executive editor), and Ms. Hatcher (editorial group manager) report no financial relationships with companies related to the field of study covered by this CME activity.

Influenza Cases Rising: What Clinicians Need to Know

Background

Influenza is an acute respiratory illness responsible for significant seasonal epidemics each year. The disease is transmitted by the influenza virus, an enveloped RNA virus that is part of the *Orthomyxoviridae* family. Despite commonly being a self-limited illness, the virus causes significant morbidity and mortality each year.

Influenza A and B are responsible for most clinically significant influenza infections. Influenza A is primarily implicated in significant pandemics that greatly affect public health. This virus is typed according to the antigenic characteristics of envelope glycoproteins, specifically hemagglutinin and neuraminidase. Influenza A has three major subtypes of hemagglutinin, H1, H2, and H3, along with two subtypes of neuraminidase, N1 and N2. Influenza B is not classified by subtypes and has not been shown to cause pandemics.

Additional subtypes of influenza, C and D, are associated with human disease less commonly. Influenza C produces a self-limited respiratory illness that is more common in children. Influenza D is believed to have originated in cattle and largely is responsible for bovine respiratory disease.[1]

The burden of influenza on the U.S. population each year is significant, with as many as 35.6 million cases since 2010 resulting in up to 56,000 deaths. Of the 35.6 million cases, as many as 710,000 patients were hospitalized secondary to influenza. The widespread use of the influenza vaccine continues to be the most effective method of prevention. The Centers for Disease Control and Prevention (CDC) estimates that the vaccine has prevented 5.1 million influenza illnesses, 2.5 million influenza-related medical visits, and 71,000 hospitalizations.[2]

Global Impact

Throughout history, several major global outbreaks of influenza have been documented. These outbreaks are due to the ability of viral cells to change their antigenic structure rapidly. While the influenza virus traditionally is regarded as a human disease entity, it is important to recognize that animals, such as birds and pigs, serve as important reservoirs for viral strains. These unique properties of the virus are responsible for the significant outbreaks that have shaped the history of public health.

Although the influenza pandemic of 1918 is perhaps the most well-known of all outbreaks, influenza has affected history for centuries. The first documented influenza outbreak may have occurred as early as 1510. While it would have been impossible for early historians to know the exact nature of the disease, this illness bore similar traits to the modern influenza virus

EXECUTIVE SUMMARY

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- The Centers for Disease Control and Prevention estimates that the vaccine has prevented 5.1 million influenza illnesses, 2.5 million influenza-related medical visits, and 71,000 hospitalizations.
- So far in the current 2018-2019 season, about 7 million Americans have been affected, with half of those people seeing a physician. Between 69,000 and 84,000 people have been hospitalized for flu-related illness.
- Influenza is spread from person to person, largely via droplet transmission when both parties are within close contact, typically less than six feet. Covering coughs and good handwashing hygiene are critical to preventing transmission.
- Typical symptoms include acute onset of fever, headache, myalgias, and malaise followed by respiratory complaints, such as cough, sore throat, and rhinorrhea.
- Antiviral medications include neuraminidase inhibitors and adamantanes administered within the first 24-30 hours of presentation.

that is well described today. Historical accounts of rapid-onset fever with respiratory symptoms that occurred via trade routes or in major population centers suggest that influenza epidemics and pandemics have been present throughout the course of human history.[3]

H1N1 Pandemic, 1918

The H1N1 avian influenza virus had a major worldwide impact from 1918-1919. Historical estimates suggest that nearly 500 million people across the globe were infected, representing roughly one-third of the entire population. In the United States, the virus emerged during the spring of 1918 when military personnel first were reported to have flu-like symptoms. Transmission of the virus resulted in the deaths of 50 million people worldwide, with roughly 675,000 deaths in the United States.[4,5] In 2005, researchers successfully recreated the virus in an effort to learn more about the emergence of pandemic viruses.[6]

H2N2 Pandemic, 1957-1958

In February 1957, the H2N2 strain of the influenza A virus resulted in the pandemic known as the Asian flu. Located predominantly in East Asia, the virus spread to coastal U.S. cities during the summer of 1957. Approximately 1.1 million deaths were documented worldwide, with close to 116,000 fatalities in the United States.[7,8]

H3N2 Pandemic, 1968

The H3N2 strain of the influenza A virus was documented to reach the United States in September 1968. The estimated number of deaths was 1 million worldwide, with roughly 100,000 fatalities in the United States.[9]

H1N1 Pandemic, 2009

In April 2009, a novel strain of the influenza A virus, H1N1, resulted in a significant outbreak of respiratory illness. The strain emerged in Mexico and quickly spread across the United States, with more than 55 million hospitalizations worldwide. Attempts to curb the infection resulted in the production of a specially formulated vaccine. The clinical impact of this virus resembled previous strains of influenza; however, there was increased morbidity among younger adults with comorbidities. In the United States, more than 10,000 patients died as a result of complications from infection. The World Health Organization declared the pandemic over in April 2010.[10,11]

H3N2 Variant Influenza, 2011

First identified in 2011, the H3N2 strain of the influenza A virus has been responsible for more than 400 cases of influenza, with the majority identified after July 2012.[12] This strain was found to be swine in origin, with the addition of the M gene from the H1N1 influenza A virus. Most affected individuals reported contact with swine prior to illness. Cases of this strain typically are milder and self-limited.

Avian H7N9 Influenza, 2013

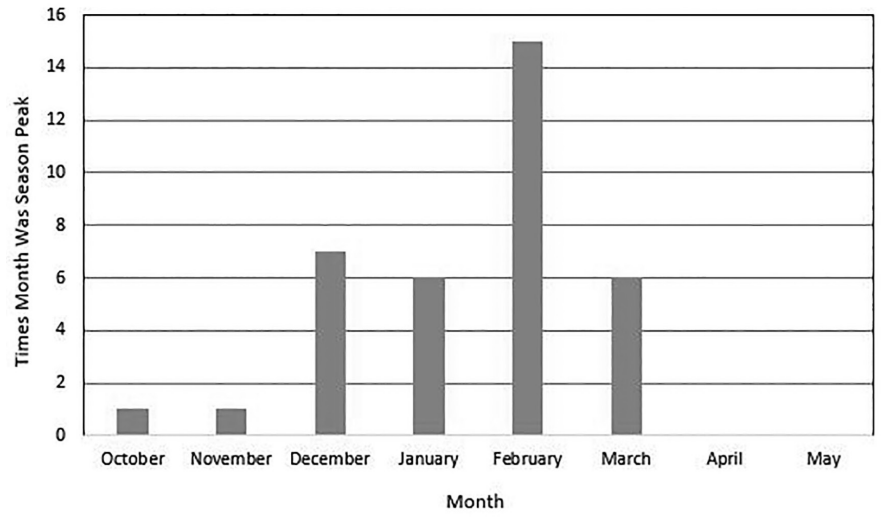
The novel avian H7N9 strain was identified first in China in 2013, and has been responsible for annual epidemics during influenza season. As with the H3N2 influenza strain, there is limited evidence of direct person-to-person transmission. Most cases have been associated with the handling of poultry prior to illness. Patients with confirmed avian H7N9 influenza had severe disease, with mortality rates from 27-36%, and pneumonia was a common complication.[13,14]

Epidemiology

The influenza virus carries a clinically significant health burden that tends to occur seasonally, with peak activity in the winter months. This phenomenon is associated with the antigenic shifts and antigenic drifts seen in the type A strain of the virus. Major changes in the virus's glycoproteins (neuraminidase and hemagglutinin) are termed antigenic shifts. These shifts are responsible for the significant epidemics and pandemics that affect large populations. Minor changes in the structure of these glycoproteins result in antigenic drift, which tends to result in more localized outbreaks.

The incidence of influenza is difficult to characterize because the infection is not always diagnosed and the incidence varies based on the disease burden during each season or unique epidemic. Furthermore, the incidence varies based on differing age groups. The World Health Organization currently estimates that annual influenza epidemics result in 1 billion infections worldwide, with 3 to 5 million cases of severe disease.[15] A meta-analysis of hospitalized patients in the United States suggests an annual incidence around 8%.[16] Seasonal disease causes between 250,000 and 500,000 deaths worldwide and between 5,000 to 50,000 deaths in the United States.[17]

Figure 1. Peak Month of Influenza Activity 1982-1983 Through 2017-2018



Source: Centers for Disease Control and Prevention

Influenza Season

Although the influenza virus circulates year-round, "influenza season" typically is defined as the period when infection with the influenza virus is the highest. In the United States, the CDC maintains annual data with weekly influenza reports available to the public. The incidence of respiratory secretions testing positive for influenza begins to rise in October and peaks throughout the winter months in the Northern Hemisphere.[18] (*See Figure 1.*) Despite this, it is important for the clinician to remember that influenza circulates continuously throughout the year and may be present at any time.

Although the influenza season typically occurs during the winter months in both the Northern and Southern Hemispheres, influenza season may occur at any period during the year in tropical regions and may affect travelers. Similarly, sporadic outbreaks may occur on cruise ships and as a result of airline travel.[19,20]

Etiology

The influenza virus (genus influenzavirus) is a negative-sense, single-strand RNA virus. Influenza A, B, C, and D have been identified, with types A and B responsible for the bulk of human pathology. The A and B viral genome contains segments of genetic material that encodes viral proteins that facilitate viral replication and entry into host cells. The hemagglutinin protein allows for viral entry, while the neuraminidase protein allows for viral release. (*See Figure 2.*)

Risk Factors for Infection

Risk factors for infection are similar to the risk factors for other viral pathologies that cause disease in humans. Children without significant previous exposure to the virus are at a higher risk for infection with more severe features. Because of their decreased immune system function and significant medical comorbidities, the elderly are at higher risk for severe illness that often requires hospitalization.[21]

Patients with neuromuscular disease and lung pathology also are more susceptible to infection. This risk is thought to be due to impaired handling of respiratory secretions.[22] Females who are pregnant have an increased risk throughout pregnancy, with a peak during the third trimester that persists through the postpartum period.[23]

Obese individuals are at higher risk of infection because of several proposed mechanisms. Reduced efficacy of vaccination and increased viral replication have been described in patients with a significantly elevated body mass index.[24]

Pathophysiology

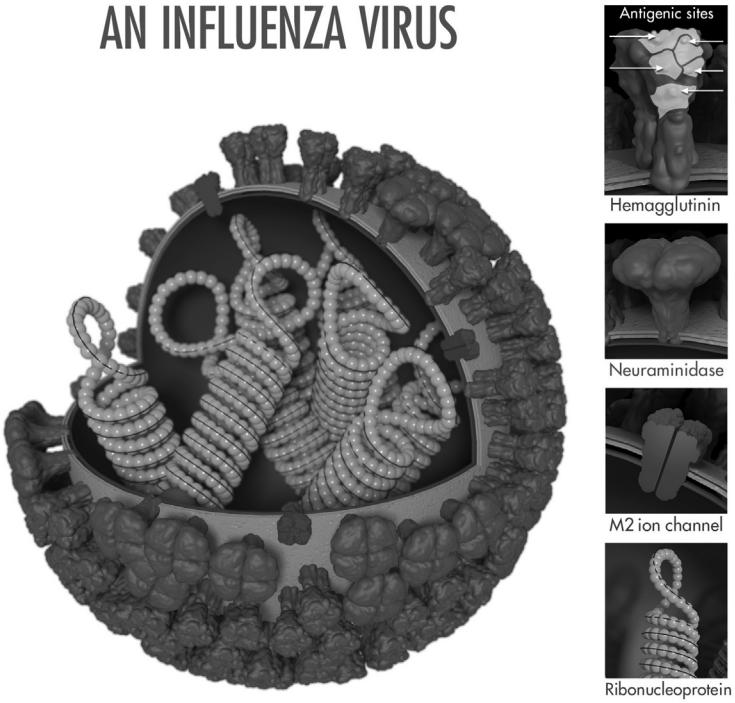
Influenza virus is spread from person to person largely via large droplet transmission that occurs during sneezing and coughing. Transmission from host to recipient occurs when both parties are within close contact, typically less than six feet, as the large droplets do not remain aerosolized for significant periods of time.[25] The virus also can spread by touching a surface contaminated with droplets and then touching mucous membranes, such as the conjunctiva of the eyes. Covering coughs and sneezes and good handwashing practices are critical to preventing transmission. The virus enters the respiratory tract and targets the epithelial cells for subsequent replication. The virus binds to the cell wall through an interaction between the virus's hemagglutinin glycoprotein and sialic acid glycoproteins on the host cell wall. Once the virus enters the cell and replicates, the neuraminidase glycoprotein aids in the release of replicated virions. This process leads to eventual apoptosis of the affected cells and subsequent spread of the virus.

Infectious Course

The incubation period for influenza typically is one to four days. Viral shedding is thought to occur within 24 to 48 hours before symptom onset, although there is less of a viral burden than when the patient is symptomatic.[25] Peak viral shedding has been shown to occur two days after transmission.[26] Longer periods of shedding may occur with certain patient populations, such as children, older adults, immunocompromised patients, or those with chronic medical conditions.[27-29]

Uncomplicated influenza infection typically manifests with an acute onset of fever, headache, myalgias, and malaise. Following these initial symptoms, patients commonly experience symptoms associated with respiratory tract disease, such as cough, sore throat, and rhinorrhea.[30] Patients

Figure 2. Influenza Virus



Source: CDC/Douglas Jordan; Dr. Ruben Donis, Dr. James Stevens, Dr. Jerry Tokars, Influenza Division; photo credit: Dan Higgins

with uncomplicated influenza usually recover from their illness within two to five days, although complete symptom resolution may take one week or more.

Clinical Presentation

The clinical presentation of uncomplicated influenza mimics other respiratory viral syndromes. Patients often present with the abrupt onset of symptoms within one to four days of exposure to the virus. Symptomatology can range from mild to life-threatening and can last for two weeks.[31,32]

Initial symptoms after infection include high fevers, intense myalgias, headaches, and anorexia. As infection progresses, patients tend to exhibit respiratory tract symptoms, such as nasal congestion, rhinorrhea, sore throat, and development of a nonproductive cough. The presence of gastrointestinal symptoms, such as vomiting and diarrhea, rarely is associated with influenza in adult patients. In contrast, nausea and vomiting may be key elements of the history elicited for pediatric patients.

The physical examination often is remarkable for fever with the presence of posterior cervical adenopathy and erythematous mucous membranes of the nasopharyngeal passages. The oropharynx may appear hyperemic, and the lung examination can vary from benign to rales secondary to superimposed pneumonia. Tachycardia may be present as a response to the febrile state or dehydration secondary to decreased oral intake. Children may demonstrate erythematous tympanic membranes suggestive of acute otitis media.

Patients at the extremes of age may present atypically. Exacerbations of underlying chronic medical comorbidities may be the initial presentation for older patients. Careful consideration should be applied when evaluating this subset of patients, as diagnosis is not always straightforward.[11,31,32]

Differential Diagnosis

Influenza carries a presentation similar to other viral syndromes and can be misdiagnosed. A thorough history and physical examination can help guide the evaluation of patients for potential etiologies. Upper respiratory infections caused by other viral agents, such as adenovirus, rhinovirus, and coronavirus, present similarly to influenza. (*See Table 1.*) Overlapping symptoms such as rhinorrhea, myalgias, and cough can predominate the clinical picture. Other infectious pathologies, such as meningitis, pneumonia, and pyelonephritis, should be considered in the evaluation of patients with influenza-like symptoms. A thorough travel history and exposure history should be pursued to screen for other etiologies such as dengue fever or Ebola. This broad differential can make diagnosis challenging.

Diagnosis and Testing

Influenza can be diagnosed clinically based on a thorough history and physical examination without the need for routine diagnostic testing. The abrupt onset of a febrile respiratory illness with systemic symptoms such as myalgias and headaches during peak months can guide clinicians toward a presumptive diagnosis.[33,34]

Laboratory testing is available and should be reserved for instances in which confirmatory testing will affect patient care. According to the CDC, testing during an acute outbreak of respiratory illness can help determine if influenza is the cause and guide implementation of prevention and control measures.[33]

In infants and young children, nasal aspirates and swabs are the preferred specimens for testing. Specimens should be obtained from the nasopharynx in older children and adults. In mechanically ventilated patients, endotracheal aspirates or bronchiolar lavage fluid should be obtained for evaluation of the lower respiratory tract.[35,36]

Suggested uses for diagnostic testing include hospitalized patients, patients with significant medical comorbidities, and documentation for institutional purposes. Individual providers should contact their laboratory for detailed information regarding the performance of the specific diagnostic test used at their institution.

Rapid Antigen Testing

The rapid antigen test can identify viral nucleoprotein antigens in

Table 1. Cold vs. Flu

Signs and Symptoms	Common Cold	Influenza
Onset of symptoms	Gradual	Abrupt
Fever	Rare	Usual
Myalgias	Slight	Usual
Chills	Uncommon	Fairly common
Malaise	Sometimes	Usual
Sneezing	Common	Sometimes
Nasal congestion	Common	Sometimes
Sore throat	Common	Sometimes
Headache	Rare	Common

Adapted from: Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). Cold versus Flu.

respiratory specimens.[35] Data suggest that this testing method carries a pooled sensitivity of 62% and specificity of 98%.[36] Although these tests can produce results in as quick as 15 minutes, they tend to have lower sensitivity than reverse transcriptase polymerase chain reaction (PCR). Rapid antigen testing in the emergency department (ED) has limited utility, as uncomplicated cases do not require diagnostic testing for presumptive treatment. Hospitalized patients should have PCR analysis performed.

Polymerase Chain Reaction

The PCR method of diagnosis typically is more burdensome because it can take approximately eight hours and is not always readily available. Despite this, PCR analysis may be useful in select patients, as sensitivity and specificity approach 100%.[37]

Viral Culture

Viral culture, typically viewed as the gold standard for diagnosis, has a turnaround time of 48-72 hours. Therefore, it is not used for initial clinical management in the emergency setting and instead may be more beneficial for public health screening.[35]

Complications

Patients with influenza also may develop more severe complications as a direct result of their infection. Well-established complications include primary influenza pneumonia, secondary bacterial pneumonia, myositis, rhabdomyolysis, acute myocardial infarction, myocarditis, pericarditis, central nervous system involvement, and toxic shock syndrome.

Although primary influenza pneumonia is one of the rarest complications of influenza infection, it is also one of the most severe. Clinicians should consider primary pneumonia in patients with persistent symptoms and recurrent fevers. Subsequent secondary bacterial pneumonia frequently is recognized as a complication in patients older than 65 years of age.[38] Radiologic imaging of the chest can assist with diagnosis. *Streptococcus pneumoniae* is the most common bacteria implicated. Clinicians also should recognize the increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* as a causative agent.[39,40]

Management

The mainstay of management for most adults and children infected with the influenza virus remains supportive care, as the disease usually is self-limited. Otherwise healthy patients without significant comorbidities may achieve symptomatic relief with over-the-counter medications and adequate oral hydration.

Antiviral therapy, when initiated promptly, has been shown to play a role in shortening the duration of influenza symptoms. The greatest benefit of these medications has been demonstrated when given to febrile patients within the first 24 to 30 hours of presentation.[41,42,43]

The two major classes of antiviral medications for influenza are the neuraminidase inhibitors (oral oseltamivir, intranasal zanamivir, and intravenous peramivir) and adamantanes (oral amantadine and rimantadine). Because of concerns that adamantanes are effective only against influenza A, and most viral strains are highly resistant to this drug class, their routine use is not recommended. (*See Table 2.*) Consequently, neuraminidase inhibitors predominate as the antiviral therapy of choice when treating suspected or confirmed cases of influenza in the overwhelming majority of patients.[44]

Current clinical guidelines from the CDC and the Infectious Diseases Society of America (IDSA) recommend initiation of neuraminidase inhibitors as soon as possible with confirmed or suspected cases of influenza in patients with severe illness, hospitalized patients, and patients at high risk of complications. The decision to administer therapy should not be delayed or depend on results of diagnostic testing.[44,45]

Otherwise healthy adults and children with presumed or confirmed

Table 2. Neuraminidase Inhibitors in the Treatment of Influenza

Drug	Indications	Contraindications	Common Adverse Effects
Oseltamivir (Tamiflu)	Seasonal influenza treatment in patients ≥ 2 weeks of age Seasonal influenza prophylaxis in patients ≥ 1 year of age	Hypersensitivity to medication or component of formulation	Headache, vomiting
Zanamivir (Relenza)	Seasonal influenza treatment in patients ≥ 7 years of age Seasonal influenza prophylaxis in patients ≥ 5 years of age	Hypersensitivity to medication or component of formulation Avoid in patients with underlying respiratory disease (chronic obstructive pulmonary disease, asthma)	Headache, sore throat, cough, rhinorrhea
Peramivir (Rapivab)	Seasonal influenza in patients ≥ 2 years of age	Hypersensitivity to medication or component of formulation	Hypertension, insomnia, increased serum glucose, constipation, diarrhea, increased alanine aminotransferase and aspartate aminotransferase

Sources: Oseltamivir. Lexi-Drugs. Lexicomp. Wolter Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com; Zanamivir. Lexi-Drugs. Lexicomp. Wolter Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com; Peramivir: Lexi-Drugs. Lexicomp. Wolter Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

Table 3. Oseltamivir Dosing for Treatment, Not for Prophylaxis

Adults	• 75 mg twice daily for 5 days
Children (> 1 year of age)	• < 15 kg: 30 mg twice daily for 5 days • 15 to 23 kg: 45 mg twice daily for 5 days • 23 to 40 kg: 60 mg twice daily for 5 days • > 40 kg: 75 mg twice daily for 5 days
Infants (< 1 year of age)	• 1 to 8 months: 3 mg/kg/dose twice daily • 9 to 11 months: 3.5 mg/kg/dose twice daily

Source: Oseltamivir. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

influenza may be treated electively as outpatients with neuraminidase inhibitors. Studies in these populations demonstrated a small decrease in length of illness by approximately one day in adults.[46] Shared decision-making with the patient on a case-by-case basis can help guide the decision to initiate medical therapy.

Oseltamivir (Tamiflu) is one of the most frequently prescribed medications used in the management of influenza. The typical dosage regimen for oseltamivir is described in Table 3. Adult patients with a creatinine clearance < 60 should have their dose adjusted to 30 mg twice daily.[47] In addition, patients with creatinine clearance ≤ 30 should have their dose reduced to 30 mg one time daily. Although the drug is considered pregnancy class C, the American College of Obstetricians and Gynecologists (ACOG) recommends presumptive treatment with antiviral medication during pregnancy.[44] Treatment should be initiated within 48 hours of onset of illness and continued for a duration of five days. Common side effects include headache, nausea, and vomiting.

Patients who require hospitalization or who are deemed to be at high risk for influenza complications should be treated with a neuraminidase inhibitor regardless of duration of symptoms. These risk factors include age older than 65 years, pregnancy, and chronic comorbid medical conditions. Initiation of therapy should not be delayed while awaiting diagnostic or confirmatory testing.[44,48]

Resuscitation of the critically ill patient initially should focus on the ABCs of emergency medicine management: airway, breathing, and circulation. A stepwise approach should be taken toward resuscitation, with prompt attention to abnormal vital signs and simultaneous expediting of therapeutic modalities. Endotracheal intubation may be necessary if patients present with profound hypoxia and/or respiratory distress that is not responsive to noninvasive management such as supplemental oxygen. The potentially septic patient should be monitored

carefully and treated with crystalloid resuscitation if hypotension and/or tachycardia are present. Initiation of vasopressors may be considered in patients who remain hypotensive despite adequate resuscitation with intravenous fluids for hemodynamic support.

Chemoprophylaxis for patients with exposure to suspected or confirmed cases of influenza remains controversial. In general, routine use of chemoprophylaxis with antivirals is not recommended. Patients exposed to influenza who are at high risk for complications and cannot be vaccinated because of contraindications should be considered as candidates.[44]

Emerging Therapy

In October 2018, the U.S. Food and Drug Administration (FDA) announced approval of single-dose baloxavir marboxil (Xofluza) for treatment of acute, uncomplicated influenza in people 12 years of age and older.[49] This oral medication works by blocking mRNA synthesis of endonucleases responsible for viral proliferation.[50] Results from a randomized, controlled trial comparing baloxavir marboxil to oseltamivir and placebo demonstrated superiority in reduction of viral load one day after initiation of pharmacotherapy for patients receiving baloxavir marboxil.[51] It remains unclear whether baloxavir marboxil is superior to oseltamivir for hospitalized or immunocompromised patients, or in those with neuraminidase inhibitor-resistant influenza infections.[52]

Prevention

Vaccination remains the cornerstone for primary prevention of influenza. Although the vaccine is effective in preventing infection with common strains of the virus, there remains significant potential for illness despite vaccination.[53]

Given the high rates of new strains that develop from significant antigenic variation, vaccines are reformulated annually to match expected circulating strains. These formulations generally are developed six months prior to influenza season based on surveillance data from the previous year.

The seasonal influenza vaccine is recommended for yearly administration in patients 6 months of age and older who do not have any known contraindications for vaccination. This includes pregnant women (regardless of gestational age) and women who are breastfeeding.[54]

Currently, three types of influenza vaccines are available in the United States:

- The inactivated influenza vaccine is administered intramuscularly and is available in tetravalent and quadrivalent forms for patients 6 months of age and older.
- The recombinant hemagglutinin vaccine is available for patients 18 years of age and older.
- The intranasal, live attenuated influenza vaccine is available for otherwise healthy and nonpregnant patients, 2-49 years of age.

These preparations typically are available in the fall to prepare for peak incidence during the winter months.[55,56] In addition, a high-dose vaccine is available for patients older than 65 years of age.

Contraindications to vaccination include severe allergy to previous formulations of the influenza vaccine in the past. Additionally, several of the available forms of the vaccine contain small amounts of egg protein. Previously, egg allergy was considered to be a contraindication to vaccination; however, recent data have demonstrated that vaccination may be given in patients with known egg allergy with appropriate precautions. These patients should be referred to an allergy specialist for additional evaluation prior to administration.

The intranasal, live attenuated vaccine should be withheld from patients who are immunocompromised. This vaccine also is contraindicated in patients who are pregnant, 50 years of age or older, and those who have taken influenza antiviral medication within the past 48 hours.[56]

Recently, research efforts have focused on the establishment of a universal vaccination. This vaccine would function to elicit the creation of protective antibodies in vaccinated patients against well-conserved viral proteins.[57,58]

Disposition

Outpatient Management

Most patients diagnosed with influenza from the ED may be discharged home safely with strong return precautions. Patients discharged from the ED should follow up with a primary care provider in two days for re-evaluation for monitoring of their clinical course. Vital signs should be re-evaluated prior to discharge planning to check for persistent hypoxia, tachycardia, or tachypnea. The febrile state is expected with the disease process, and clinicians should consider the effects of administration of antipyretics when evaluating the significance of fever.

Discharge instructions should educate patients on signs and symptoms that should prompt a patient to seek immediate medical attention. Patients should be instructed to return to the ED if they experience persistent fever, inability to tolerate oral intake, confusion, or changes in mental status. Upon discharge, patients diagnosed with influenza should be educated on hand washing, respiratory hygiene, and cough etiquette to decrease the risk of viral spread.

Supportive care with antipyretics, rest, and hydration are the mainstays of outpatient therapy. Treatment with an antiviral agent may be initiated without diagnostic testing in the appropriate clinical setting. Patients should be counseled regarding the risks and benefits of medical therapy before initiation with a neuraminidase inhibitor.

Observation

Certain patients may benefit from observation in the hospital or ED depending on institutional practices. Patients should be placed on droplet precautions to limit the spread of viral illness within the healthcare facility.[59] The observation setting may be a useful disposition for patients who may benefit from serial cardiopulmonary examinations and/or intravenous hydration secondary to clinically significant dehydration. Patients at the extremes of age without significant medical

Table 4. Comorbid Conditions That Increase Risk of Influenza Complications

- Chronic pulmonary disorders
- Chronic renal disorders
- Chronic hematological disorders, including sickle cell disease
- Metabolic disorders, including diabetes mellitus
- Immunosuppressed patients, including those with HIV/AIDS and cancer patients undergoing chemotherapy
- Pregnancy or postpartum state (within two weeks of delivery)
- Morbid obesity (body mass index > 40 kg/m^2)
- Residence in nursing home or other chronic care facilities

Source: Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60:1-24.

comorbidities may benefit from this extended period of medical observation. Prior to discharge, patients should be re-evaluated for symptomatic improvement and the ability to tolerate oral intake. If a patient's clinical response to symptomatic therapy fails to improve, strong consideration should be given for admission to the hospital for further management.

Hospitalization

During the past eight years, more than 700,000 patients have required hospitalization secondary to known or suspected influenza infection.[2] The decision to admit a patient to the hospital for influenza can be particularly challenging, as no well-validated scoring system exists to guide disposition. This decision should be based on clinical judgment in conjunction with assessment of the patient's risk factors.

A subset of patients should be considered for admission to the hospital because of concern for decompensation from the viral illness. Adults older than 65 years of age, pregnant women, children younger than 5 years of age, as well as individuals with comorbid conditions[48] should be considered for admission. (*See Table 4.*) Additionally, patients previously evaluated by a medical provider who have failed to improve with outpatient management should be considered for admission.

Patients with influenza may deteriorate and develop acute respiratory distress syndrome, requiring possible intubation and intensive care for hypoxemic respiratory failure. In these patients, extracorporeal membrane oxygenation may serve as bridge therapy during the acute illness.[60] The clinician should proceed cautiously with patients who present with hypoxia because these patients may progress to respiratory failure. Patients who are deemed to be at high risk because of comorbidities or changes in mental status should be screened for intensive care admission when available. Consultation with a pulmonologist or infectious disease specialist may be appropriate depending on the patient's clinical course or past medical history.

Summary

Influenza outbreaks occur each year, with their nature and extent largely determined by the virus's glycoprotein structure and antigenic properties. These outbreaks typically occur during the winter months and can confer high morbidity to the general patient population. Increased mortality rates are seen in young children, older adults, and those with chronic comorbid medical conditions.

During the winter months, clinicians should maintain a high suspicion for influenza in all patients presenting with an acute febrile respiratory illness. Although the differential diagnosis is broad, the history and physical examination can guide the clinicians toward a presumptive diagnosis without the need for additional testing. Laboratory testing is available and should be reserved for those cases in which the diagnosis may change the clinical management.

Treatment is indicated for patients with severe disease or those at risk for complications. Initiation of antiviral treatment should be within 48 hours of symptom onset. Most otherwise healthy patients can be managed with supportive care only. Complicated cases of influenza may require hospitalization and treatment with antiviral therapy regardless of symptom duration.

Prevention of the influenza virus is achieved primarily through the annual influenza vaccine. This vaccine is formulated to protect patients from the most commonly circulating strains of the virus. This is accomplished by obtaining routine surveillance data about viral characteristics during each influenza season.

Emerging therapy, including single-dose antiviral medications and universal vaccination, may shape the rapidly evolving nature of the influenza virus and its burden on human health.

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CME/CE Questions

1. Which of the following is true regarding the influenza virus?
   a. It is a double-stranded DNA virus.
   b. Influenza B is typed according to envelope glycoproteins.
   c. The neuraminidase glycoprotein is responsible for facilitating entry into the host cell.
   d. Influenza C is responsible for most influenza cases worldwide.
2. Which of the following patients is at increased risk of morbidity and mortality from influenza infection?
   a. A 25-year-old male with recent orthopedic surgery
   b. A 35-year-old male with history of HIV and chronic obstructive pulmonary disease
   c. A 14-year-old adolescent female with significant family history of hypertension
   d. A 52-year-old female who drinks a glass of wine two times per week
3. Which symptom of influenza is more common in pediatric patients than adult patients?
   a. High fever
   b. Myalgias
   c. Nausea and vomiting
   d. Headache
4. Which of the following is true regarding testing for influenza?
   a. All patients suspected of influenza should have polymerase chain reaction testing performed.
   b. Currently available rapid diagnostic tests have high sensitivity and specificity for influenza.
   c. Polymerase chain reaction testing is rapid and readily available at all institutions.
   d. Viral culture is the gold standard for diagnosis.
5. A 38-year-old male with no past medical history presents to the emergency department with seven days of cough and fever. He reports having a positive flu test result at his doctor's office five days ago. The chest X-ray reveals a left lower lobe infiltrate. Which of the following is the most likely causative agent?
   a. *Streptococcus pneumoniae*
   b. *Mycoplasma pneumoniae*
   c. *Klebsiella pneumoniae*
   d. *Haemophilus influenzae*

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6. Which of the following statements is true regarding antiviral therapy for the treatment of influenza?
   a. The greatest benefit has been shown for febrile patients treated within 30 hours of presentation.
   b. Adamantanes remain the recommended class of antivirals for the treatment of influenza.
   c. Chemoprophylaxis should be given to all household partners of confirmed patients.
   d. Treatment should not be initiated until confirmatory testing has been completed.

7. Which of the following is a contraindication to the influenza vaccine?
   a. Severe allergy (e.g., anaphylaxis) to previous influenza vaccine formulations
   b. Age 6 months to 1 year
   c. Pregnancy
   d. Morbid obesity

8. The antigenic shift demonstrated by the influenza virus is responsible for:
   a. significant epidemics and pandemics that affect large numbers of patients.
   b. localized outbreaks of illness in small communities.
   c. the development of erythematous rash that affects the palms and soles.
   d. diarrhea and gastrointestinal bleeding.

9. A healthy 18-year-old female currently 32 weeks pregnant asks for advice regarding the influenza vaccine. Which statement accurately reflects best practice for vaccination during pregnancy?
   a. The intranasal vaccine may be given at any time during pregnancy.
   b. The vaccine is contraindicated in patients who are pregnant.
   c. Vaccination is recommended for pregnant patients regardless of gestational age.
   d. The vaccine should not be administered to pregnant women who plan on breastfeeding.

10. According to recent studies of the past 36 years, which month has demonstrated the highest incidence of respiratory secretions testing positive for influenza in the United States?
    a. February
    b. May
    c. August
    d. September

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