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Influenza Year 2000 Update: Epidemiology, Diagnosis, and Outcome-Effective Guidelines for Neuraminidase Inhibitor Therapy

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Misery, suffering, and prostration: a distinctly unpleasant triad of sensations that say, "influenza." Every experienced clinician can recognize the classical symptoms of this common viral infection that every year, almost like clockwork, rears its unpredictable antigenic heads, in which neuraminidase and hemagglutinin surface proteins play musical chairs, thereby defying enduring host immunity.

The incentives for ameliorating the signs and symptoms of influenza are well known. The abrupt onset of fever, myalgias, malaise, sore throat, and cough that characterize influenza turn even the most robust individual into a compromised creature who begs for symptomatic relief. The bad news is the influenza season is just around the corner. The good news is we finally have a potent, well-tolerated arsenal of antiviral agents that can positively affect clinical outcomes.

From all apparent signs, the influenza season of 2000-2001 promises to be problematic. Vaccine manufacturers have experienced lower than expected yields for a component strain—the A/H3N2/Panama component has been especially difficult to grow—required for the year 2000-2001 vaccine.[1] Currently, the Centers for Disease Control and Prevention (CDC) predicts that 40-70 million doses will be available this year. Last year, more 80 million vaccine doses were available.[1] Moreover, initiation of vaccination programs will be delayed one month and it is expected they will be restricted to high-risk individuals.

Add to this looming problem that approximately 10,000-40,000 Americans die from influenza each season and that the economic and productivity costs linked to this viral infection are staggering. Even when mortality is not the outcome of influenza infection, the disease produces significant morbidity that ranges from transient, disabling symptoms to secondary bacterial infections—among them, sinusitis, bronchitis, and pneumonia. Although symptomatic relief using supportive measures and over-the-counter pain relievers were once the accepted approach for managing flu-mediated discomfort and misery, recent evidence-based studies have clarified the outcome-effectiveness and clinical value of neuraminidase inhibitors such oseltamivir and zanamivir in this patient population.

Put simply, currently approved neuraminidase inhibitors—oseltamivir, which is available in an orally administered preparation, and zanamivir, which requires inhalation—are active against their intended targets, produce minimal side effects, and are associated with low level of induction of drug resistance. To maximize the therapeutic benefits for patients, however, prompt recognition of flu symptoms and early diagnosis are required.

Moreover, it should be stressed that neither drug should be considered a substitute for proper vaccination of target populations; vaccination remains the bulwark of defense against infection, spread, and secondary complications.

With these issues in mind, the author of this evidence-based review evaluates the current clinical approach to the patient with influenza. A detailed discussion of epidemiological patterns and diagnostic strategies is complemented by a thorough assessment of therapeutic benefits offered by neuraminidase inhibitors, which range from reduction of symptom severity and duration to potential prophylactic use and reduction of intra-household viral transmission.

— The Editor

Influenza Viruses: Architecture and Action

Influenza viruses are small RNA viruses belonging to the Orthomyxoviridae family. There are three major types of influenza virus, two of which have been documented to cause infection in the human population. Influenza Type A is the most common and is responsible for major worldwide pandemics. It may infect pigs, horses, seals, whales, and birds as well as humans. Different strains of Influenza A infect some but not all hosts. Influenza Type B, a derivative strain, infects only humans. This strain is simpler and more stable, although it may cause regional epidemics. Its impact is not as global as Type A, but this virus can cause a significant public health problem. Type C belongs to an entirely different genus and does not appear to cause human disease.

Viral Architecture. The architecture of the influenza virus helps explain its unique capacity for infecting the human host and its pathogenic durability over time. Simply speaking, the influenza virus may be visualized as a ball studded with "spikes." These spikes or protuberances represent surface proteins (hemagglutinin and neuraminidase). *(See Figure 1.)* Hemagglutinin binds the virus to the target epithelial cell receptor, while neuraminidase degrades the receptor, permitting the virus to enter the cell. Neuraminidase then facilitates release of newly formed viral particles, or virions, which promote spread of the infection within the organism.

These proteins also are the antigens that initiate immune system surveillance. As would be expected, host recognition of these specific proteins by the immune system confers long-lasting immunity against the specific virus. They also reveal the specific identity of the virus and allow epidemiologists to track various strains of influenza that are infecting a population over time or from region to region. Currently, 15 hemagglutinin and nine neuraminidase subtypes have been identified. Interestingly, only three hemagglutinin and two neuraminidase subtypes are commonly associated with human infection. Individual subtypes show minor sequence differences that characterize the various strains, each of which is named according to type, geographic origin, strain sequence number, and year of isolation.[2] *(See Figure 2.)*

Antigenic Drift. The RNA core genome of the virus is composed of multiple, segmented single strands of nucleic acids. Lacking the quality control of complementary strand DNA replication, translation errors are frequent. Most mutations are lethal to the virus but some variations (e.g., hemagglutinin is particularly labile) survive and propagate new antigenic variants. These variations are recognized as new strains; they have diminished immunological recognition in the community, thereby permitting the virus to spread infection. From a temporal perspective, this antigenic drift is of clinical significance from the perspective of changes in annual infection patterns and is responsible for periodic, winter epidemics of influenza. In the case of antigenic drift, major subtypes of the hemagglutinin and neuraminidase antigens remain the same.[3]

Antigenic Shift. Antigenic shifts are characterized by major changes in surface antigens on influenza A and are associated with severe illness and worldwide pandemics. Such antigenic shifts originate from the genetic recombination of two strains within a single infected cell and subsequent propagation of the progeny virus manifesting a new configuration of surface anti-

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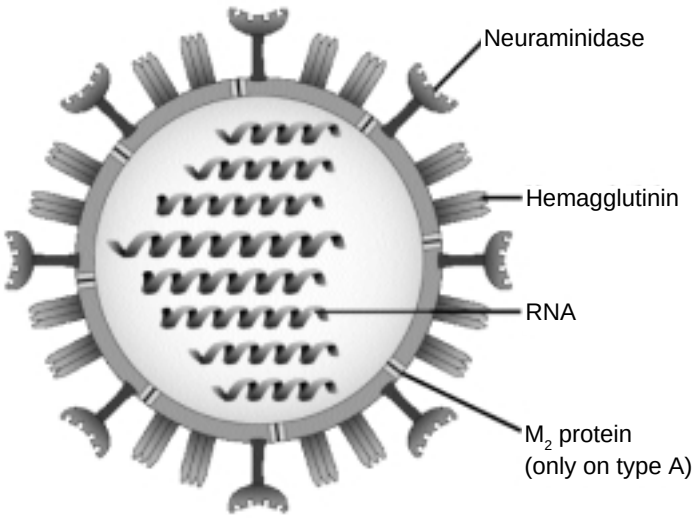
Figure 1. Influenza Surface Proteins



gens. Antigenic shift is facilitated by the segmented nature of the RNA genome. From a clinical perspective, shift is significant for its association with diminished, or complete lack of, contemporary human immunity and, as a result, sets the stage for widespread disease in the susceptible population.

The major subtype(s) of hemagglutinin and/or neuraminidase will change with antigenic shift. For example, the Asian flu pandemic of 1957 was characterized by a shift from a H1N1 to a H2N2 influenza strain. Seventy thousand deaths were reported in the United States alone. The recombination of avian and human viral subtypes within infected hogs appears to be the primary crucible for development of new strains with pandemic potential. Modern pandemics have had a propensity for originating in China, where pigs, birds, and people live in close proximity. Figure 3 illustrates the cycles of epidemics and pandemics that derive from antigenic drifts and shifts, respectively.[2,3]

The influenza B virus is more stable and does not demonstrate the antigenic shifts characteristic of influenza A. It is implicated primarily in regional epidemics rather than worldwide pandemics and, accordingly, this virus typically receives less attention from the professional and lay press. This pathogen, however, can produce widespread disease and accounted for 80% of influenza infections in the winter of 1991-1992. Military installations and schools appear especially susceptible, and specific complications, such as Reye's syndrome and myositis, are encountered more commonly with influenza B infection.

Pandemic Potential. In 1997, six people in Hong Kong died from a particularly lethal strain of influenza, which had a reported mortality rate of 30%.[4] Prior to these reported cases, the H5N1 strain isolated from these patients had been known to infect only birds.[5] Public health officials rapidly isolated the source as commercial poultry, a significant percentage of which were infected with the responsible strain. After transmission from bird to human was documented, an unprecedented public health decision was made to slaughter 2 million birds.[6]

Although person-to-person transmission was documented in some cases, the virus had not yet developed the ability to transmit readily from person to person. If the virus had acquired that capability, the consequences could have been catastrophic. Computer models estimated that up to one-third of the world's population could have died.[2] Development, manufacture, and distribution of a vaccine to contain the virus would have taken six months.[4] Unfortunately, modern transportation networks would have carried the virus around the world in epidemic proportions within four months. The case for effective therapeutic agents was made.

Epidemiology and Infectious Patterns in the Community

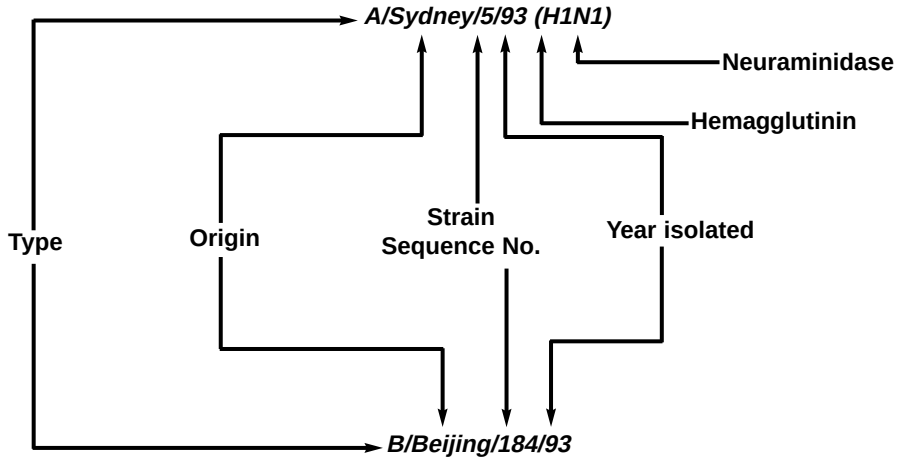
Community influenza epidemics typically are short, widespread, and infect a substantial segment of populations. In addition, the onset of a community epidemic is abrupt and peaks within several weeks, with the entire flu "season" lasting 1-2 months during the winter in temperate climates. The first sign of community involvement is an increased incidence of respiratory infection in children that is associated with widespread school absenteeism. As a rule, up to 30% of local children will be involved.

Transmission. Characteristic transmission patterns for influenza have been documented in both the adult and pediatric populations. In this regard, transmission is highest in families with school children.[7] Adults typically acquire the disease from children, a transmission pattern that is accompanied by an increase in physician and emergency room visits for "flu." Interestingly, hospitalization rates are higher at the end of the season. Up to 20% of adults in the community may be infected, with even greater penetration in closed, at-risk communities such as nursing homes, schools, and military installations.[7] While it has been customary to focus on the increased risk and complication rate among the elderly, children younger than age 1 also are susceptible to infection and have an increased mortality rate.

Respiratory secretions generated by coughing and sneezing transmit individual infections. Hand-to-hand contact also has been implicated. Infection is limited to the respiratory epithelium, and ciliated columnar cells initially are involved. Viral replication proceeds over 4-6 hours, is followed by rapid, local invasion of all cell types, and culminates with cell death and necrosis. The infection spreads by local extension throughout the respiratory tract, with clinical symptoms appearing as early as 18 hours after inoculation. The patient remains infectious for 2-5 days following the appearance of symptoms. Although extensive systemic signs, such as fever, generalized malaise, myalgias, and headache, are the hallmark of influenza, the virus rarely is found outside the respiratory tract, and viremia is not a characteristic of most infections.[7]

Host Response. The host reaction to viral invasion is rapid and complex. Humoral immunity, which is mediated by IgG and secretory IgA antibodies directed against the hemagglutinin antigen, appears early and plays an important role in immunity.[8] The antibody levels against hemagglutinin antigens are used as

Figure 2. Naming Influenza Viruses



markers for disease activity and for confirming immunity. The cell-mediated response is intense; increased concentrations of tumor necrosis factor (TNF), interferon gamma, and interleukin 6 parallel disease severity in clinical studies.[9] Immunity to a specific strain is clinically protective and long lasting. Immunological durability was confirmed by reemergence of the H1N1 "Russian" flu strain in 1977, which was identical to a strain responsible for epidemics between 1947 and 1950. The pandemic primarily affected those younger than age 25. Individuals exposed to the virus prior to 1950 had developed and maintained effective immunity.[2]

Presentation and Natural History

Overview. The clinical spectrum of influenza illness is well documented and, more often than not, is recognized by the astute clinician. The classic constellation of signs and symptoms includes sudden onset of elevated temperature, generalized malaise, headache, and fever. The initial temperature rise can be precipitous, with fever and associated systemic symptoms remitting over 2-3 days. These signs and symptoms are associated with such respiratory complaints as sore throat, cough, and sputum production, which develop several days after the initial systemic complaints. The respiratory symptoms become more prominent as the illness matures, with the cough lasting up to two weeks.

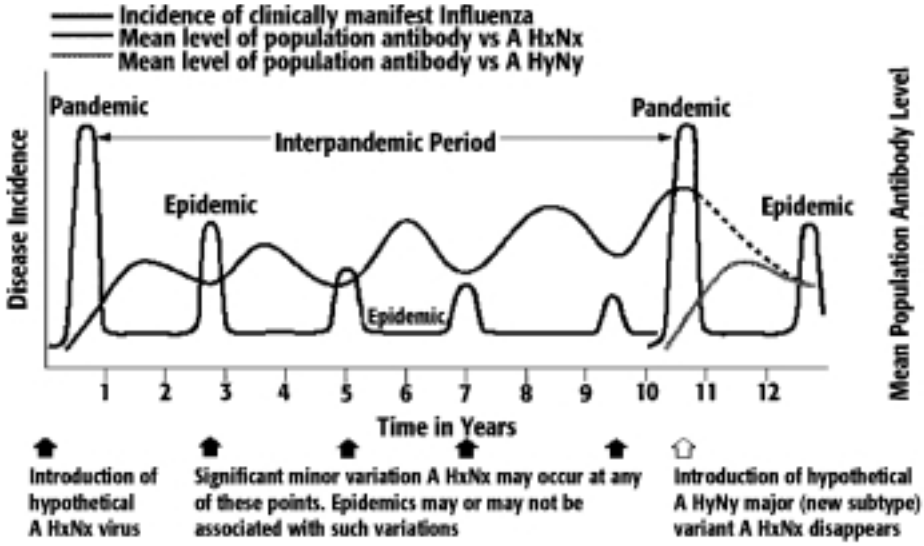
Because of fatigue, weakness, and other lingering symptoms of the respiratory tract, full recovery from influenza often takes several weeks.[10] Patients may miss an entire week of employment or school. During the 1994 influenza season, 90 million Americans contracted the disease; they spent 170 million days in bed and missed 69 million days of work.[2] Complications of influenza are not uncommon and often are the major source of morbidity and mortality. Primary influenza viral pneumonia is the most common, and also one of the most serious, complications. It occurs early and is characterized by rapid progression of fever, dyspnea, and cyanosis. Chest x-ray (CXR) demonstrates diffuse, non-focal findings and the clinical course is rapid, with findings and a clinical course similar to that seen with adult respiratory distress syndrome. Secondary bacterial pneumonia also may occur, especially in the very young and very old. *Staphylococcus aureus* and *Streptococcus pneumoniae* are common bacterial pathogens, and when suspected, require antimicrobial therapy.

Diagnosis. It may be difficult to differentiate influenza from a number of common respiratory illnesses on clinical grounds alone. Other viral illnesses or bacterial or atypical respiratory infections (e.g., *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and early bacterial pneumonia) can be difficult to rule out. Even streptococcal throat infections can present in a manner that may make it difficult, especially during the early stages, to distinguish from the flu. In the very young and elderly, differentiation from respiratory syncytial virus (RSV) infection is difficult on clinical grounds and may require laboratory confirmation.[11,12] When influenza is widespread and documented serologically and/or clinically within a community, however, the signs and symptoms of this infection usually are specific enough to permit timely diagnosis.

From a practical clinical perspective, a detailed, thorough history and physical examination usually are sufficient to make the diagnosis. Clearly, the positive predictive value of a test, laboratory measurement, or diagnostic strategy for any specific infection increases significantly as the incidence of the disease rises within the population being evaluated. This finding also applies to the predictive value of signs and symptoms elicited in the course of a history and physical examination. For example, when the influenza virus is confirmed by local authorities, state health departments, or the CDC to be present in a region or a community, persons with fever, muscle aches, and cough most likely will have influenza.[13] Several studies have shown a clinical accuracy of as high as 85% during confirmed outbreaks. During clinical trials with zanamivir, it was found that experienced physicians using key factors in the history demonstrated a diagnostic accuracy rate as high as that reported in recently marketed rapid immunoassay kits.[14]

The importance of epidemiological surveillance cannot be overemphasized. The Influenza Diagnosis Working Party (IDWP), an international expert panel, determined that epidemiological support is essential for accurate clinical diagnosis.[15] Although many studies have attempted to differentiate influenza by symptoms alone, the protean nature of this viral illness (as well as most others) hampers diagnostic distinction in the absence of supportive epidemiological data and support.[16] Knowledge of a local outbreak or known contact with a patient with influenza is key to the effectiveness of clinical diagnosis. Accordingly, local health departments and the CDC have long monitored influenza activity. Commercial monitoring by pharmaceutical companies has been initiated during the past two years and increasingly detailed information is now available to

Figure 3. Occurrence of Influenza Pandemics and Epidemics



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the practitioner. Detailed maps of influenza activity are available to the lay public via cable TV and on the Internet. Surveillance sites are noted in Table 1.

From a diagnostic perspective, the most important factors in the patient history are the presence of systemic symptoms: headache, fever, myalgias, malaise, and chills accompanied by cough and sore throat. The onset of these signs and symptoms typically is abrupt, and the patient often can tell the physician exactly when they fell ill.[11] Young, otherwise healthy patients are often surprised by how poorly they feel. In the setting of known disease, these historical features will point to the correct diagnosis. Typically, physical findings are nonspecific and often minimal.[13] The patient may look ill, but specific signs of influenza are remarkable for being unremarkable. An elevated temperature of 39°C or 40°C is present for the first 2-3 days. The skin may appear moist and flushed. The chest exam is often normal. Indeed, the presence of chest findings suggest the possibility of complications or underlying medical problems.[13]

Laboratory Examination. Typical, rapidly available laboratory findings are nonspecific in patients suspected of having influenza. For example, white blood cell (WBC) counts are variable and, not infrequently, are normal. While a low WBC with a left shift has been associated with influenza, the absolute count and differential are not diagnostic and offer little help in differential diagnosis. The virus is readily recovered from nasopharyngeal washes, but 48-72 hours are required for culture confirmation of infection. Serologic documentation requires 14 days. The CXR is normal in uncomplicated cases. As a result, obtaining a "routine" CBC and CXR in uncomplicated cases adds little to the diagnostic accuracy,[11,13] and is responsible for overloading ancillary support services better utilized for other patients.

It should be stressed that a CXR is indicated when physical findings or clinical course point to pneumonia. The presence of such underlying medical conditions as chronic obstructive pulmonary disease (COPD), asthma, or cardiac disease also may dictate the need for CXR. Rapid assay kits are now being marketed for the detection of influenza A and B; they will be useful for confirmation of clinical diagnosis. Results may be available in as little as 15 minutes, and these tests have few hands-on steps. They are regulated by the Clinical Laboratories Improvement Act and carry a rating of intermediate complexity, which limits their use in many private practice settings. These tests will be of great benefit to local community practitioners for determining local infection rates. It can be expected that rapid assay tests will subjectively enhance patient confidence in the diagnosis and will provide evidence-based support for increasing the prescription rate of antiviral therapy.

It is well appreciated that many patients with symptoms of the "flu" have come to "expect" antibiotic treatment for their illness. Positive results from on-site immunoassay tests that support a viral diagnosis may help discourage these patients from seeking inappropriate antibiotics and bolster the practitioner's resolve to withhold these medications if not indicated. Use of diagnostic kits in a children's hospital emergency department has led to a significant decrease in antibiotic use while increasing the use of appropriate antiviral therapy.[17] Table 2 outlines diagnostic kits that are currently available.

Age Considerations. Compared to the young and middle-age adult population, the elderly individual and the very young child are more likely to suffer from influenza infection and its complications. In addition, the diagnosis may be more problematic at the extremes of age. While most adults present with a classical picture, the presentation in young children is often more subtle, with signs and symptoms mimicking other common childhood diseases. In particular, the distinctive clinical picture of adult influenza often is muddied by the subjective nature of the pediatric history and its interpretation by concerned parents.

First, the child's ability to describe the myalgias, headache, and malaise of influenza is limited. Gastrointestinal symptoms of vomiting and diarrhea, which are rare in adults with influenza, are not uncommon in children. Alternatively, the infection may present to the clinician as acute laryngotracheitis/croup or classic bronchiolitis. Infants may present with severe bronchiolitis progressing to respiratory failure. Differentiation from parainfluenza or RSV infections frequently require culture or immunoassay. The very young infant/neonate may appear moribund and require a septic workup. Finally, febrile seizures are not uncommon in the infant.[18]

The elderly patient also may represent a diagnostic dilemma, because in this population, the findings of influenza may be understated. In the geriatric patient, neurological symptoms of confusion, lassitude, and decreased mental acuity with high fever

Table 1. Influenza Surveillance Networks, 2000-2001

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

www.cdc.gov/ncidod/diseases/flu/fluvirus.htm

Weekly culture and mortality reports collated with state health department reports and sentinel physician surveys.

NATIONAL FLU SURVEILLANCE NETWORK (NFSN)

www.fluwatch.com

Network of practicing physicians using ZstatFlu diagnostic kits. Uses CDC reports for specific typing of virus.

FLUTRACK

www.flutrack.com

Community level surveillance service provided by Glaxo-Wellcome. Updated weekly.

may predominate. Nasal stuffiness is common. The classic abrupt onset often is missed, and the malaise, myalgias, and cough, although present, may be dominated by the more pronounced mental symptoms.[15] The elderly patient with underlying health problems is more likely to develop complications of influenza. They also may suffer a prolonged convalescence with pronounced lassitude. Termed post-influenza asthenia, this post-acute phase can affect the patient's ability to manage his or her own affairs.[13] There may be a need to assess the living situation, with a possible need for placement, as the elderly are at risk for a progressive, gradual deterioration of multiple organ system function leading to a persistent generalized decreased level of health or death.[13]

Complications. A number of pulmonary, cardiac, and hepatic complications have been reported in patients with influenza. Viral pneumonia is a serious, potentially life-threatening complication. Mortality is high and patients do not respond to antibiotics. Bacterial pneumonia is seen in about 1-3% of patients as a secondary infection, often in the recovery phase of the illness. The findings and clinical course are that of classic lobar pneumonia in a host weakened by a prior viral infection. Typical pathogens isolated are *Streptococcus pneumoniae, Staphylococcus aureus*, and *Haemophilus influenzae*. The response to appropriate antibiotic therapy in patients suffering from bacterial infection is rewarding. It should be stressed that a "mixed" pattern of pneumonia—one showing characteristics and a time course incorporating features of both primary viral and secondary bacterial pneumonia—has been recognized with increased frequency. Therapy, which has included antibiotics and supportive care, has produced good outcomes.[10,13]

Virtually all healthy patients will suffer some transient deterioration of pulmonary function during an episode of influenza. Those with underlying problems are at higher risk. Adults with COPD frequently experience exacerbation of chronic bronchitis and are at increased risk for developing either viral or bacterial pneumonia. Patients with asthma may develop status asthmaticus. Children with cystic fibrosis (CF) may suffer severe compromise. Respiratory failure is the leading source of mortality.[13] Myositis with exquisite pain in the legs may occur. The calf muscle is most commonly involved and creatine phosphokinase (CPK) is elevated. It is most common in children with influenza B.[18]

Reye's syndrome is characterized by acute fatty deterioration of the liver with accompanying liver failure and encephalopathy. It occurs after many viral infections, especially with the use of aspirin, which is a precipitating epidemiologic cofactor. It has occurred after both influenza A and B infections but is more commonly seen after infection with influenza B. It is typically recognized as the patient recovers from the antecedent viral infection. The patient begins to vomit and may go on to have an altered mental status. Frank encephalopathy may progress to coma, decorticate posturing, brain stem abnormalities, and death.

Liver abnormalities may be encountered. Laboratory examination in these patients reflects hepatic insult and encephalopathy with elevated transaminases, serum ammonia, and prothrombin time. According to some experts, the liver biopsy is characteristic and is essential for confirming the diagnosis. Treatment is supportive and aimed at correcting biochemical abnormalities while reducing intracranial pressure. Fortunately, there has been a sharp decline in incidence as the use of aspirin had decreased, which should not be prescribed for symptoms of influenza because of the risk of Reye's syndrome in children.[18]

Other complications encountered less frequently include central nervous disease with encephalitis, Guillain-Barré syndrome, and transverse myelitis.

Cardiac complications are becoming less common. Although myocarditis and pericarditis were reported early in the 20th century, these complications have become less common in recent epidemics. ECG changes with influenza most often represent deterioration of underlying cardiac problems rather than direct invasion of the myocardium.[13]

Table 2. Rapid Diagnostic Tests

CLIA Certified Office-Based Tests*				Detect Viral Antigen		
NAME	COST (DOLLARS)	TIME (MIN.)	STEPS	SENSITIVITY‡	SPECIFICITY‡	COMMENT
Directigen Flu A	19.00	15	11	88%	92%	Flu A only
Flu OIA	16.50	15	5	95%	64%	
QuickVue	20.00	10	3	73%	95%	
ZstatFlu	18.00	20	4	62%	98%	Pharyngeal swab
Influenza Rapid Test	NA	10	4	85%	81%	

* = Average reimbursement $35.00

‡ = Nasopharyngeal swab

Prevention

Immunization with inactivated flu virus vaccines remains the cornerstone of public health efforts to reduce the effect of influenza.[19] Such

Table 3. Candidates for Influenza Vaccine

INDICATED FOR:

- Health care workers
- Homeless persons
- Persons at high risk of severe consequences of contracting influenza
- Patients > 50 years of age
- Presence of a chronic health condition including: asplenia, asthma, chronic pulmonary disease, diabetes, heart disease, hemoglobinopathy, HIV infection, immunosuppression, metabolic disease, renal disease
- Patients maintained on long-term aspirin therapy
- Pregnant women in the second or third trimester
- Public safety workers
- Staff and residents of nursing homes and residential facilities such as dormitories and prisons
- Travelers to foreign countries where influenza activity is reported

CONTRAINDICATED FOR:

- Persons with a history of anaphylactic reactions to eggs
- Persons with hypersensitivity to vaccine components
- Persons with acute febrile illness

Source: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 1999;48(RR-4); Update: Influenza activity-United States and worldwide, 1998-99 season and composition of the 1999-2000 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 1999;48:374-378.

vaccines are typically trivalent and active against the two strains of influenza A and one strain of influenza B that are predicted to be epidemic in the coming flu session. The inactivated vaccine stimulates specific humoral immunity against the selected strain. As explained earlier, antigenic drift requires new viral preparations each year and annual vaccination. The CDC publishes recommendations for annual vaccination. *(See Table 3.)* Prevention of disease is possible in nearly 80% of patients younger than 65 years and declines with age. Although vaccines are less effective in preventing illness in the frail elderly, vaccinations maintain effectiveness in the prevention of complications, hospitalizations, and death in nursing home populations.[19]

It should be stressed that manufacturers are experiencing lower than expected yields for a component strain required for the year 2000-2001 vaccine.[1] In particular, the A/H3N2/Panama component has been especially difficult to grow. Currently, the CDC predicts that only 40-70 million doses will be available this year. Last year, more than 80 million doses were available.[1] Moreover, initiation of vaccination programs will be delayed one month and it is expected that they will be restricted to high-risk individuals. The level of concern about vaccine shortfalls is demonstrated by a pilot project to determine efficacy of half-dose immunization. Volunteers at St. Louis University School of Medicine have been entered into a blinded study using a full or half-dose of vaccine. Serum antibody titers three weeks after inoculation will be used to determine immunogenicity.[20]

A live attenuated, cold-adapted, trivalent intranasal virus vaccine has undergone successful trials and has demonstrated efficacy that is as good or greater than traditional inactivated vaccines. No adverse events were reported.[21] Developed by Aviron, the live virus vaccine stimulates cellular immunity in addition to humoral immunity. The T-lymphocytes are able to respond to closely related strains of the specific selected components. The robustness of this broadened immunity has been demonstrated with induced antibody and endurable resistance to new strains in a second flu season after vaccination. Recipients developed antibody to the circulating A/Sydney strain without inclusion of this strain in the vaccine.[22] The vaccine was 86% effective in preventing infection.[22]

The intranasal delivery system is particularly attractive for the pediatric population. Acceptance of this vaccine with increased childhood immunizations may have significant effect on propagation of annual epidemics. FDA approval has been sought for the coming 2000-2001 flu season. Development of intranasal vaccines to specific immunogenic components (HA) of influenza virus also is underway. These vaccines would not be dependent on the unpredictable process of harvesting virus using fertilized eggs. The recombinant technology could produce vaccines with 2- to 3-month lead times, thereby increasing their usefulness for controlling pandemic infection.[2]

The CDC appropriately emphasizes the importance of vaccination. Treatment and/or prophylaxis with effective antiviral agents is not considered a substitute for effective prevention.[19] Unfortunately, this year's decreased vaccine inventories will likely lead to a less effective disease prevention program and an increased demand for treatment with neuraminidase inhibitors.

Treatment Strategies for Influenza: The Mandate for Neuraminidase Inhibitor Therapy

Overview. Until effective, well-tolerated, and convenient antiviral therapy became available, the treatment of influenza and "flu-like" illnesses was primarily symptomatic. In this model, the emphasis has been on bed rest, increased fluid consumption, and fever control. Supportive therapy also extended to treatment of complications. Unfortunately, many influenza patients who do not have bacterial infections as a secondary component of their flu—and who, therefore, would more likely be eligible for antiviral therapy—inappropriately are prescribed antibiotics. In one study that surveyed outpatient treatment for flu-like symptoms, investigators found that more than 50% of patients received antibiotics. The most commonly prescribed antimicrobial class was the macrolides. Only 21% received antiviral therapy.[23]

The temporal window for successful antiviral intervention in patients with influenza is relatively small. Because the illness is usually self-limited and significant resolution can be expected without therapy in most patients within 5-7 days of symptom onset, treatment must be initiated early in the course of illness if clinicians intend to limit the significant morbidity associated with influenza. The first antiviral agents, amantadine and rimantadine, were marketed for influenza with recommendations that

Table 4. Antiviral Agents for Influenza

Generic Name	Trade Name	Indications	Dosage	Wholesale Cost - Treatment	Comments
M2 INHIBITORS — INFLUENZA A					
Amantadine	Symmetrel	Treatment > age 1 Prophylaxis > age 1	100 mg bid × 7 days 100 mg qd	$6.45 (generic) $14.38 (branded)	CNS side effects > age 65 — dose decreased to 100 mg qd If CrCl < 80 mL/min — decrease dose
Rimantadine	Flumadine	Treatment > age 14 Prophylaxis > age 1	100 mg bid × 7 days 100 mg qd	$32.60	If CrCl < 20 mL/min — decrease dose
NEURAMINIDASE INHIBITORS — INFLUENZA A AND B					
Zanamivir	Relenza	Treatment > age 7	2 blisters bid × 5 days	$46.18	Dischaler inhalation device Pending indication: Prophylaxis > age 7 Caution with history of bronchospasm
Oseltamivir	Tamiflu	Treatment > age 18	75 mg bid × 5 days	$59.54	Pending indications: treatment > age 1; prophylaxis > age 1 Mild GI side effects

they be prescribed early in the course of the illness. Recently introduced neuraminidase inhibitors have indications for use within the first two days of symptoms.

Amantadine (Symmetrel). Specific antiviral therapy for influenza began about 30 years ago with the introduction of amantadine. This drug targets the M2 membrane protein of influenza A and is effective in reducing the duration of symptoms of established illness. Timely use reduces fever and other symptoms of influenza by 1-2 days.[24] It also is an effective prophylactic agent during epidemics affecting both adults and children.[24] Rapid emergence of resistance and lack of activity against influenza type B compromise its usefulness. Resistance has been documented within single households, in which treated index cases transmitted resistant virus to other family members.[25] Significant neurologic side effects associated with amantadine, including lightheadedness, nervousness, confusion, and insomnia, occur most frequently in the elderly.[26]

Rimantadine (Flumadine). This anti-influenza agent produces fewer neurologic side effects but, like amantadine, is subject to rapid emergence of resistance, lacks efficacy against type B, and is not indicated for acute therapy in children. If rimantadine is started during the first 48 hours of illness, it has been found to reduce symptoms of influenza by 1-2 days as compared to placebo in young adults.[27] Trials in elderly patients have produced similar results. Controlled trials have shown that this antiviral agent is 70-90% effective in preventing disease in populations ranging from school children to elderly nursing home residents.[28] Neither amantadine nor rimantadine has been shown to decrease mortality or complications of influenza.

Neuraminidase Inhibitors: Zanamivir and Oseltamivir. The two prominent surface proteins of the influenza virus, hemagglutinin and neuraminidase, have been investigated extensively as part of the ongoing effort to develop more effective antiviral agents. In particular, neuraminidase has proven to be a suitable target for antiviral therapy, inasmuch as inhibition of neuraminidase activity prevents spread of virus within the host and aborts the infection.[29,30] Although recognition sites for human antibodies to neuraminidase vary across strains of influenza, the active binding site for sialic acid, and hence for biologic activity, is fixed. Molecular modeling of the neuraminidase protein indicated there is conservation of the active sialic acid binding site across known types and subtypes of influenza viruses. As a result, successful inactivation of the binding site via neuraminidase inhibition will hinder virtually all strains and limit development of resistance.[29,30]

Zanamivir (Relenza). The first active neuraminidase developed was zanamivir which, because it has minimal activity against mammalian neuraminidase, limits toxicity and side effects. Clinical studies with experimental and natural infection demonstrated decreased length of viral shedding, decreased symptoms, and reduced severity in both Type A and B influenza infections.[29,31] The critical measure in clinical trials of time to relief of all symptoms was 1.5-2.0 days in several Phase III studies of patients with naturally occurring influenza. Symptom relief was 2.5 days earlier in high-risk patients and this was accompanied by a decrease in complications.[29,30,32] Specific studies also showed efficacy with influenza B infections.[33] In vaccinated elderly patients with active influenza infection, zanamivir was effective in reducing symptom duration vs. placebo suggesting synergistic benefit with vaccination in high-risk elderly patients.[34]

Zanamivir's ionic nature mandated direct delivery of the drug

to the respiratory mucosa by inhalation. Side effect profiles in trials reported such patient complaints as nasal and throat discomfort, headache, and cough; these symptoms were similar in frequency to control groups. Questions were raised about possible deterioration of respiratory function in patients with existing COPD and asthma. In this regard, bronchospasm has occurred in patients with asthma.[31,32] Moreover, the package insert contains important precautionary information regarding the use of zanamivir in patients with underlying airways disease. Drug interactions have not been reported, and no adjustment in dosage for patients with renal disease is recommended.[35] The drug is taken as a five-day course using a proven dischaler design. It is indicated for patients 7 years of age and older with fewer than 48 hours of signs and symptoms of influenza A or B.

Oseltamivir (Tamiflu). The need for an orally active drug led to the development of oseltamivir. The original compound GS 4071 proved as effective as zanamivir in early trials. Conversion of a prodrug, GS 4104 (oseltamivir), permitted oral absorption. Double blind studies in experimentally induced influenza with A/Texas/36/91 (H1N1) demonstrated this agent was effective both for prophylaxis and as an early treatment modality.[9,14,36] Phase III clinical trials evaluating naturally occurring influenza in a total of 1384 patients worldwide confirmed clinical efficacy of oseltamivir.[31]

Reducing the time required for relief of all major, acute influenza symptoms was the critical measure of therapeutic success demanded by regulatory agencies for clinical trial design and drug approval. With these end points and parameters in mind, oseltamivir reduced duration of disease by 30% (1.3 days) in the U.S. trial. In addition, measures of disease severity declined by 40% and time to resumption of usual activities declined by more than two days. Of special importance was the observation that such complications as otitis media, sinusitis, bronchitis, and pneumonia were reduced by about 50%.[31,37] Specific efficacy also was demonstrated against influenza B infection, with a decrease in symptom duration by 25%.[32,38]

Taken orally as a 75 mg dose twice daily for five days, oseltamivir was well tolerated in clinical trials and the drug's safety profile was excellent. The original trials reported nausea in 17-19% of patients and vomiting in 13 -15% of patients in the treatment group. These gastrointestinal symptoms were described as transient and mild by the recipients and led only one patient to withdraw from the study.[39,40] Subsequent studies demonstrated a significant reduction of gastrointestinal symptoms with concomitant consumption of food.[39] Moreover, resistant strains were uncommon and, when present, represented viruses with limited infectivity in humans. Drug interactions were minimal with no dosage adjustments required for concurrent medications; elderly patients also required no dosage adjustment. However, patients with renal disease should have their dosage decreased to once a day if they have a CrCl less than 30 mL/min. Oseltamivir has not been studied in patients with CrCl less than 10 mL/min.[39] Oseltamivir is indicated for patients older than age 18 with a presumptive diagnosis of influenza who present with symptoms of fewer than two days duration.

Although Phase III trials report similar efficacy with oseltamivir and zanamivir, there are no reported studies comparing these neuraminidase inhibitors in a head-to-head trial. Neither are there comparative data with respect to the established drugs, amantadine and rimantadine. Physician and patient preference will be determined by side effect profiles and mode of delivery. There are no published data evaluating the use of neuraminidase inhibitors in pregnant women.

Prophylaxis. The neuraminidase inhibitors also have been shown to be effective for prevention of influenza infection. In pivotal clinical trials, neuraminidase inhibitors showed efficacy with 1- to 2-day decreases in time to alleviation of all significant symptoms of influenza. Zanamivir once a day was 79% effective in prevention of influenza transmission within families with a confirmed index case.[41] A double blind, placebo-controlled study with 1107 patients tested the effectiveness of zanamivir for prevention of influenza over a 28-day period during a local epidemic. Laboratory examination confirmed that influenza occurred in 2% of treated patients vs. 6% of placebo recipients. Inhaled zanamivir was proven effective for reducing transmission of influenza A and B in a nursing home during an influenza outbreak.[42] Application for a prophylaxis indication was filed with the FDA in July 2000 for expedited review.

Orally administered oseltamivir, 75 mg once daily, was 92% effective in protecting close family contacts against influenza and reduced transmission within households by 89%.[40,43] Long-term studies of frail elderly patients taking oseltamivir 75 mg qd in a residential home care setting provided 92% protection against influenza.[43] Mean age of the recipients was 81 years. Application for a prophylaxis indication in adolescents and adults 13 years of age and older with oseltamivir was filed in May 2000 with consideration for expedited review.

Ongoing studies of the neuraminidase inhibitors also have shown efficacy in childhood. A double blind, placebo-controlled study of zanamivir in the 1998-1999 Northern hemisphere flu season recruited 471 children with flu-like symptoms. Among these, 346 had culture-proven influenza; dischaler therapy significantly shortened time to alleviation of symptoms and time to resumption of normal activity, and the treatment group used less relief medication. Complications and associated antibiotic use were deceased by 16% and 12%, respectively.[44]

Oseltamivir also has been studied in pediatric populations. A study of 695 patients 1-12 years of age showed a statistically significant 37% reduction in duration of influenza symptoms and allowed patients to return to normal activity 40% faster than placebo-controlled patients. The incidence of acute otitis media was reduced by 43%, and use of antibiotics to treat secondary complications was reduced by 40%.[45] Oseltamivir was well tolerated, with an incidence of gastrointestinal side effects similar to adult studies. The suspension is reported as pleasant tasting and application for a pediatric indication for children ages 1-12 was filed in June 2000.

Pharmacoeconomic Considerations. Some health maintenance organizations and other third-party payers have questioned the outcome-effectiveness of neuraminidase inhibitors, and as a

result, these drugs frequently have been excluded from such panels. The perception by some evaluators that there is only marginal efficacy with these antiviral medications stands in stark contrast to the clinical observations of patients, physicians, and investigators who have prescribed or consumed these medications and evaluated their efficacy first hand.

In an effort to reconcile clinical impressions in real world practice with trial data, investigators followed 1408 patients who were prescribed zanamivir in Australia during the 1999 flu season. Symptom relief was reported by more than 50% of patients within 24 hours and by 77% of patients within 48 hours of drug administration.[46] Of the 400 elderly patients included, 78% were satisfied with their treatment, with 59% reporting symptom relief within 24 hours.[46] The survey concluded that zanamivir was associated with early return to normal activities. They also noted the prolonged nature of residual cough in treated influenza after systemic symptoms of fever, headache, myalgia, and malaise had resolved. Investigators speculated that residual cough prolonged the temporal end point in the clinical studies and, thus, the true clinical effects of treatment may have been underestimated.

Resistance to zanamivir and oseltamivir has been induced in influenza A and B both in vitro and in vivo. In the laboratory, multiple passages through cell culture are required.[47] Resistance during clinical trials has been detected but is infrequent.[48] It appears that alterations of neuraminidase sialic acid binding site that confer resistance also diminishes the virus' ability to propagate. Post-marketing studies to detect significant resistance are under way.

Timely Therapeutic Intervention and New Standards for Influenza Treatment. Neuraminidase inhibitors represent a significant step forward in antiviral drug development. Pending new drug applications promise extension of indications for children and prophylaxis. Ongoing clinical trials are examining efficacy in high-risk patients, especially in individuals residing in long-term, skilled care facilities. Reduction of complications continues to be examined.

Emerging data, however, are very positive and suggest that this class of agents has the capacity to accomplish one or more of the following clinical, prophylactic, or epidemiological objectives:

- Reduce duration and severity of flu symptoms;
- Reduce incidence of secondary bacterial infections;
- Reduce spread of disease by making vectors less infectious;
- Possibly reduce mortality, especially in the elderly;
- Achieve pharmacoeconomic benefits including decreased use of antibiotics;
- Reduce patient load in acute care facilities; and/or
- Prevent development of flu epidemics (by reducing transmission rates).

Clearly, outcome-effective use of these medications demands prompt diagnosis of influenza and timely response by the medical care provider. The classic advice that adheres to the principles of "go home, go to bed, take a couple of aspirin, and call in the morning if you are not better," does not take advantage of the symptom—and complication—ameliorating benefits offered by neuraminidase.[18,19,30] The historical option of offering a patient an appointment with his or her personal physician or clinic in a couple of days if they do not feel better misses the window of opportunity to treat influenza with neuraminidase inhibitors, which are safe and well-tolerated agents that can positively affect the natural history of the disease. In this regard, providing relief of symptoms using only traditional over-the-counter analgesics and decongestants or even more problematic, inappropriately prescribing antibiotics, ignores the opportunity to minimize duration of symptoms afforded by neuraminidase inhibitor therapy.

Moreover, it can be expected that a reasonable standard of care for patients early in their course of influenza will consist of effective antiviral therapy that shortens illness, decreases symptoms, and reduces the risk of complications. In an age characterized by empowered health care consumers, informed patients will want, and predictably will even request, medications that permit them to return to work promptly while reducing complications, decreasing viral transmission within their household, and potentially returning children to school without prolonged absenteeism.

Inevitably, medical professionals, public health personnel, and pharmaceutical manufacturers, working cooperatively, will educate the public about new therapies that have become available for influenza. To this end, prospective patients eligible for antiviral therapy should be prepared to seek medical attention if they develop symptoms of a febrile respiratory illness in the setting of a local influenza outbreak. Recognizing the abrupt onset of flu symptoms is essential so therapy can be initiated promptly.

Summary

Those working in outpatient clinics, emergency departments, and urgent care centers, as well as office based primary care physicians should meet the prevention and therapeutic challenges presented by yearly influenza epidemics. Telephone triage systems should be established to screen for those individuals with classic symptoms of influenza and promptly direct them where they can be evaluated and treated with minimal delay.[18,19,30] The opportunity to reduce viral transmission within households should not be underestimated. Accordingly, specific time slots dedicated to prompt evaluation and treatment of afflicted patients should be established during anticipated flu seasons. Treatment protocols emphasizing clinical diagnosis, recognition of complications, and use of effective antiviral medications need to be prepared and distributed to the health care team.

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Physician CME Questions

65. Package inserts to zanamivir contain a relative caution to:
    A. patients with liver disease.
    B. children younger than age 12.
    C. patients with congestive heart failure (CHF).
    D. patients with a history of bronchospasm.
    E. elderly patients in nursing homes.

66. Primary control of influenza epidemics is dependent on:
    A. chemoprophylaxis of all susceptible persons with amantadine/rimantadine.
    B. chemoprophylaxis of high-risk patients with zanamivir/oseltamivir.
    C. an effective, timely vaccination program.
    D. quarantine of suspected cases.

67. From a diagnostic perspective, the most important factor(s) in a patient history is (are) the typically abrubt onset of which of the following systemic symptom(s)?
    A. Headache
    B. Fever
    C. Myalgias and malaise
    D. Chills accompanied by cough and sore throat
    E. All of the above

68. Early onset of respiratory distress in a previously healthy adult influenza patient indicates:
    A. presence of secondary lobar pneumonia.
    B. myocarditis and congestive heart failure.
    C. need for specific antibiotic therapy.
    D. onset of status asthmaticus triggered by viral infection.
    E. presence of progressive viral pneumonia.

69. Clinically useful confirmation of influenza infection may be obtained most efficiently by:
    A. viral culture.
    B. serum antibody titers.
    C. rapid immunoassay (or assay) kits.
    D. WBC and chest x-ray.
    E. gram stain of sputum.

70. Clinically significant side effects of oseltamivir include:
    A. CNS disturbance (confusion, vertigo, lassitude).
    B. exacerbation of COPD or asthma.
    C. GI upset, with nausea and vomiting.
    D. significant drug interactions.
    E. known teratologic effects.

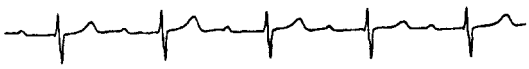
71. The elderly often present with which of the following symptom complex, which is uncommon in other age groups?
    A. Respiratory distress
    B. Generalized malaise with myalgias
    C. Depressed CNS function with lassitude, confusion, and memory loss
    D. Reye's syndrome
    E. Acute laryngotracheobronchitis

72. Infants with influenza may present to the emergency room with symptoms of:
    A. acute laryngotracheobronchitis/croup.
    B. ckassuc bronchiolitis.
    C. sepsis.
    D. febrile seizures.
    E. All of the above

Correction

In the September 11, 2000 (2000;21:208), *Emergency Medicine Reports'* issue on bradycardia, the ECG shown in Figure 4 was incorrect. The correct figure is shown below. We apologize for any inconvenience this error may have caused.

Figure 4. First-Degree Atrioventricular Block



The PR interval is prolonged with a duration greater than 0.20 sec and is constant without progressive change with both a normal P wave and QRS complex. Every atrial impulse is conducted to the ventricles.

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In Future Issues: Acute Coronary Syndromes