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An Urgent Care Approach to Influenza—Before Onset

Urgent message: The urgent care clinician must have a thorough understanding of different influenza types and strains, disease course, and preventive measures—including, but not limited to, vaccination—at the outset of flu season.

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Introduction

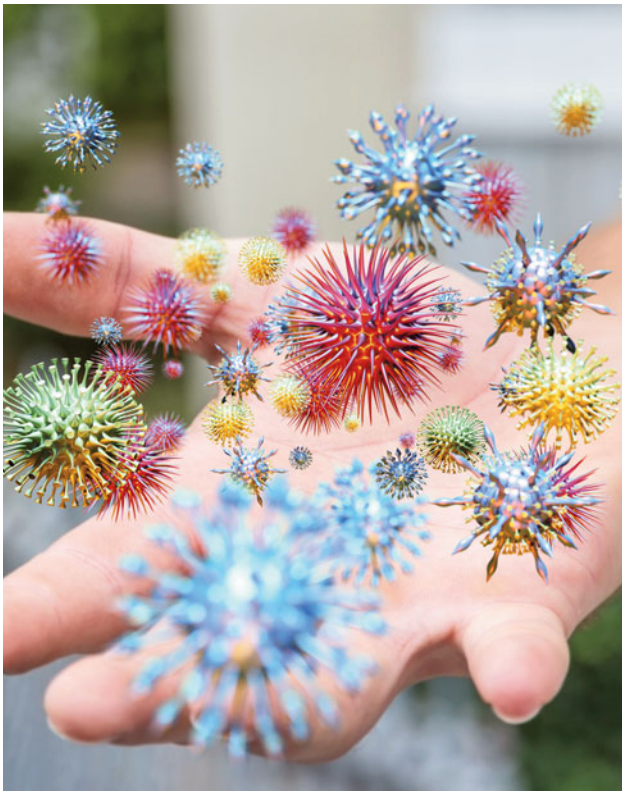
Influenza is most deadly in the very young, very old, and those with comorbid conditions. Typically, onset is rapid and seasonal, though patients may initially present with few or nonspecific symptoms. Complicating things further, there are many different strains of the flu. Spread can occur from the host even before the onset of symptoms, and current treatments may be only marginally effective.

Flu Types and Strains

The Centers for Disease Control and Prevention has adopted an international naming convention for influenza based on the antigenic type (A-D), origin, and strain number. Seasonal flu epidemics are caused by the two main human influenza virus types: A and B. Type C generally does not cause true epidemics and is self-limited to mild respiratory illnesses. Type D influenza affects cattle and has no known effect on humans.[1]

Influenza A has two different subtypes which are defined as the hemagglutinin (H) and the neuraminidase (N) protein markers. There are different subtypes which can correspond to influenza A (H1-18) and (N1-11), respectively. Perhaps one of the most well-known influenza subtypes is influenza A (H1N1), which has been known to cause disease in humans for many years but in 2009 changed and caused the first pandemic influenza outbreak in more than 40 years.[1]

This strain of influenza surprised the CDC because it was a combination of flu genes that had never been seen before in animals or humans, being a combination from four separate influenza sources. In just 2 months, it became a true pandemic, with CDC estimates of infection in over 1 million people.[2] Though large, that does not compare with the 1918 influenza pandemic which affected 500 million people and had death tolls



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upwards of 50 million. This pandemic caused the average life expectancy in the U.S. to fall by 12 years. It was termed the Spanish flu, as Spain was one of the few countries that remained neutral during WW I and they reported the influenza news around the world.[3]

Influenza B is not divided into subtypes, but rather has different strains and lineages: Yamagata and Victoria.

There are key differences, both biological and clinical, between the flu virus types. About 75% of influenza infections are caused by influenza A, with influenza B making up the other 25%.[4] Influenza A infections are associated with more serious complications, such as pneumonia and deaths in children and the elderly. Influenza B tends to be more prevalent later in the season and does not cause pandemics. It causes symptoms similar to influenza A, but they are milder and rarely cause the life-threatening complications seen with influenza A.

The Changing Nature of Influenza

Influenza viruses change periodically by a process call antigenic drift, which is a slow but continuous change resulting in a new strain that is not recognized by the host's immune system. This is a more abrupt, sudden, and complete change which produces a completely new subtype with new H/N that leaves patients without antibody protection.[5] A prime example of this "antigenic shift" is the 2009 H1N1 virus that combined genes in a new way to affect humans and resulted in the 2009 influenza A pandemic. When these shifts happen, most people have very little immunity against the newly formed virus because the change happened so suddenly.[6]

Time from Exposure to Onset

Influenza is highly contagious. Symptoms start, on average, 2 days after exposure to the virus. Adults can start to spread the infection 24 hours before symptoms develop and up to a week after becoming sick. Children can spread the virus for more than 1 week.

Influenza is spread through respiratory droplets such as a cough or sneeze and can be spread up to 6 feet. The virus can be transmitted onto surfaces, as well, then transmitted to a person who touches the surface and then their own mucosal surfaces (mouth/nose).

"Influenza is spread through respiratory droplets such as a cough or sneeze and can be spread up to 6 feet. It can also be transmitted via contact with tainted surfaces."

Clinical Course

The abrupt onset of fever, cough, malaise, myalgia, nasal congestion, and sore throat is characteristic of influenza. In immunocompetent patients, symptoms should start resolving within 1 week, but cough and malaise may last up to 2 weeks.

Signs/Symptoms/Duration

Sensitivity and specificity

Several studies have attempted to isolate or help predict the most likely symptoms associated with influenza illness. A study out of Taiwan in 2015 suggested that the combination of fever and cough had the best sensitivity (86%), and fever, cough, and sneezing had the best specificity at 77%.[7] Another study out of Kenya also showed fever and cough as the most sensitive.[8]

What clinical findings are most reliable?

There are several symptoms associated with influenza illness. They generally include fever, myalgias, sore throat, cough, headaches, fatigue, chills, and runny/ stuffy nose. Some strains of influenza also can cause nausea, vomiting, and/or diarrhea. It is possible to have influenza and not have a fever.[9]

Many of these symptoms are also associated with other viral illnesses, so it would be beneficial to know which symptoms are most suggestive of influenza. In 2000, Monto, et al looked at 3,700 patients suspected to have the flu, noting:[10]

- 93% had cough
- 91% had nasal congestion
- 68% had fever
- Cough + fever during flu season had a positive predictive value of 79%

Symptoms of influenza are similar to the symptoms of other viral respiratory infections, making a definitive clinical diagnosis difficult. Establishing a pretest probability and assessing the importance of a definitive diagnosis (such as in the elderly, pregnant, or immunosuppressed) will aid in the decision to pursue further testing.

Testing

Indications

Early season

Influenza testing early in the season may be useful to establish when the virus is starting to increase in prevalence. It can also be used to help further characterize what symptoms or subtleties of this season's virus is producing.

Late season

Testing later in the season is less useful if the patient fits into the pre-established risk group and may benefit from treatment.

Diagnosis

Diagnostic testing is not always necessary, as the diagnosis can often be suspected on a clinical basis. This is especially true during "flu season" when the virus is more prevalent.

The virus is spread through respiratory droplets and can be found in nasal, oral, or respiratory mucosa. Testing in the urgent care center occurs with a nasal swab. These tests may use molecular assays such as rapid molecular assays, reverse transcription polymerase chain reactions (RT-PCR), nucleic acid amplification tests, and antigen detection (rapid influence diagnostic tests [RIDTs] or immunofluorescence assays).

- *Rapid molecular assays* detect influenza-specific nucleic acids from an upper respiratory sample. Sensitivity is 90%-95%, with results within 30 minutes.
- *RT-PCR* recognizes influenza RNA or nucleic acids (again, in a respiratory sample) with high sensitivity and specificity. The tests can isolate whether the virus is influenza A or B. Some tests can even identify specific subtypes, such as influenza A (H1N1). These tests take a little longer (from 45 minutes to several hours), which is seen as an acceptable compromise due to the increased sensitivity/specificity.
- *Rapid influenza diagnostic* tests are antigen tests specific to influenza, and produce results within 15 minutes with 50%-70% sensitivity and high specificity (90%). Some tests can have up to 80% sensitivity.[11] A limitation is that these tests don't differentiate between viable and nonviable infections or ongoing infections. Another key consideration is that influenza A subtypes cannot be obtained from the RIDTs.
- *Immunofluorescence assays* also use antigen detection but, as the name implies, require the use of a fluorescent microscope to provide results. This does take longer (2-4 hours) and produces moderate sensitivity and high specificity. These types of tests can differentiate between influenza A and B, but cannot further differentiate different influenza A subtypes.
- *Viral cultures* are not timely enough to effect clinical management, as they can take anywhere from 3 to 10 days. The strength of these cultures is that one can characterize the antigenic and genetic makeup of the specific influenza virus causing the patients infection. These are generally, at least in part, used to determine the following year's influenza vaccine.

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The key to ordering and proper clinical use of these tests requires knowledge of the reliability and timing of the tests. For example, RDITs have moderate sensitivities, meaning that false-negative results are common, but high sensitivity of 90%-95%, which means false-positives are uncommon. This makes it useful for confirming an influenza infection, but not in ruling it out. This is in contrast to viral cultures, which have a 90%-95% specificity—false-positive are uncommon.[12,13]

To sum up, the rapid nucleic acid amplifications tests and digital immunoassays have higher sensitivities for both influenza A and B while maintaining equally high specificities when compared to traditional point-of-care testing.[13]

Prevention of Spread

Other than getting the yearly flu vaccine, the best ways to avoid getting the flu include the following:[14]

- Avoid close contact with people who are ill
- Stay at home when you are sick
- Minimize the spread of respiratory droplets by covering the mouth and nose when sneezing or coughing
- Do not touch the face (eyes, nose, mouth)

- Disinfect commonly touched surfaces
- Wash hands frequently

A 2007 meta-analysis in the *American Journal of Public Health* showed a 21% reduction in the transmission of respiratory illness just by hand hygiene alone.[15]

The Flu Vaccine

There are over 100 national influenza centers in over 100 countries.[16] These centers conduct year-round research on influenza by analyzing thousands of virus samples. In the U.S., the Food and Drug Administration has the final approval for vaccines to be produced and sold here. This takes place in February each year for the upcoming flu season. The CDC generally chooses a vaccine to protect against three or four influenza viruses based on these research center data. Now, the vaccine always includes influenza A (H1N1), A (H3N2), and one or two flu B viruses.[1]

These vaccination choices are based on the influenza centers' predictions of which viruses have been and will be circulating during the upcoming season. The ideal vaccine would contain viruses that are easily isolated and can be grown, which occurs in chicken eggs. Additionally, the vaccine virus must have enough similarity to the circulating viruses to provide immunity and also have adequate time to be tested and produced.[16]

The influenza vaccine takes about 7 months to become available after the virus vaccine combination is chosen. One complication from this long time frame is that the influenza virus can change between the time the vaccine was chosen and when it became available. A perfect example of this, again, is the 2009 H1N1 pandemic that became one of the worst influenza pandemics since the 1918 Spanish flu. Generally, if these viruses are not antigenically significant, it won't cause an issue. However, if they do become different, the vaccination may not allow the patient's immune system to detect these changes and the patient would get the flu. Currently, work is being done to shorten production time to help reduce this effect.

Who should get the influenza vaccine?

Anyone can get the influenza vaccine, but certain groups are at much higher risk, including:

- The elderly (>65 years of age)
- Those with neurological, heart, lung, liver, renal, endocrine, blood, or metabolic diseases
- Very young children (<2 years of age)
- Pregnant women

Also, less commonly thought of but of clinical importance to note, are Alaska Natives and Native American, as these populations are more susceptible to significant flu complications.

"Patients with significant illness and a fever should wait until they are over their current illness prior to being vaccinated."

Patients with significant illness and a fever should wait until they are over their current illness prior to being vaccinated. The thought process behind this recommendation is that if the patient were to develop a fever immediately following vaccine administration, it would be difficult, if not impossible, to tell if the fever was due to the preceding illness or a reaction to the vaccine.

If it is a reaction to the vaccine, this would cause the patient to be unable to get the vaccine in the future. Another common reason is more speculative and based on physiology that during an active illness, the body is already developing an immune response to another bug and may not achieve a maximal immune response to influenza when compared to the patient being healthy and receiving the vaccine.[17] Additionally, patients with a history of Guillain-Barre syndrome after receiving the influenza vaccine in the past and who are not currently at risk for severe illness from the flu should not receive the vaccine.[18]

New Nasal Indication (What's Different vs Old Nasal Vaccine)

Previously, the nasal live attenuated influenza vaccine (LAIV) was indicated for all nonpregnant patients 2-years-old through 49-years-old without significant comorbidities. Those with certain diseases and comorbidities should not receive this form of the vaccine because safety and effectiveness in these people have not been established. Additionally, a key difference between this route of administration and the injection is that the

LAIV can be shed for up to 2 weeks. However, according to the 2017-2018 and current recommendations, the LAIV is not recommended for use.[19]

Does the flu vaccine decrease mortality?

During the 2016-2017 season alone, the CDC estimated that the influenza vaccination "prevented an estimated 5.29 million illnesses, 2.64 million medical visits, and 84,700 hospitalizations."[1]

To calculate this, the expected outcome of people at risk was compared with the expected outcome if no one was vaccinated. Then, the averted outcomes (assumed to be from vaccination) were calculated by the difference between outcomes in the hypothesized unvaccinated and vaccinated populations.[1] The data are generated from studies conducted by the U.S. Influenza Vaccine Effectiveness Network, a group of academic institutions.[20]

The problem with these data, however, is multifactorial. First, flu-related deaths of people over the age of 18 are not required to be reported. Second, flu-related deaths often occur weeks after the initial illness due to deadly secondary infections (eg, pneumonia) or exacerbated chronic respiratory illnesses such as COPD or CHF. Further complicating this scenario is that by the time a life-threatening diagnosis is made, the virus can no longer be detected in respiratory samples. Finally, "influenza" is rarely listed as a cause of death on death certificates, making it difficult to track.[21] ■

[This article is the first in a two-part series. In next month's JUCM, *we will examine how urgent care providers and operators can prepare for the influx of patients with influenza—including treatment, patient education, and vigilance for patients who may be prone to complications and poor outcomes.]*

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Summary

- Influenza can be spread from the host 24 hours before symptoms develop, and up to a week after the host becomes sick.
- Influenza A infections are associated with more serious complications, such as pneumonia and death in children and the elderly.
- Early-season testing may be useful in establishing when the virus is starting to increase in prevalence. Conversely, late-season testing is less useful if the patient fits into a pre-established risk group.
- Because rapid nucleic acid amplification tests and digital immunoassays have higher sensitivities for both influenza A and B while maintaining equally high specificities compared with traditional point-of-care testing, they are effective in assessing patients with symptoms of influenza.