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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 on the speakers bureau for the Medicines Company. Dr. Sivasankar (author), Dr. Wang (author), Dr. Marco (peer reviewer), Ms. Coplin (executive editor), and Mr. Springston (associate managing editor) report no financial relationships relevant to this field of study.

AHC Media

Diagnosis and Management of Influenza

"If the epidemic continues its mathematical rate of acceleration, civilization could easily disappear from the face of the earth within a few weeks." — Victor Vaughn, Surgeon General of the Army in reference to the Spanish Flu, October 1918[1]

Clinical Case

A 7-year-old male with no significant past medical history comes to the office in the middle of December. For the past 36 hours, the patient has had a sore throat and a fever with a maximum temperature of 102.3° F (39.1° C). His vaccines are up to date, but he has not received the current influenza vaccine. A classmate of the patient was recently diagnosed with influenza. Currently, the patient is complaining of mild, non-specific abdominal pain and muscle aches throughout his body. He has no rhinorrhea, difficulty breathing, chest pain, diarrhea, vomiting, or rash. The patient's physical exam is unremarkable. The patient's mother brought him to the doctor because she heard that if caught within the right timeframe, he could be treated with medications.

Scope of Problem

From the Spanish influenza of 1918-1919 to the recent pandemic of H1N1 in 2009-2010, influenza has developed a contradictory public reputation. Although generally viewed as a simple common illness, influenza also generates a fear of epidemics and pandemics. In the United States, on average, influenza infects 5-15% of the population annually. Hospitalizations and deaths occur mainly in high-risk groups such as the elderly (> 65 years of age), the very young, and the chronically ill.[2] Influenza results in approximately 40,000 deaths in the United States per year.[3] In contrast, during the 1918 pandemic, 20-40% of the world's population developed the infection. More than 600,000 people died in the United States and 50 million people died worldwide; the majority of those who died were young adults.[4] The 2009 pandemic affected 1.6 million people worldwide, with 3433 deaths in the United States. However, 100 years after the Spanish flu pandemic, the effects were mitigated by modern public health efforts and the availability of a vaccine, antibiotics, as well as modern medicine. The estimated case fatality rate was 0.03% compared to 2% in 1918.

Etiology

The influenza virus is categorized into three genera — influenza A, B, and

EXECUTIVE SUMMARY

- Influenza epidemics are caused by "antigenic drift" or point mutations of the influenza hemagglutinins and neuraminidases over time.
- Antigenic shift has the potential to cause pandemics because a population has no prior exposure or immunity to the new strain of virus and the infection will spread very rapidly through the population.
- Influenza typically presents with an abrupt onset of systemic manifestations — fever, headache, myalgia, and malaise, along with respiratory symptoms including cough, rhinorrhea, and sore throat.
- The neuraminidase inhibitors, oseltamivir and zanavimir, are recommended for treatment for both influenza A and B *if symptom onset is within 48 hours.*
- Neuraminidase inhibitors should be initiated for high-risk patients regardless of the timeframe for the onset of symptoms, including for prophylaxis.

C. Of the influenza genera, influenza A is the most virulent human pathogen. In addition to humans, influenza A infects other mammals and birds. The ability of different strains of influenza A virus to be transmitted from other animals to humans has given rise to eponyms such as the swine flu and the avian flu. If zoonotic influenza A strains mutate so that not only animal-to-human but also human-to-human transmission occurs, influenza A infection can result in virulent pandemics. Influenza B occurs in humans primarily and causes less severe disease than influenza A. Influenza C only infects humans, but it is an uncommon strain and will not be discussed here.

The influenza virus is an RNA virus with two large glycoproteins, hemagglutinin (H) and neuraminidase (N), on its surface. Hemagglutinin mediates viral binding and DNA entry into host cells. Neuraminidase is involved in release of the virus from the host cell. These glycoproteins characterize the subtype of the virus and give them their name (e.g., H1N1). These subtypes are further divided into strains based on other virulence factors. Although there are 16 hemagglutinins and nine neuraminidases known, only H1, H2, and H3, and N1 and N2 are commonly found in humans.[5] Antiviral drugs target hemagglutinin and neuraminidase function. Vaccines consist of antibodies to the hemagglutinin and neuraminidase antigens.

Epidemiology

In North America, influenza season typically is defined as the months between November and April. This highly contagious disease is spread as an aerosol and is transmitted from person-to-person through respiratory secretions from coughing, sneezing, and talking, as well as through fomites.[6] After gaining access to the respiratory tract, the virus replicates within the epithelium. It is most commonly found in the upper respiratory tract, but may also infect the lower respiratory tract.

The typical incubation period of the virus is between 1-4 days. Infected individuals may shed the virus 24 hours prior to symptom onset and are considered contagious up to 10 days after symptoms start, although most viral shedding occurs within the first 24-48 hours of illness onset.[7] Children tend to shed the virus for longer periods than adults, making them major causes of infection in the community.

Epidemics and Pandemics

An epidemic is defined by the Centers for Disease Control and Prevention (CDC) as "the occurrence of more disease than expected in a given area or among a specific group of people over a particular period of time."[8] This predetermined "epidemic threshold" is based on data collected from previous influenza seasons. A pandemic is a worldwide epidemic — one that occurs within several countries, usually involving a new influenza strain and affecting a certain percentage of the population in each country.[8]

Influenza epidemics are caused by "antigenic drift" or point mutations of the influenza hemagglutinins and neuraminidases over time. These mutations slowly create an increasing variety of influenza strains until a strain is different enough that it can infect some people who were immune to pre-existing influenza strains. The new strain will then infect the population, causing an epidemic (although the strain will still be similar enough to other strains that some members of the population will still be immune).

Antigenic shift occurs when strains from different species combine through independent reassortment to create entirely new antigens or an entirely new strain of influenza. Antigenic shift has the potential to cause pandemics because a population has no prior exposure or immunity to the new strain of virus and the infection will spread very rapidly through the population.

Differential Diagnosis

Although influenza tends to occur during winter months and local public health surveillance reports can heighten suspicion of the diagnosis of influenza, it is difficult to differentiate influenza infection from any of the respiratory viruses clinically. Influenza can infect any part of the respiratory tract and can cause symptoms similar to many of the respiratory viruses. Thus, influenza infection can mimic respiratory syncytial virus (RSV) bronchiolitis as well as laryngotracheitis.

Bacterial infection must always be on the differential of febrile respiratory illness. Febrile neonates and infants should be worked up in a systematic manner to exclude serious bacterial illness. Ill-appearing children and those in respiratory distress should be treated

initially with empiric antibiotics appropriate for respiratory bacterial pathogens until the precise etiology is known. Children with documented influenza infection who deteriorate should be considered to have a bacterial superinfection and treated accordingly.

Clinical Course and Complications

In children, the symptoms of influenza are difficult to differentiate from other winter viral illnesses. Influenza typically presents with an abrupt onset of systemic manifestations — fever, headache, myalgia, and malaise, along with respiratory symptoms including cough, rhinorrhea, and sore throat.[9] In children, abdominal pain, nausea, vomiting, and diarrhea are more likely to be seen in comparison to adults with influenza. In a study of children younger than 13 years of age who were diagnosed with the influenza virus, the predominant symptom was fever — found in 95% of the population. Cough (77%), rhinitis (78%), headache (26%), and myalgia (7%) were the most commonly reported symptoms, similar to what is seen in the adult population.[10]

The symptoms typically last between 2 to 5 days. Improvement in symptoms tends to occur within the first 48 hours. Among children who are generally healthy with no medical comorbidities, influenza tends to be a self-limited condition with no complications.[9,11] A post-viral cough may linger, and post-influenza asthenia, manifested by fatigue and weakness, may last for weeks, especially in older children.[12]

Although the majority of influenza cases are self-limited in healthy children, complications occur, particularly in high-risk patients. Common complications include viral pneumonia, acute otitis media, and bacterial co- or superinfections. Less common are neurologic and cardiac consequences.

The populations with greater probability for severe courses of influenza or those who may have a complicated course include the elderly (> 65 years), pregnant or recently postpartum women, children younger than 5 years of age, and those defined as "high risk."[13] (*See Table 1.*) In particular, children younger than 2 years of age and children with neurologic disorders, sickle cell disease, immunosuppression, and diabetes are at a high risk for complications from influenza.[14]

Table 1. Groups at High Risk for Influenza Complications

Children < 2 years of age
Persons with chronic disease including: pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), metabolic (including diabetes mellitus), neurologic, neuromuscular, and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate-to-severe developmental delay, muscular dystrophy, or spinal cord injury)
Immunosuppression (including immunosuppression caused by medications for HIV)
Women who are pregnant or postpartum (within 2 weeks after delivery)
Children on current long-term aspirin therapy
Native Americans and Alaskan Natives
Body mass index > 2.33 kg/m^2 standard deviations above the mean
Residents of chronic care facilities

Adapted from: Influenza Division, National Center for Immunization and Respiratory Diseases, CDC. Prevention and control of seasonal influenza with vaccines. *MMWR Recomm Rep* 2013; 62:1.

The most common complication of influenza infection is bacterial otitis media.[15]

As with other viral infections, bacterial co-infections or superinfections may occur. One theory is that a weakened immune system, as well as a denuded respiratory epithelium, provide an easy target for bacterial colonization and entry. Bacterial pneumonia tends to be severe when caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*.[16]

Neurologic complications (aseptic meningitis, cerebellar ataxia, Guillan-Barre syndrome, transverse myelitis, encephalopathy, and acute disseminated encephalomyelitis) are uncommon, with an incidence of 4 per every 100,000 person-years.[17] These complications are more prevalent in children with pre-existing neurologic disorders and tend to occur in younger children with an incidence of 4 per 100,000 person-years.[17,18]

Cardiac complications, including pericarditis and myocarditis, are quite rare.

Pediatric death is usually due to a complication from a superinfection with a bacterial pathogen.[19] According to the CDC, there were 109 laboratory confirmed influenza-related deaths during the 2013-14 influenza season. The mean age for death was 6.0 years and the median age was 4.6 years.

Diagnostic and Adjunct Testing

According to the CDC, testing should be undertaken if results will change the clinical care for the patient, affect clinical practice for other patients, or change outbreak-control strategies within the population.[20] Admitted patients should be tested for influenza along with a respiratory viral panel for cohorting purposes. In general, treatment should be based on clinical suspicion for influenza rather than laboratory test results. Sometimes, influenza testing can help with decreasing antibiotic use.

Multiple modalities exist for influenza testing, and include PCR testing, immunofluorescence, enzyme immunoassay, viral culture, and serologic testing. (*See Table 2.*) The gold standard for diagnosis is viral culture, which takes 48-72 hours for results. Immunofluorescence and enzyme immunoassays often are batched in large hospitals and run at multiple intervals during a day. Rapid testing

Table 2. Diagnostic Tests for Detecting the Influenza Virus

Test	Time to Result	Acceptable Specimen Source	Sensitivity/ Specificity	When Do I Use This?
Viral culture (gold standard)	3-10 days	Nasopharyngeal swab or wash, nasal or endotracheal aspirate, sputum, bronchial wash	Moderately high sensitivity, highest specificity	Research purposes
Rapid cell culture	1-3 days			Research purposes
PCR (can differentiate between viral subtypes)	1-6 hours	Nasopharyngeal swab or wash, throat swab, nasal or endotracheal aspirate, sputum	High sensitivity, very high specificity	Primary care setting, emergency department, hospital setting
Immunofluorescence	1-4 hours	Nasopharyngeal swab or wash, bronchial wash, nasal or endotracheal aspirate	Moderately high sensitivity, high specificity	Emergency department, hospital setting
Rapid diagnostics (antigen testing)	< 30 minutes	Nasopharyngeal swab, throat swab, nasal wash, nasal aspirate	Low-to-moderate sensitivity, high specificity	Primary care setting, emergency department, hospital setting

Adapted from: Centers for Disease Control and Prevention. Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests. Available at: http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed Jan. 25, 2015.

provides results within 30 minutes,[21] usually using enzyme immunoassay methods. Rapid testing is less sensitive and specific than gold-standard testing options, but can be useful to guide treatment. Accordingly, providers should use both laboratory testing, especially if negative, and clinical gestalt to decide the need for treatment in suspected influenza. As with any illness, if the incidence is low, the false-positive rates tend to be higher and the positive predictive value is decreased.

There are no specific adjunct studies recommended for the suspicion of influenza. Rather, ordering of adjunct studies should be guided by history, physical exam, and differential diagnosis. For example, appropriate septic workups should be pursued for those younger than 2 months of age. If the patient appears to be tachypneic, toxic, or has focal findings on a lung exam, a chest X-ray should be obtained. Those with comorbid pulmonary or cardiac conditions should have a more detailed workup due to the increased risk of complications. Routine chemistries and complete blood counts should not be obtained in healthy patients.

Management and Treatment

Supportive therapy tends to be the mainstay of therapy in the primary care setting. This includes treating fevers, myalgia, and headache with antipyretics and dehydration with anti-emetics and rehydration. As a general rule, aspirin therapy should be avoided in children because of the risk of Reye syndrome (Reye syndrome had an all-time high incidence in 1980 [555 cases], which has since declined to less than five cases per year once its association with aspirin was identified and reported in 1982). Over-the-counter decongestants and cough suppressants are not recommended based on FDA reviews regarding safety and efficacy, especially in infants and young children.

Antibiotics should only be used for children with high likelihood for bacterial superinfection, such as those with a lack of improvement of symptoms within 48 hours, worsening symptoms, increasing difficulty of breathing, or continued deterioration of oxygenation status.

Antivirals: The neuraminidase inhibitors, oseltamivir and zanamivir, are recommended for treatment for both influenza A and B *if symptom onset is within 48 hours.* Neuraminidase inhibitors should be initiated for high-risk patients regardless of the timeframe for the onset of symptoms, including for prophylaxis. According to the CDC, chemoprophylaxis may serve as an adjunct to vaccination in the following populations: prevention in persons at high risk of influenza complications during the first 2 weeks following exposure to an infectious person, prevention for those with severe immune deficiencies or those who may not respond well to vaccination because they are on immunosuppressive medications, prevention for those at high risk who cannot receive the vaccination due to a contraindication, and prevention among residents at long-term care facilities in the midst of an outbreak.[22]

Oseltamivir is approved for children older than 2 weeks of age and zanamivir is approved for anyone older than 7 years of age.[23,24] Dosages for oseltamivir are found in Table 3. Dosing for zanamivir is 10 mg or two inhalations twice daily for anyone older than 7 years of age.[25]

In 2014, a meta-analysis found that oseltamivir reduced the risk of symptomatic influenza by a risk difference of 3.1% and zanamivir by a risk difference of 12.0%.[12] Oseltamivir reduces illness duration by 1 to 1.5 days. Studies did not show that risk of hospitalization was reduced.

The major side effects of this class

Table 3. Oseltamivir Dosing Information

Age	Weight	Oseltamivir Dosing
0-8 months		3 mg/kg/dose twice daily for 5 days
9-12 months		3.5 mg/kg/dose twice daily for 5 days
	≤ 15 kg	30 mg twice daily for 5 days
	> 15-23 kg	45 mg twice daily for 5 days
	> 23-40 kg	60 mg twice daily for 5 days
	> 40 kg	75 mg twice daily for 5 days

Weight-based dosing is preferred over age based dosing.

Adapted from: Lexicomp. Available at: www.gene.com/download/pdf/tamiflu_prescribing.pdf Accessed Jan. 25, 2015.

of antiviral medications include gastrointestinal symptoms: nausea, vomiting, and rashes with oseltamivir and diarrhea, nausea, headache, and upper respiratory infection symptoms with zanamivir.[24] Rare adverse events include neuropsychiatric conditions, severe skin reactions, and death.[23]

In December 2014, the FDA approved the use of another neuraminidase inhibitor, peramivir (trade name Rapivab). However, its use is currently limited to a single intravenous dose in adults presenting with influenza symptoms for less than 48 hours.

The CDC no longer recommends the use of adamantane drugs (amantadine and rimantadine) given the high resistance patterns shown by current strains.[26]

Disposition

There is no national standard or set clinical decision rule to help determine which patients with confirmed or suspected influenza merit admission to the hospital. A study published in 2009 looked retrospectively at children admitted to hospitals with confirmed influenza and found that four predictors within broader categories of historical information, radiographic studies, clinical examination and laboratory tests were independently strongly associated with hospitalization.[27] These included history of a high-risk medical condition (2 points), respiratory distress on physical exam (1 point), confirmed influenza B virus (2 points), and radiographic evidence of pneumonia (3 points). Each of these was assigned a score, and a total score between 3 and 8 predicted an 86% chance of hospitalization. Given that routine testing for influenza and obtaining radiographic studies are not routine for most patients presenting with influenza, these criteria may not be universally applicable. (*See Table 4.*)

High-risk patients, especially those with congenital heart defects and chronic pulmonary diseases with influenza-like symptoms (even if they are well appearing), should be managed in conjunction with the consulting specialist. These patients may be admitted under an observation status or discharged home with close specialty follow-up.

For patients with stable vital signs and no other complications (medical, social, etc.), close follow-up with a primary care provider should be stressed and discharge home is appropriate.

Immunizations, Prevention, and Public Health Implications

Infection control and vaccination remain at the forefront of preventive treatment for influenza. Beyond the goal of individual protection, the goals of vaccination include herd immunity. Patients with family members who are elderly or chronically ill should be encouraged to obtain an influenza vaccine to protect their loved ones.

Table 4. Scoring Guidelines for Factors Associated with Hospitalization in the Setting of Influenza

Predictor	Points Awarded
High-risk medical condition	2
Respiratory distress on exam	1
Radiographic evidence of pneumonia	3
Lab confirmed influenza B infection	2

Adapted from: Bender JM, Ampofo K, Gesteland P, et al. Development and validation of a risk score for predicting hospitalization in children with influenza virus infection. *Pedatr Emerg Care* 2009;25:369-375..

The influenza vaccine is created annually according to World Health Organization predictions of the strains likely to be circulating the following year. It consists of three (trivalent) to four (tetravalent) viral strains. According to the CDC, the effectiveness of the 2013-2014 vaccine was 61% (95% confidence interval, 52-68%).[28] The strains used in the 2014-15 vaccine are identical to those used in the 2013-2014 season, but have so far only been found to have a 23% success rate according to the CDC.

In the United States, two forms of the vaccine are currently licensed — the inactivated vaccine for intramuscular use and the live-attenuated, cold-adapted vaccine administered intranasally. (*See Table 5.*) The American Academy of Pediatrics recommends annual influenza vaccination for anyone older than 6 months of age. Vaccines should be administered prior to influenza season, usually in the October and November timeframe, but can be given anytime during influenza season. Children with moderate-to-severe febrile illnesses should not be vaccinated until after recovery.

Starting in the 2014-2015 influenza season, the CDC now recommends use of the intranasal vaccine for healthy

Table 5. Comparing Live Attenuated Influenza Vaccine (LAIV) with Inactivated Influenza Intramuscular Vaccine (IIMV)

	LAIV	IIMV
Route of administration	Intranasal	Intramuscular
Approved ages	2-49 years	≥ 6 months
Interval between the two doses administered to children between the ages of 6 months to 8 years	≥ 4 weeks	≥ 4 weeks
Okay to give simultaneously with other vaccines?	Yes	Yes
Okay to give in those with medical risk factors for influenza-related complications*?	No	Yes
Can be given to to children with asthma or in children aged 2-4 years with wheezing in the past year?	No	Yes
Can be given to those in close contact with immunosuppressed persons requiring a protected environment?	No	Yes

* See Table for high-risk population.

Adapted from: Grohskopf LA, Olsen SJ, Sokolow LZ, et al. Prevention and control .of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014-15 influenza season. *MMWR Morb Mortal Wkly Rep* 2014;63:691-697.

children ages 2-8 years. According to the CDC, "recent studies suggest that the nasal spray influenza vaccine may work better than the influenza shot in younger children." It is also emphasized that vaccination should not be delayed if the intranasal formulation is unavailable. The intranasal vaccine should be avoided in children with metabolic diseases, chronic renal disease, neuromuscular disorders, immunosuppression, hemoglobinopathies, cardiac disease, and pregnancy.[29,30]

Physicians should also be aware that certain populations are eligible for palivizumab (Synagis) to prevent respiratory tract disease caused by RSV. These include anyone younger than 2 years of age with a history of bronchopulmonary dysplasia, chronic lung disease of prematurity, or hemodynamically significant congenital heart disease, as well as premature infants with a gestational age < 35 weeks.[31]

Summary Case Conclusion

A rapid influenza test was ordered for this patient, and results were positive for influenza A. Oseltamivir was given since he was within the 48-hour window for its administration.

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CME Questions

1. Which statement is true about influenza?
   a. Influenza A is the most common genera of influenza that affects humans.
   b. Influenza B is the most virulent genera of influenza.
   c. Currently available antivirals target the hemagglutinin moiety on the viral surface.
   d. Influenza C affects cats and can be transmitted to humans.
2. Which of the following viruses is least likely to be on the differential in the child presenting with cough, rhinitis, and fever?
   a. Respiratory syncytial virus
   b. Parainfluenza
   c. Enterovirus
   d. Coronavirus
3. In which patient is the use of oseltamivir most indicated?
   a. A 10-year-old with congenital HIV infection with 3 days of influenza-like symptoms
   b. An otherwise healthy 3 year-old with 4 days of influenza-like symptoms
   c. An otherwise healthy 8-year-old with 1 day of influenza-like symptoms
   d. A 14-year-old with a lobar pneumonia
4. What is the most common complication of influenza?
   a. Acute otitis media
   b. Pneumonia
   c. Aseptic meningitis
   d. Myocarditis
5. Which of the following is more commonly seen in children with influenza vs adults?
   a. Longer course of illness
   b. More severe upper respiratory tract symptoms
   c. More gastrointestinal symptoms
   d. Abrupt onset
6. In which patient is the use of intranasal influenza vaccine indicated?
   a. A 52-year-old with medical history of cholelithiasis
   b. A healthy 3-year-old
   c. An 8-year-old with poorly controlled asthma
   d. A 4-month-old presenting with fevers, rhinitis, and difficulty breathing

PRIMARY CARE REPORTS

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Summarize recent, significant studies related to the practice of primary care medicine;
- Evaluate the credibility of published data and recommendations related to primary care medicine;
- Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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