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Clinical Review



CLINICAL MIMICS: AN EMERGENCY MEDICINE–FOCUSED REVIEW OF INFLUENZA MIMICS

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Abstract—Background: Influenza viruses are a significant cause of morbidity and mortality in the United States. Given the wide range of symptoms, emergency physicians must maintain a broad differential diagnosis in the evaluation and treatment of patients presenting with influenza-like illnesses. **Objective:** This review addresses objective and subjective symptoms commonly associated with influenza and discusses important mimics of influenza viruses, while offering a practical approach to their clinical evaluation and treatment. **Discussion:** Influenza-like symptoms are common in the emergency department (ED), and influenza accounts for > 200,000 hospitalizations annually. The three predominant types are A, B, and C, and these viruses are commonly transmitted through aerosolized viral particles with a wide range of symptoms. The most reliable means of identifying influenza in the ED is rapid antigen detection, although consideration of local prevalence is required. High-risk populations include children younger than 4 years, adults older than 50 years, adults with immunosuppression or chronic comorbidities, pregnancy, obesity, residents of long-term care facilities, and several others. The Centers for Disease Control and Prevention recommends treatment with neuraminidase inhibitors in these populations. However, up to 70% of patients with these symptoms may have a mimic. These mimics include infectious and noninfectious sources. The emergency physician must be aware of life-

threatening mimics and assess for these conditions while beginning resuscitation and treatment. **Conclusions:** The wide range of symptoms associated with influenza overlap with several life-threatening conditions. Emergency physicians must be able to rapidly identify patients at risk for complications and those who require immediate resuscitation. Published by Elsevier Inc.

Keywords—influenza; mimic; viral illness; upper respiratory infection; viral syndrome

INTRODUCTION

Emergency physicians play a significant role in the evaluation, diagnosis, and treatment of viral respiratory illnesses. Fever, headache, cough, and complaints related to the throat are among the 10 most commonly cited reasons for patient presentation to United States (US) emergency departments (EDs) (1–3). From 2007 to 2009, approximately 1.3 million individuals experiencing the symptoms mentioned were assigned a formal diagnosis of influenza by an emergency physician (1–4). Each year, nearly 220,000 patients require hospitalization secondary to influenza; an infection with a mortality rate of 1.4 deaths per 100,000 laboratory-confirmed cases (5,6).

Influenza A, B, and C, named for their respective viral surface proteins, are single-stranded ribonucleic acid viruses belonging to the *Orthomyxoviridae* family (7–9).

This review does not reflect the views or opinions of the United States government, Department of Defense, or United States Air Force.

While all of the influenza viruses possess the capability for human infectivity, influenza types B and C are primarily responsible for the majority of illness observed in the human population (8,9). Of the influenza viruses, only influenza A (commonly affecting birds, horses, swine, and dogs) is characterized by subtype based on the composition and morphology of its envelope glycoproteins (7,8).

Influenza viruses are unique in their ability to generate antigenic variability. Minor (antigenic drift) and major (antigenic shift) genomic changes are responsible for several historical and recent influenza epidemics and pandemics (7–9). Given the socioeconomic cost associated with influenza infection (annual direct costs of care estimated as \$4.6 billion, with approximately \$7 billion lost to sick days/productivity), primary prevention remains a significant public health concern (10). Risk factors predisposing to a severe clinical course include extremes of age, numerous medical comorbidities, and pregnancy; therefore, the Centers for Disease Control and Prevention (CDC) has published recommendations for influenza vaccination, as detailed in Table 1 (11,12).

DISCUSSION

Influenza is a respiratory virus primarily transmitted by aerosolized viral particles. Infection by influenza A subtypes can occur through direct contact with an infected animal, exposure to contaminated environment, or ingestion of inadequately prepared food stuffs (7). Upon failure of host immunologic defenses (immunoglobulin A secretory antibody and mechanical respiratory mucociliary clearance), influenza viruses invade columnar respiratory epithelium, triggering a molecular cascade responsible for the inactivation of host-cell protein synthesis (9,13,14). Local destruction of respiratory epithelium, resulting in the release of pro-inflammatory

cytokines, in addition to viral invasion of polymorphonuclear leukocytes, lymphocytes, and monocytes, are responsible for systemic symptoms (9,15). Table 2 discusses the affected systems in infection.

Signs of Influenza

Signs and symptoms of influenza commonly begin after a 1- to 2-day incubation period and are highly variable (7–10). The majority of adolescent and adult patients present with complaints of fever, headache, myalgias, malaise, anorexia, rhinorrhea, pharyngitis, cough, and chest discomfort (9,10). Abdominal pain, nausea, and emesis are also commonly reported among the pediatric population (15). At the extremes of age, influenza can manifest as malaise, lethargy, or altered mental status (9,13).

While symptoms of influenza may be caused by a number of respiratory viruses (respiratory syncytial virus, parainfluenza virus, adenovirus, rhinovirus, and coronavirus), in the setting of a local outbreak, the accuracy of clinical diagnoses in healthy adolescent and adult patients approximates 80%–90% (9,23,24). It is recommended that confirmatory testing be performed in all populations at high risk for complications secondary to infection (see Table 1) and in closed settings in which an influenza outbreak is suspected (e.g., long-term care facilities, inpatient treatment centers) (9,25).

Methods for influenza detection include antigen detection (rapid influenza diagnostic tests [RIDTs]), direct immunofluorescence, reverse transcription polymerase chain reaction (RT-PCR), viral culture, and serology (9,26). Ideally, samples should be obtained within 4–5 days after the onset of symptoms, before the decline in viral replication and shedding (9). Processing time varies according to laboratory and manufacturer. The majority of RIDTs provide results within approximately

Table 1. Centers for Disease Control and Prevention's Recommendations for Influenza Vaccination (11)

Populations at risk for influenza complications in whom vaccination should be prioritized

- Children \geq 6 months of age to 4 years (59 months)
- Adults \geq 50 years of age
- Individuals with chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Individuals who are immunosuppressed
- Women who are or will be pregnant during influenza season and up to 2 weeks postpartum
- People ages 6 months to 18 years receiving long-term aspirin therapy and might be at risk for Reye syndrome after influenza infection
- Residents of nursing homes or long-term care facilities
- American Indians/Alaska Natives
- The super obese (body mass index $>$ 40)
- Health care personnel
- Caregivers of children $<$ 5 years and adults \geq 50 years of age

Populations in whom caution must be utilized

Severe egg allergy: Should be vaccinated in a medical setting and supervised by a health care professional

History of Guillain-Barré syndrome associated with vaccination: physician discretion advised

Table 2. Organ System Effects of Influenza

Organ System	Influenza Pathophysiology
Respiratory	Most common system affected. Destruction of respiratory epithelium by the influenza virus results in edema of the tracheobronchial tree (9,15,16).
Neurologic	Influenza infection can result in direct damage to the thalamus, tegmentum, or cerebellar medulla, resulting in encephalopathy, seizures, or coma. Cellular dysfunction in the setting of viral-associated apoptosis has also been associated with myelitis, Guillain-Barré syndrome, and encephalitis. Reye syndrome can occur in the setting of aspirin administration (9,17).
Cardiovascular	Pericarditis and myocarditis are uncommonly associated with influenza A and B infections (9,18).
Gastrointestinal	Patients with influenza can experience emesis and diarrhea. Although the pathophysiology of this infectious manifestation is poorly understood, researchers hypothesize a role for the hematogenous spread of infected lymphocytes (19).
Hematologic	Leukocytosis is a common cell-mediated immune response to influenza infection. In patients with a white blood cell count >15,000/mm ³ (15 × 10 ⁹ /L) with or without a left shift, pneumonia, or secondary bacterial infection should be suspected (20,21).
Musculoskeletal	Myositis and myoglobinuria are frequently observed in the pediatric population and associated with elevated serum creatinine phosphokinase levels (9,22).

15 min, with a reported sensitivity of 50%–70% and specificity > 90% (9,26). Positive and negative predictive values of RIDTs should be interpreted with respect to the local prevalence of influenza infection and patient presentation. False negatives are likely to occur at the height of the influenza season, when prevalence is high. If diagnosis is likely to alter clinical decision making, the CDC recommends confirmation of a negative RIDT with RT-PCR (27).

Direct immunofluorescence testing, RT-PCR, and viral culture require clinical laboratory handling, with processing time ranging from 1–8 h (direct immunofluorescence and RT-PCR) to 3–10 days (rapid viral culture and traditional viral culture) (9,26). While individual sensitivities of the 26 Food and Drug Administration–approved RT-PCR assays vary, several studies have demonstrated the superiority of RT-PCR in the detection

of influenza viruses, making it the gold standard for diagnostic evaluation (28–30). Serologic testing allows for the retrospective confirmation of influenza infection, rendering it of little diagnostic utility in the emergency setting (9).

TREATMENT RECOMMENDATIONS

In the majority of immunocompetent individuals, influenza is self-resolving and does not require treatment (9). In persons who are at high risk for influenza complications, however, initiation of antiviral therapy can significantly reduce morbidity and mortality (9,30). Populations in which antiviral treatment is recommended are detailed in Table 1 (31). Double-blinded, placebo-controlled studies of influenza antiviral agents reported a mean reduction in febrile influenza

Table 3. Recommendations for the Treatment and Chemoprophylaxis of Influenza (31)

Antiviral	Delivery Method	Recommendations for Use	Not Recommended for Use	Adverse Effects
Oseltamivir (Tamiflu®)	Per os	Treatment: age ≥ 14 days* Chemoprophylaxis: age ≥ 3 months*	Not applicable	Nausea and emesis. Post-marketing surveillance: rare cutaneous reactions and transient neuropsychiatric events.
Zanamivir (Relenza®)	Inhalation	Treatment: age ≥ 7 years Chemoprophylaxis: age ≥ 5 years	Persons with underlying respiratory diseases (asthma, chronic obstructive pulmonary disease). Contraindicated in persons with a history of allergy to milk protein.	Allergic reactions: oropharyngeal or facial edema. Adverse effects: diarrhea, nausea, sinusitis, bronchitis, headache, and ear, nose, and throat infections.
Peramivir (Rapivab®)	Intravenous	Age ≥ 18 years	Not applicable	Diarrhea. Post-marketing surveillance: rare cutaneous reactions and transient neuropsychiatric events.

* Food and Drug Administration–approved indication. The use of oral oseltamivir in the treatment of influenza in infants < 14 days old and chemoprophylaxis in infants 3 months to 1 year of age is recommended by the Centers for Disease Control and Prevention and American Academy of Pediatrics.

Table 4. Infectious Mimics of Influenza

Patient Presentation	Clinical Condition	Infectious Etiologies	
		Diagnosis	Treatment
Hemodynamic instability or altered mental status	Sepsis (43–45)	<ul style="list-style-type: none"> • Suspected or identified infection in patients meeting two or more of the following Systemic Inflammatory Response Syndrome (SIRS) criteria: <ul style="list-style-type: none"> • Temperature > 38.0°C or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or PCO₂ < 32 Torr • White blood cell count (WBC) > 12,000/mm³ or < 4000 per mm³ or > 10% immature forms • Patient probability of mortality may be assessed with the Sequential Organ Failure Assessment (SOFA) scoring system. The quick SOFA (qSOFA) criteria are utilized to identify those patients who require further evaluation for multi-organ dysfunction. qSOFA criteria include the following: <ul style="list-style-type: none"> • Respiratory rate ≥ 22 breaths/min • Altered mentation • Systolic blood pressure ≤ 100 mm Hg 	<ul style="list-style-type: none"> • Obtain i.v. access and initiate diagnostic studies as appropriate: complete blood count (CBC), basic metabolic panel, urinalysis, chest x-ray study (CXR), blood cultures, and lactate. • Administer a fluid bolus to augment preload and improve peripheral perfusion. • If sepsis is suspected, broad-spectrum antimicrobials should be initiated (45).
	Dyspnea or chest pain	<p>Pneumonia (46,47)</p> <ul style="list-style-type: none"> • Predominant clinical findings include cough, dyspnea, chest pain, sputum production, and fever. • Patients with medical comorbidities (diabetes, congestive heart failure, chronic obstructive pulmonary disease), and those who are immunosuppressed have an increased likelihood for the development of pulmonary infections (46). • Evaluate for health care–associated pneumonia (more likely to be caused by multi-drug–resistant pathogens) (47). <p>Pericarditis (48–50)</p> <ul style="list-style-type: none"> • Typical clinical manifestations include chest pain, pericardial friction rub, electrocardiogram (ECG) changes, and pericardial effusion (49). • Viruses are the most common etiology in adults (Coxsackie viruses, echoviruses, adenoviruses, influenza viruses) (48). • Bacterial pericarditis disproportionately affects children and most commonly occurs secondary to hematogenous spread (<i>Staphylococcus aureus</i>, <i>Haemophilus influenzae</i>, and <i>Neisseria meningitidis</i>) (50). <ul style="list-style-type: none"> • Pediatric patients with bacterial pericarditis commonly present with hemodynamic instability secondary to sepsis. • Obtain ECG to evaluate for characteristic findings (diffuse PR depression with ST elevation). • A troponin level should be obtained to rule out concomitant myocarditis. <p>Infectious endocarditis (IE) (51–53)</p> <ul style="list-style-type: none"> • Patients present with fever, fatigue, anorexia, dyspnea, chest pain, and myalgias. Hematuria and neurologic manifestations less frequently. • Occurs most commonly in patients > 65 years of age (incidence in the United States: 20.4 cases per 100,000); patients with congenital heart defects, and i.v. drug abusers (51). 	<ul style="list-style-type: none"> • Evaluate and address serious respiratory compromise (use of accessory muscles, sternal retraction, nasal flaring, hypoxia). • Evaluate for signs and symptoms consistent with sepsis and manage as appropriate. • Evaluate for signs and symptoms consistent with acute respiratory distress syndrome and manage as appropriate. • Initiate antimicrobial therapy. • Viral pericarditis: nonsteroidal anti-inflammatory drugs are first-line therapy and are generally continued from 1–2 weeks post diagnosis. • Bacterial pericarditis: likely to present with systemic illness and decreased myocardial function. Initiate broad-spectrum antibiotics and admit for further evaluation and treatment. • Initiate broad-spectrum parenteral antibiotic therapy; patients require admission for evaluation and treatment. <ul style="list-style-type: none"> • Transthoracic echocardiogram (TTE) should be performed as a noninvasive screening technique (52): • Prosthetic valve or intracardiac device: poor quality TTE or positive TTE requires transesophageal echocardiography (TEE).

- *Staphylococcus* (acute presentation: symptoms days to 6 weeks) and *Viridans streptococcus* (subacute/chronic presentation: symptoms > 6 weeks to months) most common pathogens.
 - *Enterococcal* organisms up to 20% of cases (51).
 - Polymicrobial infection < 2% of all IE cases (51).
 - History should include queries regarding conditions predisposing to IE:
 - Palliative conduits, shunts, unrepaired congenital heart defect (CHD).
 - Repair of a CHD with a prosthetic material within the previous 6 months.
 - Residual defects in a repaired CHD.
 - Transplanted heart in which valvulopathy develops.
 - Previous IE.
 - Diagnosis: Duke Criteria (Sensitivity 66%–100%) (52).
 - Major criteria:
 - Positive blood cultures: for organisms known to cause IE from two separate cultures, or persistently positive findings for organisms known to cause IE (*Viridans streptococci*, *Streptococcus bovis*, *S aureus*, enterococci and HACEK [*Haemophilus*, *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella*] species).
 - Blood cultures must be drawn; all three cultures must be positive (the first and last should be drawn at least 1 h apart) (52).
 - A single positive culture for *Coxiella burnetii*.
 - Evidence of endocardial involvement.
 - Positive echocardiogram (intracardiac mass, abscess, new partial dehiscence of a prosthetic valve, new valvular regurgitation).
 - Minor criteria:
 - Fever (38.0°C)
 - Condition predisposing to IE (i.v. drug abuse, CHD).
 - Vascular phenomenon (arterial embolus, septic pulmonary infarct, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions).
 - Immunologic phenomenon (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor).
 - Microbiologic evidence (positive blood culture, but does not meet major criteria or provide serologic evidence of active infection with IE-causing organism).
 - Diagnostic studies: three sets of venous blood cultures obtained over 24 h, echocardiography, histologic analysis of endomyocardial tissue.
 - Ancillary studies: CBC, comprehensive metabolic panel, C-reactive protein (CRP), troponin, ECG, and CXR. Computed tomography (CT) and magnetic resonance imaging (MRI) may be considered (51).
 - Meningitis and encephalitis may present with fever, neck stiffness (lower sensitivity in the elderly), headache, myalgias, or change in mental status (54).
- TTE negative with a high suspicion of IE: requires TEE.
- TTE negative with a low clinical suspicion of IE: no further evaluation.
- If initial TEE is negative but suspicion for IE remains: repeat TEE within 7–10 days.
- In the setting of bacterial meningitis, empiric antibiotic therapy should not be delayed for imaging or LP.

Headache,
back pain,
or myalgias

Central nervous
system infection
(CNS) (54–57)

Table 4. Continued

		Infectious Etiologies	
Patient Presentation	Clinical Condition	Diagnosis	Treatment
		<ul style="list-style-type: none"> • Pediatric patients: Evaluate for hypothermia, hypoglycemia, poor feeding, seizures, irritability, increased general body tone, bulging fontanelles (55). • Pathogens of adult bacterial meningitis: <i>Streptococcus pneumoniae</i>, <i>N. meningitidis</i>, <i>H. influenzae</i> type B, <i>Listeria monocytogenes</i>. Pediatrics < 2 months of age: <i>Group B Streptococcus</i> (56). • Etiologies of viral meningitis: Enteroviruses (50%–75%) (54). • Etiologies of encephalitis: herpes family viruses, varicella zoster virus, arboviruses (La Crosse virus, St. Louis virus, West Nile virus, Western Equine virus, Eastern Equine virus) (55): <ul style="list-style-type: none"> • Herpes simplex virus (frontal and temporal lobe involvement): taste and smell hallucinations, seizures; syndrome of inappropriate antidiuretic hormone secretion (SIADH). • West Nile (anterior horn cell involvement): tremors, myoclonus, parkinsonism, flaccid paralysis. • La Crosse (cortical areas involved), most commonly in school-aged children; late spring to fall: seizures, disorientation, focal neurologic signs. • St. Louis (substantia nigra, pons, thalamus, cerebellum involved): tremor, opsoclonus, nystagmus, ataxia, SIADH and urinary symptoms (dysuria, urgency, incontinence). • Eastern Equine (basal ganglia, thalamus, brainstem involvement), primarily in summer months: seizures. • CT before lumbar puncture (LP): immunosuppressed, history of CNS disease, new-onset seizure, focal neurologic deficit, papilledema, altered mental status. • Laboratory studies: <ul style="list-style-type: none"> • LP • CBC: elevated WBC with left shift (unless immunosuppressed) • Electrolytes: hyponatremia in 30% of bacterial meningitis cases • Lactate: evaluation for SIRS/sepsis, early goal-directed therapy • Blood cultures: positive in 50%–75% of patients with bacterial meningitis if obtained before antibiotic therapy (57) • Spinal epidural abscess may present with fever, back pain, myalgias, and focal neurologic deficit. Hematogenous spread of infection is the most common etiology (<i>S. aureus</i> indicated in 60%–90% of cases). Discitis or vertebral osteomyelitis is an associated finding in 80%–100% of patients. <ul style="list-style-type: none"> • Adults: often localized to the thoracic spine (50%–80% of cases) (57). • Pediatrics: abscesses localize to the cervical and lumbar spine. 	<ul style="list-style-type: none"> • Dexamethasone should be given to all patients > 1 month of age to reduce neurologic sequelae (0.5 mg/kg, max 10 mg per dose every 6 h).⁵⁵ • Consider antibiotic prophylaxis for close contacts. • Acyclovir if suspicion for viral encephalitis. • Epidural abscess: broad-spectrum antibiotic therapy. <ul style="list-style-type: none"> • Consult neurosurgery as soon as the diagnosis is suspected.

Mosquito-borne illnesses (58–64)

- Risk factors: spinal surgery, instrumentation, trauma (10%–30% of cases), advanced age, pregnancy, sickle cell disease, i.v. drug abuse, diabetes, immunosuppression (57).
- Laboratory studies:
 - Fluoroscopy-guided LP with Gram stain and cell culture.
 - CBC: the absence of leukocytosis does not rule out an epidural abscess.
 - Erythrocyte sedimentation rate: commonly elevated; may be falsely low in the setting of hyperglycemia, systemic corticosteroid therapy and in the setting of high-dose aspirin (57).
 - CRP: often elevated.
 - Blood cultures: If positive, cultures reveal the etiology of infection.
- Diagnostic imaging: MRI of the spine with and without contrast.
- Dengue, Yellow fever, and Zika viruses are arboviruses commonly transmitted by the mosquitos of the *Aedes* genus (58).
 - Dengue: Most prevalent of the arboviruses. Mortality rate 20% if untreated (59). In the United States, outbreaks reported in Louisiana, Hawaii, Florida, and Texas (60).
 - 50% of patients present with fever, myalgias, arthralgias, headache, and rash. Approximately 5% progress to develop a severe hemorrhagic diathesis, end-organ dysfunction, and hemodynamic collapse (58).
 - Laboratory studies: anemia, thrombocytopenia, transaminitis, elevated lactate. Polymerase chain reaction (PCR) and serology utilized for definitive diagnosis.
 - Yellow fever: Endemic to Africa and Central America, rarely occurring in unvaccinated American travelers (61).
 - Presentation ranges from subclinical infection to systemic disease (fever, jaundice, hemorrhage, and renal failure).
 - Laboratory studies: anemia, thrombocytopenia, transaminitis. Serology utilized for definitive diagnosis.
 - Transaminitis is proportional to the severity of the disease: peak observed early in the second week of illness in patients who recover (61).
 - Zika virus: Flavivirus closely related to dengue. Unlike other arboviruses, Zika virus may also be transmitted through sexual contact and bodily secretions. Initially isolated to Brazil and Micronesia, local outbreaks have been reported in Florida. Symptomatic patients (only 20% of those infected) may report headache, arthralgias, and fever. A strong association between maternal Zika virus infection and fetal malformations has been identified (61). Diagnosis: PCR and serology.
 - Chikungunya: Prevalent throughout Africa and Asia, the first case identified in the United States was reported in Florida. Patients are most often symptomatic and report high-grade fevers with disabling arthralgias. Migratory polyarthritis with joint effusions (wrists, fingers, ankles) is common. Vesiculobullous eruptions and ulcers may be present (58).
- Malaria: Affects 0.6/100,000 population per year in the United States, with nearly all cases occurring in the setting of recent travel (63,64).
- Dengue: initiate treatment based on clinical suspicion and travel history (supportive care, consideration of transfusion as appropriate).
- Yellow fever: supportive care. Extremes of age associated with increased lethality of the illness.
- Zika: Most commonly a self-resolving illness. Pregnant patients in whom Zika virus infection is a concern should undergo serial ultrasounds (every 3–4 weeks) to identify potential anatomic abnormalities (62). Women of child-bearing age who are presumed to be infected with Zika virus should abstain from unprotected intercourse until 8 weeks after resolution of symptoms (62). Zika virus has been associated with the development of Guillain-Barré syndrome.
- Chikungunya: Most often self-resolving. The majority of patients do not require admission. Rarely, neurologic complications including seizures, meningo-encephalitis, and encephalopathy may occur (more common in children) (58).
- Malaria: If suspected, begin treatment with chloroquine or mefloquine, depending on geographical region of infection, immediately to avoid complications (cerebral malaria, renal failure, pulmonary edema, hemolysis, and splenic rupture) (63).
- If *P. vivax* or *P. ovale* are identified, chloroquine treatment should be followed by primaquine to eradicate the hypnozoite form.

(Continued)

Table 4. Continued

		Infectious Etiologies	
Patient Presentation	Clinical Condition	Diagnosis	Treatment
	Acute retroviral infection (65–67)	<ul style="list-style-type: none"> • Endemic areas: Haiti, Dominican Republic, Mexico, central and South America, Areas of North and West Africa, India, Asia, and New Guinea (63). • History should include discussion of clinical course: <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> cause relapses months after initial infection. <ul style="list-style-type: none"> • Laboratory studies: leukopenia, anemia, thrombocytopenia, transaminitis, and elevated bilirubin. Diagnosis: thick and thin peripheral smears (Giemsa stain) or PCR. • 50,000 incident human immunodeficiency virus (HIV) infections in the United States per year; males who have sex with males represent those at highest risk for HIV contraction (65). • Only half of all individuals infected with HIV manifest symptoms during the acute phase (fever, sweats, malaise, lethargy, headache, myalgias). • Risk of HIV transmission is highest during acute infection (43%–50% of all new infections caused by transmission from an acutely infected sexual partner) (66). • Diagnosis: <ul style="list-style-type: none"> • Six Food and Drug Administration (FDA)–approved rapid HIV detection tests available; sensitivities ranging from 97.6%–100%; can be utilized as a screening tests (66). • All patients with concern for HIV infection should receive diagnostic enzyme immunosorbent assay, and Western blot testing. • Positive test results may not occur for up to 12 weeks post exposure (time to generate a detectable humoral response) (66). 	<ul style="list-style-type: none"> • Consensus guidelines support the strategy of offering antiretroviral therapy to anyone with HIV-related signs or symptoms (67). • Treatment includes initiation of a non-nucleoside reverse-transcriptase inhibitor in combination with two nucleoside reverse-transcriptase inhibitors (67).
Pharyngitis and dysphagia	Epiglottitis (68,69)	<ul style="list-style-type: none"> • Pediatric epiglottitis rare in the United States secondary to <i>H. influenza</i> type B vaccination. <ul style="list-style-type: none"> • Pediatric patients with epiglottitis are often toxic-appearing: drooling, leaning forward in the tripod position with hyperextension of the neck. • Adult epiglottitis is commonly due to infection by <i>S. pneumoniae</i>, <i>Streptococcus pyogenes</i>, or <i>N. meningitides</i>. <ul style="list-style-type: none"> • 80%–95% of adults with epiglottitis present reporting sore throat and odynophagia (68). • Laboratory studies: leukocytosis common. • Imaging: lateral neck x-ray studies demonstrating the “thumb-print sign.” • Definitive diagnosis: laryngoscopy or nasopharyngeal endoscopy. <ul style="list-style-type: none"> • Pediatric patients: ideally performed in a controlled setting, immediately before securing the airway. 	<ul style="list-style-type: none"> • Initiate antibiotic therapy with cefotaxime, ceftriaxone, or ampicillin-sulbactam. <ul style="list-style-type: none"> • Add vancomycin if bacterial tracheitis cannot be excluded for <i>S. aureus</i> coverage. • Chemoprophylaxis recommended for household contacts of pediatric patients with suspicion of <i>H. influenza</i> type B epiglottitis (69).
	Deep space infection (70)	<ul style="list-style-type: none"> • Peritonsillar abscess, Lemierre’s syndrome, retropharyngeal abscess, and Ludwig’s angina commonly present with fever, generalized malaise, sore throat, neck pain, and dysphagia. 	<ul style="list-style-type: none"> • Initiate antibiotic therapy with directed activity against <i>Streptococcus</i> and oral anaerobes. • Retropharyngeal abscess: include <i>S. aureus</i> coverage.

Nausea, emesis, diarrhea	Gastrointestinal infections (71,72)	<ul style="list-style-type: none"> • <i>S. aureus</i> is frequently the pathogen associated with retropharyngeal abscesses; anaerobes are uncommon (70). • Lemierre's syndrome, septic thrombophlebitis of the internal jugular vein, is associated with <i>Fusobacterium necrophorum</i>, in 90% of cases (70). • Examination: <ul style="list-style-type: none"> • Inspect and palpate the entirety of the head and neck. • Trismus, "hot potato" voice, and stridor are often signs of impending airway compromise. • Peritonsillar abscess: evaluate for uvular deviation. • Cranial neuropathies may indicate contiguous spread of infection to the cavernous sinus. • Evaluation: <ul style="list-style-type: none"> • If dysphonia is present and the patient is stable, consider fiber-optic laryngoscopy. • Concern for retropharyngeal abscess: anteroposterior and lateral neck x-ray study. • Concern for peritonsillar abscess: CT neck with i.v. contrast or ultrasound with endocavitary probe. • Lemierre's syndrome or Ludwig's angina: CT neck with i.v. contrast. <ul style="list-style-type: none"> • CXR in the setting of Lemierre's may reveal septic emboli. 	<ul style="list-style-type: none"> • Lemierre's syndrome: metronidazole is first line. • Most-feared complications of deep space infections: airway compromise and mediastinitis. • Lemierre's syndrome, retropharyngeal abscess, Ludwig's angina: require admission and parenteral antibiotic therapy. • Peritonsillar abscess: if the patient is nontoxic and per os (p.o.) tolerant, aspiration or incision and drainage may be performed and the patient discharge with oral antibiotic therapy.
	Genitourinary infections (73,74)	<ul style="list-style-type: none"> • Diverticulitis, diverticular abscess, and appendicitis may present with fever, nausea, emesis, and diarrhea. • Lifetime risk of appendicitis is 8.6% in males and 6.7% in females (71). • History and physical examination guide evaluation and management: <ul style="list-style-type: none"> • Patients presenting with signs/symptoms suggestive of peritonitis: immediate surgical consult. Consider upright CXR or abdominal series to evaluate for perforation. • Laboratory studies: leukocytosis and elevated acute phase inflammatory proteins (71,72). • Systemically ill patient with concern for complicated diverticulitis (requiring surgical evaluation and management) or those who are immunosuppressed, have numerous medical co-morbidities or are elderly: CT with i.v. and p.o. contrast: 100% sensitive in identifying pathology (71). • Uncomplicated diverticulitis: patients with a history of diverticular disease or diverticulitis who are not systemically ill do not require imaging. • Appendicitis: ultrasound and MRI (pediatric patients, pregnant females) may be utilized for definitive diagnosis. • High fever, abdominal pain, and nausea are the hallmarks of tubo-ovarian abscesses (TOAs) and salpingitis. • The majority of TOAs result from salpingitis, both predominately associated with exposure to sexually transmitted infections (STIs) (gonorrhea and chlamydia) (74). • History taking should include queries regarding concern for exposure to STIs, history of STI treatment, and multiple sexual partners, as these are associated with increased risk of salpingitis and subsequent TOA (73,74). 	<ul style="list-style-type: none"> • Uncomplicated diverticulitis: patients who are p.o. tolerant may be discharged home with antibiotic therapy (71). • Complicated diverticulitis: fluid resuscitation, parenteral antibiotic therapy, and surgical consultation with consideration for Interventional Radiology (IR) if localized abscess. • Colonoscopy required 3–6 weeks post resolution of diverticulitis/diverticular abscess. • Appendicitis: fluid resuscitation, i.v. antibiotics, and surgical consult. • Parenteral i.v. antibiotic therapy is indicated in patients with suspected salpingitis/TOA and should be continued until the patient is asymptomatic, has been afebrile for 24–48 h, and laboratory studies demonstrate resolution of leukocytosis (73).

(Continued)

Table 4. Continued

Infectious Etiologies			
Patient Presentation	Clinical Condition	Diagnosis	Treatment
		<ul style="list-style-type: none"> • Evaluation: <ul style="list-style-type: none"> • Cervical samples should be obtained for gonorrhea and chlamydia testing. • Laboratory studies often reveal a leukocytosis > 20,000/mm³. • Imaging: Ultrasound or CT with i.v. contrast are both highly sensitive for the diagnosis of TOA and salpingitis (73). 	

illness of 1–1.6 days compared with placebo when therapy was initiated within 48 h of symptom onset (32–35). For patients at risk of influenza complications presenting within 48 h of symptom onset, the CDC recommends treatment during the 2016–2017 influenza season as detailed in Table 3 (36).

Two antiviral classes are commonly utilized in the treatment of influenza. The neuraminidase inhibitors oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®) inhibit viral aggregation and release of infectious nucleic acids to nearby host cells, therefore limiting infection (9,36). Amantadine (Symmetrel®) and rimantadine (Flumadine®), M2 inhibitors, are responsible for halting viral replication by inhibiting the release of infectious viral nucleic acids into host cells (9,36). Although amantadine and rimantadine have previously been utilized in the treatment of influenza, the CDC does not recommend their use for the 2016–2017 influenza season because of viral resistance (36).

CHEMOPROPHYLAXIS RECOMMENDATIONS

Individuals to be considered for chemoprophylaxis include family and close contacts of persons with suspected or confirmed cases of influenza at high risk for complications secondary to influenza infection, but have not been vaccinated against influenza strains circulating at the time of exposure (37,38). In randomized, placebo-controlled trials, oseltamivir and zanamivir were efficacious in the prevention of influenza among persons administered chemoprophylaxis after exposure to a household member of close contact with laboratory confirmed influenza (oseltamivir 68%–89%, zanamivir 72%–82%) (37–41). Chemoprophylaxis should continue for no longer than 10 days after the most recent exposure (see Table 3 for chemoprophylaxis recommendations) (42).

MIMICS OF INFLUENZA

Current studies indicate that up to 70% of patients presenting with influenza-like illnesses are not infected with the influenza virus (37). Tables 4 and 5 address clinical conditions that commonly present as an influenza-like illness, along with diagnostic and treatment pearls and pitfalls.

ED Approach

Identifying individuals infected with the influenza viruses, specifically those at risk for adverse outcomes secondary to infection, is paramount in limiting the morbidity and mortality associated with influenza. Due to the extensive variability of influenza symptoms, and

Table 5. Noninfectious Mimics of Influenza

Patient Presentation	Noninfectious Etiologies		
	Clinical Condition	Diagnosis	Treatment
Hemodynamic instability or altered mental status	Thyroid storm (75,76)	<ul style="list-style-type: none"> • Characterized by fever, tachydysrhythmias, diaphoresis, nausea, vomiting, confusion, and delirium. • In patients with known thyroid disease, thyroid storm may occur in the setting of trauma, infection, pulmonary embolism, myocardial infarction, and diabetes ketoacidosis. • Even when promptly recognized, mortality is estimated as 20%–30% (75). • Burch & Wartofsky Diagnostic Criteria may be utilized for diagnosis (76). • Evaluation: <ul style="list-style-type: none"> • Obtain thyroid-stimulating hormone and free thyroxine levels. 	<ul style="list-style-type: none"> • Treatment includes: β-blockade, systemic corticosteroid therapy, administration of thionamides, and iodine. • Supportive care with fluid resuscitation, external cooling methods as indicated. • Consider antibiotic therapy, as sepsis or infection (pulmonary source most common) is the most likely underlying trigger.
Dyspnea or chest pain	Pulmonary embolism (PE) (77,78)	<ul style="list-style-type: none"> • Dyspnea is reported as the earliest symptom of PE, and tachypnea the earliest sign. Patients may report pleuritic chest pain, fever, and hemoptysis. • Evaluation: <ul style="list-style-type: none"> • Perform a thorough history and examination utilizing the Wells Criteria or Revised Geneva score for risk stratification (78). • Chest x-ray study and electrocardiogram (ECG) are commonly nonspecific. • Echocardiography may be used for rapid triage in the unstable patient (evidence of right ventricular strain), as well as risk stratification. • Utilize D-dimer and PERC (Pulmonary Embolism Rule-out Criteria) as appropriate. computed tomography (CT) pulmonary angiography remains the gold standard for diagnosis (sensitive and specific for emboli localized to the main, lobar, and segmental pulmonary arteries) (78). 	<ul style="list-style-type: none"> • Anticoagulate as indicated.
	Acute respiratory distress syndrome (ARDS) (79–81)	<ul style="list-style-type: none"> • Rapidly progressive dyspnea, tachypnea, and hypoxemia. • Diagnostic Criteria as published by the American-European Consensus Conference: <ul style="list-style-type: none"> • Symptoms acute in onset. • Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) \leq 200. • Bilateral infiltrates seen on frontal chest x-ray study. • Pulmonary artery wedge pressure of \leq 18 mm Hg when measured, or no clinical evidence of left atrial hypertension. 	<ul style="list-style-type: none"> • Treatment of ARDS is supportive with mechanical ventilation, nutrition management, and stress ulcer and venous thromboembolism prophylaxis. • Utilize the ARDSnet protocol (81): <ul style="list-style-type: none"> • Low tidal volumes with control of plateau pressure to avoid further lung injury.

(Continued)

Table 5. Continued

Patient Presentation	Noninfectious Etiologies		
	Clinical Condition	Diagnosis	Treatment
	Myocardial infarction (MI) (82,83)	<ul style="list-style-type: none"> Annual incidence in the United States (ST-elevation MI [STEMI] and non-ST-elevation MI [NSTEMI]) is > 600,000. <ul style="list-style-type: none"> Etiologies include rupture of plaques in the coronary arteries, coronary dissection, coronary aneurysm, coronary embolism (secondary to atrial fibrillation (afib) or infective endocarditis), Takayasu arteritis, and acute cocaine use. Inferior wall and right ventricular infarcts commonly present with hypotension. Inferior wall and anterior wall infarcts may present with variable degrees of heart block. Evaluation: <ul style="list-style-type: none"> Obtain and interpret an ECG within 10 min of patient arrival. If no evidence of STEMI or NSTEMI, continue serial ECGs every 5–10 min in individuals persistently experiencing chest pain. Cardiac biomarkers should be interpreted in the context of the clinical onset of symptoms (if present). 	<ul style="list-style-type: none"> Administer aspirin (if contraindicated, clopidogrel should be considered, unless evidence of multivessel disease on ECG). Activate the catheterization laboratory or transport as appropriate. <ul style="list-style-type: none"> In the setting of a STEMI, if door to catheterization time is anticipated to be > 90 min, consider thrombolysis (82). <ul style="list-style-type: none"> If door-to-catheterization time will be < 90 min, door-to-balloon time target: 30 min (82).
Headache and myalgias	Cerebral vascular pathology (84–91)	<ul style="list-style-type: none"> The differential diagnosis for patients presenting with headache and myalgias should include subarachnoid hemorrhage (SAH). Cerebral vascular accident (CVA), cavernous venous sinus thrombosis (CVST), and venous sinus thrombosis commonly present with headache and focal neurologic deficit. Evaluation: <ul style="list-style-type: none"> SAH: noncontrast CT head and lumbar puncture vs. noncontrast CT head and CT angiogram (CTA) of the head and neck CTA identified as 98% sensitive and 100% specific in detecting bleeding from aneurysms \geq 3 mm; approximately 85% of SAHs are due to aneurysmal bleeding) (84–87). CVA: noncontrast CT head as screening tool. magnetic resonance imaging (MRI), MR angiography, CTA, Doppler ultrasound of the carotid arteries is helpful for further diagnostic evaluation. CVST: MRI of the brain with and without contrast is the gold standard. Cerebral angiography and CT may be utilized if MRI unavailable (88). <ul style="list-style-type: none"> Laboratory studies: Majority of patients with CVST demonstrate leukocytosis (88). A coagulation panel should be obtained. CVST: MRI with venography recommended first line. CT angiography and venography if MRI unavailable (90). <ul style="list-style-type: none"> Laboratory studies: Up to 90% of patients with CVST have an elevated D-dimer (91). 	<ul style="list-style-type: none"> SAH: identify underlying etiology of bleed, obtain neuro-surgical consultation, consider administration of nimodipine for prevention of cerebral vasospasm. Target systolic blood pressure (SBP) of \leq 160 mm Hg (labetolol considered first line) (84). CVA: if ischemic, consider thrombolytic therapy (appropriate National Institutes of Health [NIH] Stroke Scale, appropriate time frame, absence of contraindications) after discussion with patient or family. <ul style="list-style-type: none"> Do not treat hypertension in the first 24 h unless blood pressure > 220/120 mm Hg in patients who are not candidates for thrombolysis or > 185/110 mm Hg in those who are (86). CVST: Heparin often administered. An extended-spectrum penicillin and third-generation cephalosporin should be utilized if concern for infectious etiology (88). VST: anticoagulation is the primary treatment. Thrombolectomy or thrombolysis may be required (90).

Nausea, emesis,
diarrhea

Intestinal ischemia
(92–94)

- Abdominal pain out of proportion to examination in addition to nausea, emesis, and diarrhea may be presenting signs.
- Risk factors: hypotension, afib, severe cardiovascular disease, and recent MI.
- Mesenteric ischemia may occur secondary to: acute arterial embolus, acute arterial thrombosis, venous thrombosis, and nonocclusive mesenteric ischemia.
- Mortality is estimated as ranging from 63% to 100% (93).
- Evaluation:
 - No laboratory study is sensitive or specific to exclude the diagnosis of bowel ischemia (92). Leukocytosis and elevated lactate often noted on laboratory analysis (92).
- Imaging: CT angiography is sensitive (74%–100%) and specific (100%) for the diagnosis of mesenteric ischemia (94).

Toxin ingestion or
withdrawal
state (95,96)

- Obtain a thorough history to include prescription medications, homeopathic remedies, over-the-counter medications, and illicit drug abuse.
- Perform a physical examination. Pay particular attention to the patient's generalized appearance (diaphoresis), vital signs (hyperthermia, hypopnea, or bradypnea), neurologic findings (altered mental status, pinpoint or dilated pupils, hyper or hyporeflexia, and clonus).
- Sympathomimetic toxidrome: agitation, delirium, hypertension, hyperthermia, nausea, and muscle rigidity.
- Anticholinergic: mydriasis, urinary retention, tachycardia, and hyperthermia.
- Serotonin syndrome: altered mental status, autonomic instability, myoclonus, and tremor.
- Neuroleptic malignant syndrome: lead pipe rigidity, hyperthermia, altered mental status.
- Monoamine oxidase inhibitor (MAOI) toxicity may present with severe hyperthermia, nausea, emesis, and cardiovascular collapse. Excessive ingestion of tyramine containing food stuff during MAOI therapy may result in hypertensive crisis.
- Patients experiencing benzodiazepine, opioid, and alcohol withdrawal may present with agitation, hypertension, tachycardia, and gastrointestinal upset.
- Carbon monoxide poisoning may present with headache, nausea/vomiting, neurologic deficit, ischemia, syncope, or seizure. Seek history on others with similar symptoms and use of indoor heating device.

- Initiate fluid resuscitation and oxygen supplementation as necessary.
- Administer broad-spectrum antibiotics.
- Anticoagulation often required.
- Consult surgery as soon as the diagnosis is suspected (early angiography and surgical intervention improve mortality).

- Primary treatment includes addressing airway, breathing, and circulation.
- Benzodiazepines are the treatment of choice for agitation, anticholinergic toxicity, sympathomimetic toxicity, and serotonin syndrome.
- Dopamine agonists have been demonstrated to improve symptoms in neuroleptic malignant syndrome.
- Provide fluid resuscitation in the setting of seizure and muscular rigidity to avoid complications secondary to rhabdomyolysis.
- Carbon monoxide poisoning requires supplemental oxygen. Patients with confusion, altered mental status, seizure, stroke, chest pain, pulmonary edema, or syncope require hyperbaric chamber.

that the influenza virus circulates concurrently with other respiratory viruses, the emergency physician must be acutely aware of influenza mimics and their evaluation and treatment (97,98).

1. The assessment of a patient presenting with fever, headache, chills, myalgias, sore throat, and influenza-like symptoms (or in the case of the pediatric patient: decreased appetite, decreased per os tolerance, or decreased urinary output) begins with evaluation of airway, breathing, and circulation (3). A definitive airway should be obtained in all toxic-appearing patients with signs of impending airway compromise including stridor, "hot potato voice," trismus, seated in the tripod position, or in those presenting with an inability to protect their airway (altered mental status) (70). An assessment of systemic inflammatory response syndrome criteria should be performed, and diagnostic testing ordered as appropriate, given the physician's clinical suspicion regarding the etiology of the systemic illness. Potential studies include a complete blood count, serum electrolytes, urinalysis, chest x-ray study, blood cultures, and lactate. If sepsis is suspected, the provider should initiate fluid resuscitation to improve peripheral perfusion and administer broad-spectrum antimicrobials (44–46,98).
2. After initial resuscitation and stabilization of the toxic-appearing patient, a focused history and examination allows for the development of a differential diagnosis based on targeted questioning regarding immunization status, medical comorbidities, daily medication use, sexual practices, and recent travel (e.g., high-risk areas for mosquito-borne illness, such as Southeast Asia, Africa, South/Central America). A determination regarding the requirement for adjunct testing and advanced imaging (point-of-care blood glucose, respiratory viral panel, serology, peripheral smear, head noncontrast computed tomography [CT], abdomen/pelvis CT) can then be made.
3. In the nontoxic, immunocompetent adolescent or adult patient, the clinical diagnosis of influenza is accurate in up to 90% of cases (23,24,97). Patients, or caregivers of patients older than 1 month of age, presenting for evaluation and treatment within 48 h of symptoms onset should be counseled about the benefits (reduced duration of illness up to 1.6 days), and common side effects (gastrointestinal upset) of antiviral therapy (31–33,35).
4. In patients at high risk for complications secondary to influenza infection (e.g., elderly [50 years and older], immunosuppressed, health care workers,

pregnant females; detailed in Table 3), confirmatory testing for influenza should be performed. RIDT has a sensitivity of 50%–70% and specificity > 90%, and testing should be interpreted in terms of the community prevalence of influenza infection (9,26). The utility of performing direct immunofluorescence and RT-PCR testing in the ED may be limited by required laboratory processing times (1–8 h) (9,26). RT-PCR is recognized as the gold standard for the definitive diagnosis of influenza (28–30,97).

In approaching the patient with influenza-like symptoms, the emergency physician must make a determination regarding the severity of illness. Identification of the need for immediate airway management and resuscitation is paramount. Any concern for an infection other than influenza, such as pneumonia, warrants antimicrobials and fluid resuscitation. Ultimately, a thorough history and physical examination allow for the directed performance of evaluation and treatment.

CONCLUSIONS

Fever, headache, cough, and sore throat—a myriad of chief complaints associated with influenza and influenza-like illnesses—represent the most common reasons for presentation to US EDs (3). Given the significant overlap in the presenting signs and symptoms of influenza and influenza mimics, and the plethora of infectious and noninfectious influenza mimics, the emergency physician must be able to quickly identify patients as toxic-appearing or non-toxic-appearing, perform initial resuscitation as appropriate, and collect an adequate history and perform a physical examination to determine necessary methods for patient evaluation and treatment.

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ARTICLE SUMMARY

1. Why is this topic important?

Influenza and upper respiratory infections account for a large amount of emergency department (ED) presentations. However, many critical conditions can present with similar symptoms.

2. What does this review attempt to show?

This review evaluates influenza symptoms and diagnosis, while discussing mimics and an approach to evaluation and management.

3. What are the key findings?

Influenza can present with a variety of symptoms, and providers demonstrate a diagnostic accuracy approaching 90% in the correct setting. Rapid antigen detection can be useful in the ED, and treatment is warranted for several populations within 48 h of symptom onset. Approximately 70% of patients with influenza-like symptoms are experiencing a mimic. Several of these conditions that mimic the presentation of influenza require rapid management.

4. How is patient care impacted?

This evaluation of influenza and its mimics discusses the presentation, diagnosis, and management of influenza, while detailing the presentation and diagnosis of several deadly conditions requiring rapid diagnosis and treatment.