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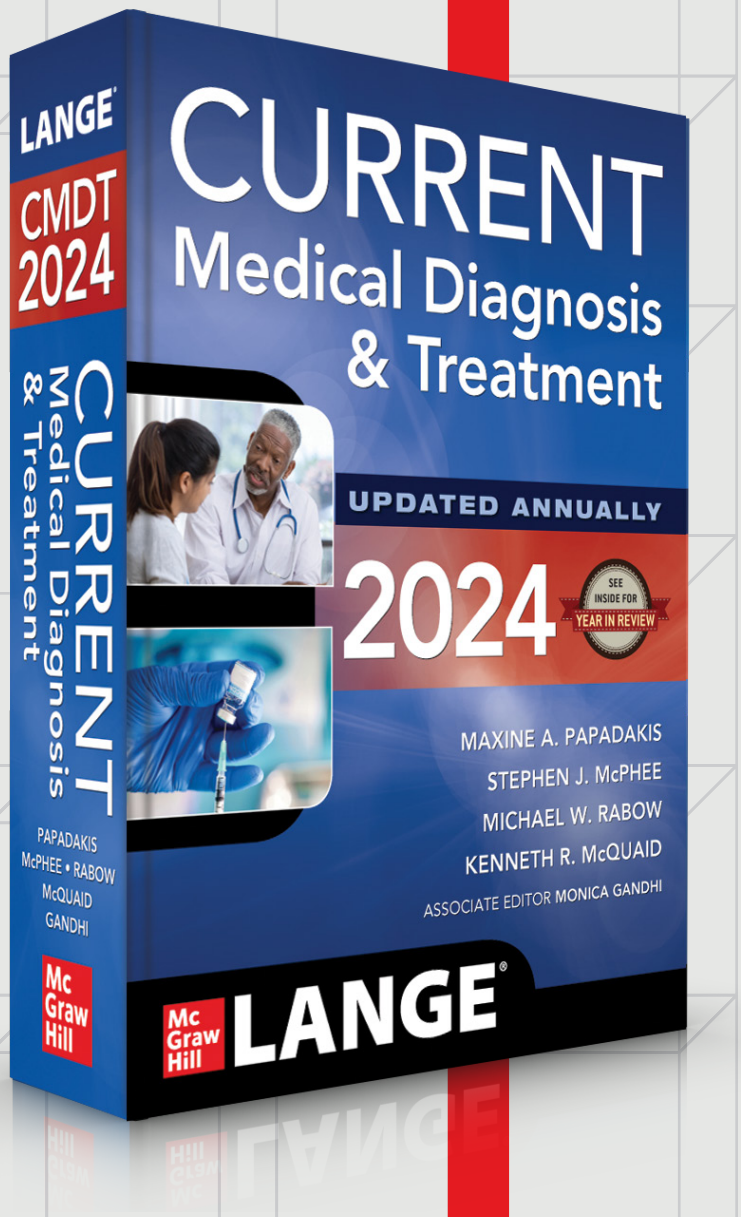
# Sample Excerpt

## Seasonal Influenza

*From Chapter 34*

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that bind to the surface F protein (such as rilematovir, presatovir, ziresovir, and sisunatovir). Compounds targeting viral replication also have been under study, including AZ-27, PC786, JNJ-64417184, and EDP-938.

The prophylactic monoclonal antibody palivizumab, while recommended for and effective in high-risk infants (premature infants less than 32 weeks' gestation as well as infants 32- to 25-weeks' gestation with additional risk factors such as congenital heart and lung diseases and Down syndrome), is not of proven efficacy among adults with RSV. The monoclonal antibody nirsevimab is also effective in preventing RSV-associated lower respiratory tract infections in premature and term infants. Another monoclonal antibody, clesrovimab, is undergoing phase 3 trials.

In 2023, an RSV vaccine from GSK was approved in the United States for people older than 60. Other vaccine candidates are in phase 3 clinical trials, including two protein subunit vaccine (by Pfizer) and two recombinant vector vaccines (one by Janssen and one by Bavaria Nordic).

Prevention in hospitals entails rapid diagnosis, hand washing, contact isolation, and perhaps passive immunization. (Passive immunization is costly but is associated with improved antiviral titers in hematologic stem cell transplant recipients.) The use of conjugated pneumococcal vaccination appears to decrease the incidence of concomitant pneumonia associated with viral infections in children in some countries. Viral shedding averages 11 days and correlates inversely with age and directly with severity of infection.

Therapeutic modalities for human metapneumovirus and parainfluenza virus infections under investigation include intravenous ribavirin administration.

Cunningham S et al. Nebulised ALX-0171 for respiratory syncytial virus lower respiratory tract infection in hospitalised children: a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9:21. [PMID: 33002427]

Elawar F et al. Pharmacological targets and emerging treatments for respiratory syncytial virus bronchiolitis. Pharmacol Ther. 2021;220:107712. [PMID: 33121940]

# Seasonal Influenza

**ESSENTIALS OF DIAGNOSIS**

- Cases usually in epidemic pattern.
- Onset with fever, chills, malaise, cough, coryza, and myalgias.
- Aching, fever, and prostration out of proportion to catarrhal symptoms.
- Leukopenia.

## General Considerations

Influenza (an orthomyxovirus) is a highly contagious disease transmitted by the respiratory route in humans. Transmission occurs primarily by *droplet nuclei* rather than fomites or direct contact. Three types of influenza viruses infect humans. While type A can infect a variety of mammals (humans, swine, horses, etc) and birds, types B and C almost exclusively infect humans. Type A viruses are further divided into subtypes based on the hemagglutinin (H) and the neuraminidase (N) expressed on their surface. Eighteen subtypes of hemagglutinin and 11 subtypes of neuraminidase are identified.

Annual epidemics usually appear in the fall or winter in temperate climates. Up to 5 million cases of severe influenza are estimated by the WHO to occur annually, with approximately 0.5 million annual deaths. Influenza epidemics affect 10–20% of the global population on average each year and are typically the result of minor antigenic variations of the virus, or **antigenic drift**, which occur often in influenza A virus. On the other hand, pandemics—associated with higher mortality—appear at longer and varying intervals (decades) as a consequence of major genetic reassortment of the virus (**antigenic shift**) or adaptation of an avian or swine virus to humans (as with the pandemic H1N1 virus of 1918).

The highly pathogenic avian influenza subtypes are discussed in the next section. The novel swine-origin influenza A (pandemic H1N1) virus emerged in Mexico in 2009 and quickly spread throughout North America and the world causing a pandemic. This virus originated from triple-reassortment of North American swine, human, and avian virus lineages and Eurasian swine virus lineages and replaced the previous H1N1 seasonal virus.

## Clinical Findings

### A. Symptoms and Signs

Type A and B seasonal influenza viruses produce clinically indistinguishable infections, whereas type C usually causes mild illness. The incubation period is 1–4 days. In unvaccinated people, uncomplicated influenza often begins abruptly. Symptoms range widely from nearly asymptomatic to a constellation of systemic symptoms (including fever, chills, headache, malaise, and myalgias) and respiratory symptoms (including rhinorrhea, congestion, pharyngitis, hoarseness, nonproductive cough, and substernal soreness). GI symptoms and signs may occur, particularly among young children with influenza B virus infections. Fever lasts 1–7 days (usually 3–5). Older patients especially may present with lassitude and confusion, often without fever or respiratory symptoms. Signs include mild pharyngeal injection, flushed face, and conjunctival redness. Moderate enlargement of the cervical lymph nodes and tracheal tenderness may be observed. The presence of fever (higher than 38.2°C) and cough during influenza season is highly predictive of influenza infection in those older than 4 years.

### B. Laboratory Findings

Rapid influenza diagnostic tests for detection of influenza antigens from nasal or throat swabs are widely available, highly specific, and produce fast results but have low sensitivity leading to high false-negative results. Because of this, *the CDC recommends empirically treating patients in whom influenza is suspected*. Not all commercial rapid influenza

diagnostic tests can differentiate between influenza A and influenza B, and none of the available rapid influenza diagnostic tests can provide information on influenza A subtypes. Newer digital immunoassays and rapid nucleic acid amplification tests are more sensitive than traditional rapid influenza diagnostic tests; however, the sensitivity of newer PCR techniques is compromised early in the season during low prevalence periods. A nasopharyngeal swab, nasal aspirate, combined nasopharyngeal swab with oropharyngeal swab, or material from a bronchoalveolar lavage can be tested for any influenza strain. When influenza pneumonia is suspected, lower respiratory tract specimens should be collected and tested for influenza viruses by RT-PCR or the above assays.

## Differential Diagnosis

The differential diagnoses for influenza-like infections include a variety of viral respiratory infections (SARS-CoV-2, parainfluenza, RSV, atypical dengue, adenovirus, enterovirus, coronavirus) or other viral infections (flavivirus, CMV, EBV, acute HIV infection), as well as bacterial infections such as mycobacterial infection (atypical pneumonia), pertussis, and Legionnaire disease. Epidemiologic factors can suggest Legionnaire (older adult smokers). Chronicity of cough may suggest adenovirus, mycobacterial, or pertussis infection. Leukocytosis and lymphadenopathy are more often seen with CMV and EBV. Distinguishing influenza from dengue requires attention to rhinitis (influenza) and thrombocytopenia (dengue).

## Complications

Hospitalization or ICU admission for influenza is often a consequence of diffuse viral pneumonitis with severe hypoxemia and sometimes shock. Patients with asthma, residents of nursing homes and long-term care facilities, adults aged 65 years or older, persons who have morbid obesity, and persons with underlying medical conditions (pulmonary, renal, cardiovascular, hepatic, hematologic, neurologic, and neurodevelopmental conditions; and immune-deficient conditions, such as HIV, diabetes, and cirrhosis) are at high risk for complications. Infection during pregnancy increases the risk for hospitalization and may be associated with severe illness, sepsis, pneumothorax and respiratory failure, spontaneous abortion, preterm labor, and fetal distress.

Influenza causes necrosis of the respiratory epithelium, increased adherence of bacteria to infected cells, and ciliary dysfunction, which predispose to secondary bacterial infections. Pneumococcal pneumonia is the most common secondary infection, and staphylococcal pneumonia is the most serious. *Haemophilus* spp infections also occur. Other frequent complications are acute sinusitis, otitis media, and purulent bronchitis.

CVDs are a complication of influenza infection, in particular among older adults, and influenza is postulated to be a significant trigger for MI, cerebrovascular disease, and sudden death. Several studies suggest that influenza vaccination has protective effect against major adverse cardiovascular events. Neurologic complications, including seizures and encephalopathy, may occur. Encephalopathic complications of influenza are uncommon.

**Reye syndrome** is a rare and severe complication of influenza (usually B type) and other viral diseases (especially varicella), particularly in young children. It consists of rapidly progressive hepatic failure and encephalopathy, and the mortality rate is 30%. The pathogenesis is unknown, but the syndrome is associated with aspirin use in the management of viral infections.

## Treatment

Treatment is supportive. Antiviral therapy should be considered for all persons with acute illness, in particular those at high risk for developing complications who have a suggestive clinical presentation or with laboratory-confirmed influenza. Clinical trials show a reduction in the duration of symptoms, hospital admissions, as well as secondary complications, such as otitis, sinusitis, or pneumonia, but not mortality when using these agents. Maximum benefit is expected with the earliest initiation of therapy. Although the benefit of antiviral therapy after 48 hours of illness is reduced, it should be initiated if the patient is hospitalized or critically ill. Benefit has been noted up to 4–5 days into illness.

The antiviral treatment of choice should be based on the susceptibility of the circulating virus. Since high levels of resistance to the adamantanes (amantadine and rimantadine) persist among seasonal H1N1 and H3N2 influenza A viruses and these agents are not effective against influenza B viruses, amantadine and rimantadine are not recommended for treatment.

Three neuraminidase inhibitors are FDA-approved for treatment of influenza A and B: oral oseltamivir, inhaled zanamivir, and intravenous peramivir. The CDC recommends treatment with **oral oseltamivir** (75 mg twice daily for 5 days) as the medication of choice for patients of any age, pregnant women, and patients who are hospitalized or have complicated infection. Absorption of oral oseltamivir is considered reliable, except in patients with impaired gastric motility or GI bleeding.

**Inhaled zanamivir** (10 mg, two inhalations twice daily for 5 days) is indicated for uncomplicated acute influenza in patients aged 7 years or older, is relatively contraindicated among persons with asthma because of the risk of bronchospasm and is not formulated for use in mechanically ventilated patients. Inhaled zanamivir lacks efficacy in pneumonia, probably due to poor bioavailability in the peripheral lungs.

**Intravenous peramivir** (600 mg in single dose) is used for outpatient treatment of uncomplicated infection in patients aged 18 years or older. It is also recommended if concern exists about inadequate oral absorption of oseltamivir. The efficacy of peramivir in patients with severe illness and in patients with influenza B is not well established. Some studies demonstrated that repeated doses for up to 5 days of intravenous peramivir are safe, effective, and shorten the duration of influenza illness.

Resistance to neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) can occur during or after prolonged use in immunocompromised patients, particularly

in persons who have undergone hematopoietic stem cell transplant. **Intravenous zanamivir** is an investigational drug that could be requested for clinical use if concern exists for an oseltamivir-resistant influenza strain. **Laninamivir** is a long-acting inhaled neuraminidase inhibitor used for the treatment of seasonal influenza, including infection caused by oseltamivir-resistant virus. It is licensed in Japan and South Korea but not in the United States.

**Baloxavir** (a selective inhibitor of influenza cap-dependent endonuclease that is given as a single oral dose) is FDA-approved for treatment of uncomplicated influenza A and B infections and postexposure prophylaxis. It is given as 40 mg or 80 mg orally as a single dose depending on weight (the higher dose for persons 80 kg or more) and should be given within the first 48 hours of infection. Its side effects include diarrhea, headache, and bronchitis. Baloxavir's unique mechanism of action may be beneficial as part of multidrug therapy for resistant or severe disease, however, an RCT (FLAGSTONE) of patients hospitalized with severe influenza, comparing baloxavir plus a neuraminidase inhibitor versus placebo plus a neuraminidase inhibitor did not indicate that combining antivirals improved outcomes. For complicated disease, especially in immunosuppressed patients, the combination of oseltamivir, amantadine, and ribavirin appears to produce faster viral clearance but no definite clinical improvement.

Updated advice is available at http://www.cdc.gov/flu/index.htm.

## Prognosis

The duration of the uncomplicated illness is 1–7 days, and the prognosis is excellent in healthy adults and children. Hospitalization typically occurs in those with underlying medical disease, at the extremes of age, and in pregnant women. *Most fatalities are due to bacterial pneumonia, although exacerbations of other disease processes, in particular cardiac diseases, occur.* Pneumonia resulting from influenza has a high mortality rate among pregnant women and persons with a history of rheumatic heart disease. Mortality among adults hospitalized with influenza ranges from 4% to 8%, although higher mortality (greater than 10–15%) may be seen during pandemics and among immunocompromised individuals. At least 64% of pneumonia and influenza deaths occurred among older persons in the United States, who comprised only 15% of the population.

If the fever recurs or persists for more than 4 days with productive cough and white cell count over 10,000/mcL ($10.0 \times 10^9$/L), secondary bacterial infection should be suspected.

## Prevention

*Annual administration of influenza vaccine is the most effective measure for preventing influenza and its complications.* Seasonal influenza vaccines can reduce influenza hospitalizations by an estimated 61%. Vaccination of health care workers is associated with decreased mortality among hospitalized patients and those in long-term care facilities. Vaccination prevents influenza illness among pregnant women and their infants during the first months of life.

The ACIP and the American College of Obstetricians and Gynecologists' Committee recommend annual influenza vaccination for all persons over 6 months of age with no contraindications. Vaccination is emphasized for high-risk groups and their contacts and caregivers.

Several Cochrane database analyses have examined the efficacy of the influenza vaccines in select populations. The studied groups include patients with COPD (a documented reduction in exacerbations with inactivated vaccine), older adults (where vaccination shows some efficacy), adults with cancer (weak evidence, some lower mortality and influenza-related outcomes), healthy adults (established efficacy with inactivated vaccine, but only modest effects in pregnant women and newborns), and healthy children (where both live and inactivated vaccines lower the rate of influenza infections).

Other reviews establish the efficacy and safety of influenza vaccination in patients with rheumatoid arthritis, asthma, or myasthenia gravis, and older nursing home patients. Patients with obesity have an impaired response to the influenza vaccine.

Multiple influenza vaccine products are licensed in the United States and available from different manufacturers (see Table 32–8). These include inactivated influenza vaccines (standard- or high-dose, quadrivalent [IIV4], adjuvanted or unadjuvanted), recombinant vaccines (quadrivalent [RIV4]), and live attenuated influenza vaccine (LAIV4). Available quadrivalent vaccines contain antigens from two strains of influenza A (H1N1 and H3N2) and two strains of influenza B (Victoria lineage and Yamagata lineage). The CDC does not endorse one influenza vaccine product over another, although each influenza vaccine product has different age indications and contraindications. The CDC publishes its annual influenza recommendations in the late summer (www.cdc.gov/mmwr).

LAIV4 (which was not recommended by the CDC during the 2016–2017 and 2017–2018 seasons in the Northern Hemisphere due to concerns about its effectiveness against influenza viruses in prior years) is considered an acceptable option for groups in whom it is indicated.

Adults over the age of 18 years, including pregnant women, can receive any influenza vaccine, with few exceptions. Patients 65 years or older should receive a high-dose quadrivalent inactivated influenza vaccine, which contain several times more hemagglutinin than standard dose influenza vaccines. Some data suggest intradermal vaccination is more effective than intramuscular vaccination in older adults. *The COVID-19 vaccines can be safely coadministered with the inactivated seasonal influenza vaccines with an acceptable reactogenicity profile and without evidence of immunointerference.* Several combined influenza and SARS-CoV-2 vaccines are under study.

Vaccination is contraindicated for persons with a history of severe allergic reaction to an influenza vaccine. Precautions should be taken if patients report a history of Guillain-Barré syndrome 6 weeks following an influenza vaccine and if patients have a moderate to severe acute illness with or without fever until clinical improvement. Persons with a history of egg allergy with hives only may receive any recommended influenza vaccine. Those with

more severe allergic reactions to eggs may receive any recommended vaccine under close observation in a health care facility under the supervision of a provider with experience treating severe allergic reactions. Two completely egg-free influenza vaccine options are licensed in the United States for the 2022–2023 season, the recombinant vaccine (Flublok Quadrivalent) and the cell culture-based inactivated (Flucelvax Quadrivalent, ccIIV4). Additional vaccine information can be found at https://www.cdc.gov/flu/professionals/index.htm.

When antiviral chemoprophylaxis is used, it prevents 70–90% of influenza infections. *Chemoprophylaxis is not routinely recommended and is not recommended prior to exposure to prevent development of resistance.* Chemoprophylaxis may be considered for persons at increased risk for complications from infection who are exposed to an infected patient within 2 weeks of vaccination, for persons unlikely to respond to vaccination because of immunosuppression after exposure to an infected person, for persons for whom vaccination is contraindicated and who are at high risk for complications after exposure to an infected person, and for prevention of infection in residents of institutions during an outbreak. Alternatively, a person can be monitored closely, and antiviral therapy initiated at the first onset of symptoms after exposure. Initiation of chemoprophylaxis is not recommended more than 48 hours after exposure. Patients taking chemoprophylaxis should seek urgent medical care if an influenza-like illness develops.

Chemoprophylaxis against influenza A and B is accomplished with daily administration of the neuraminidase inhibitors oseltamivir (75 mg/day, oral) or zanamivir (10 mg/day, inhaled) to continue through 7 days after last known exposure. For outbreak control in long-term care facilities and hospitals, a minimum of 2 weeks is recommended, including in vaccinated persons if the seasonal vaccine is not well matched to the circulating strain, to continue until 1 week after identification of the last known case. Zanamivir should not be given as chemoprophylaxis to asthmatic persons, nursing home residents, or children younger than 5 years.

Breakthrough infections with influenza occur with neuraminidase inhibitors (in a study with zanamivir) and with vaccination. The efficacy of chemoprophylaxis is proven for individuals and households but not community settings.

Hand hygiene and surgical facemasks appear to prevent household transmission of influenza virus isolates when implemented within 36 hours of recognition of symptoms in an index patient. Such nonpharmaceutical interventions assist in mitigating the spread of pandemic and interpandemic influenza to unvaccinated persons. In one study, patients with seasonal H1N1 influenza infection were infectious from 1 day before to about 7 days following illness onset. Children and immunosuppressed persons exhibit prolonged viral shedding and may be infectious longer. Winter school breaks during periods of high influenza transmission appear to decrease rates of visits to primary care practitioners for influenza illness among children and adults.

Any hospital patient in whom the infection is suspected should be isolated in an individual room with standard and droplet precautions. CDC guidelines recommend the equivalent of N95 masks for aerosol-generating procedures (eg, bronchoscopy, elective intubation, suctioning, administering nebulized medications). For such procedures, an airborne infection isolation room can be used, with air exhausted directly outside or recirculated after filtration by a HEPA filter. Strict adherence to hand hygiene with soap and water or an alcohol-based hand sanitizer and immediate removal of gloves and other equipment after contact with respiratory secretions is essential. Precautions should be maintained until 7 days from symptom onset or until 24 hours after symptom resolution, whichever is longer. Postexposure prophylaxis or close monitoring and early treatment should be considered for close contacts of patients who are at high risk for complications of influenza and may be considered for health care personnel, public health workers, or first responders who experienced a recognized, unprotected close contact exposure to a person with influenza virus infection during that person's infectious period.

### When to Admit

- Limited availability of supporting services.
- Pneumonia or decreased oxygen saturation.
- Changes in mental status.
- Consider with pregnancy.

Centers for Disease Control and Prevention (CDC). FluView: a weekly U.S. influenza surveillance report. https://www.cdc.gov/flu/weekly

Cohen C et al. Vaccinating mothers to protect their babies against influenza. J Infect Dis. 2020;221:5. [PMID: 31671176]

Grohskopf LA et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2022-23 influenza season. MMWR Recomm Rep. 2022;71:1. [PMID: 36006864]

Ikematsu H et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. N Engl J Med. 2020;383:309. [PMID: 32640124]

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Loeb M et al. Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational randomised, double-blind, placebo-controlled trial. Lancet Glob Health. 2022;10:e1835. [PMID: 36400089]

## 4. Avian Influenza

### ESSENTIALS OF DIAGNOSIS

- Most human cases occur after exposure to infected poultry.
- Clinically indistinguishable from seasonal influenza.
- Epidemiologic factors assist in diagnosis.
- Rapid antigen assays confirm diagnosis but do not distinguish avian from seasonal influenza.