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Influenza: Diagnosis and Management in the Emergency Department

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Abstract

Emergency clinicians must be aware of the current diagnostic and therapeutic recommendations for influenza and the available resources to guide management. This comprehensive review outlines the classification of influenza viruses, influenza pathophysiology, the identification of high-risk patients, and the importance of vaccination. Seasonal variations of influenza are discussed, as well as the rationale for limiting testing during periods of high prevalence. Differences between strains of influenza are discussed, as well as the challenges in achieving optimal vaccine effectiveness. Recommendations for use of the currently available oral, intranasal, and intravenous antiviral treatments are provided, as well as utilizing shared decision-making with patients regarding risks and benefits of treatment.

Case Presentations

A 20-month-old boy presents to the ED with a cough and fever for 3 days. He has no past medical history, and his routine vaccinations are up-to-date. His parents say he has been eating less than usual; however, his urine output is normal, and he has had no vomiting or diarrhea. Vital signs are: temperature, 39.6°C (103.2°F); heart rate, 156 beats/min; respiratory rate, 32 breaths/ min; and oxygen saturation, 100% on room air. He is well-appearing, although his left tympanic membrane is erythematous and bulging, with apparent middle-ear purulence. You make the diagnosis of otitis media in the setting of a presumed viral upper respiratory infection. While preparing the discharge papers, you consider the many patients you've seen during the current flu epidemic and wonder whether treatment for influenza would be appropriate . . .

Your next patient is a 32-year-old man with the same chief complaints: cough and fever. His maximum temperature over the past 5 days was 40°C (103.9°F). He has been taking over-the-counter cold remedies without relief, and today he is markedly short of breath. The patient has no regular primary care provider and has no significant past medical history. His initial vital signs are: temperature 39.2°C (102.5°F); heart rate, 118 beats/min; respiratory rate, 28 breaths/min; blood pressure, 134/78 mm Hg; and oxygen saturation, 88% on room air. On examination, he appears uncomfortable, with notable tachypnea. The oropharynx is clear and the neck supple. Crackles are noted in the right lower lung field, without any wheezing. The abdomen is soft and nontender. The patient is given oxygen via face mask, with an improvement in saturation to 100%. Chest x-ray reveals a right lower lobar pneumonia with a small pleural effusion. You start IV antibiotics and request an inpatient bed, as he is hypoxic with his pneumonia. You wonder whether influenza testing is indicated, and if so, what type of test, and how reliable would it be?

Introduction

During the 1918–1919 influenza pandemic, approximately one-third of the world's population was infected and approximately 50 million people died.[1] At that time, influenza pandemics were not new occurrences, but their mortality and morbidity had not been well documented and the causative organisms had not been identified. Fifty years later, it was estimated that the 1968 "Hong Kong" influenza pandemic (H3N2) caused between 1 and 4 million deaths worldwide. Despite advances in diagnostic and treatment strategies, mortality from influenza continues to increase, with over 30,000 deaths annually in the United States, partly related to the aging of the population.[2] With globalization, the need to contain regional influenza outbreaks has assumed more urgency to prevent an emerging pandemic. The emergency department (ED) plays a key role in disease outbreaks, since containment of a potential epidemic relies on early and rapid identification, treatment, and—in some cases—prophylaxis.

The medical costs and lost wages from influenza are substantial. According to the United States Centers for Disease Control and Prevention (CDC), influenza epidemics cost $10.4 billion per year in direct medical expenses and an additional $16.3 billion in lost earnings annually in the United States.[3,4] An influenza epidemic is responsible for 3.1 million hospitalized days, and 31.4 million outpatient visits annually (during the epidemic), with a total economic burden of $87.1 billion in the United States alone.[4]

As the public health community commemorates the 50th and 100th anniversaries of historic and tragic influenza pandemics, this issue of *Emergency Medicine Practice* presents an update based on a critical appraisal of the most current literature on influenza. Recent studies on clinical presentation, diagnosis, and treatment are reviewed, and recommendations on the evaluation and management of patients with suspected symptoms of influenza are provided.

Critical Appraisal of the Literature

PubMed, ISI Web of Knowledge, and the Cochrane Database of Systematic Reviews resources from 2012 to 2018 were accessed using the keywords: *emergency department, epidemic, pandemic, influenza, novel H1N1,* and *H3N2*. The CDC[5] and the World Health Organization (WHO)[6] websites were accessed. Guidelines from the American College of Emergency Physicians (ACEP),[7] the Infectious Diseases Society of America (IDSA),[8] and the American Academy of Pediatrics (AAP)[9] were also reviewed. References from the literature were searched to identify additional content.

Epidemiology

Although precise data for influenza-related illness and sequelae are difficult to obtain, up to 20% of the United States population has been estimated to be infected with the influenza virus during the winter season.[2] Influenza disproportionately affects young children and elderly persons, and influenza deaths have increased substantially in the last 2 decades, in part due to the aging of the population.[2] Annual mortality in the United States from influenza typically ranges from 12,000 to 56,000 deaths; 140,000 to 710,000 patients are hospitalized each year; and 9.2 to 35.6 million patients present for treatment.[4,10]

Morbidity and mortality from influenza can vary depending on a given population's immunity to previous strains.[11] Historically, mortality from seasonal outbreaks disproportionately affects the elderly, with up to 90% of deaths occurring in people aged 65 years and older. In the pandemic of 2009, more significant outbreaks of disease were

seen in the younger population, who had no (or weaker) immunity.[11,12]

Types of Outbreaks

Seasonal influenza is the typical outbreak of the infection that occurs at varying times in a given year. When the number of cases of influenza exceeds what would normally be expected within a circumscribed region, an epidemic is declared.[13] According to the WHO, the term *pandemic* is reserved for the occurrence of worldwide disease outbreaks and not for the emergence of a new strain (as was once the case). Declaration of a pandemic by the WHO raises global awareness of a disease outbreak and allows for aggressive preparedness and response planning.[10,14] In the United States, the CDC publishes a weekly report (https://www.cdc.gov/flu/weekly/fluactivitysurv.htm) that includes laboratory surveillance data, the frequency of influenza-like illness, and region-based estimates of laboratory-confirmed cases of influenza.[5]

Seasonality and Transmission

Influenza is diagnosed every month of the year somewhere in the world. In the Northern Hemisphere, the virus is most active between November and March. In tropical regions, the virus is present year-round.[13] Much of its spread is attributed to direct person-to-person contact via expelled respiratory secretions. This may explain, in part, the more rapid transmission during the colder months, when people are often confined to poorly ventilated spaces.[14]

The 2017–2018 Influenza Epidemic

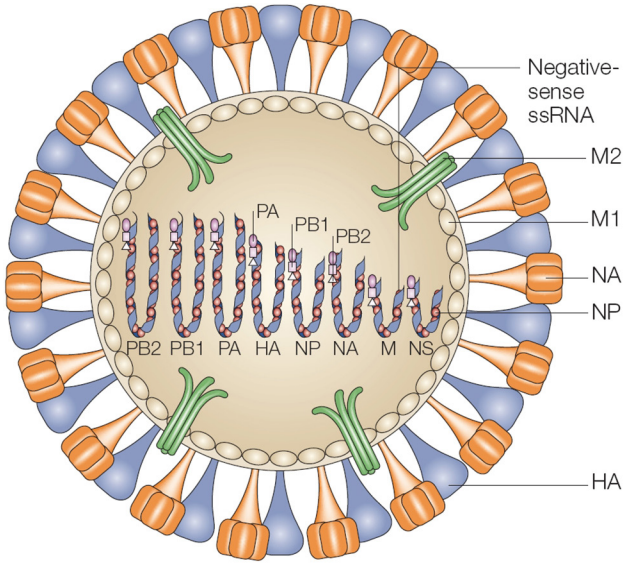
The CDC initially stated that, although the 2017–2018 influenza season was very severe, it did not meet their criteria for a pandemic, despite news reports of record-breaking ED visits.[15,16] However, recent CDC data have shown that it was the deadliest season since 1976, with at least 80,000 deaths attributed to the illness and its complications.[17] The 2017–2018 season was the proverbial "perfect storm," with a convergence of factors that contributed to the high morbidity and mortality.[17] In addition to the highly mutagenic nature of the prevalent H3N2 species and the resultant low vaccine effectiveness, that season arrived on the heels of a severe hurricane, which limited intravenous (IV) fluid and antiviral medication production at several pharmaceutical companies in Puerto Rico.[10,18-20] Additionally, there were significant gaps in supply chain management for the production and distribution of oseltamivir (Tamiflu®), leading to further disruption of treatment and lengthening the time course of the disease.

Classification of Influenza Viruses

The influenza virus is a spherical, RNA-based organism of the Orthomyxoviridae family. The RNA core of the virus particle is associated with a nucleoprotein (NP) antigen. Variations of this nucleoprotein have led to categorization of influenza viruses into 3 primary subgroups known as influenza types A, B, and C. Influenza A is the most common subtype of influenza and is most frequently associated with pandemics. Influenza B virus infection occurs with less frequency but sometimes results in epidemics.[10-14] Influenza C is the form of the virus least likely to infect humans. Influenza C illness is typically milder than A or B, so diagnosis, prevention, and treatment are not generally pursued.

Influenza A viruses are further grouped based on specific transmembrane or surface proteins: hemagglutinin (H) and neuraminidase (N).[21] **(See Figure 1.)** There are 16 different hemagglutinin subtypes and 9 different neuraminidase subtypes, of which 3 subtypes of hemagglutinin (H1, H2, and H3) and 2 subtypes of neuraminidase (N1 and N2) have caused epidemic disease in the human population.[22] Viral strains are classified based on the type of influenza, site of origin for that particular strain, isolate

Figure 1. Schematic Diagram of an Influenza Virion



Virion schematic: 2 surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA); M2 ion channel (M2); core viral nucleoprotein (NP); 3 polymerase proteins (PA, PB1, PB2); and matrix protein (M1).

number, year of isolation, and subtype. For example, the influenza pandemic of 1968 was designated "A/Hong Kong/03/1968(H3N2)."

Antigen Variations

The surface proteins, hemagglutinin and neuraminidase, play an important role in antigenic variation of the virus over time, which leads to the occurrence of epidemic and pandemic outbreaks. There are 2 types of antigen variation: *antigenic drift* and *antigenic shift*. All 3 virus subgroups (influenza A, B, and C) undergo antigenic drift, which involves small point mutations to the viral genes that code for hemagglutinin and neuraminidase. This is clinically significant because these mutations are subtle enough that some immunity may be maintained within the population infected previously by influenza viruses of a similar subtype. Antigenic shift, by contrast, is a much more radical change, with reassortment of the viral genes such that the surface proteins less closely resemble those of viral strains that previously caused infection. Antigenic shift results in loss of immunity even when one is exposed to the same type of influenza. When cells are infected by 2 or more different influenza strains at once, a new strain can emerge after genetic reassortment.

Evidence suggests that the reassortment of genes that results in production of new influenza strains often involves an animal host. Pigs, horses, and birds are some of the most common intermediate hosts, thus explaining the respective nomenclature of "swine," "equine," and "avian" influenza strains. This explanation would account for the influenza epidemics in China, where close living conditions between animals and humans facilitate co-infection and genetic reassortment. Because animal co-infection with influenza types B and C is infrequent, the phenomenon of antigenic shift is limited to influenza type A, which accounts for the more frequent epidemics and pandemics involving this viral subtype. Historically, pandemics have emerged at intervals of approximately 15 to 30 years.[1,23] **(See Table 1.)**

Table 1. Influenza Pandemics Over the Past 100 Years

Years	Name	Subtype	Estimated Deaths
1918-1919	Spanish flu	H1N1	USA: 675,000 Worldwide: 50 million
1957-1958	Asian flu	H2N2	USA: 70,000 Worldwide: 1 to 2 million
1968-1969	Hong Kong flu	H3N2	USA: 34,000 Worldwide: 700,000
2009-2010	Swine flu	H1N1	USA: 12,469[24] Worldwide: 284,000[25]

Pathophysiology

The primary route of transmission of influenza is through respiratory secretions released during coughing or sneezing. The virus initially infects the epithelial cells of the upper respiratory tract and the alveolar cells of the lower respiratory tract. Viral replication occurs within 4 to 6 hours, with a typical incubation period of 18 to 72 hours, depending on the size of the initial inoculum.[21] Peak viral replication is typically reached by the second or third day, with viral shedding usually complete approximately 7 days after infection. However, in children and immunocompromised hosts, viral shedding can be prolonged, lasting up to 2 weeks, according to some studies.[26,27]

During active infection, pathologic changes can be found throughout the respiratory tract. Changes in the lower respiratory tract are most significant, and bronchoscopy reveals diffuse mucosal inflammation and edema of the bronchi. Subsequent epithelial cell necrosis leads to desquamation of the epithelial cells that line the respiratory tract. Spread of the virus into the lung parenchyma can lead to viral pneumonia and occasionally secondary bacterial pneumonia.

The most common secondary bacterial pathogens associated with influenza infections are *Staphylococcus aureus*, *Streptococcus pneumonia*e and *Haemophilus influenzae*. Although uncommon, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has been found in fatal cases of pneumonia in patients with confirmed skin CA-MRSA or in patients living with someone who had the infection, with most reported cases leading to fatality within 4 days.[28] These organisms often colonize the respiratory tract, but then gain access to the lung parenchyma through the depletion of bronchopulmonary defenses.[21] In fact, *H influenzae* was found with such frequency in the respiratory secretions of influenza victims during the 1918 epidemic that it was initially thought to be the primary etiologic agent. Only later did further study characterize this organism as the cause of a secondary bacterial infection.[29,30]

Vaccination

There are currently 3 methods approved by the United States Food and Drug Administration (FDA) to produce influenza vaccines: egg-based, cell-based, or recombinant influenza vaccine. Once the season's candidate vaccine viruses have been determined, they can be introduced into fertilized hens' eggs and incubated for several days, allowing the virus to replicate. The influenza viruses are then inactivated and the viral antigen is purified and made available for injection or nasal spray. In cell-based vaccines, the viruses are harvested from mammalian cells instead

of hens. In recombinant-based vaccines, manufacturers isolate specific proteins from a naturally occurring candidate virus, which are then combined with another virus that grows well in insects, and they are allowed to replicate. These viral proteins are then harvested and purified for vaccine use.

Vaccination initiatives are fundamental to preventing and/or reducing illness. The influenza vaccine for the 2017–2018 season was comprised of antigenic representations from the 4 major circulating strains, namely influenza A (H3N2), influenza A (H1N1), influenza B/Yamagata, and influenza B/Victoria.[10] H1N1 and H3N2 were the predominant strains during the 2009 and 1968 pandemics, respectively; however, since the 2009 H1N1 pandemic, H3N2 has been the most dominant strain, with the exception of the 2015–2016 season.[10,31] **(See Figure 2.)** The CDC has also implicated the H3N2 strain as being the most virulent, volatile, and mutagenic of all the dominant strains, which leads to its poor prophylaxis when incorporated into vaccines, as compared to the other viral strains.[10] A meta-analysis on the vaccine effectiveness in ambulatory care settings from 2004 to 2015 found that the pooled vaccine effectiveness against the influenza B viruses was 54%; the pooled vaccine effectiveness against the H1N1 pandemic 2009 viruses was 61%; and the pooled vaccine effectiveness against the H3N2 viruses was 33%.[10,32] H3N2-dominant seasons are associated with the highest rates of influenza cases, hospitalizations, and deaths.[31]

Despite the poor protection from the H3N2 strain specifically, vaccination still prevents influenza cases, hospitalizations, and deaths. Vaccine effectiveness is typically around 50% in preventing severe influenza morbidity and mortality.[18] **(See Table 2.)** The 2017–2018 season's vaccine effectiveness was approximately 40%.[10,18] However, even with this seemingly poor prevention rate, this translates to 40% less severe outpatient influenza cases, and thus a significant decrease in hospitalizations and deaths.[10,18]

Figure 2. Seasonal Impact of Influenza

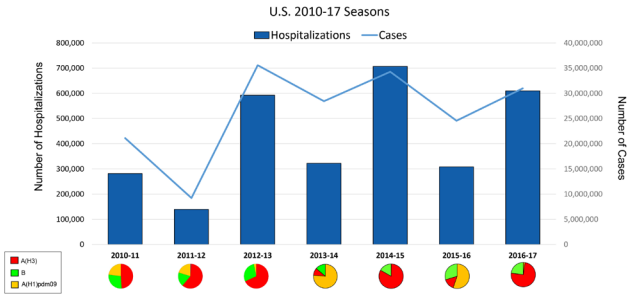


Image source: https://www.cdc.gov/grand-rounds/pp/2018/20180116-severe-influenza-H.pdf

Data source: https://www.cdc.gov/flu/about/disease/2015-16.htm

For 2018–2019, the trivalent (3-component) vaccines contained:

- A/Michigan/45/2015 (H1N1) pdm09-like virus
- A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus (updated)
- B/Colorado/06/2017-like (Victoria lineage) virus (updated)

The quadrivalent (4-component) vaccines, which protect against a second lineage of B viruses, contained:

- The 3 viruses in the 3-component vaccine, plus B/Phuket/3073/2013-like (Yamagata lineage) virus.[33]

Differential Diagnosis

The CDC defines *influenza-like illness* as a temperature > 37.8°C (100°F), plus either cough or sore throat, in the absence of a known cause other than influenza.[34] The signs and symptoms of influenza are not specific; hence, the broad definition of influenza-like illness by the CDC. Influenza should be included in the differential diagnosis of any febrile patient who presents to the ED with symptoms of an upper respiratory infection. Given the nonspecific symptoms of influenza, the differential diagnosis must include a wide range of bacterial and viral infectious processes. Such organisms include *Mycoplasma pneumoniae, S pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, *Legionella* species, and, less commonly, CA-MRSA.

Prehospital Care

Evaluation and management of patients with influenza-like illness in the prehospital setting require an accurate, age-appropriate assessment; stabilization; and management of the patient's respiratory status. Efforts to stabilize the patient could range from

Table 2. Yearly Vaccine Effectiveness

Season	VE Against A/B Influenza Viruses (95% CI)
2010–2011	60% (53, 66)
2011–2012	47% (36, 56)
2012–2013	49% (43, 55)
2013–2014	52% (44,59)
2014–2015	19% (10, 27) [Mismatched]
2015–2016	48% (41,55)
2016–2017	40% (32,46)
2017–2018	40% (34,46)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

Data source: https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

simple oxygen supplementation to more advanced airway management techniques. The use of face masks by patients and providers is indicated to minimize viral spread. Because influenza is contagious and patients with comorbidities are at highest risk for complications, efforts by emergency medical services providers to limit patient transport is a growing area of interest and one actively being studied, using community paramedicine to treat patients at home or to transport them to healthcare facilities other than crowded EDs.

Most communities have strategic plans for the evaluation and management of large numbers of patients in the event of a major influenza outbreak. Local, state, and federal protocols are designed to facilitate effective triage, stabilization, and transport of patients in the prehospital setting. These protocols are published by the National Highway Traffic Safety Administration.[35] **(See Table 3.)**

Emergency Department Evaluation

Appropriate management of patients with influenza-like illness includes taking infection control measures within the ED, including the isolation of patients with suspected infection, as well as the use of personal protective equipment for healthcare staff.[8] All patients with suspected influenza should be managed according to standard isolation and contact precautions.[36] The Clinical Pathways (pages 12-13) summarize the clinical approach to patients who present to the ED with an influenza-like illness.

Influenza infections are associated with a range of symptoms and presentations that vary by age. **(See Table 4.)** The typical history of influenza is 2 to 5 days of fever, nasal congestion, sore throat, and myalgias. Usual signs include fever, tachycardia, cough, dyspnea, and chills. Van Wormer et al performed a prospective analysis of subjective symptoms of patients presenting with acute respiratory illness to determine correlation with laboratory-confirmed influenza illness and severity. They found that the most common symptoms were cough (92%), fatigue (91%), and nasal congestion (84%) ($P < .001$), whereas sneezing was identified as a negative predictor of influenza in adults.[37] In a retrospective study, Monto et al concluded that the best multivariate predictors of influenza infections were cough and fever, with a positive predictive value (PPV) of 79% ($P < .001$).[38] The PPV rose with the increase in the temperature at the time of recruitment. Furthermore when influenza is circulating within the community, patients with an influenza-like illness who have both cough and fever within 48 hours of symptom onset are likely to have influenza.[8]

A study of children aged ≤ 13 years found that the predominant symptoms among those with influenza were fever, cough, and rhinitis, which were reported in 95%, 77%, and 78% of the study population, respectively.[39] This study also suggested that the range of fever (> 39˚C [102.2°F]) was significantly higher in children with influenza. Associated gastrointestinal symptoms (vomiting and diarrhea) are also noted more frequently in children than in the adult population.[40] Numerous potential complications can result from a primary influenza infection.[41] **(See Table 5, page 7.)**

Table 4. Most Frequent Clinical Symptoms of Seasonal Influenza, by Age Group

Adults	Children
Fever	Fever
Cough	Cough
Sore throat	Sore throat
Nasal congestion	Nasal congestion
Headache	Vomiting
Myalgia	Diarrhea

Table 3. Online Resources for Evaluation/Management of Influenza

Organization	Topic	Website
CDC	Up-to-date information on influenza	https://www.cdc.gov/flu/professionals/index.htm
CDC	Weekly flu activity and surveillance	https://www.cdc.gov/flu/weekly/fluactivitysurv.htm
CDC	Influenza infection in pregnancy	https://www.cdc.gov/flu/protect/vaccine/pregnant.htm
CDC	Antiviral medication treatment recommendations and susceptibility information	http://www.cdc.gov/flu/professionals/antivirals/index.htm
American College of Emergency Physicians	Strategic plan for ED management of outbreaks of novel H1N1 influenza	https://www.acep.org/globalassets/uploads/uploaded-files/acep/clinical-and-practice-management/resources/publichealth/h1n1/h1n1-strategicplan.pdf
National Highway Traffic Safety Administration	Strategic plan for prehospital evaluation and management of an influenza pandemic	https://icsw.nhtsa.gov/people/injury/ems/pandemicinfluenzaguidelines/Task61136Web/PDFs/FrontMatterOverview.pdf

Abbreviations: CDC, United States Centers for Disease Control and Prevention; ED, emergency department.

Diagnostic Studies

Rapid influenza diagnostic tests may impact medical management by decreasing ancillary tests and antibiotic use. The diagnostic tests for influenza include viral culture, immunofluorescence, reverse transcription polymerase chain reaction (RT-PCR), and rapid antigen testing. During an epidemic, formal testing may not be indicated because the decision to treat is based on treatment criteria such as age, comorbidities, severity of illness, etc. The reliability of laboratory tests varies greatly, depending on the type of test performed, the quality of the sample, and the laboratory.

Table 5. Complications Associated With Influenza Infection in Adults

Complication(s)	Incidence	Comments
Respiratory		
Acute bronchitis	Common	More common in elderly and those with chronic respiratory medical conditions.
Primary viral pneumonia	Uncommon	Onset within 48 hours of start of fever.
Secondary bacterial pneumonia	Common	Typically occurs 4-5 days after onset of illness.
Cardiovascular		
Electrocardiogram abnormalities	Common	Nonspecific T wave and rhythm changes; ST segment deviation. Mostly not associated with cardiac symptoms
Myocarditis/pericarditis	Rare	—
Muscle		
Myositis	Uncommon	Occurs during early convalescence.
Myoglobinuria and renal failure	Rare	—
Central nervous system		
Encephalitis/ encephalopathy	Rare	Occurs within first week of illness. More common in children and in Japan.
Transverse myelitis	Very rare	—
Guillain-Barré syndrome	Very rare	—
Other		
Otitis media	Common	Much more common in children.
Toxic shock syndrome	Rare	—
Parotitis	Very rare	—

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There are 3 major categories of tests for influenza. The first type detects influenza A only; the second detects either A or B but cannot distinguish between them; and the third type detects both influenza A and B and is subtype-specific. The influenza strain is typically determined by the local epidemiologic pattern because of the lack of specificity of most current tests.[42]

Rapid diagnostic testing currently consists of commercially available kits that detect viral influenza antigen. The majority of the currently available kits will detect influenza A and B, but not all will distinguish between the two. Fluorescent antibody testing offers relatively rapid results by direct fluorescent antibody staining, yielding results within 2 to 4 hours.

Although viral culture and RT-PCR remain the gold standards for influenza testing, both require more time and expense as well as a specialized laboratory to process the specimens. Testing modalities that allow for more-rapid processing and identification of influenza-positive patients have become the mainstay of diagnostic testing, since they provide more-immediate results and thus decrease delays in treatment and management decisions. Numerous studies support the usefulness of obtaining a positive result on rapid influenza testing in deciding whether to perform additional tests, prescribe an antibiotic or an antiviral medication, and consider additional medical management for both pediatric and adult populations.[43-49] However, as previously mentioned, during epidemics, formal testing may not be required.

The sensitivity and specificity of a given diagnostic test remain stable, but its PPV and negative predictive value (NPV) are affected by disease prevalence. This is an important factor to keep in mind when deciding whether a particular patient with an influenza-like illness should have rapid diagnostic testing performed.

When influenza prevalence is relatively low, the PPV is low and false-positive test results are more likely. By contrast, the NPV will be high and negative results more likely when influenza prevalence is low. When influenza prevalence is relatively high, the NPV is low and false-negative test results are more likely. When influenza prevalence is high, the PPV is high and positive results are more likely to be true.

In periods of low influenza activity (typically during the summer months), a rapid test will have its lowest PPV and its highest NPV and is more likely to yield false-positive results—up to 50%, in 1 study—when the disease prevalence drops below 5%.[50] Conversely, in times of peak influenza activity (eg, during an epidemic or pandemic), a rapid test will have a higher PPV and lower NPV and is more likely to produce a false-negative result.[51,52] **(See Tables 6 and 7, page 8.)**

In a prospective study of adults who presented with influenza-like illness when the prevalence of seasonal influenza was high, rapid testing was found to be no better than clinical judgment alone in making the diagnosis of influenza.[53] It may be better to reserve testing for more seriously ill patients in whom a confirmed diagnosis of influenza is more critical. In this patient population, rapid testing should always be confirmed by either viral culture or RT-PCR. Even these gold standard tests will not reliably exclude influenza virus infection 100% of the time, since the quality of the specimen and the experience of the technician can affect these assay results greatly. Thus, empiric treatment of the critically ill patient must be considered until a clear alternative etiologic explanation can be found.

Treatment

For patients with evidence of mild-to-moderate disease severity and no underlying high-risk conditions, treatment with supportive therapy alone is reasonable at all times, even with variations in disease prevalence. Antiviral therapy is best reserved for those with a more severe disease course or in whom a high-risk condition (such as extremes of age, chronic pulmonary disease, pregnancy, or immunosuppressive conditions) predicts increased morbidity and mortality resulting from an influenza virus infection. **(See Table 8, page 9.)** Early treatment with antiviral medications for patients with high-risk chronic medical conditions has been shown to reduce the rate of influenza-related complications in both children and adults.[54,55]

There are 2 primary classes of antiviral medications for influenza: adamantane derivatives and neuraminidase inhibitors. However, the FDA recently approved a new, single-dose oral antiviral medication, baloxavir marboxil (Xofluza™), which is in a new class, called the polymerase acidic endonuclease inhibitors.

The oldest class of antivirals is the adamantane derivatives: amantadine and rimantadine. The neuraminidase inhibitors are a newer class of antiviral drugs and include oseltamivir, zanamivir (Relenza™), and peramivir (Rapivab™). Oseltamivir is taken by mouth; zanamivir is inhaled orally, and peramivir is administered intravenously. Oseltamivir and zanamivir can be used for influenza prophylaxis in certain clinical situations. (See the "Chemoprophylaxis" section, page 11.)

The Neuraminidase Inhibitors

The neuraminidase inhibitors— oseltamivir, zanamivir, and peramivir—inhibit the spread of newly formed virus particles within the host cell by blocking the function of neuraminidase, a viral cell surface protein. This enzyme is necessary to cleave newly formed viral particles that are bound by their hemagglutinin surface proteins to the sialic acid receptors of the host cell. Since these medications inhibit neuraminidase, they are effective in patients infected with either type A or type B influenza virus. These drugs tend to be well tolerated; the most frequently noted side effects are oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhea.

Oseltamivir

Oseltamivir is taken orally and is currently approved for the treatment of influenza in patients of all ages. **(See Table 9, page 10.)** In a 2015 meta-analysis by Dobson et al, the intention-to-treat infected population had a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio, 0.79; 95% confidence interval [CI], 0.74-0.85; $P < .0001$). The median times to alleviation were 97.5 hours for oseltamivir and 122.7 hours for placebo groups (difference -25.2 hr; 95% CI, -36.2 to -16.0). For the intention-to-treat population, the

Table 6. Clinical Considerations of Testing When Influenza Prevalence is Low

If Influenza Prevalence is…	And Specificity is…	Then PPV is…	False-Positive rate[1] is…
Very low (2.5%)	Moderate (80%)	Very low (6%-12%)	Very high (88%-94%)
Very low (2.5%)	High (98%)	Low (39%-56%)	High (44%-61%)
Moderate (20%)	Moderate (80%)	Low (38%-56%)	High (44%-62%)
Moderate (20%)	High (98%)	High (86%-93%)	Low (7%-14%)

[1]The false-positive rate is the number of false-positives divided by the number of total positives, or 1-PPV.

Source: https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

Table 7. Clinical Considerations of Testing When Influenza Prevalence Is High

If Influenza Prevalence is…	And Sensitivity is…	Then NPV is…	False-Negative rate[2] is…
Moderate (20%)	Low (50%)	Moderate (86%-89%)	Moderate (11%-14%)
Moderate (20%)	High (90%)	High (97%-99%)	Low (2%-3%)
High (40%)	Low (50%)	Moderate (70%-75%)	Moderate (25%-30%)
High (40%)	High (90%)	High (93%-94%)	Low (6%-7%)

[2]The false-negative rate is the number of false-negatives/number of total positives, or 1-NPV.

Source: https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

estimated treatment effect was attenuated (time ratio 0.85) but remained highly significant (median difference -17.8 hr). In the intention-to-treat infected population, they found fewer lower respiratory tract complications requiring antibiotics > 48 hours after randomization (risk ratio [RR], 0.56; 95% CI, 0.42-0.75; $P = .0001$; 4.9% oseltamivir vs 8.7% placebo; risk difference, -3.8%; 95% CI, -5.0 to -2.2) and also fewer admissions to hospital for any cause (RR, 0.37; 95% CI, 0.17-0.81; $P = .013$; 0.6%, oseltamivir; 1.7%, placebo; risk difference, -1.1%; 95% CI, -1.4 to -0.3). Regarding safety, oseltamivir increased the risk of nausea (RR, 1.60; 95% CI, 1.29-1.99; $P < .0001$; 9.9% oseltamivir vs 6.2% placebo; risk difference, 3.7%; 95% CI, 1.8-6.1) and vomiting (RR, 2.43; 95% CI, 1.83-3.23; $P < .0001$; 8.0% oseltamivir vs 3.3% placebo; risk difference, 4.7%; 95% CI, 2.7-7.3).[56]

Table 8. CDC Antiviral Treatment Recommendations

- Early antiviral treatment can reduce the risk of complications from influenza (eg, pneumonia, respiratory failure, and death). Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who:
  - is hospitalized;
  - has severe, complicated, or progressive illness; or
  - is at higher risk for influenza complications.
- Persons at higher risk for influenza complications recommended for antiviral treatment include:
  - Children aged < 2 years;
  - Adults aged ≥ 65 years;
  - Persons with chronic pulmonary disease (including asthma); cardiovascular disease (except hypertension alone); renal, hepatic, hematological disease (including sickle cell disease); metabolic disorders (including diabetes mellitus); or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
  - Persons with immunosuppression, including that caused by medications or by HIV infection;
  - Women who are pregnant or post partum (within 2 weeks after delivery);
  - Persons aged < 19 years who are receiving long-term aspirin therapy;
  - American Indians/Alaska Natives;
  - Persons who are morbidly obese (ie, body-mass index ≥ 40); and
  - Residents of nursing homes and other chronic-care facilities.
- Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. When indicated, antiviral treatment should be started as soon as possible after illness onset.
- The greatest benefit is when antiviral treatment is started within 48 hours of influenza illness onset. However, antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patients when administered > 48 hours from illness onset.
- 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.

Excerpted from:
https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm

Zanamivir

Zanamivir is administered via inhalation because of its poor bioavailability. It is approved for the treatment of influenza in patients aged ≥ 7 years and for prevention of the disease in patients aged ≥ 5 years. Due to its possible association with bronchospasm, the manufacturer of zanamivir has recommended it not be used in patients with underlying reactive airway disease; however, in a multicenter randomized clinical trial, no direct causality between its use and bronchospasm was made.[57,58]

Peramivir

Peramivir is the newest drug of this class and is administered intravenously as a single dose for patients with uncomplicated influenza who have been sick for no more than 2 days. It is approved for use in patients aged ≥ 2 years. Efficacy has not yet been established in patients with influenza B; however, the benefit of a single IV dose medication in a vomiting influenza A patient has been shown to justify its cost in symptom reduction when compared to placebo or oseltamivir.[59-62]

The Adamantane Derivatives

Amantadine and rimantadine inhibit activity of the M2 protein within the influenza A virus. This protein is a transmembrane polypeptide involved in the viral replication process through its actions as an ion channel. Because the genetic sequence of this protein channel within the influenza B virus is significantly different, this class of medications is effective only for the treatment and prevention of influenza A.[63]

Though amantadine and rimantadine have similar clinical antiviral activities, their side-effect profiles and pharmacokinetics differ significantly. Amantadine clearance depends on adequate renal function, so careful dose adjustment is required for patients with renal insufficiency. This agent has also been associated with more significant central nervous system and psychiatric side effects, such as hallucinations, insomnia, headaches, dizziness, and depression—symptoms that have proved to be especially problematic in elderly patients.

Although rimantadine is primarily metabolized in the liver, it may also require dose adjustments in patients with renal insufficiency. It does not have the same degree of central nervous system activity and the associated side-effect profile as amantadine.

Baloxavir Marboxil

On October 24, 2018, the FDA approved a new orally administered, single-dose influenza antiviral drug, baloxavir marboxil (Xofluza™). A polymerase acidic endonuclease inhibitor, it is effective for treatment of influenza from type A or type B strains. The safety and efficacy of baloxavir marboxil have not been established in patients aged < 12 years or those weighing < 40 kg. Its use in pregnant and lactating patients has not been established.[64] For more information, go to: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf

Antiviral Resistance

The recent discovery of increasing mutations in the gene that encodes the M2 protein in avian influenza viral isolates has suggested the potential for human pandemics with drug-resistant strains.[65] This was a concern during the influenza season of 2005–2006, during which up to 92% of viral isolates were found

Table 9. CDC Recommendations for Antiviral Medications for Treatment and Chemoprophylaxis of Influenza

Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended For	Adverse Events
Oral oseltamivir	Influenza A and B	Treatment	Any age[1]	N/A	Adverse events: Nausea, vomiting, headache. Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemoprophylaxis	Ages ≥ 3 months[1]	N/A	
Inhaled zanamivir	Influenza A and B	Treatment	Ages ≥ 7 years[3]	People with underlying respiratory disease (eg, asthma, COPD)[3]	Allergic reactions: Oropharyngeal or facial edema, skin rash. Adverse events: risk of bronchospasm, especially in the setting of underlying airways disease; sinusitis, dizziness, and ear, nose and throat infections. Postmarketing reports of sporadic, transient neuropsychiatric events[2]
		Chemoprophylaxis	Ages ≥ 5 years[3]	People with underlying respiratory disease (eg, asthma, COPD)[3]	
Intravenous peramivir	Influenza A and B[4]	Treatment	Ages ≥ 2 years[4]	N/A	Adverse events: Diarrhea. Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemoprophylaxis	N/A	N/A	
New Drug Information					
Oral baloxavir marboxil	Influenza A and B	Treatment	Ages ≥ 12 years, weight ≥ 40 kg	N/A	FDA approved October 2018.[5] Adverse events: Diarrhea, bronchitis, headache, nausea, and nasopharyngitis
		Chemoprophylaxis	Not studied	N/A[5]	

[1]Oral oseltamivir is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in persons 14 days and older, and for chemoprophylaxis in persons 1 year and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants aged < 14 days, and for chemoprophylaxis in infants 3 months to 1 year of age, is recommended by the CDC and the American Academy of Pediatrics. If a child is aged < 3 months, use of oseltamivir for chemoprophylaxis is not recommended unless the situation is judged critical, due to limited data in this age group.

[2]Self-injury or delirium; mainly reported among Japanese adolescents and adults.

[3]Inhaled zanamivir is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in persons aged ≥ 7 years, and for chemoprophylaxis of influenza in persons aged ≥ 5 years. Inhaled zanamivir is contraindicated in patients with history of allergy to milk protein.

CDC Antiviral Drug Recommendations

[4]Intravenous peramivir is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in persons aged ≥ 2 years. Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

[5]Use in human pregnant and lactating patients has not been studied. Studies were not conducted in patients aged > 65 years, so it is unclear how this age group will respond to baloxavir. Data are limited on the pharmacokinetics of baloxavir in patients with renal and/or hepatic impairment; its use should be avoided in those patients until more data become available. For full prescribing information, go to: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf or scan the QR code at right with an enabled smartphone.

Baloxavir Marboxil Prescribing Information

Abbreviations: CDC, United States Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; FDA, United States Food and Drug Administration; N/A, not applicable.

Source: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm or scan the QR code above with a smartphone.

to have point mutations within the M2 gene, conferring resistance to the adamantane class of medications.[66] The restriction of these medications to the treatment of influenza A, the rapid emergence of drug resistance, and their side-effect profiles have limited the usefulness in clinical practice of the adamantane class of medications.[67] Two 2006 systematic reviews discouraged the primary use of these medications in the treatment and prophylaxis of influenza except in select situations when viral isolate susceptibility has been documented and determined to be resistant to the neuraminidase inhibitors.[68,69]

When the neuraminidase inhibitors were first developed and used in clinical practice, the emergence of resistant viral isolates was rare. However, continuous changes in gene sequences within the influenza viral genome have led to an increase in the number of drug-resistant viral strains. During the 2007–2008 influenza season, oseltamivir-resistant H1N1 seasonal influenza emerged globally at rates of up to 68% in some regional populations.[70] This led to a resurgence of the adamantane derivatives as the recommended primary agent in regions of the world where the rates of oseltamivir-resistant H1N1 seasonal virus isolates were high. However, the last 3 seasons of influenza demonstrated relatively low resistance to oseltamivir and the other neuraminidase inhibitors, and the CDC continues to recommend treatment with only the neuraminidase inhibitors.[61]

Cross-resistance between the recently FDA-approved antiviral drug, baloxavir marboxil, and neuraminidase inhibitors, or between baloxavir marboxil and M2 proton pump inhibitors (adamantanes), is not expected because these drugs target different viral proteins.[64]

Close, consistent monitoring of local influenza strain prevalence and susceptibility patterns is paramount. **See Table 3, page 6** for links to online information and resources to monitor influenza activity and susceptibility.

Chemoprophylaxis for Influenza

Although the CDC does not recommend seasonal or pre-exposure antiviral prophylaxis for influenza, chemoprophylaxis with oseltamivir and zanamivir can be considered for patients who:

- Are at high risk for complications and were exposed to influenza in the first 2 weeks following vaccination;
- Are at high risk for complications and cannot receive the vaccination; and/or
- Are immunosuppressed.

Chemoprophylaxis in Institutional Settings

For patients who live in institutional settings such as long-term care and skilled nursing facilities, the CDC recommends immediate antiviral chemoprophylaxis for all residents in the following circumstances:

- When there have been 2 or more ill residents, or
- 1 laboratory-confirmed positive influenza case,
- regardless of vaccination status.

The CDC further recommends that antiviral chemoprophylaxis:

- Should be given for a minimum of 2 weeks and should continue for at least 7 days after the last known case was identified.
- May be considered or offered to healthcare personnel who care for patients at high risk for complications.

For more information, go to: https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm

Antiviral Use in Pregnant Patients

According to the CDC, oseltamivir is the recommended treatment for pregnant women.[68] The use of oseltamivir as postexposure prophylaxis among household contacts had an efficacy rate of 58.5%, with a range of efficacy of 68% to 89% among direct contacts of index cases.[68] Oseltamivir also led to a statistically significant decrease in viral nasal titers as well as a reduction in secondary lower respiratory tract complications, particularly bronchitis and pneumonia.[68]

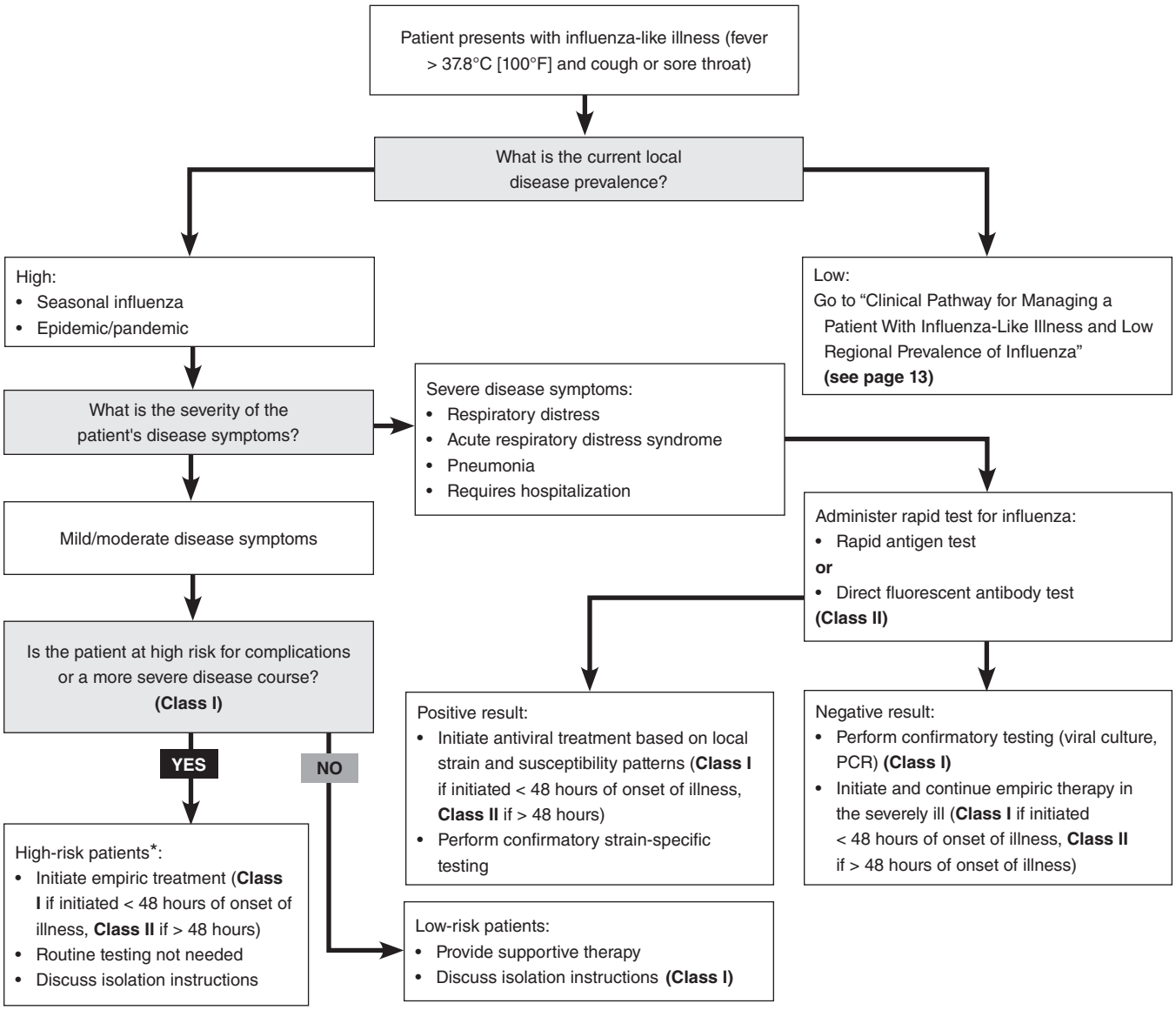
Controversies and Cutting Edge

Efficacy of Treatment With Antiviral Medications

There is some controversy regarding the cost versus benefit of antiviral medications in treating influenza, yet a growing body of evidence supports the effectiveness of these agents in decreasing symptom duration and complications. In a meta-analysis, using the time to alleviation of symptoms as the primary efficacy endpoint, oral oseltamivir resulted in an efficacy rate of approximately 73% (95% CI, 33-89) against symptomatic influenza when given in a dose of 150 mg/day.[66] Inhaled zanamivir at 10 mg/day has been found to be 62% efficacious (95% CI, 15-83).[60,61,68] Numerous studies have compared the efficacy of oral oseltamivir with IV peramivir; however, other than peramivir slightly reducing the time to alleviate fever compared to oseltamivir, there are no significant benefits other than its route of delivery and single dosing (mean difference, -7.17 hr; 95% CI, 11.00 to -3.34).[60,62]

In a 2014 meta-analysis by Muthuri et al, comparing no treatment with neuraminidase inhibitor treatment, the antivirals were associated with a reduction in mortality risk (adjusted odds ratio [OR], 0.81; 95% CI, 0.70-0.93; $P = .0024$).[71] When compared with later treatment, early treatment (within 2 days

Clinical Pathway for Managing a Patient Who Presents to the ED With an Influenza-Like Illness



*For conditions indicating high risk for a more severe disease course, see the Clinical Pathway on page 13.

Abbreviations: ED, emergency department; PCR, polymerase chain reaction.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

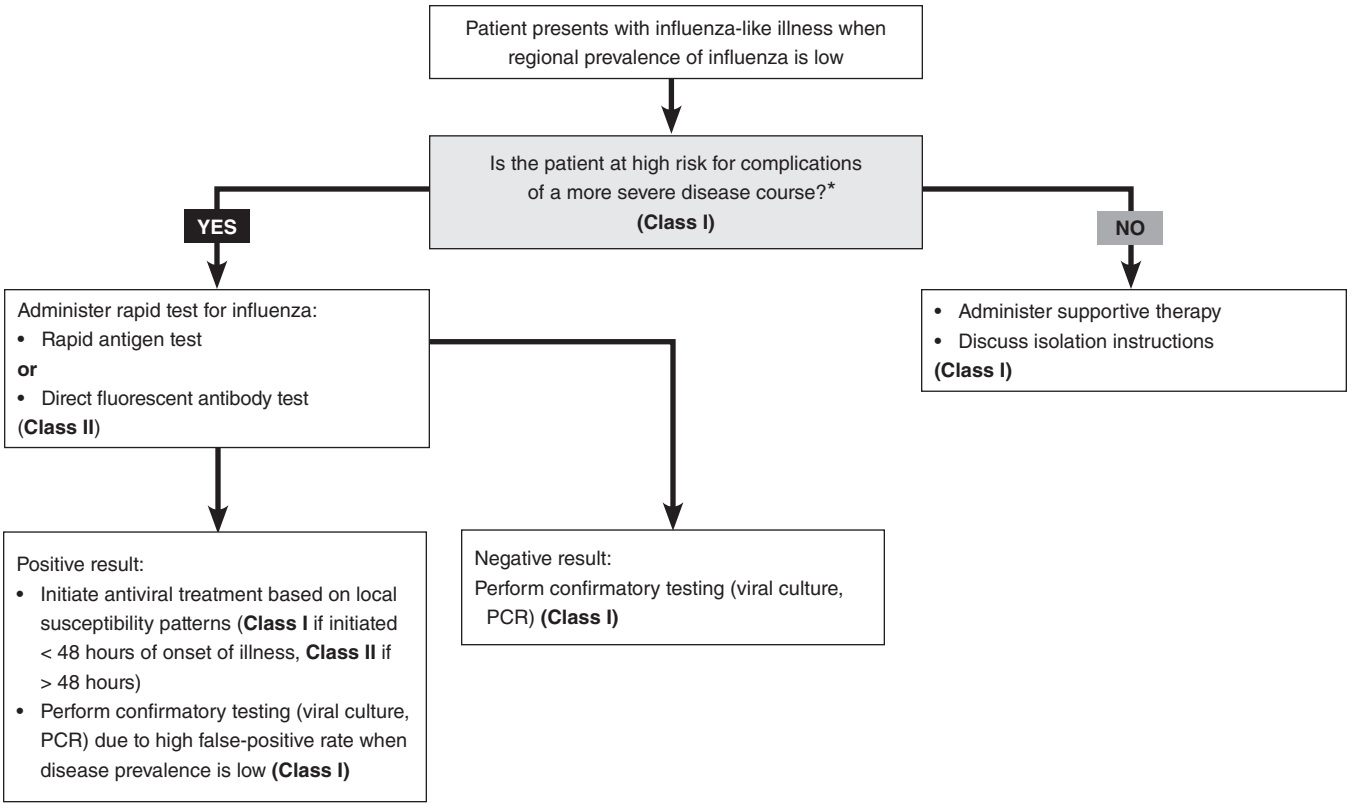
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway for Managing a Patient Who Presents to the ED With an Influenza-like Illness When There is Low Regional Prevalence of Disease



***Conditions Indicating High Risk for More Severe Disease Course**

- Age ≥ 65 years
- Age < 2 years
- Chronic pulmonary disease (eg, asthma or chronic obstructive lung disease)
- Chronic cardiovascular, renal, and/or hepatic disease
- Hematologic disease (eg, sickle cell disease)
- Metabolic disorders (eg, diabetes mellitus)
- Immunosuppression secondary to either disease (eg, HIV) or a medication
- Compromised respiratory function or other conditions that increase risk of aspiration
- Pregnancy and up to 2 weeks post partum
- Long-term aspirin therapy for chronic medical conditions in patients aged < 19 years
- Neuromuscular disorders, seizure disorders, or other cognitive dysfunction that may compromise handling of respiratory secretions

Abbreviations: ED, emergency department; PCR, polymerase chain reaction.

For Class of Evidence Definitions, see page 12.

of symptom onset) was associated with a reduction in mortality risk (adjusted OR, 0.48; 95% CI, 0.41-0.56; $P < .0001$). Early treatment versus no treatment was also associated with a reduction in mortality (adjusted OR, 0.50; 95% CI, 0.37-0.67; $P < .0001$). These associations with reduced mortality risk were less pronounced and not significant in children.[71] They further found that there was an increase in the mortality hazard rate with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted hazard ratio [HR], 1.23; 95% CI, 1.18-1.28; $P < .0001$ for the increasing HR with each day's delay).[71] A similar review of neuraminidase inhibitor therapy in children aged < 12 years found that the duration of clinical symptoms was reduced by 36 hours among previously healthy children taking oseltamivir and by 30 hours among those taking zanamivir.[8,9,27]

Therefore, based on the best available evidence, use of neuraminidase inhibitors is associated with decreased duration of symptoms and complications, especially if started within 2 days of symptom onset, and is thus recommended, especially in the elderly and in patients with comorbidities.

Disposition

Final disposition of the patient with a suspected or confirmed influenza infection will depend on many clinical factors, including (but not limited to) respiratory status and work of breathing, oxygen saturation, age, comorbid medical conditions, and reliability of obtaining follow-up care. Admission to the hospital may be needed to manage not only the primary viral infection but also complications that may arise. For patients who can be safely discharged from the ED, the emergency clinician must engage with the patient in shared decision-making regarding the risks and benefits of the available treatments, encourage a follow-up visit with the patient's primary care provider, and discuss specific reasons for return to the ED. The CDC recommends that patients stay home for at least 24 hours after their fever has dissipated.

Time- and Cost-Effective Strategies

- Be familiar with the available Internet-based public health resources that can inform the clinician about local influenza strain prevalence as well as strain-specific medication susceptibilities.
- The clinical presentation of influenza is nonspecific, and not every patient requires formal testing. Reserve formal diagnostic testing for patients who are severely ill or during periods of low disease prevalence.
- Patients with severe illness who require hospitalization should be tested to help guide treatment and management decisions. In times of high disease prevalence, many patients who are at high risk for complications and a more severe disease course can be treated empirically without formal diagnostic testing. Many patients who are otherwise healthy and at low risk for disease complications can be treated with supportive therapy.
- Testing is appropriate in times of low disease prevalence, since the signs and symptoms of influenza can mimic many other upper respiratory infections. For patients with an influenza-like illness in which influenza testing and antiviral treatment are not warranted, a shared-decision strategy with close follow-up with the patient's primary care provider are important, as is a discussion of reasons to return to the ED.
- Prescribe antiviral medications for patients who are more severely ill or at high risk for a more severe disease course. In healthy patients, antiviral medications can be prescribed on the basis of clinical judgment if treatment can be initiated within 48 hours of symptom onset.
- Document clearly the presenting signs and symptoms as well as any past medical history or smoking history that could increase the risk of more-severe complications from influenza, especially if the choice is made not to treat.
- Careful ED infection control and/or vaccination are important for the protection of both patients and healthcare personnel and will reduce absenteeism among staff.
- Influenza virus infection is associated with greater morbidity and mortality in children and adults with chronic diseases such as asthma and chronic obstructive pulmonary disease.[72,73] This increased morbidity risk supports the recommendation for vaccination of very young children even in the absence of comorbid medical conditions.[74]

Summary

Because influenza infections can present with a wide range of nonspecific clinical signs and symptoms and numerous possible complications, emergency clinicians must be keenly alert to this possible diagnosis. A knowledge of the local seasonal prevalence of influenza as well as the specific strains circulating within a particular region are crucial for appropriate diagnostic and treatment decisions and will help to limit unnecessary testing when empiric therapy would be more appropriate. Such considerations will improve efficiency in the ED while still ensuring that patients who are at increased risk for a more severe disease course will receive timely and appropriate therapy. With the evolution of new influenza strains through genetic reassortment, combined with

the globalization of disease, the world is at greater risk than ever before for pandemics. Today's emergency clinician must be both an epidemiologist and a clinician to recognize emerging pathogens and make the complex shared decisions required for individual and community health.

Case Conclusions

A colleague reminds you that the CDC has guidelines for the evaluation and treatment of patients who present with an influenza-like illness. A visit to the CDC website confirms your impression that your area is experiencing an epidemic of influenza, with a disease prevalence well above that of the typical seasonal outbreak. You note that children aged < 2 years are at increased risk for a more severe disease course if infected with influenza, and that an influenza A strain sensitive to oseltamivir is most prevalent in your region. Therefore, you decide that initiating treatment with this antiviral agent would be appropriate for your 20-month-old patient, in addition to amoxicillin for his secondary otitis media. You are interested to learn that this ear infection is a common secondary complication of influenza in the pediatric population.

Delving further into the CDC website, you find that the false-negative rate with rapid antigen testing for influenza can be significant, especially when disease prevalence is high, as it is in your region. Based on this information, you decide to start your more seriously ill 32-year-old patient on oseltamivir 75 mg twice a day for 5 days despite the initially negative result reported by the hospital laboratory.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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Risk Management Pitfalls For Managing Influenza in the Emergency Department (Continued on page 17)

1. **"The fever was low-grade; I thought the baby just had a cold."**
   The presenting signs and symptoms of influenza infection are nonspecific, and a diagnosis based on clinical presentation alone becomes less accurate in children aged < 3 years. Although many children will experience a mild disease course and can be managed with supportive therapy, patients aged < 2 years are at high risk for a more severe clinical course. Be vigilant and have a high index of suspicion for possible influenza infection in high-risk populations, especially when disease prevalence is high.

2. **"The patient had an infiltrate on chest x-ray, so bacterial pneumonia appeared to be the clear diagnosis."**
   Numerous secondary complications can stem from a primary influenza infection. When addressing and treating these complications, do not overlook the possibility of a primary influenza infection and the need for medical management. In certain clinical situations, treatment with antiviral medications as well as antibacterial medications may be indicated.

3. **"I thought I would just let it run its course."**
   Many previously healthy people can be treated with supportive therapy alone; however, you must be aware of the numerous risk factors that are likely to result in a more severe disease course. For patients deemed well enough to be safely discharged from the ED, utilize shared decision-making with the patient and ensure a follow-up strategy is in place.

4. **"It is the summer. Influenza occurs in the fall and winter, so I do not need to be concerned about it at this time of the year."**
   Although influenza certainly exhibits seasonal fluctuations and regional outbreaks, the disease can occur year-round. Testing and possible empiric treatment of patients with an influenza-like illness are influenced by the regional prevalence of the disease, so monitor medical agencies that track the prevalence of influenza on a regional and national level, such as the CDC.

5. **"My patient is pregnant and has influenza. The side-effect profile of antiviral medications concerns me, so I feel better treating her with supportive care."**
   Pregnancy is a risk factor for a more severe disease course during an influenza infection. Initial CDC epidemiologic data from the last 10 influenza seasons indicate that some of the highest rates of morbidity and mortality are among pregnant women, which confirms the necessity of antivirals in this population.

6. **"Medical knowledge has advanced over the past few decades, and now we have great antiviral medications. I do not need to worry about a devastating influenza infection today."**
   While it is true that medical science has advanced considerably since the pandemic of 1918, influenza remains a significant threat. The ability of the virus to undergo genetic reassortment allows for the rapid development of new influenza strains to which the population has little or no immunity. Resistance to antiviral medications has been known to develop quickly for certain influenza strains and appears to be a rapidly increasing concern over time.

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Risk Management Pitfalls For Managing Influenza in the Emergency Department (Continued from page 16)

7. **"Flu is everywhere. I don't have the time to consult the CDC website. I will just give oseltamivir to my patient and be done with it."**
Even in times of epidemic influenza infection, numerous strains can be circulating at a given time within a particular region. In past epidemics, there have been reports of influenza strains resistant to oseltamivir. Thus, without knowing the prevalence of local strains, one might mistakenly choose an antiviral agent that will prove less effective on those strains. Treatment with more than 1 agent may even be indicated in some regions until more formal strain-specific diagnostic testing can be undertaken. Since certain medications are effective against only influenza type A, the local prevalence of any type B influenza should be determined in order to select the appropriate drug therapy.

8. **"I see so many patients in the ED every hour. I can't possibly wear a mask and wash my hands for every patient. Plus, I must have been exposed to influenza 100 times already."**
Maintaining effective infection control is crucial to protecting not only other patients in the ED but also healthcare staff. Patients suspected of having influenza require appropriate isolation, and strict hand-washing as well as personal protective equipment (eg, masks) are necessary to protect healthcare staff who are in direct contact with patients. The Strategic Plan for Management of an Influenza Outbreak, published by the American College of Emergency Physicians, is a good resource to ensure the highest level of preparedness on the part of the ED staff as well as their ability to handle a surge in patient volume that can be expected during a disease pandemic.

9. **"The WHO has declared a pandemic. I feel better giving all my suspected influenza patients antiviral therapy, since I don't want anyone to have a poor outcome."**
Declaration of a pandemic does not necessarily mean that the particular infectious organism is more virulent. It merely recognizes that the disease is spreading worldwide. Pandemics can occur during both mild and more severe disease outbreaks.

10. **"I performed a rapid influenza test and it was negative, so I am safe sending my patient home on supportive therapy alone."**
Numerous forms of testing are available to detect influenza infection. Rapid diagnostic tests help guide clinicians in their immediate management decisions, but the quality of the specimen and the skill of the technician performing the assay can influence results. Certain rapid assays are specific for influenza type A, so knowing which strains are circulating locally is important. In times of high disease prevalence, the chance that a given patient with an influenza-like illness actually has the disease is increased, as are the number of false-negative results obtained from rapid diagnostic testing. At such times, empiric therapy based on clinical presentation alone is advised for patients at high risk. In more severely ill patients, viral culture and PCR testing are indicated when the initial rapid test yields a negative result.

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1. **Declaration of an influenza pandemic implies that:**
   a. Influenza has been isolated on every major continent
   b. The strain is more virulent then the typical strain of influenza
   c. There are more cases of the disease occurring over a worldwide distribution than would typically be expected
   d. There is no vaccine available for that particular strain of influenza

2. **Which type of antigen variation causes radical changes that cause reassortment of the viral genes, leading to loss of immunity and epidemics and pandemics?**
   a. Antigenic drift
   b. Antigenic shift

3. **Currently, seasons dominated by which influenza virus strain are associated with the highest rates of influenza cases, hospitalizations, and deaths?**
   a. H1N1
   b. H2N2
   c. H3N2

4. **Which of the following symptoms is NOT included in the CDC clinical presentation definition for an "influenza-like illness?"**
   a. Muscle aches
   b. Cough
   c. Sore throat
   d. Fever > 37.8°C (100°F)

5. **Which of the following symptoms is NOT among the most common for influenza in adult patients?**
   a. Cough
   b. Sneezing
   c. Nasal congestion
   d. Fatigue

6. **Regarding rapid influenza diagnostic testing, which of the following is TRUE?**
   a. Rapid testing may increase the need for additional ancillary testing
   b. Rapid testing may increase antibiotic use
   c. Rapid testing may decrease delays in treatment and management decisions
   d. Rapid testing is more likely to yield false-negative results during periods of low influenza activity

7. **Which of the following is NOT a common complication of an influenza infection?**
   a. Otitis media
   b. Guillain-Barré syndrome
   c. Bacterial pneumonia
   d. Acute bronchitis

8. **Which of the following can be used for chemoprophylaxis in a child aged 1 year?**
   a. Oseltamivir
   b. Beloxavir marboxil
   c. Peramivir
   d. Zanamivir

9. **A severely ill pregnant patient is hospitalized with confirmed influenza, but the local strain-specific epidemiologic and culture data are not yet available. Which antiviral (if any) should be prescribed?**
   a. Oseltamivir
   b. Beloxavir marboxil
   c. Amantadine
   d. An antiviral is not recommended

10. **Which of the following is NOT a patient group at risk for a more severe disease course during an influenza infection?**
    a. A child aged < 2 years
    b. A pregnant patient at 30 weeks' gestation
    c. A patient who has had recent surgery
    d. A patient with a history of asthma

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this article, you should be able to: (1) discuss the epidemiology and spread of the strains and subtypes of influenza, (2) describe when to consider antiviral drug treatment for influenza based on clinical presentation alone and when more formal testing is indicated, (3) list the factors that place a patient at higher risk for a more severe disease course, (4) list the testing modalities available for influenza diagnosis and their accompanying deficiencies, and (4) identify the antiviral agents available for influenza, their pharmacologic effects, and how to select the best agent for a particular patient in a particular location.

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