

TERMINOLOGY

CLINICAL CLARIFICATION

- Influenza is an acute, seasonally epidemic, highly contagious, febrile respiratory illness caused by infection with influenza virus

CLASSIFICATION

- By type:¹
 - Influenza A and B cause most clinical disease in humans; type C rarely causes significant illness
 - Influenza A viruses are named according to the viral surface hemagglutinin (H or HA) and neuraminidase (N or NA) antigens, the geographic area of origin, the isolate number, and the year of isolation (eg, A/Texas/50/2012 for a variant of H3N2)
 - Influenza B viruses are named by lineage (eg, B/Victoria)

DIAGNOSIS

CLINICAL PRESENTATION

- History
 - Presentation varies from mild to profound and life-threatening illness
 - Abrupt onset of symptoms is a hallmark of influenza, beginning 1 to 4 days after exposure and lasting up to 14 days
 - First symptoms typically include:
 - Fever, chills, and diaphoresis (common)
 - Myalgia (may be intense)
 - Headache (often prominent)
 - Malaise and fatigue (may be profound)
 - Anorexia (common)
 - Subsequent symptoms may include the following respiratory tract complaints:
 - Rhinorrhea and nasal congestion, with or without sneezing (prominent)
 - Sore throat (common)
 - Deep, hacking, nonproductive cough resulting in progressive chest discomfort
 - Dyspnea may be present with influenzal pneumonia
 - Gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) occur sometimes in children but rarely in adults
- Physical examination
 - Fever is usual but is less common in children and elderly people
 - Tachycardia may be present if fever is high or patient is dehydrated
 - Tachypnea may indicate pneumonia or more severe disease
 - Erythema of nasal and oropharyngeal mucous membranes
 - Thin nasal discharge
 - Cervical adenopathy (usually posterior)
 - Lung examination may find clear lungs; rales or rhonchi suggest viral or secondary bacterial pneumonia

CAUSES AND RISK FACTORS

- Causes
 - 1 or 2 strains of influenza A and B cause seasonal epidemics each year; type C strains cause only sporadic illness
- Risk factors and/or associations
 - Age
 - Attack rates are higher in children than in adults, but all ages are affected¹
 - Elderly people are also at higher risk¹
 - Other risk factors/associations
 - Seasonal pattern
 - Occurs from mid-fall to early spring in temperate climates
 - Seen sporadically throughout the year in tropical climates
 - Risk factors for severe manifestations:
 - Immunocompromised status
 - Comorbid chronic illness (eg, diabetes; heart failure; chronic pulmonary, renal, hepatic, hematologic, or neurologic disease)
 - Morbid obesity
 - Pregnancy

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DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - History and physical examination are usually sufficient to make the diagnosis in the setting of seasonal epidemics^{2,3}
 - Use a rapid influenza diagnostic test if it will change the care of the patient or of other patients. The following factors warrant such testing:⁴
 - Hospitalized patients
 - Patients with high-risk conditions
 - Documentation of institutional outbreaks
 - Atypical timing (eg, summer months in temperate climates)
 - Under these circumstances, viral culture is recommended to confirm positive results from rapid tests and to identify strain
- Laboratory
 - Antigen detection tests: rapid influenza diagnostic tests are usually available at the point of care³
 - Performed on nasal or nasopharyngeal swab or aspirate
 - Some can distinguish influenza A from influenza B but cannot identify specific strain
 - Sensitivity is 50% to 70%³
 - Specificity is 90% to 95%³
 - Polymerase chain reaction testing for viral nucleic acid: available at commercial laboratories
 - Recommended for hospitalized patients, especially if rapid antigen test result is negative³
 - Turnaround time is longer
 - Sensitivity and specificity approach 100%⁵
 - Viral culture
 - Recommended only in unusual cases, primarily for epidemiologic purposes; turnaround time is too long for management decisions. Useful for the following:³
 - Document and characterize an outbreak
 - Determine source (eg, poultry, pigs) in nonepidemic settings
- Imaging
 - Chest radiograph is not indicated in most cases
 - Often no chest radiographic findings even in symptomatic patients⁶
 - Obtain if either primary influenzal pneumonia or secondary bacterial pneumonia is suspected on the basis of physical examination findings
 - Chest radiograph findings suggestive of pneumonia due to influenza are as follows:⁶
 - Peribronchial patchy interstitial infiltrates
 - Centrilobular nodules
 - Lobar ground-glass appearance
 - Consolidation

DIFFERENTIAL DIAGNOSIS

- Most common
 - Common cold
 - Prevalent during winter months, overlapping with influenza epidemics
 - Clinically, onset is more gradual, and patient appears only mildly ill
 - Fever is absent or lower than with influenza; patients are less likely to have severe myalgia and fatigue
 - Predominant symptoms are in upper respiratory tract in common cold, as opposed to lower respiratory tract (eg, cough) in influenza
- Diagnostic groups
 - Other respiratory tract viral infections
 - Respiratory syncytial virus infection
 - Seasonality overlaps that of influenza; infection mostly affects infants and small children
 - Often nosocomial (patients develop symptoms after being in a health care environment)
 - Lower respiratory tract symptoms predominate, with prolonged expiratory phase, rales, and wheezes
 - Diagnosis is confirmed by polymerase chain reaction assay
 - Parainfluenza virus infection
 - Seasonality overlaps that of influenza; infection causes both upper and lower respiratory tract disease in infants and small children and mostly upper respiratory tract disease in adults
 - Croup and hoarseness are predominant symptoms
 - Diagnosis is confirmed by polymerase chain reaction assay or antigen detection test

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- Adenovirus infection
 - Usually not seasonal; more common in children
 - Most prominent symptoms are sore throat, hoarseness, and conjunctivitis
 - Diagnosis is confirmed by polymerase chain reaction assay or antigen detection test
- Epstein-Barr virus infection (mononucleosis)
 - Occurs sporadically (not seasonally); most common in adolescents and young adults
 - Most prominent symptoms are sore throat and fatigue; physical findings include pharyngeal exudates and prominent posterior cervical adenopathy; cough is not predominant symptom
 - Diagnosed by laboratory testing (monospot rapid test or Epstein-Barr virus antibody testing)
- o Bacterial infections
 - Pneumonia
 - May occur sporadically or may be a complication of influenza
 - Symptoms are similar, but cough is productive and there is more likelihood of pleuritic chest pain and dyspnea
 - Rales and rhonchi, egophony, and/or dullness to percussion suggest a pneumonic infiltrate
 - Diagnosed by chest radiograph and microscopy and culture of sputum
 - Meningococcal meningitis
 - Tends to occur in epidemics; occurs most commonly in children and young adults living in close quarters (eg, dormitories, barracks)
 - Begins abruptly, as influenza does, and with high fever
 - Predominant symptoms initially are severe headache, neck stiffness, photophobia, and vomiting
 - Rash may be present; cough is unusual
 - Diagnosis is confirmed by cerebrospinal fluid analysis and culture

TREATMENT

GOALS

- Symptom relief
- Prevention of complications, such as viral pneumonia, in patients at higher risk

DISPOSITION

- Admission criteria
 - o Admit pregnant women, children younger than 5 years, and adults older than 65 years with severe illness or with moderate illness that appears to be rapidly worsening
 - o Criteria for ICU admission
 - Patients likely to need ventilator support
 - Severe or rapidly progressive illness with dyspnea and/or hypoxia
 - Bilateral diffuse pneumonia
 - Patients with hemodynamic instability
- Recommendations for specialist referral
 - o Refer to an infectious disease specialist, pulmonologist, or critical care specialist for severe illness requiring hospitalization
 - o Consider consultation with an allergist for high-risk patients who would benefit from immunization but are allergic to the vaccine

TREATMENT OPTIONS

- Supportive care with rest and maintenance of adequate hydration
 - o Common symptomatic treatments involve relief of fever, pain, and nasal congestion (eg, OTC forms of NSAIDs are often used; avoid aspirin in children owing to risk of Reye syndrome)
- Neuraminidase inhibitors are recommended as soon as possible with confirmed or suspected influenza for the following 3 groups of patients:^{5,7}
 - o Patients with severe or progressive illness
 - o Hospitalized patients
 - o Patients at high risk of complications
 - Children younger than 5 years (especially those younger than 2 years)
 - Adults aged 65 years and older
 - Residents of nursing homes and other long-term care facilities
 - Persons with certain medical conditions or demographic characteristics, as follows:
 - Asthma and other chronic pulmonary diseases
 - Cardiovascular disease (except hypertension alone)
 - Renal disease

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- Hepatic disease
- Hematologic conditions (including sickle cell disease)
- Immunosuppression due to medication, HIV infection, or other causes
- Long-term aspirin therapy if younger than 19 years
- Metabolic disorders (including diabetes mellitus)
- Neurologic and neurodevelopmental conditions
- Morbid obesity (BMI of 40 or more)
- Pregnant or recent (2 weeks) postpartum status
- American Indian or Alaska Native ethnicity
- Decision to administer therapy need not depend on test results⁸
 - In particular, in very ill patients or those at high risk, do not delay treatment while awaiting test results
- Drug therapy
 - Neuraminidase inhibitors
 - May be prescribed electively for healthy adults and children not at high risk of complications; associated with small decrease in length of illness in adults; results in children are inconsistent⁹
 - Observational studies of hospitalized children and adults suggest that significant decrease in mortality is most pronounced when an inhibitor is started *within 48 hours*^{10, 11, 12}
 - If treatment is elected, start antiviral treatment as soon as possible after illness onset, ideally *within 48 hours* of symptom onset, and continue for 5 days⁸
 - In hospitalized or otherwise severely ill patients, institute treatment regardless of duration of symptoms
 - Oseltamivir is favored over zanamivir in this population
 - For patients unable to absorb oseltamivir because of gastrointestinal malfunction, IV peramivir may be administered
 - If oseltamivir resistance is suspected, IV zanamivir (an investigational formulation) is an option
 - Extended courses may be considered for patients who remain severely ill
 - Oseltamivir¹³
 - Oseltamivir Phosphate Oral suspension; Premature Neonates greater than 40 weeks postmenstrual age† and Term Neonates 0 to 13 days†: 3 mg/kg/dose PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Premature Neonates 38 to 40 weeks postmenstrual age†: 1.5 mg/kg/dose PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Premature Neonates younger than 38 weeks postmenstrual age†: 1 mg/kg/dose PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Term Neonates and Infants 14 days and older: 3 mg/kg/dose PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Children weighing 15 kg or less: 30 mg PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Children weighing 16 kg to 23 kg: 45 mg PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral suspension; Children and Adolescents weighing 24 kg to 40 kg: 60 mg PO twice daily for 5 days; consider extended course for severely ill patients.
 - Oseltamivir Phosphate Oral capsule; Children weighing more than 40 kg and Adolescents: 75 mg PO twice daily for 5 days; consider extended course for severely ill patients.
 - Zanamivir, inhaled
 - Infants and children younger than 7 years: Safety and efficacy have not been established. Clinical studies have indicated that young children do not produce the peak inspiratory flow rates needed for the proper use of dry powder inhalers such as the Diskhaler device, which limits the systemic absorption and clinical efficacy of zanamivir.
 - Zanamivir Inhalation powder; Adults, Adolescents, and Children 7 years and older: 2 inhalations (one 5-mg blister per inhalation for total dose of 10 mg) PO 2 times daily (roughly every 12 hours) for 5 days. Take 2 doses on first day provided there are at least 2 hours between doses. CDC suggests potential longer treatment course in severely ill.
 - Zanamivir, IV
 - IV zanamivir is available only through enrollment in an ongoing clinical trial or through a compassionate use program; follow dosage recommendations from the clinical trial or provided by the manufacturer.
 - Peramivir
 - Peramivir Solution for injection; Adults: 600 mg IV as a single dose. Administer within 48 hours of influenza symptom onset.

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- Nondrug and supportive care
 - Rest and adequate fluid intake to offset insensible losses during fever are recommended
- Comorbidities
- Special populations
 - Pregnant women
 - Increased risk for hospitalization but not mortality¹⁴
 - Increased risk of preterm birth and small-for-gestational-age infants
 - Inactivated influenza vaccine is recommended for all pregnant women without contraindications, regardless of trimester or season of due date.¹⁵ Live, attenuated influenza vaccine is not recommended for use during pregnancy
 - Strongly consider prophylactic neuraminidase inhibitors (category C drugs) for unimmunized women; administer within 48 hours of exposure^{15,10}
 - Provide neuraminidase inhibitors at standard adult dose, preferably within the first 48 hours of symptoms¹⁵
 - However, it is recommended that these drugs be started even if the 48-hour mark has passed
 - Hospitalize pregnant women if illness appears to be severe or is worsening, with a low threshold for admitting to ICU with signs of respiratory distress

MONITORING

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Direct influenza virus complications
 - Influenzal pneumonia is the most common viral complication
 - Rarely, the following may occur:
 - Aseptic meningitis and/or encephalitis
 - Myositis and/or rhabdomyolysis
 - Transverse myelitis
- Suppurative complications
 - Bacterial pneumonia
 - Otitis media
 - Sinusitis
- Worsening of comorbid conditions
 - Asthma
 - Chronic obstructive pulmonary disease
 - Congestive heart failure

PROGNOSIS

- For patients in low-risk groups who do not develop complications, prognosis is good and a full recovery is expected
- Patients in high-risk groups have an increased incidence of severe illness, hospitalization, and death
- Overall mortality is 1.4 deaths per 100,000 population in the United States¹⁶

SCREENING AND PREVENTION

SCREENING

PREVENTION

- Vaccination
 - Seasonal influenza vaccine is recommended yearly, in autumn, for all persons aged 6 months and older (including pregnant women) for whom there is no contraindication^{17,18}
 - Children aged 6 months through 8 years require 2 doses of influenza vaccine (administered 4 or more weeks apart) during their first season of vaccination to optimize immune response^{18,17}
 - Children aged 6 months through 8 years who have received 2 or more doses of trivalent or quadrivalent influenza vaccine previously (regardless of whether they were given during the same season or consecutive seasons) do not require 2 doses of vaccine
 - Children who have received only 1 vaccine dose in a previous season should receive the 2-dose initial regimen; the interval between the 2 doses should be at least 4 weeks
 - 3 types of vaccines are produced in the United States¹⁹
 - Inactivated influenza virus vaccine, available in trivalent and quadrivalent forms: for patients aged 6 months and older
 - Not all commercially available vaccines are approved for all age groups
 - High-dose trivalent and adjuvanted trivalent forms are available for adults older than 65 years

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- Recombinant hemagglutinin influenza vaccine, available in trivalent and quadrivalent formulations for patients aged 18 years and older
- Live attenuated influenza vaccine, quadrivalent (administered intranasally)
 - CDC Advisory Committee on Immunization Practices does not recommend this vaccine for the 2017/2018 season^{18, 17, 19}
- Antiviral prophylaxis
 - Pre- or postexposure chemoprophylaxis with the neuraminidase inhibitors oseltamivir and zanamivir may be given for the following reasons:⁴
 - Protect vaccinated high-risk patients who have recently been immunized (less than 2 weeks before) but have not had time for vaccine-induced antibodies to develop
 - Protect unvaccinated high-risk patients and their household contacts with recent exposure to influenza
 - Protect immunocompromised patients who cannot develop an antibody response to vaccine
 - Prevent or control large outbreaks in closed settings
 - Begin postexposure prophylaxis within 48 hours of exposure⁷
 - Antiviral drugs may be given concurrently with inactivated influenza virus vaccine²⁰
 - Live attenuated influenza vaccine is not currently recommended; however, in the event that its use is resumed, it should not be administered concurrently with antiviral medication or within 48 hours after the last dose of antiviral medication
 - Zanamivir dosage for prophylaxis is the same as for treatment; oseltamivir prophylaxis is given once a day at half the total daily treatment dosage⁷
 - Duration of chemoprophylaxis varies with the circumstances, as follows:⁷
 - Postexposure prophylaxis is usually maintained for 10 days following the most recent exposure
 - In persons at high risk who cannot be immunized, continue pre-exposure prophylaxis for the duration of the influenza season
 - For management of institutional outbreaks, continue prophylaxis for a minimum of 2 weeks and for at least 10 days after onset of illness in the last patient
- Hand washing and avoiding contact with infected persons also help prevent infection

SYNOPSIS

KEY POINTS

- Influenza causes seasonal epidemics of an acutely debilitating febrile respiratory illness of up to 2 weeks' duration
- During epidemics, recognition of the classic symptoms of abrupt onset of high fever, myalgia, headache, and cough is diagnostic for most patients. Confirm with rapid diagnostic tests in patients with high medical risk. Laboratory testing (viral culture) is most useful in nonepidemic settings or for epidemiologic uses
- Yearly influenza vaccine is recommended for all persons older than 6 months^{18, 17}
 - Special caution is needed in those with severe egg allergy; the vaccine is contraindicated in persons who have previously experienced an allergic reaction to influenza vaccine
- Prophylactic use of neuraminidase inhibitors is indicated in some situations (eg, high medical risk)
- Persons at higher risk for severe illness and complications (eg, viral or bacterial pneumonia) include children younger than 5 years, adults older than 65 years, pregnant women, and those with many chronic medical conditions
 - Treatment of influenza with neuraminidase inhibitors is recommended for these patients and for all patients who have severe or progressive illness or are hospitalized with influenza
- Neuraminidase treatment is best begun within 48 hours of illness but may be beneficial up to day 5⁸
- Treatment is primarily supportive for persons without severe disease and without elevated risk of complications

URGENT ACTION

- Identify patients at higher risk of complications and start neuraminidase treatment as soon as possible
- Hospitalize very young children, elderly people, and pregnant women if illness is severe or is rapidly worsening

PITFALLS

- Not all vaccine formulations are approved for all age groups; be sure to select an age-appropriate product
- Egg allergy is not necessarily a contraindication for seasonal influenza vaccine¹⁸
 - Recombinant hemagglutinin influenza vaccines, available in trivalent and quadrivalent formulations, are considered egg-free
 - Persons whose allergic reaction to eggs is limited to hives may receive any age-appropriate, inactivated-virus vaccine
 - Persons who have experienced more severe reactions to eggs (eg, angioedema, respiratory distress) may receive any age-appropriate inactivated vaccine in a health care setting under supervision of a provider experienced in managing severe allergic reactions
 - A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine

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