CME

EARN CATEGORY I CME CREDIT by reading this article and the article beginning on page 46 and successfully completing the posttest on page 52. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of December 2009.

LEARNING OBJECTIVES

- Describe the epidemiology of influenza outbreaks and the pathophysiology of influenza viruses
- Discuss the signs and symptoms of influenza and the patients who are at risk for complications
- Explain the tests used to diagnose influenza
- Describe treatment for influenza, including the guidelines for treating H1N1

H1N1 in perspective: The clinical impact of a novel influenza A virus

A swine-origin influenza A virus is poised to challenge how we treat influenza. This update explains what PAs should know about novel and seasonal influenza viruses.

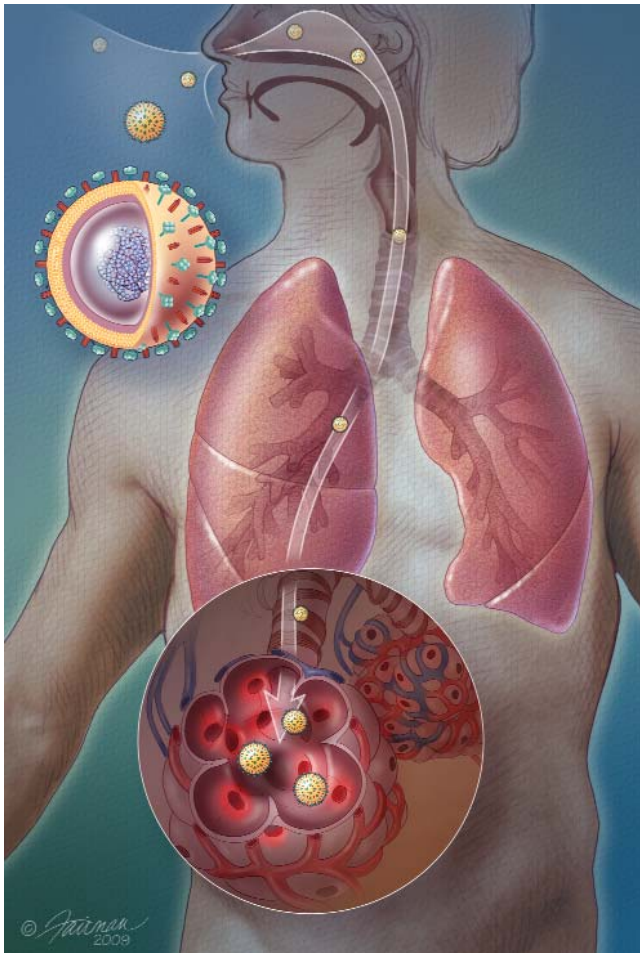
Kristine Himmerick, MS, MPAS, PA-C

The H1N1 influenza virus burst onto the global media stage this year and brought to the foreground viruses that have caused human disease on a pandemic scale since 1918. Clinicians who encounter patients with influenzalike illness (ILI) are responsible for identifying those who are at risk for flu complications, judiciously ordering laboratory studies, and dispensing antiviral medications. The goals of this article are to provide a clinically based review of influenza and to place the current H1N1 flu outbreak in historical and clinical context with other influenza viruses.

EPIDEMIOLOGY

Seasonal influenza outbreaks of widely varying severity are recorded annually. In the past century, however, three major influenza pandemics were recognized as a result of a genetic reassortment of human influenza A viruses with animal influenza A viruses.[1] The most severe pandemic, in which an estimated 40 to 50 million people died, occurred in 1918. Other influenza pandemics occurred in 1957 and 1968 and to a lesser extent in 1977.[2] In 1997, the discovery of avian influenza illness in humans in Hong Kong generated fear of a pandemic. **Avian influenza** is a highly pathogenic influenza A(H5N1) found in birds and, occasionally, in pigs. The virus transmitted easily from bird to bird but poorly from bird to human and human to human; therefore, the originally feared pandemic did not occur. Although pandemic influenza outbreaks do not appear to have any temporal pattern, they do seem to be decreasing in severity.[3]

On April 29, 2009, the World Health Organization (WHO) declared a human influenza pandemic. The pan-



Influenza A virus infection in the lungs

demic is the result of an influenza A virus that originated in pigs and has been categorized as a **novel swine-origin influenza A(H1N1) virus** (S-OIV).[4] Although swine H1N1 viruses and human H1N1 viruses have been documented in the past, the term *novel* refers to a genetically unique influenza virus that transmitted from pig to human and is now able to transmit rapidly from human to human.[5] The first cases of this novel S-OIV were discovered in Mexico and the United States in March and April 2009; by June 2009, all 50 US states had reported cases of the virus. At press time, the United States was on the cusp of influenza season, and the full impact of this S-OIV was not known.

CLASSIFICATION AND PATHOPHYSIOLOGY

Influenza is a single-strand RNA virus found in the family Orthomyxoviridae (**Figure 1**). Influenza viruses are subdivided into three genera: A, B, and C. **Influenza B and C viruses** are not typically categorized further because they demonstrate very little genetic change and are not thought to cause disease in species other than humans.[6,7] In contrast, influenza A virus is capable of rapid genetic evolution in multiple species. It requires further categorization by the species in which the virus resides (primarily avian, swine, or human) and by the genetic makeup of the two prominent surface glycoproteins (hemagglutinin [H] and neuraminidase [N]).

Influenza A viruses evade host antibodies to hemagglutinin and neuraminidase through mutations in the genes that code for these surface antigens (referred to as *genetic drift*). These minor mutations cause the yearly variation in influenza A viruses that circulate the globe. A more substantial mutation occurs when the genes that code for hemagglutinin and neuraminidase recombine with influenza virus segments from another animal species. The reassortment of genes between two species (called a *genetic shift*) may produce more severe infections because the surface antigens are wholly unrecognizable by the antibodies circulating in the immune system. A pandemic can occur when the influenza virus genes recombine between different species.[7]

CLINICAL MANIFESTATIONS

Signs and symptoms of influenza A infection usually manifest 1 to 4 days after exposure. The patient typically presents with sudden onset of fever and cough but may also report chills, malaise, myalgias, headache, nasal congestion, coryza, sore throat, nausea, vomiting, and diarrhea. Classic presentations are less likely to be seen in children, adults older than 60 years, and immunosuppressed patients. Symptoms of more severe illness may include shortness of breath, chest pain, headache, debilitating myalgias, or neurologic dysfunction.

Influenza B and C infections typically manifest with mild clinical symptoms and are most commonly found in children and people who reside in group settings. Healthy adult immune systems are able to develop an antibody response that confers future resistance because influenza B and C viruses demonstrate little genetic variation.

Clinical **signs of uncomplicated influenza** are few but may include pharyngeal injection, conjunctival injection, facial flushing, and cervical lymph node enlargement. Frequently, the patient's complaint of a severe sore throat is not consistent with the mild pharyngeal injection seen on examination. Findings that indicate a more severe illness may include frank dyspnea, hypoxia, cyanosis, diffuse rales, pulmonary consolidation, a fever that lasts for more than 5 days, or symptoms that last for more than 10 days.

The influenza virus causes the respiratory epithelium to break down, which increases the risk of a secondary bacterial infection (ie, acute bacterial sinusitis, otitis media, bronchitis, or pneumonia). Clinicians should be alert for these secondary bacterial infections when patients present with prolonged illness or worsening symptoms. The influenza virus itself can cause primary viral pneumonia, which has a significant mortality rate, particularly in high-risk populations.

Extrapulmonary complications of influenza include myositis; transverse myelitis; rhabdomyolysis; myocarditis; pericarditis; encephalitis; transverse myelitis; Guillain-Barré syndrome; and gradual deterioration of underlying cardiovascular, pulmonary, or renal function. The medical condi-

KEY POINTS

- On April 29, 2009, the World Health Organization declared a human influenza pandemic. The pandemic is the result of an influenza A virus that originated in pigs and has been categorized as a novel swine-origin influenza A(H1N1) virus. The term *novel* refers to a genetically unique influenza virus that transmitted from pig to human and is now able to transmit rapidly from human to human.
- Signs and symptoms caused by influenza A infection usually manifest 1 to 4 days after exposure. The patient typically presents with sudden onset of fever and cough, but may also report chills, malaise, myalgias, headache, nasal congestion, coryza, sore throat, nausea, vomiting, and diarrhea.
- Influenza can be diagnosed with throat swabs, nasopharyngeal washes, or sputum by rapid viral tests or reverse transcriptase-polymerase chain reaction. The subtype of influenza A virus can only be determined accurately in a designated laboratory with the use of subtype-specific antiserum.
- Antiviral medications reduce the severity and duration of influenza symptoms if they are started within 48 hours of the onset of illness. If antiviral treatment is initiated, the first dose should be administered as soon as possible and should not be delayed awaiting laboratory confirmation of infection.
- Specific guidelines for the treatment of novel H1N1 influenza may have changed by the time this article is published; therefore, PAs should refer to www.cdc.gov/h1n1flu/recommendations.htm for the most up-to-date recommendations.

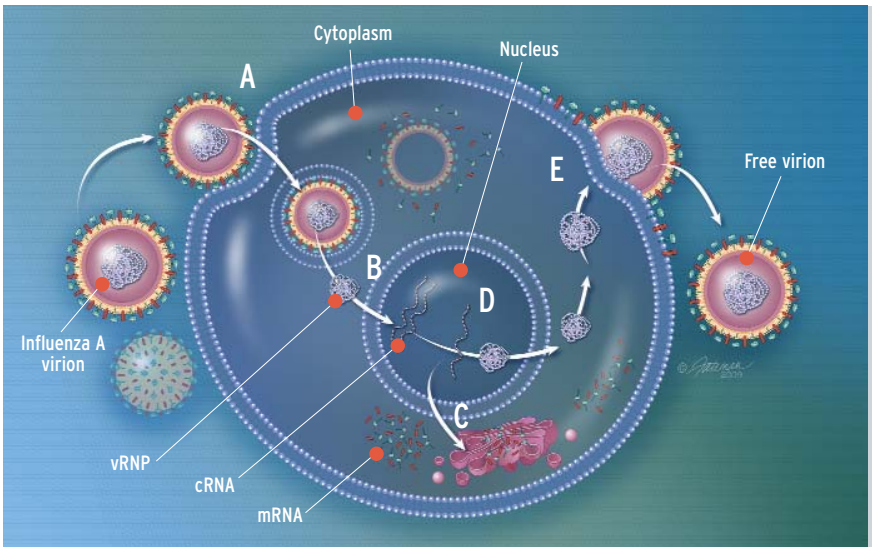


FIGURE 1. Influenza virus is an RNA virus that is capable of replication and transcription in the nucleus of a host cell. This process begins with entry of the virus into the host cell (a). The virus is then exposed to the cytoplasm, and the viral ribonucleoprotein complex (vRNP) is released and transported into the nucleus (b). Two types of viral RNA are produced in the nucleus: messenger RNA (mRNA) and complementary RNA (cRNA). Viral mRNAs are capped, polyadenylated, and exported from the nucleus (c). Viral cRNAs form the template for synthesis of viral RNA segments. Viral RNA segments are then packaged into newly synthesized RNPs (d), which are directed toward the surface of the host cell for assembly into new virions (e) and are released.

tions that predispose patients to the highest risk of death from influenza virus infection are chronic cardiopulmonary diseases; pregnancy; advanced age; and, to a lesser extent, chronic metabolic, renal, or immunosuppressive diseases.

DIAGNOSIS

Influenza can be diagnosed with throat swabs, nasopharyngeal washes, or sputum via rapid viral tests or reverse transcriptase-polymerase chain reaction. The subtype of influenza A virus can be determined accurately only in a designated laboratory with the use of subtype-specific antiserum. Leukocyte counts correlate poorly with the severity of illness and are often low in early illness and normal or slightly elevated in later illness. A leukocyte count greater than 15,000 cells/μL suggests the presence of a secondary bacterial infection.

Although many clinics are equipped with rapid influenza tests, influenza illness can be diagnosed clinically in patients presenting with ILI in the setting of a known community-wide outbreak. Confirmatory testing in qualified hospital or state laboratories should be prioritized for hospitalized patients with ILI.

TREATMENT

Testing every person with ILI or treating every fever and cough with an antiviral is impracticable. Patients with uncomplicated influenza can be treated symptomatically with rest, hydration, antipyretics, analgesics, humidified air, and/or cough suppressants. Children younger than 18 years should not be given salicylates because of their association with Reye's syndrome.

Antiviral medications reduce the severity and duration of influenza symptoms if they are started within 48 hours of the onset of illness. These advantages must be weighed against the cost, potential adverse effects, and the risk for development of viral resistance. If antiviral treatment is initiated, the first dose should be administered as soon as possible and should not be delayed awaiting laboratory confirmation of infection.

Amantadine and rimantadine inhibit influenza A viral reproduction; however, emerging resistance has become problematic. The neuraminidase inhibitors oseltamivir and zanamivir are effective against influenzas A and B.[8,9] Currently circulating novel H1N1 viruses are susceptible to oseltamivir and zanamivir but resistant to amantadine and rimantadine. WHO laboratories have received case reports of novel H1N1 resistance to oseltamivir, but the virus is still susceptible to zanamivir.[10]

Specific **treatment guidelines for novel H1N1 influenza** may have changed by the time this article is published; therefore, PAs should refer to www.cdc.gov/h1n1flu/recommendations.htm for the most up-to-date recommendations.[11] As of October 16, 2009, the recommendations are to reserve antiviral treatment for people with suspected or confirmed influenza who are at higher risk for complications (eg, children younger than 2 years, adults 65 years and older, pregnant women, persons with certain chronic medical or immunosuppressive conditions, persons younger than 19 years who are receiving long-term aspirin therapy, hospitalized patients, and patients with warning signs and symptoms of severe illness [dyspnea, tachypnea, hypoxia]).[11] Early manifestation of severe symptoms should be treated aggressively. Of note, these recommendations are the same as for seasonal influenza.

Preliminary research in the United States and in Europe indicates that there may be an association between obesity and increased risk of hospitalization and death as a result of infection with the current novel H1N1 influenza virus. Patients with morbid obesity should also be considered for antiviral treatment of ILI.[12,13]

PREVENTION

The first line of defense for preventing the spread of influenza is the practice of good health habits, including thorough

and frequent hand washing. Chemoprophylaxis should be reserved for patients who are at high risk for influenza complications and are suspected to have had contact with an influenza-infected person.

Two influenza vaccines are available for the 2009-2010 flu season. The novel H1N1 vaccine is not intended to replace the seasonal flu vaccine. It is intended to be used in conjunction with the seasonal flu vaccine to protect people at high risk. Seasonal flu and novel H1N1 vaccines can be administered on the same day. The CDC **recommendations for seasonal influenza vaccination** for the 2009-2010 flu season remain the same as those for the previous season and include vaccinating

- Children from age 6 months to their 19th birthday
- Pregnant women
- People 50 years and older
- People of any age with certain chronic medical conditions
- People who live in nursing homes and other long-term care facilities
- People who live with or care for persons at high risk for complications from flu and/or children younger than 6 months (these children are too young to be vaccinated), including health care workers, household contacts, and out-of-home caregivers.[14]

The **recommendations for the novel H1N1 influenza vaccination** apply to an estimated 159 million high-risk people in the United States.[15] The H1N1 high-risk group is defined more strictly than the seasonal influenza high-risk group. Those recommended for vaccination include

- People aged 6 months to 24 years
- Pregnant woman
- People aged 25 to 64 years with chronic health disorders or compromised immune systems
- Health care and emergency medical services personnel
- People who live with and/or care for children younger than 6 months.[16]

In the event of an H1N1 vaccine shortage, the CDC recommends prioritizing the vaccine to pregnant women, people who live with or care for children younger than 6 months, health care and emergency medical services personnel with direct patient contact, children aged 6 months to 4 years, and children aged 5 to 18 years who have chronic medical conditions.[17]

CONCLUSION

Although the CDC provides periodically updated guidelines for diagnosis, treatment, and prevention of influenza, nothing takes the place of informed clinical judgment and thorough patient education. All patients with ILI should be instructed to return for further evaluation if their symptoms do not improve within 3 days of onset. The patient should also be educated about the potential complications and encouraged to return if concerned, particularly those patients with underlying chronic diseases or immunodeficiency.

One result of the heightened level of public awareness during the current influenza season is that patients with ILI are just as likely to present with concerns to specialty practices as they are to present to primary care and emergency care settings. Therefore, all clinicians should develop an understanding of influenza viruses and attempt to keep up with the rapidly changing guidelines. This is essential patient-care knowledge for clinicians both in the setting of this current influenza outbreak and for future flu seasons. **JAAPA**

Kristine Himmerick is on the faculty of the FNP/PA program, Department of Family and Community Medicine, University of California Davis School of Medicine, Sacramento, California. She has indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Amantadine (Symmetrel, generics)
Oseltamivir (Tamiflu)
Rimantadine (Flumadine, generics)
Zanamivir (Relenza)

REFERENCES

1. Zimmer SM, Burke DS. Historical perspective–emergence of influenza A (H1N1) viruses. *N Engl J Med.* 2009;361(3):279-285.
2. Kilbourne ED. Influenza pandemics of the 20th century. *Emerg Infect Dis.* 2006;12(1):9-14.
3. Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. *N Engl J Med.* 2009;361(3):225-229.
4. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med.* 2009; 360(25):2605-2615.
5. Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science.* 2009;325(5937):197-201.
6. Palese P, Young JF. Variation of influenza A, B, and C viruses. *Science.* 1982;215(4539):1468-1474.
7. Webster RG, Bean WJ, Gorman OT, et al. Evolution and ecology of influenza A viruses. *Microbiol Rev.* 1992;56(1):152-179.
8. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA.* 2000;283(8):1016-1024.
9. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet.* 1998;352(9144):1877-1881.
10. Centers for Disease Control and Prevention (CDC). Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis–North Carolina, 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(35):969-972. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5835a1.htm. Last reviewed September 9, 2009. Accessed November 4, 2009.
11. Centers for Disease Control and Prevention (CDC). Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. CDC Web site. http://www.cdc.gov/H1N1flu/recommendations.htm. Updated October 16, 2009. Accessed November 4, 2009.
12. Vaillant L, La Ruche G, Tarantola A, Barboza P; epidemic intelligence team at InVS. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. *Euro Surveill.* 2009;14(33). pii:19309.
13. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection–Michigan, June 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(27): 749-752.
14. 2009-10 Influenza prevention & control recommendations: recommendations of the Advisory Committee of Immunization Practices (ACIP). CDC Web site. http://www.cdc.gov/flu/professionals/acip/index.htm. Updated August 3, 2009. Accessed November 4, 2009.
15. Pandemic (H1N1)–update 65. World Health Organization Web site. http://www.who.int/csr/don/2009_09_11/en/index.html. Accessed November 4, 2009.
16. 2009 H1N1 vaccination recommendations. CDC Web site. http://www.cdc.gov/h1n1flu/vaccination/acip.htm. Updated October 15, 2009. Accessed November 4, 2009.
17. CDC advisors make recommendations for use of vaccine against novel H1N1 [CDC Online Newsroom]. CDC Web site. http://www.cdc.gov/media/pressrel/2009/r090729b.htm. July 29, 2009. Accessed November 4, 2009.

SUGGESTED READINGS

1. Cotran RS, Kumar V, Collins T, Robbins SL. *Robbins Pathologic Basis of Disease, Sixth Edition.* Philadelphia, PA: WB Saunders; 1999.
2. Dolin R. Chapter 180. Influenza. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, eds. *Harrison's Principles of Internal Medicine, 17th ed.* New York, NY: McGraw-Hill; 2008. McGraw Hill's AccessMedicine Web site. http://www.accessmedicine.com/content.aspx?aID=2895663. Accessed November 4, 2009.
3. Shandera WX, Corrales-Medina VF. Chapter 32. Viral & rickettsial infections. In: McPhee SJ, Papadakis MA. *CURRENT Medical Diagnosis & Treatment 2009.* New York, NY: McGraw Hill; 2008. McGraw Hill's AccessMedicine Web site. http://www.accessmedicine.com/content.aspx?aID=17051. Accessed November 4, 2009.