



Treating Patients Infected with Influenza Virus in the Urgent Care Setting

Urgent message: As patients start to feel the effects of the 2018–2019 influenza season, urgent care centers can expect to see visits by patients with related symptoms increase. Providers must be prepared to identify and treat patients most at risk for complications and poor outcomes—armed with old standbys and a newly approved antiviral agent.

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Introduction

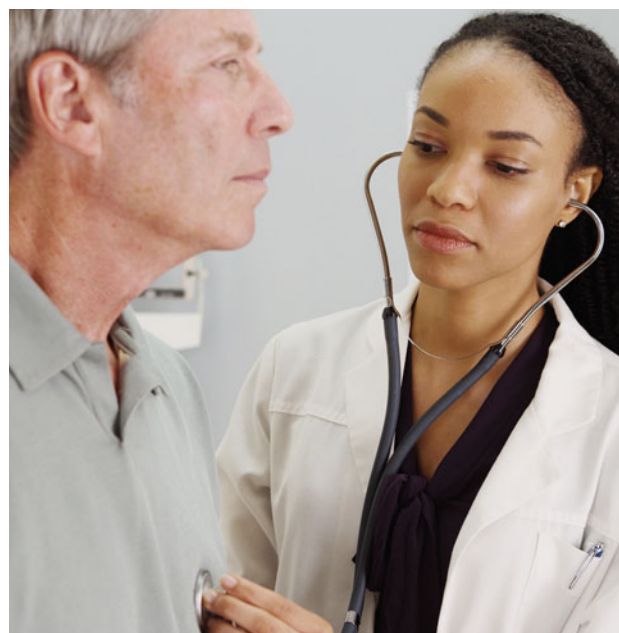
Last month, *JUCM* explored prevention, diagnosis, and testing for influenza. In this issue, we focus on management of patients who have been diagnosed with influenza, with attention to duration of infectivity, complications of influenza, symptomatic treatment, and indications and side effects of medications.

Complications of Influenza

Symptoms of influenza may range from mild to severe, and may include fever, cough, myalgias, sore throat, nasal congestion, headache, and nausea or vomiting. In the healthy adult, these symptoms are typically self-limited; however, thousands of patients in the United States die every year from “the flu.”

Most complications of influenza reflect co-infection of the flu virus and microbes, including “nuisance” illnesses such as sinus infection and ear infection. However, life-threatening complications such as pneumonia may also occur. Other serious potential complications include myocarditis, encephalitis, myositis, rhabdomyolysis, sepsis, and kidney failure. Influenza infection can also lead to decompensation in chronic medical problems such as asthma, chronic obstructive pulmonary disease, or chronic heart disease.

One of the most serious complications of influenza is acute respiratory distress syndrome (ARDS), which is characterized as an inflammatory lung injury with



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increased pulmonary vascular permeability and loss of aerated lung tissue. Typically, chest x-ray shows bilateral radiographic opacities in patients with ARDS.

Despite recent progress in managing ARDS, the mortality rate is nearly 50%. Influenza infection is often responsible for severe ARDS whose clinical course is more prolonged and has a high mortality.¹

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Patients at High Risk for Developing Influenza-Related Complications

According to the Centers for Disease Control and Prevention, populations at high risk for developing influenza-related complications include:

1. Children younger than 5 years old, especially those under 2 years old
2. Adults aged 65 and older
3. Pregnant women and women up to 2 weeks postpartum
4. Residents of nursing homes or long-term care facilities
5. American Indians and Alaska Natives
6. Those with chronic medical conditions such as asthma, heart disease, diabetes, chronic renal disease, liver disease, any weakened immune system (such as AIDS or immunosuppression from chemotherapy or chronic steroid use)
7. Morbid obesity with BMI>40

Indications for Referral to the Emergency Department

Referral or transfer to the emergency department is warranted for some patients presenting to urgent care with symptoms (or a confirmed case) of influenza. These include patients with:

1. *Respiratory distress*, including hypoxemia with oxygen saturation <90%, increased work of breathing with use of accessory muscles and nasal flaring, tachypnea, or significant tachycardia
2. *Hypotension* with consideration of septic shock
3. *Altered level of consciousness*
4. *Myocarditis*; this can be difficult to diagnosis in the urgent care, but red flags include a febrile patient with chest pain and unexplained tachycardia
5. *Encephalitis*, whose manifestations can include confusion, hallucinations, seizures, weakness, and loss of sensation; this is more common in patients over 60 years old but can present at any age
6. *Myositis*, with the most common presenting symptom being muscle weakness. This may only be found with muscle strength testing. Myalgias may or may not be present
7. *Rhabdomyolysis*, whose symptoms include dark red urine, decreased urine, weakness, and muscle aches
8. *Acute renal failure*, which may include decreased urinary output, fluid retention leading to swelling of the lower extremities, shortness of breath, nausea, and confusion
9. *Diagnostic uncertainty*

Mechanisms in Influenza: Why Do Healthy People Die?

Patients who are immunosuppressed, elderly, very young, or pregnant are more likely to develop complications of influenza, but healthy young men and women also may die of influenza. This is likely due to cytokine storms, an immune response so large that the body's own cells, particularly those in the respiratory tract, are damaged, leading to severe complications of influenza including pneumonia and ARDS.

Cytokine storms are a result of an overactive immune system. When the immune system is fighting a microbe, cytokines activate T-cells and macrophages which then stimulate more cytokine production. Normally, this system is kept in check with a feedback loop. However, when this reaction becomes uncontrolled, too many immune cells are activated in a single place, leading to damage. The exact reason is not entirely understood, but this is thought to occur when a new and highly pathogenic microbe is encountered. For example, in patients with influenza, cytokine storms occurring in the lungs may lead to accumulation of immune cells, causing blockage of the airway and leading to ARDS.¹¹

It is thought that the older population may have at one time been exposed to or infected with a similar virus in the past, making their body much more adept at fighting off the infection due to an immune-related memory.² Although the older population is considered high-risk for developing complications from influenza, younger patients are more likely to develop a cytokine storm response leading to ARDS.

Treatments—Indications, Efficacy, and Precautions

Very similar to overuse of antibiotics, increasing use of antiviral medications has led to an increase of resistance. When this occurs, our most vulnerable patients are at risk for increased morbidity and mortality. Therefore, use of antivirals in influenza should be carefully considered. Any individual with severe disease or who is at higher risk of complications should be considered for treatment with antiviral therapy. Unfortunately, many of the studies completed on current antiviral therapies do not show a clear decrease in mortality. Even though recent studies question the effectiveness of antiviral therapies, the CDC still does recommend antiviral therapy in specific patient populations, including those who are considered high risk or who have other comorbid conditions.

When indicated, antiviral therapy should be initiated when the initial diagnosis is made, as it is most likely to provide benefit when initiated in the first 48 hours of

illness. In high-risk patients, therapy may be started after 48 hours. Patients who have had a negative rapid influenza test, for whom clinical suspicion of influenza remains high, should be treated, as well, as the sensitivity of these tests may be low.³ While working directly with patients with high clinical suspicion of having influenza there are broad recommendations from OSHA for direct staff safety. These include getting vaccinated, following the steps for hand hygiene and cough etiquette, staying home if you are ill, following infection control practices, and using the appropriate personal protective equipment as decided by your employer.

Three oral medications are approved by the Food and Drug Administration for patients diagnosed with influenza. These include the oral agents oseltamivir (available as a generic or under the trade name Tamiflu) and baloxavir marboxil (Xofluza) and inhaled zanamivir (Relenza). According to the CDC, recommended treatment should be initiated in the patients described in **Table 1**.

Oseltamivir (Tamiflu)

Researchers within the Cochrane Collaboration completed an assessment of 20 studies on efficacy of oseltamivir that included almost 10,000 children and adults. They did not find any evidence that oseltamivir would prevent serious cases and complications in the event of a flu epidemic. They did find that oseltamivir shortens the duration of flu symptoms by about 17 hours. Without oseltamivir, symptoms last 7 days on average in otherwise healthy children and adults. However, duration of symptoms was shortened to 6.3 days in adults who took oseltamivir, and by about 1 day in children who took oseltamivir.⁴

This collaboration also showed that the most common side effects of oseltamivir were nausea and vomiting, occurring in 4% of the patients.

With all of this information, it is important to engage in shared decision making (SDM) with the patient about use of oseltamivir. CDC recommendations, patient presentation, and patient preference should all come into play when considering whether to prescribe antiviral medications for influenza. The risk of GI side effects and increased risk of resistance should be balanced with the possibility that the duration of symptoms may be shortened. Additionally, over-the-counter medications such as antipyretics should be recommended for symptom relief.

Note that generic oseltamivir became available in 2016. Dosing reduction is needed in patients with decreased creatinine clearance. Recommended dose from the CDC are shown in **Table 2**.

Table 1. Persons at Higher Risk for Influenza Complications Recommended for Antiviral Treatment

- Children younger than 2 years of age
- Adults 65 years and older
- Persons with:
 - chronic pulmonary (including asthma)
 - cardiovascular (except hypertension alone)
 - renal
 - hepatic
 - hematological (including sickle cell disease)
 - metabolic disorders (including diabetes mellitus)
 - neurologic conditions
 - neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate-to-severe developmental delay, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression, including that caused by medications or HIV infection
- Woman who are pregnant or postpartum (2 weeks after delivery)
- Persons younger than 19 years of age who are receiving long-term aspirin therapy
- American Indians/Alaska Natives
- Persons who are extremely obese (ie, body mass ≥ 40)
- Residents of nursing homes and other chronic care facilities

Adapted from Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians.

A New Vaccine, a New Antiviral

In May 2018, the National Institute of Allergy and Infectious Disease (NIAID) launched a Phase 2 clinical trial of a universal influenza vaccine called M-001. The vaccine, which was developed and produced by BiondVax Pharmaceuticals based in Ness Ziona, Israel, contains antigenic peptide sequences shared among many different influenza strains.⁹

That same month, health authorities in Japan approved a new influenza medication called Xofluza (baloxavir marboxil). Baloxavir aims to stop the virus within 1 day. According to the manufacturers, the drug works by blocking the influenza virus's ability to use the host cell for replication. Its mechanism of action differs from oseltamivir's. The World Health Organization has stated that it could be the breakthrough needed to help reduce the morbidity and mortality associated with the influenza virus.

Just days before this article went to press, Genentech received approval from the FDA to sell Xofluza in the United States. The approval states Xofluza is to be used only in patients 12 years of age and older, and taken as

Table 2. Recommended Dosage and Duration of Influenza Antiviral Medications for Treatment or Chemoprophylaxis

Antiviral agent	Use	Children	Adults
Oral oseltamivir	Treatment (5 days)	If younger than 1 year: 3 mg/kg/dose twice daily If 1 year or older, dose by weight: ≤15 kg, 30 mg twice daily >15 to 23 kg, 45 mg once daily >23 to 40 kg, 60 mg once daily >40 kg, 75 mg once daily	75 mg twice daily
	Chemoprophylaxis (7 days)	If younger than 3 months, not recommended unless situation is judged critical, due to limited data in this age group. If 3 months or older but younger than 1 year, 3 mg/kg/dose once daily If 1 year or older, dose varies by weight: ≤15 kg, 30 mg once daily >15 kg to 23 kg, 45 mg once daily >23 kg to 40 kg, 60 mg once daily >40 kg, 75 mg once daily	75 mg once daily
Inhaled zanamivir	Treatment	Approved in children ≥7 years of age only: 10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) twice daily
	Chemoprophylaxis (7 days)	Approved in children ≥5 years of age only: 10 mg (two 5 mg inhalations) once daily	10 mg (two 5 mg inhalations) once daily
Oral baloxavir	Treatment (1 day)	Approved in children ≥12 years of age only, varies by weight: 40 kg to <80 kg, single dose of 40 mg ≥80 kg, single dose of 80 mg	Varies by weight: 40 kg to <80 k, single dose of 40 mg ≥80 kg, single dose of 80 mg

Adapted from Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians; and Xofluza [Package Insert]. South San Francisco, CA: Genentech USA, Inc.; 2018.

a single oral dose within 48 hours of symptoms onset.⁵ According to *The New York Times*, Genentech expects to price the product at \$150 per dose, though it plans to offer coupons that would effectively lower the cost to \$30 for insured patients and roughly \$90 for patients who do not have insurance.⁶

The safety and efficacy of Xofluza were demonstrated in a pair of randomized, controlled trials of 1,832 patients who were assigned to Xofluza, placebo, or another antiviral flu treatment within 48 hours of first symptoms of flu. In both trials, symptoms for patients in the Xofluza group were alleviated in less time than those in the placebo group. It worked more quickly than the other antiviral in one of the two studies, while there was no difference between the two products in the second trial. The most common side effects seen in patients taking Xofluza were diarrhea and bronchitis.

Data from the drug maker show that Xofluza works days faster than oseltamivir in stopping the influenza virus, but that symptoms are completed in about the same timeframe for both medications.

Dosage information is shown in **Table 2**.

Other Symptomatic Management—What Works?

Each year, Americans spend over \$2 billion on over-the-counter medications designed to treat the common cold. So, as practitioners, what are we able to confidently tell our patients to use?

Resting and drinking fluids remain the standard treatments. Critical reviews of clinical trials have been completed on over-the-counter cold remedies and have found some evidence to support the use of antihistamines, decongestants, and anticholinergic drugs in adults. There has not been any strong evidence to sup-

port the use of these remedies in children.⁷ In general, recommendations should be patient-specific to address their complaints and minimize side effects.

Many holistic approaches are becoming popular in treatment of influenza and other common viral infections.

Zinc is thought to prevent the formation of viral proteins and therefore, theoretically, can inhibit replication of rhinoviruses. Zinc may also have immunomodulating properties by inducing production of interferon. But, evidence from clinical trials for zinc have been inconsistent.⁷ One study by Hemila does show a 33% to 54% reduction in cold-like symptoms such as nasal discharge and congestion, scratchy throat, and myalgias with a daily dosing of zinc at 80–92 mg/day. They did not show a decrease in duration of sneezing, headache, or fever. Even though this small study (199 participants) shows decrease in some symptoms, one must also consider the side effects of zinc, including indigestion, diarrhea, headache, nausea, and vomiting. Also, when used long-term, high doses of zinc can cause copper deficiency, leading to neurological issues. Considering there is no definitive proof of decrease in symptoms and that multiple adverse effects of over-the-counter zinc are known to occur, it should not be recommended at this time.

Another holistic treatment that is gaining popularity is echinacea. This is an herb that reportedly exerts its action through nonspecific immunomodulatory properties. Three species are used in medicine, including *Echinacea purpurea*, *E pallida*, and *E angustifolia*. Despite its widespread use, there are limited data from well-designed clinical trials that support its use.⁷ A study from 2011 completed by Barrett, randomized 719 patients to blinded or open-label echinacea, or to blinded placebo or no pills at all. It did not show a clinical or statistical effect in treatment for symptoms of the common cold. Until more controlled studies are completed, we cannot state its effectiveness.

Do Flu Patients Need to Miss School and Work, and for How Long?

Patients are contagious for the time span of 1 day before development of symptoms through the following 1 week, though children may remain contagious even longer. According to the CDC, patients should stay home for at least 24 hours after resolution of fever; symptoms vary widely in severity and duration, however, so avoiding contact with others needs to be individualized.¹⁰

The Future of Influenza Prevention

Looking back at the effectiveness of the seasonal

influenza vaccine, it is easy to understand why there has been a push into further research and planning for a universal influenza vaccine. During the 2017–2018 influenza season, vaccine effectiveness was only 36%. In 2004, it was as low as 10%. The highest effectiveness rate we've had in the past 15 years was in 2010, when effectiveness was 60%.⁸

Consequently, the NIAID has focused on research programs to develop a universal flu vaccine. This would, potentially, eliminate the need to update the vaccine annually. According to the NIAID, a universal flu vaccine should do the following:

1. Be at least 75% effective
2. Protect against group I and II influenza A viruses
3. Have durable protection that lasts at least 1 year
4. Be suitable for all age groups

Take-Home Points

- Neuraminidase inhibitors may shorten the duration of flu symptoms, and are recommended for populations at high risk. Common side effects include nausea and vomiting.
- As of October 2018, three antiviral agents—Relenza, Tamiflu, and Xofluza—have received approval by the FDA for patients who have been diagnosed with influenza infection.
- Symptomatic medications such as acetaminophen and ibuprofen may be helpful, but zinc and echinacea cannot be recommended at this time.

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