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Complications of Viral Influenza

Michael B. Rothberg, MD, MPH,^{a,c} Sarah D. Haessler, MD,^{b,c} Richard B. Brown, MD^{b,c}

From the Divisions of ^aGeneral Medicine and ^bInfectious Diseases, Baystate Medical Center, Springfield, Mass; ^cTufts University School of Medicine, Boston, Mass.

ABSTRACT

Viral influenza is a seasonal infection associated with significant morbidity and mortality. In the United States more than 35,000 deaths and 200,000 hospitalizations due to influenza occur annually, and the number is increasing. Children aged less than 1 year and adults aged more than 65 years, pregnant woman, and people of any age with comorbid illnesses are at highest risk. Annual vaccination is the cornerstone of prevention, but some older patients may derive less benefit from immunization than otherwise fit individuals. If started promptly, antiviral medications may reduce complications of acute influenza, but increasing resistance to amantadine and perhaps neuraminidase inhibitors underscores the need for novel prevention and treatment strategies. Pulmonary complications of influenza are most common and include primary influenza and secondary bacterial infection. Either may cause pneumonia, and each has a unique clinical presentation and pathologic basis. *Staphylococcus aureus*, including methicillin-resistant strains, is an important cause of secondary bacterial pneumonia with high mortality. During influenza season, treatment of pneumonia should include empiric coverage for this pathogen. Neuromuscular and cardiac complications are unusual but may manifest in persons of any age.

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Viral influenza is a well-established cause of seasonal illness, generally characterized by acute onset of fever, myalgias, and respiratory symptoms. In healthy persons, disease usually resolves inconsequentially. However, influenza is estimated to cause 36,000 deaths and more than 200,000 hospitalizations annually in the United States.^{1,2} Although many hospitalizations are for pneumonia, influenza also is associated with a general increase in admissions for pulmonary and cardiovascular disease, and less frequently, neuromuscular complications. An appreciation of complications of influenza should spur the clinician toward more aggressive attempts at prevention and treatment.

Because influenza is rarely tested for in patients admitted to the hospital, and because most pneumonia cases related to influenza are secondary bacterial pneumonia rather than primary influenza pneumonia, estimates of hospitalization and mortality rates are modeled comparing outcomes for pneumonia and influenza (or respiratory and circulatory diseases) during months when influenza is circulating to

rates during the rest of the winter. On the basis of this methodology, hospitalizations attributable to influenza vary from 50,000 to 400,000,² depending on the duration of the season and predominant strain. Recently, influenza A (H1N1) seems to be the mildest, influenza B is intermediate, and influenza A (H3N2) is most severe, accounting for 66, 81, and 99 hospitalizations per 100,000 persons, respectively, with 80% of deaths due to influenza A (H3N2).²

Although estimates of influenza mortality are indirect, they are remarkably consistent when different models are compared.³ They all demonstrate an increase in mortality during the past 30 years.^{4,5} One explanation is the rapid aging of the US population. The mortality rate for persons aged more than 85 years is 16 times greater than that of persons aged 65 to 69 years.² Similarly, the median length of stay increases from 6 days (patients 50-64 years old) to 8 days (>75 years old).²

RISK STRATIFICATION

Assessing individual risk can help target vaccination during normal influenza seasons and prioritize during vaccine shortages.⁶ Chronic medical conditions, such as heart dis-

Requests for reprints should be addressed to Michael B. Rothberg, MD, MPH, Division of General Internal Medicine and Geriatrics, Baystate Medical Center, Springfield, MA 01199.

E-mail address: michael.rothberg@bhs.org

ease, lung disease, diabetes, renal disease, rheumatologic disease, dementia, and stroke, are all risk factors for influenza complications. Regardless of age, those with high-risk conditions have increased rates of hospitalization and death (Figure).^{7,8} Thus, high-risk patients aged 45 to 64 years have a risk equivalent to that of all patients aged more than 65 years.⁷ Because of the high incidence of occult cardiopulmonary disease in older persons, the Advisory Committee on Immunization Practices has extended its vaccination recommendation to include all persons more than 50 years old.⁹ For patients aged more than 65 years, high-risk conditions are particularly dangerous. According to one clinical prediction rule, those at highest risk demonstrate a 30-fold greater risk of influenza-related hospitalization or death than otherwise healthy elderly persons.¹⁰

Other groups at risk for influenza complications include those who are pregnant or immune suppressed. Compared with non-pregnant women, both high and low-risk pregnant women—especially during the third trimester—have more cardiopulmonary events during influenza season.¹¹ Nevertheless, pregnant women have low vaccination rates, with only 13% reporting vaccination in 2004.⁹ This is at least

partially related to a reluctance to vaccinate on the part of obstetricians.^{12,13}

Influenza is an important cause of morbidity and mortality among selected populations with altered immune response. Patients with human immunodeficiency syndrome (HIV) and influenza have a typical clinical presentation and fever is common, despite vaccination.^{14,15} Both the rate and duration of hospitalization are greater in HIV-infected persons, as is mortality.¹⁶⁻¹⁸ Infection with influenza virus did not influence the progression of HIV disease during 5 months of follow-up.¹⁹

Organ transplant recipients are at even higher risk from influenza with two thirds demonstrating either viral pneumonia or secondary bacterial pneumonia, with a related 50% mortality rate.²⁰ Influenza also triggered allograft rejection in 62% of patients in one study.²¹

CLINICAL SIGNIFICANCE

- Influenza virus is a common cause of morbidity and mortality.
- Complications of influenza include pneumonia and exacerbations of underlying pulmonary and cardiac disease.
- The very young, the elderly, and those with comorbid illnesses are at highest risk.
- Annual vaccination is the cornerstone of prevention but might not be as effective in the elderly.
- Antiviral therapy can be an adjunct to vaccination in high-risk patients.

PULMONARY COMPLICATIONS OF VIRAL INFLUENZA

The most frequent serious complications of influenza are pulmonary and fall into 4 categories: primary influenza pneumonia, secondary bacterial pneumonia, pneumonia due to unusual pathogens or in immunocompromised hosts, and exacerbations of chronic pulmonary diseases.

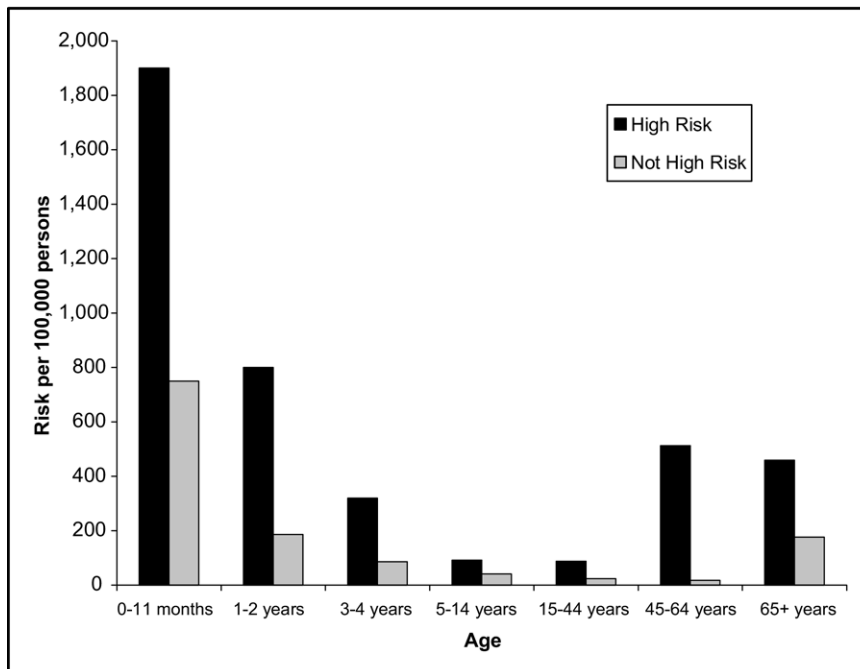


Figure Annual risk of hospitalization for high-risk and non-high-risk persons.

Primary Influenza Virus Pneumonia

The first conclusive evidence that influenza virus could cause pneumonia came during the 1958 to 1959 pandemic.²² Patients with primary influenza pneumonia accounted for 18% of those admitted to hospitals with evidence of lower respiratory complications of influenza. All were aged more than 45 years, had underlying cardiac disease, and presented with classic influenza symptoms including high fever, non-productive cough, and myalgia. Soon all appeared seriously ill, with extreme dyspnea and cyanosis. Findings on physical examination included diffuse rales and wheezing. Laboratory studies demonstrated leukocytosis and normal erythrocyte sedimentation rate. Bacteriologic studies were negative, and sputum samples did not induce bacterial peritonitis when injected into rodents. Radiographs revealed diffuse infiltrates that mimicked pulmonary congestion. Mortality was 80%.²² During interpandemic periods, patients with influenza pneumonia are more likely to have underlying cardiopulmonary disease, and mortality is 6% to 29%.^{23,24} Pathologic findings in pure influenza pneumonia include necrotizing bronchitis, hyaline membranes, intra-alveolar hemorrhage and edema, and interstitial inflammation—changes identical to those seen with acute respiratory distress-like syndrome associated with influenza pneumonia in 1918.²⁵

More recently, influenza A caused by an H5N1 virus (“avian flu”) has been associated with large avian epidemics spreading from Southeast Asia, with more than 250 cases reported in humans.²⁶ Victims are often young, previously healthy persons, and the fatality rate is approximately 60%, usually due to respiratory failure.²⁶ Spread appears to be primarily bird to human via droplet inhalation. Illness occurs after an incubation of 3 to 8 days; initial symptoms include high fever and lower respiratory symptoms.^{26,27} Cough, which may be productive, is common and hemoptysis has been described. Severe dyspnea and respiratory distress are noted within 1 week. Complete blood count often shows leucopenia and thrombocytopenia.²⁷ The most common x-ray presentation is patchy or interstitial infiltrates, and infrequently, pleural effusion. Adult respiratory distress syndrome and multiorgan dysfunction are seen in patients with severe illness and often precede death. Post-mortem investigations confirm that death is most commonly associated with diffuse lung injury.^{26,27} Vascular congestion and formation of hyaline membranes are noted. Findings are most consistent with primary viral pneumonia, rather than secondary bacterial complications.

Secondary Bacterial Pneumonia

Bacterial pneumonia complicating viral influenza was reported during the pandemic of 1918 and multiple subsequent epidemic and inter-epidemic periods.^{22,23} Typical viral influenza infection is followed by near resolution of symptoms, subsequently complicated 4 to 14 days later by a recurrence of fever, dyspnea, productive cough, and pulmonary consolidation.²⁸ The most common pathogens are

Streptococcus pneumoniae, *Staphylococcus aureus*, *Haemophilus influenzae*, and occasionally other gram-negative bacilli.²⁹

S. aureus pneumonia following influenza was first described during the 1918 pandemic. Striking features included a fulminant course, unusual cyanosis (“cherry-red indigo-blue”), lack of consolidation on pulmonary examination, dirty salmon-pink purulent sputum, leucopenia, multiple micro-abscesses on autopsy, and a near-universal fatality.³⁰ Subsequent reports confirmed an increased incidence of *S. aureus* pneumonia during the epidemic of 1968 to 1969.²⁹ Staphylococcal toxic shock syndrome arising from the respiratory tract during influenza infection also has been described.³¹ During the 2003 to 2004 and 2006 to 2007 influenza seasons, cases of severe community-acquired pneumonia due to methicillin-resistant *S. aureus* (MRSA) were reported with 33% mortality.^{32,33}

The mechanisms by which bacteria act synergistically with influenza virus include increased binding and invasion of bacteria, increased viral replication, and modification of the host inflammatory response. The interactions between influenza virus and bacteria have most thoroughly been established with streptococcus pneumoniae. As the viral neuraminidase cleaves sialic acid to release new viral particles from host cells, damage to the epithelial layer of the airways occurs, exposing binding sites necessary for adherence of the pneumococcus.³⁴

Pulmonary Complications with Unusual Pathogens

Multiple reports describe secondary pneumonia caused by less common microorganisms. These include *Aspergillus* sp., *Chlamydia pneumoniae*, B-hemolytic streptococci, and *Legionella pneumophila*.³⁵⁻³⁸ Six cases of invasive aspergillosis have been reported, all in immunocompetent persons, with 5 deaths.

Noninfectious mimics of infection that may be incited by influenza include bronchiolitis obliterans organizing pneumonia,³⁹ usual interstitial pneumonia,⁴⁰ and transient Goodpasture’s syndrome.⁴¹ Influenza-related bronchiolitis obliterans organizing pneumonia has been described in lung transplant recipients and was associated with allograft rejection. Goodpasture’s syndrome resolved with cure of influenza.

Exacerbations of Chronic Lung Diseases

Although rhinoviruses and coronaviruses account for the majority of pathogens that exacerbate chronic lung disease, influenza also may account for as much as 25%.⁴² Mechanisms by which influenza virus and other respiratory viruses induce exacerbations of chronic respiratory diseases are incompletely understood but are likely related to inflammatory mediators, including interleukins, cytokines, and modifications in the ratio of T-cell subsets that lead to increased sensitivity to other allergens.⁴³

Miscellaneous Complications of Viral Influenza

In addition to the systemic and respiratory effects of viral influenza, and the pulmonary complications that can arise from the direct effects of influenza virus on the lung, this virus can exert direct and indirect effects on other body systems. Myositis and rhabdomyolysis have been rarely reported associated with either influenza A or B.⁴⁴ In one study, more than 50% of patients hospitalized with influenza A were noted to have elevations of creatine phosphokinase, and 2 of these demonstrated muscle necrosis on biopsy. Clinical severity varies but can include renal failure and problems with ambulation involving proximal leg muscles. Symptoms generally resolve in 4 to 6 weeks.

Neurologic complications of influenza include encephalopathy (Reye's syndrome), encephalomyelitis, transverse myelitis, aseptic meningitis, focal neurologic disorders, and Guillain-Barré syndrome. Central nervous system involvement is most common in children.⁴⁵ Pathogenesis includes direct viral invasion and development of antigen/antibody complexes, but is often uncertain. Presentation is generally rapid, and mortality may reach 30%. Acute necrotizing encephalopathy has been reported primarily from Japan, most commonly in association with influenza A. Disease is often fulminant and fatal.

Diagnosis of central nervous system involvement is based on clinical and laboratory findings. Lumbar puncture demonstrates elevated protein and lymphocytic pleocytosis. Computed tomography and magnetic resonance imaging scanning should be performed in cases of focal or severe neurologic symptoms; abnormalities predict adverse outcomes.⁴⁵

Reye's syndrome is an acute, noninflammatory encephalopathy documented by the clinical picture and a record of cerebrospinal fluid containing less than 8 leukocytes/mm³ or histologic sections of the brain demonstrating cerebral edema without perivascular or meningeal inflammation, associated with either (a) fatty liver or (b) a 3-fold elevation of transaminases or serum ammonia.⁴⁶ A correlation with influenza activity has existed for several decades; more than 90% of cases occur in white children less than 14 years of age. Confirmed adult cases have been associated primarily with influenza A and have resulted in death. Up to 500 cases annually were reported in the 1970s with a 33% mortality rate. Incidence has dramatically declined during the past 2 decades, likely because of the appreciation of the role of salicylates in causation.

Psychiatric complications after influenza infection are considered controversial. Several studies note increased rates of schizophrenia in offspring of women who developed influenza during the second trimester of pregnancy,⁴⁷ implying fetal developmental brain abnormalities. This was especially related to the influenza epidemic of 1957 but has been associated with other influenza seasons.

Although influenza frequently exacerbates underlying heart problems, such as congestive heart failure and isch-

emic heart disease, direct cardiac complications are considered uncommon. Both pericarditis and myocarditis have been noted. In a prospective study, abnormal electrocardiographic findings were present in 50% of adults without cardiac symptoms.⁴⁸ Alterations were seen at presentation, and most resolved by 28 days. No patients had muscle damage or reduced ejection fractions. Influenza pneumonia seems to predispose one to myocardial infarction, and congestive heart failure exacerbations are more common during influenza season.

IMPACT OF PREVENTION AND TREATMENT ON COMPLICATIONS

Vaccine

Given the tremendous health and economic burden of influenza, preventing both illness and complications are public health concerns. The cornerstone of prevention remains annual vaccination with trivalent killed virus vaccine. Recommendations are for yearly vaccination for all adults aged more than 50 years, children aged 6 to 59 months, patients of any age with chronic medical conditions, women who will be pregnant, immune-suppressed patients, caretakers of high-risk patients, and health care workers.⁹

In healthy adults and children, influenza vaccine prevents 50% to 80% of influenza illness depending on the adequacy of match with circulating virus.⁴⁹ It is less effective in preventing influenza-like illness. Vaccination also may have a modest impact on work loss, preventing 0.13 days of work lost per worker vaccinated. Even considered in aggregate, trials have been too small to demonstrate a reduction in influenza complications.

There is less direct evidence about vaccine efficacy in elderly and high-risk patients. A Cochrane review of all 5 randomized trials including more than 5000 patients demonstrated a rate of vaccine effectiveness of 58% against influenza and 43% against influenza-like illness.⁵⁰ There were few participants aged more than 70 years, but there seemed to be little efficacy in this group. Observational cohort studies offer conflicting data. For elderly individuals living in the community (>1 million patients in 15 studies), vaccination failed to protect against influenza-like illness, influenza, or pneumonia, but was associated with a 26% reduction in hospitalization from influenza and pneumonia, and a 42% reduction in all-cause mortality.⁵⁰ Vaccinated patients were older and had more comorbid disease than nonvaccinated patients. After adjustment for confounders, vaccination was associated with a reduced risk of hospitalization from respiratory diseases (odds ratio 0.78), cardiac disease (odds ratio 0.76), and all-cause mortality (odds ratio 0.53). For the subset of patients at high risk of complications, there was no effect of vaccination on influenza, pneumonia, or hospitalization, but there was a 61% reduction in all-cause mortality.

Reductions in all-cause mortality during winter months have been challenged on several grounds. First, the antibody

response of elderly patients to influenza vaccine is blunted⁵¹ and T-cell responses are short-lived.⁵² Second, it is unclear how a vaccine that does not protect against influenza, pneumonia, or death from respiratory causes reduces all-cause mortality.⁵³ Finally, it has been proposed that if vaccination did decrease all-cause winter mortality by more than 50%, such a decline should be noticeable in age-adjusted mortality rates as the proportion of the population vaccinated against influenza increased from 15% in 1980 to 65% in 2001.⁴ During seasons dominated by the more severe H3N2 strain, pneumonia and influenza deaths did indeed decline as vaccination levels increased, whereas age-adjusted all-cause mortality remained flat.⁴

One explanation is selection bias—that frail elderly patients at highest risk of death are less likely to be vaccinated, but that available administrative data do not capture frailty. Indeed, data from 2 cohort studies^{54,55} demonstrated that vaccinated high-risk persons had lower mortality before, during, and after influenza season, and that adjusting for diagnosis code variables did not affect this relationship. In a companion case-control study,⁵⁶ adjusting for functional status as identified through chart review negated the mortality effects of influenza vaccination, whereas adjustment for diagnosis codes enhanced the effect of vaccination. Although influenza vaccination undoubtedly provides some benefit for the elderly, more research needs to be done on ways to improve the efficacy in older persons. Potential methods include alternative modes of delivery, immune adjuvants, strategies for indirect protection through immunization of family and caregivers, and greater use of antiviral medications.⁵⁷ Immunization of health care workers is particularly important because influenza is common in this group⁵⁸ but often unrecognized,⁵⁹ and vaccination of health care workers has been associated with decreased mortality among patients in long-term care facilities.^{60,61}

Antiviral Medications

During an influenza outbreak, medications can prevent influenza illness, lessen symptoms, and prevent complications. Two adamantanes (amantadine and rimantadine) and 2 neuraminidase inhibitors (oseltamivir and zanamivir) are available in the United States. Because of high levels of resistance to amantadine during the 2005 to 2006 season (resistance increased from 1.9% in 2002 to 91% in 2006),⁶² adamantanes are not currently recommended. Resistance to oseltamivir has been reported in Japan but remains low worldwide.^{63,64} Avian influenza (H5N1) may be resistant to all available agents.⁶⁵

Clinical trials of anti-influenza medications have mostly enrolled healthy adults and children.⁶⁶⁻⁶⁹ All agents shorten illness by approximately 1 day. Treatment must be started within 48 hours of symptoms and is most effective when started within 6 hours.⁷⁰ Treatment also seems to be more effective in high-risk patients.⁷¹ Neuraminidase inhibitors decrease antibiotic use by 25% and rates of lower respiratory tract infections by 40% to 55%.⁷² Pooled analyses of oseltamivir trials demonstrated a 59% decrease in hospitalizations among treated patients relative to placebo, both for

average-risk and high-risk patients.⁷² There are no studies in hospitalized patients.

There are no clinical trials of anti-influenza medications for avian influenza. Although oseltamivir and zanamivir appear active against avian influenza in vitro, observational studies found that treated and untreated patients have similar mortality,²⁷ and resistance to oseltamivir has been reported in Vietnam.⁷³ On the basis of ferret models, earlier treatment or higher dosing might improve the efficacy of oseltamivir.⁷⁴

Secondary bacterial pneumonia should be treated promptly with antibiotics.⁷⁵ Because of the recent increase in rates of MRSA pneumonia after influenza infection, clinicians in countries where MRSA is prevalent should strongly consider using empiric vancomycin or another antimicrobial with efficacy against MRSA pending bacteriologic data.

Influenza outbreaks can occur in long-term care facilities, despite high levels of vaccination.^{76,77} Seasonal prophylaxis with adamantanes^{78,79} or neuraminidase inhibitors⁸⁰ have been shown to prevent new cases of influenza illness, but control also can be achieved once an outbreak is detected by administering prophylaxis to asymptomatic individuals.^{81,82} Adamantanes are not currently recommended because of resistance.⁹

Future studies may examine the role of antiviral therapy in patients hospitalized with complications of influenza. Another candidate for this indication is HMG-CoA reductase inhibitors (“statins”). Observational trials found these agents to reduce the risk of pneumonia hospitalization^{83,84} or mortality,⁸⁵ although these results may be confounded by a “healthy user” effect.⁸⁶ Randomized trials are needed, but given the paucity of treatments potentially available for pandemic flu, statins may be a low-cost option available to all countries.⁸⁷

CONCLUSIONS

Complications of viral influenza involve numerous organ systems. An appreciation of those at risk and the role of prevention and treatment may allow more timely management strategies. Better use of influenza vaccines and antivirals may decrease risks of pulmonary complications, but novel prevention and treatment strategies are needed to improve outcomes for those at highest risk and if new strains of influenza virus emerge.

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