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Hospitalist Update:

10 Things to Know About Influenza

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1. **Introduction:** Influenza is an acute, contagious and usually self-limited febrile illness caused by infection of the respiratory tract with the influenza virus. The most common clinical manifestations are fever, malaise, and cough. The epidemic nature of influenza results in outbreaks every winter (seasonal influenza) but it is important to remember that the potential to become a pandemic always exists, as in the 2009 H1N1 influenza pandemic (this virus was a unique combination of influenza virus genes never previously identified in either animals or people). Influenza viruses spread mainly by direct contact or inhalation of aerosols or large droplets from persons with influenza during a cough, sneeze or talk. Less often, infection is acquired from indirect contact of a person's mouth, eyes or nose with contaminated environmental surfaces (fomites) that contain the viruses. The incubation period is 1-4 days (average: 2 days). The infective period begins 1 day before onset of

symptoms and extends to 5-7 days after becoming sick. Mortality from influenza infection is related mainly to its pulmonary complications.

2. Know the enemy: Influenza viruses are RNA viruses that belong to the family Orthomyxoviridae and are classified into three distinct types, influenza A, influenza B, and influenza C virus, on the basis of major antigenic differences. Influenza A viruses are further divided into subtypes on the basis of their hemagglutinin (HA) and neuraminidase (NA) activity (e.g., H1N1 or H3N2). Currently, infections during influenza season are usually caused by influenza types A (2009 H1N1), A (H3N2), and B. A recent CDC health advisory alerted clinicians about a number of reports of severe respiratory illness among young and middle-aged adults, many of whom were infected with influenza A (2009 H1N1) or pH1N1. Multiple pH1N1-associated hospitalizations, including many requiring intensive care unit (ICU) admission, and some fatalities have been reported. The pH1N1 virus that emerged in 2009 caused more illness in children and young adults, compared to older adults, although severe illness was seen in all age groups. While it is not possible to predict which influenza viruses will predominate during the entire 2013-14 season, pH1N1 has been the predominant circulating virus so far. For the 2013-14 season, if pH1N1 virus continue to circulate widely, illness that disproportionately affects young and middle-aged adults may occur. Reports of new subtypes are in the news. For example, human infections with a new avian influenza A (H7N9) virus were first reported in China in March 2013. Most of these infections are believed to result from exposure to infected poultry or contaminated environments. Most patients had a severe respiratory illness, with about one-third resulting in death. No cases of H7N9 outside of China have been reported. Influenza viruses that normally circulate in pigs are called "variant" viruses when they are found in humans. Influenza A H3N2 variant viruses (also known as "H3N2v" viruses) with the matrix (M) gene from the 2009 H1N1 virus were first detected in humans in July 2011. In 2012, 309 cases of H3N2v infection across 12 states were detected. These infections have been mostly associated with prolonged exposure to pigs at agricultural fairs. Another subtype is the highly pathogenic avian influenza (HPAI) A (H5N1) virus. Human infections with this subtype are rare, although sporadic cases have been reported. Indonesia, Vietnam and Egypt have reported the highest number of human HPAI H5N1 cases to date. The mortality rate is 60%. In the majority of cases, the person got HPAI H5N1 virus infection after direct or close contact with sick or dead infected poultry. This is one difference with H7N9, in which the infected poultry may be asymptomatic.

3. A little history: Influenza has caused pandemics as a result of antigenic shift (replacement of HA and NA) resulting in "new" viruses to which the population has no immunity. Only influenza A can experience antigenic shift. A pandemic can be devastating. In fact, the most significant infectious disease outbreak known to man was the Spanish Flu of 1918 that caused more than 50 million deaths; 50% of deaths were in people 20-40 years old. Other known influenza pandemics were the Asian Flu of 1957, the Hong Kong Flu of 1968, the Russian Flu of 1977 and the most recent 2009 H1N1 Flu.

4. Epidemiology: There are 25-50 million cases per seasonal influenza epidemic, causing more than 200,000 hospitalizations per year, more than 36,000 deaths per year and annual cost of approximately $87 billion. While any person is at risk of getting the infection, those older than 65 years have increased rates of severe illness, hospitalization and death. American Indians, Alaskan Natives, young children and pregnant women are also at increased risk of complications. Other comorbid conditions that predispose to complications are: asthma, neurological disorders (cerebral

palsy, epilepsy, stroke, muscular dystrophy, spinal cord injury), chronic lung disease (COPD, CF), cardiovascular disease (CHF, CAD), hematological disorders (sickle cell disease), diabetes mellitus, kidney disorders, liver disorders, immune deficiencies, BMI >40.

5. Complications: Uncomplicated influenza illness typically resolves after 3-7 days in most cases, although cough and malaise can persist for >2 weeks. However, influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease); lead to secondary bacterial pneumonia (typically Streptococcus pneumoniae and Staphylococcus aureus), sinusitis, or otitis media; or contribute to coinfections with other viral or bacterial pathogens. Influenza virus infection also has been uncommonly associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.

6. Diagnosis: Influenza illness can include any or all of these symptoms: fever, muscle aches, headache, lack of energy, dry cough, sore throat, and runny nose. However, not everyone with influenza will have a fever. Respiratory illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone. Hence, the differential diagnosis includes, but is not limited to, infections caused by Mycoplasma pneumoniae, Legionella spp., adenoviruses, RSV, rhinovirus, parainfluenza viruses, metapneumovirus. Sensitivity and predictive value of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity. For example, clinical assessment can have a positive predictive value up to 88% in adults living in areas with confirmed influenza virus circulation. Accurate and timely diagnosis of influenza is important because it can reduce the inappropriate use of antibiotics and provide the option of using early antiviral therapy. Several tests can help in the diagnosis of influenza as seen in the table below.

Method	Acceptable specimens	Test time
Viral culture	Nasopharyngeal swab Throat swab Bronchial wash Sputum	3-10 days
	Endotracheal aspirate	
Immunofluorescence Direct (DFA) or indirect (IFA)	Nasopharyngeal swab Bronchial wash	1-4 hours
	Endotracheal aspirate	
RT-PCR Singleplex or multiplex	Nasopharyngeal swab Throat swab Bronchial wash Sputum	1-6 hours
	Endotracheal aspirate	
Rapid influenza diagnostic tests	Nasopharyngeal swab Throat swab	<30 minutes
	Nasal wash	

Influenza testing should be done when results will affect clinical decision making (for example, a hospitalized patient with respiratory symptoms) and ideally within 4 days of onset of symptoms. The most commonly used testing method is the rapid antigen test, which provides results within 30 minutes and is 50-70% sensitive when compared with viral culture or PCR. It is important to remember that false positives occur when prevalence is low (beginning/end of influenza season) and false negatives occur when prevalence is high. It is 90-95% specific. In other words, the rapid tests are useful for confirming infection with influenza but not for ruling out infection. If the rapid test is negative and clinical suspicion persists and a positive testing would change management, a molecular test such as the multiplex RT-PCR (commonly called "respiratory viral panel") can be sent, which is more sensitive and has the advantage of testing for other respiratory viruses and bacteria (Influenza A, Influenza A Subtypes H1, H1-2009, & H3, Influenza B, Parainfluenza Types 1, 2, 3, Respiratory Syncytial Virus, Human Metapneumovirus, Rhinovirus, Adenovirus, Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Coronavirus 229E, Coronavirus OC43, Coronavirus HKU1, and Coronavirus NL63). This is probably the preferred test in severely immunocompromised patients (e.g., stem cell transplant recipients) or critically ill patients with an unexplained respiratory illness.

7. Treatment: Four antiviral drugs are available for treatment of influenza: M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir). The M2 inhibitors are active against influenza A only. Widespread M2 inhibitor resistance among influenza A (H3N2) virus strains has made this class less useful clinically. In addition, circulating 2009 H1N1 virus strains are resistant to M2 inhibitors. The neuraminidase inhibitors are active against influenza A and B. For the reasons above, only oseltamivir and zanamivir are currently recommended for use during the influenza season. Studies have shown that neuraminidase inhibitors reduce duration of symptoms by 1-1.5 days when administered within 2 days of illness onset. They also reduced risk of complications (pneumonia, hospitalization, respiratory failure, death). Antiviral therapy is indicated in any patient with influenza who: is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications (see Epidemiology). Although the greatest benefit is achieved when antiviral is started within 48 hours of illness onset, antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patient when administered >48 hours from illness onset. Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza. Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.

8. Postexposure prophylaxis: In randomized, placebo-controlled trials, both oseltamivir and zanamivir were efficacious in the prevention of influenza illness among persons who were administered chemoprophylaxis after a household member or other close contact had laboratory-confirmed influenza. Postexposure chemoprophylaxis with neuraminidase inhibitors generally should be reserved for those who have had recent close contact with a person with influenza. Antiviral chemoprophylaxis can be considered in family or close contacts of a person with a suspected or confirmed case if they are at higher risk for influenza complications and have not been vaccinated against influenza at the time of exposure. Persons who receive an antiviral medication for chemoprophylaxis might still acquire influenza virus infection and be potentially able to transmit influenza virus, even if clinical illness is prevented. Decisions on whether to administer antivirals for chemoprophylaxis should take into account the exposed person's risk for influenza complications, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. Generally,

postexposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure and is typically administered for a total of no more than 10 days after the most recent known exposure to a close contact known to have influenza. Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available (see below).

9. Influenza vaccination: According to the Advisory Committee on Immunization Practices (ACIP) for 2013-2014, routine annual influenza vaccination of all persons aged 6 months and older continues to be recommended. 2013-14 U.S. trivalent influenza vaccines contain an A/ California/7/2009 (H1N1)-like virus, an H3N2 virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2012-like virus (Yamagata lineage). Quadrivalent vaccines will include an additional vaccine virus, a B/Brisbane/60/2008-like virus (Victoria lineage). There are several vaccine products currently available in 5 categories:

a. Inactivated Influenza Vaccine, Trivalent (IIV3), Standard Dose
b. Inactivated Influenza Vaccine, Trivalent (IIV3), High Dose
c. Inactivated Influenza Vaccine, Quadrivalent (IIV4), Standard Dose
d. Recombinant Influenza Vaccine, Trivalent (RIV3)
e. Live-attenuated Influenza Vaccine, Quadrivalent (LAIV4)

Please visit the Centers for Disease Control and Prevention (CDC) website for the complete list of vaccine products (www.cdc.gov). Other considerations: the IIV3 High Dose is recommended for people 65 years of age and older; it contains 4 times the dose of antigen compared to the standard dose for a better immunogenic response (studies showed 24.2% more effectiveness in this population). The RIV3 is egg-free and can be used in people with history of severe allergic reactions to eggs, if aged 18-49 years. If the reaction is only hives, administer IIV and observe for reaction for at least 30 minutes. Women who are or will be pregnant during influenza season should receive IIV. Pregnant and postpartum women do not need to avoid contact with persons recently vaccinated with LAIV. Administration of IIV to persons receiving influenza antiviral drugs for treatment or chemoprophylaxis is acceptable. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines.

10. Resources: The CDC website has a robust influenza section with information for health professionals. I recommend checking regularly FluView, a weekly influenza surveillance report and case counts per region. You can also visit the Missouri Department of Health & Senior Services for weekly influenza reports in the state of Missouri. It provides information by county and comparisons with previous years. See the hyperlinks below.

Useful References:

- Centers for Disease Control and Prevention (CDC) website: www.cdc.gov/flu/professionals
- FluView: www.cdc.gov/flu/weekly
- Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the ACIP — United States, 2013–2014. MMWR; September 20, 2013 / 62(RR07);1-43.
- MMWR: Evaluation of 11 Commercially Available Rapid Influenza Diagnostic Tests — United States, 2011–2012, November 2, 2012. MMWR; November 2, 2012 / 61(43);873-876.

- Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR; January 21, 2011/60 (RR01);1-24.
- www.health.mo.gov/living/healthcondiseases/communicable/influenza/reports.php
- Treanor, J. Influenza viruses, including avian influenza and swine influenza. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th edition. Philadelphia: Chnurchill Livingston Elsevier. 2010.

HEMATOLOGY UPDATE

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ASH Choosing Wisely®:

After attending the American Society of Hematology (ASH) meeting a few weeks ago, it is time to discuss the Choosing Wisely campaign®. This is a quality improvement project led by the American Board of Internal Medicine (ABIM) Foundation in collaboration with the leading national medical professional societies. This campaign aims to encourage open discussion among patients, physicians and the community regarding the costs and benefits of medical care, taking into account the increasing health care costs.

The Choosing Wisely® campaign challenges medical societies to identify 5 tests, procedures, or treatments within each specialty's clinical domain that are offered to patients despite an absence of evidence demonstrating benefit or, in some cases, despite evidence demonstrating disutility or harm.

ASH has identified 5 tests/intervention practices that can be improved and provided these recommendation so the care provider teams actually consider the anticipated benefits of these interventions before choosing to perform them.

ASH Choosing Wisely® Recommendations:

1. In situations where transfusion of RBCs is necessary, transfuse the minimum number of units required to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (7-8 g/dL in stable, non-cardiac in-patients)
2. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility)
3. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism
4. Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e., outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)