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CHAPTER 39

INFLUENZA

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1. What is influenza?

Influenza is a respiratory illness caused by an RNA virus that comes in two forms: influenza A and influenza B. Although generally self-limited, influenza can cause significant morbidity and mortality especially in those at risk (see answer 4 below). Influenza is most common during the fall and winter months because of increased indoor crowding and low humidity, though illness can continue through April and May in the Northern hemisphere.

2. How are influenza A strains designated?

Influenza A is described by the surface glycoproteins: hemagglutinin (H) and neuraminidase (N). The hemagglutinin, of which there are 16 structurally different types, allows attachment to host respiratory epithelium. The neuraminidase, of which there are nine different types, acts as an enzyme that facilitates release of newly replicated viruses from the infected cell. Humans are most often infected with influenza viruses having H1, H2, or H3 and N1 or N2.

The H and N terminology is also used to name the influenza strains spreading yearly. Generally each year one or two influenza A strains and an influenza B strain circulate. During the 2010-2011 season, the circulating strains included A H1N1, A H3N2, and influenza B.

3. What are the symptoms of influenza?

Influenza is characterized by the abrupt onset of fever, nonproductive cough, sore throat, rhinitis, headache, myalgia, and fatigue. Children may also have otitis media. Symptoms generally resolve within 5 to 7 days though the cough may persist for several weeks. During the flu season, an otherwise healthy adult with fever and cough has an 80% to 90% chance of having influenza. Such a simple case definition though may not accurately diagnose influenza in young children, the elderly, or those with comorbid cardiopulmonary illness.

4. Who is at risk for more severe or complicated influenza?

The Centers for Disease Control and Prevention (CDC) has warned that influenza can be especially serious and life threatening for patients with the risk factors as follows:

- Aged 6 months to 4 years
- Aged 50 years and older
- Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Immunosuppression caused by medications, organ transplantation, malignancy, or HIV
- Pregnancy during the influenza season
- Aged 6 months to 18 years and receiving long-term aspirin therapy (Reye syndrome)
- Residents of nursing homes and other long-term–care facilities
- American Indians and Alaska Natives
- Morbidly obese (body mass index is 40 or greater)

5. What complications can occur from influenza?

According to the CDC on average in excess of 36,000 deaths and 226,000 hospitalizations are attributable to influenza during each yearly flu season. Influenza can cause a primary viral hemorrhagic pneumonia characterized by progressive dyspnea and leukocytosis, potentially progressing to

respiratory failure and acute respiratory disease syndrome. A secondary bacterial pneumonia may develop in older patients and those with chronic cardiopulmonary illness. After a period of improvement the patient appears to worsen with signs and symptoms of bacterial pneumonia, most often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae,* or *Staphylococcus aureus*.

In addition, patients may have exacerbations of chronic cardiopulmonary illnesses. Less-common complications include myositis, myocarditis, pericarditis, encephalitis, a toxic shock–like illness, Guillain-Barré syndrome, and Reye syndrome.

6. What other infections can mimic influenza?

The symptoms of influenza are very nonspecific and can be caused by a large array of viruses and bacteria. Because these pathogens can cause an illness similar to influenza, any febrile respiratory illness may be referred to as influenza-like illness (ILI). Causes of ILI, in addition to influenza, include respiratory syncytial virus, parainfluenza, rhinovirus, and coronavirus (agents of the common cold); adenovirus; metapneumovirus; group A streptococcus; mycoplasma; chlamydia; and *Bordetella pertussis*.

7. How do you diagnose influenza?

Influenza is often a clinical diagnosis. For those without risks for complications or requiring hospitalization, no further diagnostics are required. The most accurate way to confirm that a patient does or does not have influenza is to obtain a nasopharyngeal swab. The swab is the same one used to collect and transport bacterial culture samples. The swab needs to be inserted through the nose to the pharynx. Testing by polymerase chain reaction (PCR) is most accurate. Testing by rapid influenza diagnostic tests (RIDT) is not very sensitive (50%-70%) but is reasonably specific (90%-95%). A negative RIDT is not helpful. A positive RIDT can be helpful, and most people with a positive RIDT have influenza A.

8. What is the approach to the patient with an ILI?

The approach to the patient with ILI can progress in a stepwise manner. The patient should be assessed for degree of illness and presence of risk factors for complications.

Those with mild symptoms (no shortness of breath and able to maintain hydration) and no risks for complications do not need further testing and can be treated symptomatically. Those with moderate symptoms (some shortness of breath, difficulty maintaining hydration, signs and symptoms of pneumonia) should be tested and treated with antiviral medications. Those with severe symptoms (respiratory distress, altered mental status) need immediate assessment in the emergency department. Pregnant women with influenza, especially those in the third trimester, have a high rate of complications and should be urgently assessed in the emergency department also. See Figure 39-1.

9. How do you treat influenza?

M2 channel blockers, such as amantadine and rimantadine, are not often used because of emergence of resistance and central nervous system toxicity. Neuraminidase inhibitors such as oseltamivir and zanamivir act by blocking the surface neuraminidase. Both are active against influenza A and B. Oseltamivir is oral and dosed at 75 mg twice daily for 5 days for treatment. Zanamivir is a nasal spray and has been approved for persons aged $\geq$7 years. These agents have been shown to shorten the duration of influenza symptoms but only modestly; if started within 48 hours of symptoms, the duration of the illness may be decreased by approximately 1 day. Several intravenous (IV) formulations are in research such as IV zanamivir and peramivir that may be used in critically ill persons who are unable to use or absorb the conventional agents.

10. How do you manage a patient admitted to the hospital with ILI?

All patients with ILI during the fall-winter flu season admitted to the hospital should be presumed to have influenza until ruled out by nasopharyngeal PCR. Until that test result is back, they should:

- Be isolated in a private room.
- Have standard and droplet precautions used.

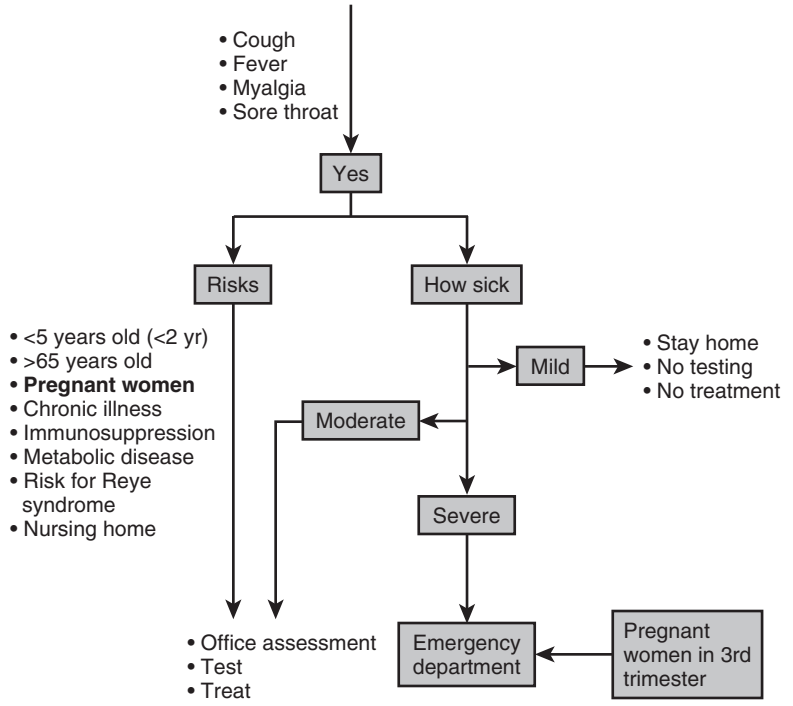

Figure 39-1. Approach to the patient with an ILI. When testing and treatment are being decided on, the patient's risk for complications and severity of illness need to be taken into account.

- Be treated with neuraminidase inhibitors. Consideration should be given to treating with antibiotics such as ceftriaxone and vancomycin to cover potential streptococcal, staphylococcal, and *Haemophilus* superinfection.

If the nasopharyngeal PCR returns negative, influenza treatment and isolation can be stopped. Keep in mind that a negative RIDT does not rule out influenza.

11. What are epidemics and pandemics?

The hemagglutinin (H) and neuraminidase (N) undergo small changes in structure called antigenic drift on a yearly basis, which allows the virus to partially evade humans' past immune response and cause yearly epidemics. Larger changes in the H and N, called antigenic shift, occur infrequently. When antigenic shift occurs, much of the population has essentially no or limited immunity to the new strain, and a pandemic may occur as was seen in 1918, 1956, 1967, and 2009. Pandemic refers to a new viral type and worldwide spread but not severity. The 1918 pandemic was very severe, causing an estimated 50 to 100 million deaths worldwide, whereas the 2009 pandemic was no more severe than a usual epidemic year, though it disproportionately affected younger adults and children.

12. What have we learned from past pandemics?

The influenza virus can mutate and reassort frequently and randomly making occurrence of pandemics unpredictable. Over the past 300 years there has been no regular periodicity with

times between pandemics varying from 8 to 42 years. Pandemics often unfold in waves of severity over several years as occurred in 1918. Pandemics disproportionately affect the young as occurred in both 1918 and 2009. Pandemics may not follow seasonal (fall-winter) patterns as evidenced by the 2009 pandemic's springtime arrival.

13. What is "bird flu"?

Viral strains that affect predominately birds including aquatic fowl and domestic poultry are referred to as bird flu and generally do not infect humans. In 1997, a bird flu, H5N1, infected 18 people in Hong Kong, resulting in six deaths. It reappeared in 2003 infecting persons in Vietnam, Cambodia, Laos, Thailand, Indonesia, China, Egypt, and central Asia. As of March 16, 2011, there have been 534 confirmed human infections with H5N1 with 316 deaths, a startling 59% mortality. The great majority of these patients had extensive direct contact with infected poultry. Several limited episodes of human-to-human transmission have occurred but no sustained transmission. Although the H5N1 virus is still circulating and continues to cause illness and death in these countries, it has not attained the ability, yet, to be easily transmitted to or between people.

14. What was the pandemic of 2009?

During the 2009-2010 influenza season, a large change in the H and N structure occurred, leaving much of the population, especially those younger than 65 years old, with inadequate immunity. This new structure was the result of a reassortment of bird, swine, and human influenza strains resulting in an antigenically new H1N1 strain. It appeared to start simultaneously in Southern California and Mexico in the spring of 2009 and spread rapidly worldwide with the World Health Organization declaring a pandemic on June 11, 2009. Young adults and children were particularly affected. In Argentina, for example, pediatric hospitalization rates doubled. Of hospitalized children, 19% were admitted to the intensive care unit (ICU), 17% required mechanical ventilation, and 5% died. In the United States, 45% of patients admitted to the hospital were under the age of 18 years. Seventy-three percent of patients had at least one underlying condition including asthma, diabetes, heart, lung and neurologic diseases, and pregnancy.

15. How severe was the pandemic of 2009?

Fortunately the 2009 pandemic was a *mild* pandemic as compared with that in 1918. The severity has been estimated to be similar to that of the 1957 and 1968 pandemics. Many countries including Australia, Spain, and the United States reported more ICU admissions, patients requiring mechanical ventilation, and deaths. Those admitted to ICUs often had extensive multifocal pneumonias on chest radiograph. In one study of those admitted to the ICU, 36% had pulmonary emboli on chest computed tomography. Early in the pandemic, Spain noted that 91% of the patients admitted to the ICU had primary viral pneumonia, 75% had multiorgan failure, 75% required mechanical ventilation, and 22% needed renal replacement therapy. In the Australia and New Zealand experience, one third of patients receiving mechanical ventilation were treated with extracorporeal membrane oxygenation (ECMO), and 21% died. In Canadian experience, 81% of critically ill patients received mechanical ventilation for a median of 12 days. The 28-day mortality of these patients was 14.3%. Lung rescue therapies included neuromuscular blockade (28%), inhaled nitrous oxide (13.7%), high-frequency oscillatory ventilation (11.9%), ECMO (4.2%), and prone-positioning ventilation (3.0%). The 90-day mortality was 17.3%.

16. How should the patient admitted to the ICU be managed?

Any patient admitted to the ICU with a respiratory illness during the influenza season should be presumed to have influenza until proved otherwise by nasopharyngeal swab PCR. Patients may be seen with exacerbations of underlying cardiopulmonary diseases, primary viral pneumonia, or secondary bacterial pneumonias. All patients should be given treatment with a neuraminidase inhibitor and antibiotics. Antibacterial therapy should be directed primarily

against *S. pneumoniae*, *S. aureus*, and *H. influenzae*. Possible initial regimens may include ceftriaxone and vancomycin. Once respiratory and blood culture results are known, the empiric antibiotics should be narrowed or stopped.

17. What infection control measures are needed?

Influenza is most often spread by large-particle respiratory droplets created by patient coughing or sneezing. This mode of transmission generally requires close contact (3-6 feet) because these larger and heavier respiratory particles quickly fall out of the air. Hand contact with environmental surfaces contaminated with the virus can also transmit influenza when those hands come in contact with mucosal surfaces such as touching the eye, nose, or mouth. Concern has been expressed that influenza may be airborne transmitted by small-particle aerosols, though it is not clear how much this mode of transmission contributes to community spread. For the office and hospital, the CDC recommends standard and droplet precautions as follows:

- Placing the patient in a private room.
- Wearing a surgical mask when entering the patient room.
- Wearing gloves and gowns if you should expect contact with patient's blood, body fluids, or secretions (including respiratory).
- If participating in an aerosol-generating procedure such as intubation, extubation, bronchoscopy, or autopsy, a fit-tested N95 respirator or a powered air-purifying respirator (PAPR) should be worn.

All health care workers need to practice good hand hygiene before and after patient contact.

18. Who should get the influenza vaccine?

The CDC now recommends that all persons older than 6 months get yearly vaccination. This is especially true for those at high risk for complications of influenza as outlined earlier. The subcutaneous injectable form uses inactivated hemagglutinin antigen from three circulating vaccine strains. For those between 2 and 49 years of age who are in good health and not pregnant, a nasal aerosol of live attenuated viruses is available. Both forms are safe and effective. In children and adults younger than 65 years, approximately 90% developed protective levels of antibodies, though that may be less effective in the elderly and immune compromised. All health care workers need to be vaccinated yearly so as to remain healthy and not risk spreading influenza to the more vulnerable patients.

KEY POINTS: INFLUENZA

1. Influenza can cause severe respiratory illness requiring ICU care.
2. Influenza may exacerbate underlying cardiopulmonary conditions.
3. All patients admitted to the hospital for presumed influenza should be treated with antiviral medications.
4. Secondary bacterial pneumonias may develop and should be looked for and treated.
5. All persons aged older than 6 months should be vaccinated yearly.

BIBLIOGRAPHY

1. Fiore AE, Fry A, Shay D, et al: Antiviral agents for the treatment and chemoprophylaxis of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 60:1-24, 2011.
2. Girard MP, Tam JS, Assossou OM, et al: The 2009 A (H1N1) influenza virus pandemic: a review. Vaccine 28:4895-4902, 2010.

3. Homsi S, Milojkovic N, Homsi Y: Clinical pathological characteristics and management of acute respiratory distress syndrome resulting from influenza A (H1N1) virus. South Med J 103:786-790, 2010.
4. Kumar A, Zarychanski R, Pinto R, et al: Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 302:1872-1879, 2009.
5. Tang JW, Shetty N, Tsan-Yuk Lam T: Features of the new pandemic influenza A/H1N1/2009 virus: virology, epidemiology, clinical and public health aspects. Curr Opin Pulm Med 16:235-241, 2010.