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Epidemics of influenza—a highly infectious, acute viral illness—were reported in detail as early as 1510, but even earlier accounts of epidemic respiratory illness from the 10th and 11th centuries probably also were a reflection of influenza's influence on early societies. One hypothesis holds that the circa 430 BC plague of Athens was caused by a co-infection of influenza and the toxic shock producing phage of Staphylococcus aureus.[1] *The epidemiologic concept of "excess mortality" initially was developed to describe the effect of an 1847 influenza epidemic in London.[2] Later, the systematic evaluation of excess mortality became an index for recognizing the course of an influenza epidemic.[3]*

There are several types of influenza and many subtypes. For some types, humans are not the only host. Influenza virus first was isolated from chickens suffering from "fowl plague" in 1901—a subtype we now call H7N7.[4] In 1931, an influenza virus closely related to the virus that caused the Great Pandemic of 1918 was identified in swine.[5] The first influenza B virus was isolated in 1940, and the first influenza C virus in 1947. The ability to isolate these viruses and grow them in embryonated eggs eventually led to the ability to develop and test influenza vaccines and antiviral medications, as well as to perform careful seasonal surveillance.

—The Editor

Influenza and Influenza Vaccination 2004-2005

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Influenza Disease

Epidemiology. *Incidence and Prevalence.* Influenza can lead to death from pneumonia as well as exacerbations of underlying diseases of the heart, lungs, or other organ systems. More than 90% of deaths attributed to influenza and pneumonia occur in the elderly. In the United States, the mortality rate has been rising. According to a recent study, the average number of influenza-associated deaths was approximately 19,000 per year from 1976 to 1990, but 36,000 per year from 1990 to 1999.[6] It is considered probable that this increase was due in part to the increasing number of seniors and because the relatively virulent H3N2 subtype predominated in 90% of the more recent influenza seasons. Death from influenza is uncommon among children, even those with high-risk medical conditions. Overall, an estimated average of 92 deaths occur annually from influenza among children younger than 5 years of

age,[6] a number that is dwarfed by the incidence of influenza death later in life. However, as demonstrated during the 2003-2004 influenza season (143 pediatric deaths reported as of April 2004), illness resulting in childhood mortality can draw enormous national media attention and lead to parental panic.[7]

Rates of hospitalization depend upon the predominant influenza virus subtype, as well as host factors such as age, underlying medical conditions, and socioeconomic status. Infants and seniors both have been shown to have high rates of influenza-associated hospitalization. In a study of healthy infants and young children with Medicaid insurance from 1973-1993, the influenza-associated hospitalization rate per 100,000 varied: 1,038 (birth to 5 months of age), 496 (6-11 months of age), and 186 (12-23 months of age). In the same study, children with high-risk conditions had higher hospitalization rates than healthy children: 1900 (birth to 11 months) and 800 (12-23 months of age).[8] In a more recent study (1992-1997) of healthy infants and young children enrolled in a health maintenance organization, the influenza-associated hospitalization rate per 100,000 was 144 to 187 in those from birth to 23 months of age.[9] Based on National Hospital Discharge Data, the hospitalization rate for persons 65 or older was 228 per 100,000 from 1969 to 1995 when H3N2 predominated.[10]

Less severe morbidity may be experienced by both children and adults. For children, influenza is a major cause of fevers, ear infections, and other upper respiratory infections that lead to medical visits. These visits, in turn, lead to antibiotic prescriptions and, it can be speculated, a rising incidence of antibiotic resistance. Both the visits and the prescriptions contribute to health care costs.

Epidemic Behavior. Influenza epidemics are an annual event, and usually one or two influenza viruses predominate. It previously was believed that only one influenza A subtype could circulate at a time, but since 1978 both H1N1 and H3N2 viruses have circulated concurrently. It appears that influenza viruses do not continue to spread within a population between epidemics,[11] but must be reintroduced each season.

Geographic Distribution. Influenza has worldwide distribution, including tropical regions. Airplane travel makes circulation of the infectious agent rapid.

Temporal Distribution. In temperate climates, influenza is a cold weather disease. In the United States between 1976 and 2004, peak influenza activity was documented from November through April, with the most frequent peaks occurring in January (21%) and February (43%). Because 14% of the peaks were noted in March and April, the Advisory Committee on Immunization Practices reminds readers that influenza vaccine can continue to be offered in December and throughout the influenza season while supplies last.[7]

Host Factors. Rates of serious morbidity and mortality from influenza are highest in persons aged 65 years and older, but school-age children (age 5-14 years) are the age group most often infected. These young people may be the major source of infection for older people. Settings in which there is daily mixing of large numbers of susceptible people—such as day care, schools and colleges, military barracks, and nursing homes—create a fertile setting for the spread of influenza infection. There is no special susceptibility for any racial group or sex. The children of low income families are at greater risk for influenza infection than are those of middle income families[12,13] presumably because of greater crowding. However, this intense exposure in childhood may lead to protection that persists into adulthood as suggested by lesser risk for influenza infection among low income as compared to middle income adults.[14]

Nosocomial Infections. Because large numbers of community members are infected during influenza season (including health care workers, hospital staff, patients, and patient visitors) and because influenza easily is transmitted from person to person, the potential for spread of influenza within a hospital is considerable. The occurrence and serious consequences of nosocomial influenza outbreaks are well documented.

Influenza Viruses. Influenza virus was the first human virus to be isolated and characterized. Influenza viruses are single-stranded RNA viruses, categorized as orthomyxoviruses. There are three types of influenza viruses: A, B, and C. Influenza A and B are the two types that cause epidemics in humans; influenza C tends not to cause significant disease. Both influenza A and B have two surface glycoproteins that are important both for immune recognition and categorization: hemagglutinin and neuraminidase. For example, A/Hong Kong/1/68 (H3N2) represents an influenza A virus first isolated in a laboratory in Hong Kong (strain number 1) in 1968 and determined to have a specific combination of hemagglutinin and neuraminidase antigens.[15]

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The nucleus of influenza A contains eight gene segments that code for 10 proteins. The segmented nature of the genome allows for the frequent genetic reassortment that is considered the basis for the emergence of new subtypes of type A viruses (antigenic shift). When cells are simultaneously infected with two influenza A viruses with different genetic properties (e.g., a human and an avian virus), RNA assembly may incorporate gene segments from either parent virus. Minor antigenic changes (antigenic drift) occur when there are progressive alterations in antigenic sites for reactivity with human antibodies. The constant antigenic flux of influenza viruses make them particularly difficult to control. An antigenic shift would be the basis for a pandemic.

Mechanism and Route of Transmission. The virus is shed in respiratory secretions of an infected person for 5-10 days.[16] The virus is highly contagious and generally spread from person to person via inhalation of airborne droplets elaborated during coughing or sneezing. Less commonly it is spread by contact with an infected person's secretions, for example from hand to mouth via a doorknob or other inanimate object that has been recently handled by an influenza-infected person. Because influenza passes from person to person, it spreads easily during seasons when people stay indoors, such as winter in northern climates and the rainy season in the tropics.

Pathophysiology

Mechanism of Disease Process.[14] Influenza is an acute infection of the respiratory tract. Influenza virus inhalation can lead to viral deposition in the upper or lower respiratory tract, the latter probably being more susceptible. The influenza hemagglutinin attaches to influenza-specific receptors on mucoproteins in the airway's mucous coating. The influenza neuraminadase probably liquefies mucosal secretions and promotes influenza's access to the epithelial cells of the mucosa.

The incubation phase from exposure to shedding is 1-5 days. Shedding may precede symptoms by a day. Viral concentrations increase over the next 1-2 days and peak during the symptomatic peak of illness. Viral concentrations and disease severity correlate directly.

Disease Course. A simple case of influenza starts suddenly, causing fever, headache, muscle aches, and exhaustion, as well as respiratory tract symptoms such as sore throat, runny or stuffy nose, and dry cough. Very young children also may experience nausea and vomiting,[17] but these symptoms are uncommon in adults with true influenza. (The term "stomach flu" is a misnomer; other viruses and bacteria cause nausea and diarrhea in adults.) Influenza infection usually is short-lived, averaging two to three days, but in some cases it can persist for weeks, especially among the elderly.

It should be noted that influenza B, which primarily affects children, generally causes milder disease than influenza A. This is, in large part, because the Type B virus shows more immunologic stability than Type A.

Potential Complications. Pneumonia is the chief complication of influenza. Pneumonia may be either related primarily to influenza or to a bacterial complication from *S. pneumoniae*, *S. aureus*, or *H. influenza*. Infection of cells by influenza A requires cleavage of the virus hemagglutinin by proteases. Some strains of *S. aureus* produce such proteases, possibly accounting for the frequency with which *S. aureus* pneumonia complicates influenza infections.[18] Influenza may induce an exacerbation of chronic obstructive pulmonary disease or chronic bronchitis. In young infants, influenza infection may lead to croup or bronchiolitis. Upper respiratory infections such as sinusitis and otitis media may complicate the course.

Influenza has been implicated in cardiac disease such as myositis and myocarditis. Though the mechanism is not understood, the virus may induce neurologic symptoms including acute viral encephalitis, Reye's syndrome, and Guillain-Barré syndrome. Miscellaneous other complications attributed to influenza infection include a sepsis picture in infants, toxic shock syndrome, and myoglobinuria.

Immunity. Immunity to influenza depends upon immunity to its surface antigens, including hemagglutinin. Immunity reduces both the likelihood of being infected and, if infected, the severity of clinical symptoms.[19] Immunity to one antigenic variant does not guarantee protection against others, and immunity to one influenza virus type confers limited or no protection against other types.

Clinical Features

Patients may present with high fever, chills, malaise, myalgia, and headache. The chief complaint is typically respiratory, for example nasal congestion, rhinitis, sore throat, conjunctivitis, and nonproductive cough. Photophobia and shivering may be present. Gastrointestinal symptoms are not common in adults, but are reported more frequently in children. Cervical and general adenopathy may be present.

Diagnostic Studies[20]

The purpose of making an early diagnosis of influenza is to prevent unnecessary use of bacterial antibiotics and maintain the opportunity for more directed antiviral therapy. From a public health perspective, laboratory diagnosis makes surveillance feasible, announcing the presence of influenza viruses in the community and identifying the predominant circulating types, subtypes, and strains.

Tests for influenza include viral culture, rapid antigen testing, serology, polymerase chain reaction (PCR), and immunofluorescence (IF).[21-23] There is a wide range of eligible specimens for viral isolation, including nasopharyngeal swab, throat swab, nasal wash, nasal aspirate, bronchial wash, and sputum. It should be kept in mind that bronchial wash and sputum should not be used for rapid diagnostic testing, and that the nasopharyngeal specimens are more effective than throat swab specimens. Samples should be collected within the first four days of illness.

• Viral cultures remain the gold standard. They are important adjuncts to rapid tests because they provide information on subtypes and strains and help monitor the emergence of antiviral resistance and novel influenza A subtypes that may become pandemic threats. Results typically take 5-10 days and are not useful in the acute situation.

• Rapid antigen tests can detect the virus within 30 minutes to 1 hour, but have a lower sensitivity than culture. Some brands of rapid tests only detect influenza A. If confirmation is necessary, a viral culture should be sent.

• Serology requires two samples per person—one obtained during the first week of illness and another 2-4 weeks later. The length of time necessary to note an antibody level rise excludes this test from helping in the decision to start antiviral treatment.

• PCR may be used to detect viral RNA in respiratory secretions. The full range of specimens used for culture may be used for PCR. Results usually are available in 1-2 days.

• Immunofluorescence DFA antibody staining and enzyme immuno assays (EIA) both can detect influenza A and B and take about two hours.

Differential Diagnosis

Influenza often is difficult to distinguish based solely on clinical symptoms because the early influenza symptoms are similar to those of other infectious agents such as *Mycoplasma pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and Legionella.

Prevention

The most efficacious means to combat influenza is via prevention. As often is stated, good hand washing is one of the cornerstones of prevention. The influenza virus is heavier than tuberculosis and it does not stay airborne for prolonged periods; airborne/TB precautions are not necessary in hospitals if influenza is the infecting agent. However, health care workers are advised not to touch their eyes or nose after contact with an infected patient. Vaccination (detailed below) also is an important and cost effective preventive tool. Avoidance of ill persons and crowds seems prudent as a means for the general public to prevent influenza, but such methods have not been shown to be effective[14] and may not be practical in modern society. It has been shown, however, that epidemics do not spread extensively unless schools are in session,[14] so school closings may be in order for severe outbreaks.

Management

Symptomatic. As with all illness, the mantra "airway, breathing, circulation" is of key importance for patients with influenza. Supplemental oxygen and other supportive measures should be used as needed. Antipyretic therapy may include acetaminophen or ibuprofen. Aspirin should be withheld from patients younger than 16 years of age due to the risk of Reye's syndrome.

Antiviral Medications[24] (*See Tables 1 and 2*). In the United States, four prescription medicines are licensed for preventing or treating influenza. Although they may prevent symptoms and shorten the course of the illness by a day or two, they do not interfere with the development of immunity to the infecting influenza strain. It must be kept in mind that these are not panaceas. Their use may cause side effects, and none of them are licensed for use in children younger than 1 year. Some strains of influenza virus already have mutated enough to be resistant to one of these antiviral drugs. More resistant strains may develop.

Two of the antiviral medications, amantadine (Symmetrel) and rimantadine (Flumadine), are related to the adamantanes. They are only effective against influenza A. Both are approved for prophylaxis in children and adults. Both also are approved for treatment, but rimantadine is not approved for treatment of pediatric patients. The two other antiviral medications, zanamivir (Relenza) and oseltamivir (Tamiflu), are neuraminadase inhibitors. They are effective against both influenza A and B. Both are approved for treatment, but zanamivir is only approved for persons 7 years or older. Additionally, oseltamivir is approved for prophylaxis of adults. Table 2 shows the recommended daily dosage of influenza antiviral medications for treatment and prophylaxis by age.

Interim chemoprophylaxis and treatment guidelines have been prepared by the CDC and can be accessed at the CDC influenza website.[25]

Influenza Vaccine

Two Types of Vaccines. There are two main types of influenza vaccine: the injectable inactivated and live intranasal spray vaccines. They are alike in that the viruses for both are grown in eggs, so anaphylactic type allergic reaction to chicken eggs is a true contraindication to all influenza vaccines produced currently. Also, both types of vaccines must be given annually to achieve optimal protection.

Inactivated Influenza Vaccine. Description. The trivalent inactivated vaccine (TIV) is an injectable vaccine made from inactivated or killed influenza viruses. Different manufacturers use different compounds to inactivate the virus, but all manufacturers add antibiotics to prevent bacterial contamination. Because of heated controversy around the use of thimerosal (a mercury-based preservative) in vaccines, a new pediatric formulation that does not contain thimerosal as a preservative has been licensed.[26]

Dose. An intramuscular dose of 0.5 mL of inactivated vaccine is recommended for children 3 years of age or older and for adults (irrespective of body weight). Children 6-35 months of age should receive only 0.25 mL. Children younger than 9 years who have never been immunized should receive two doses at least four weeks apart, optimally timed so that the second dose is administered before December.

Vaccine Efficacy. The effectiveness of TIV depends on two main factors: host characteristics and the degree of similarity between circulating influenza virus and the vaccine virus. If there is a good match, the vaccine prevents influenza in 70-90% of healthy adults younger than 65.[27,28] Among children younger than 16 years, a five-year study found TIV to be 77-91% efficacious in preventing influenza symptomatic illness culture positive for H1N1 and H3N2, respectively, but considerably less efficacious against influenza seroconversion (44% and 49% for children 1-5 years of age; 74% and 76% for those 6-10; and 70% and 81% for adolescents 11-15).[29] Conflicting results regarding the reduction of otitis media have been reported.[30,31]

Among non-institutionalized persons age 60 years or older, influenza vaccine efficacy may be as low as 58% against influen-

Table 1. Antiviral Medications: Trade Names, Routes of Administration, Precautions, and Toxicities

DRUG ROUTE	PRECAUTIONS*	TOXICITY
Chemically related to adamantanes, these therapies prevent penetration of virus into the host by inhibiting uncoating of influenza A. They are effective only against influenza type A (prophylaxis and treatment within 24-48 hours of symptom onset).		
Amantadine (Symmetrel) Oral	Elderly, seizure disorders, psychiatric illness, anticholinergic drugs Eczematoid dermatitis CNS stimulants Reduce dose in renal disease, liver disease. Effective only against type A	Among some healthy adults and children, side effects can include: CNS effects (nervousness, anxiety, difficulty concentrating, and lightheadedness) GI effects (nausea and loss of appetite) Among some other persons with long-term illnesses, more serious side effects, such as delirium, hallucinations, agitation, and seizures, can occur. Side effects usually diminish or disappear after 1 week.
Rimantadine (Flumadine) Oral	Reduce dose to 100 mg QD if severe renal or hepatic disease Cimetidine increases plasma levels Effective only against type A	CNS side effects happen more often among persons taking amantadine than among persons taking rimantadine.
Chemically related to neuraminidase inhibitors: Release of viruses from infected cells is decreased. They are effective against influenza A and B.		
Oseltamavir (Tamiflu) Oral	Decrease dose for CrCl < 30 mL/min Chronic cardiac or respiratory disease	Nausea, vomiting (may be less severe if taken with food)
Zanamivir (Relenza) Oral inhalation	Children older than 7 yrs Contraindication: COPD, asthma Not approved for influenza prophylaxis	This drug is inhaled; more side effects in those with asthma or other chronic lung disease (e.g., decreased respiratory function and bronchospasm). Other side effects reported by < 5% of those who used this drug are diarrhea, nausea, sinusitis, nasal infections, bronchitis, cough, headache, and dizziness.

* All four of these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturers' package inserts).

za respiratory illness and even lower among that portion of the population more than 70 years of age.[32] Among HMO patients age 65 years or older, inactivated influenza vaccine was 30-50% effective in preventing hospitalization for influenza and pneumonia[33] and as much as 80% effective in preventing influenza-related death.

Adverse Reactions. Allergic reactions could occur after any vaccine or medicine. These are the other risks and side effects that have been known to occur after influenza vaccines:

• Minor pain or tenderness, swelling, or warmth at the injection site may begin soon after the shot and usually resolve within two days. Between 10% and 64% of people will experience these mild reactions.

• General side effects, including fever, muscle aches, or malaise may begin 6-12 hours after the shot and can persist for a day or two. More children than adults experience these symptoms. Overall, fewer than 1% of vaccine recipients report these side effects.

• Guillain-Barré syndrome, or GBS, causes potentially severe motor peripheral neuropathy. Unrelated to influenza vaccination, GBS affects 10-20 adults out of 1 million. In 1976, the swine influenza vaccine was associated with an increase in the basal incidence of GBS. Since then, influenza vaccines have not been clearly linked to GBS. According to the CDC, "…if there is a risk of GBS from current influenza vaccines, it is estimated at 1 or 2 cases per million persons vaccinated."[34] However, if a patient has a history of GBS and is at high risk of influenza complications, CDC does not consider use of the inactivated vaccine as contraindicated.

• A recent study showed a possible association between inactivated influenza vaccines and an increased risk of Bell's palsy. The authors concluded that a population-based controlled study is needed to determine whether this association could be causal and to quantify the risk.[35]

Table 2. Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis (from www.cdc.gov/flu/professionals/antiviralback.htm)

ANTIVIRAL AGENT	AGE GROUPS (YRS)				
	1-6	**7-9**	**10-12**	**13-64**	**≥ 65**
Amantadine*					
Treatment, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Rimantadine¶					
Treatment, ** influenza A	NA††	NA	NA	100 mg twice daily§§§	100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	100 mg/day¶¶
Zanamivir*††††					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,§§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel–tablet and syrup) and Geneva Pharms Tech (Amantadine HCL–capsule); USL Pharma (Amantadine HCL–capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL–syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine–tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL–tablet), and Amide Pharmaceuticals (Rimantadine HCL–tablet). Zanamivir is manufactured by Glaxo SmithKline (Relenza–inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu–tablet). Information based on data published by the U.S. Food and Drug Administration at www.fda.gov.

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤ 50 mL/min/1.73 m^2.

† 5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§ Children ≥ 10 years who weigh < 40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤ 10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

** Only approved by FDA for treatment among adults.

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate also for treatment among children. (See American Academy of Pediatrics, 2000 Red Book.)

¶¶ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥ 65 years if they experience possible side effects when taking 200 mg/day.

***Zanamivir is administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

†††Zanamivir is not approved for prophylaxis.

§§§A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance < 30 mL/min.

¶¶¶The dose recommendation for children who weigh ≤ 15 kg is 30 mg twice a day; for >15 to 23 kg children, the dose is 45 mg twice a day; for > 23 to 40 kg children, the dose is 60 mg twice a day; and for children > 40 kg, the dose is 75 mg twice a day.

There has been some publicity about fear of the use of influenza vaccine during pregnancy because of the presence of thimerosal, a mercury-containing preservative, used in minute amounts in the influenza vaccine. Experts believe that related mercury compounds should be avoided in pregnancy, but no clear-cut data are available on the use of thimerosal-containing vaccines during pregnancy. It is very likely that the small amounts and rapid excretion[36] make influenza vaccine safe for pregnant women. The Advisory Committee on Immunization Practices, which advises the CDC, has recommended that women who will be pregnant during influenza season receive the injectable vaccine because of their risk of serious complications from influenza.[7] In previous years, only a minority of pregnant women have been vaccinated.[37]

Live Attenuated Influenza Vaccine. An influenza vaccine in the form of a nasal spray—used for years in Russia—was licensed in the United States in 2003 for use by people between 5 and 49 years of age who are free of chronic illness. The potential advantages of such a vaccine are great. No needle is used, so there is no risk of sharps injury, there is no pain at the injection site, and immunity develops in the lining of the nose as well as systemically. The disadvantages also have been notable—onerous storage and handling requirements as well as greater cost.

Description. The live attenuated influenza vaccine (LAIV) is an intranasal spray comprised of live influenza virus that is attenuated or weakened because it is, through serial culturing, cold-adapted. That is, it replicates in the cooler temperatures of the upper respiratory tract, but not in the warmer lower airways.[15] The fact that this vaccine does contain a living organism makes it quite different than the injectable vaccine. There is only one intranasal influenza vaccine currently licensed for use in the United States influenza virus vaccine (nasal), trade name FluMist.[38]

Dose. Each syringe-like sprayer contains a 0.5 mL dose; 0.25 mL to be sprayed into each nostril. Previously un-immunized children 5-8 years old should receive two doses at least six weeks apart.

Vaccine Efficacy. In one pre-licensure study of the intranasal influenza vaccine during a season in which the circulating virus strains were well matched with those in the vaccine, efficacy was 93% among children receiving two doses.[39] Among adults 18-49 years of age, when compared to placebo recipients, LAIV recipients had fewer upper respiratory infection episodes (26%) and consequently fewer lost days of work (27%), as well as fewer days of health care visits for febrile illness and antibiotic use.[40]

Adverse Reactions. Clinical signs and symptoms that occurred more frequently among children receiving LAIV than among those receiving placebo included nasal congestion or runny nose, headache, fever, vomiting, abdominal pain, and myalgias.[41-43] In contrast, signs and symptoms that occurred more frequently among adults receiving LAIV than among those receiving placebo included nasal congestion or runny nose, headache, and sore throat. The incidence of serious adverse events that would be expected to complicate influenza (e.g., pulmonary or central nervous system events) were not statistically different between LAIV and placebo recipients in the many pre-licensure trials. A study of an inactivated intranasal influenza vaccine used in Switzerland (fundamentally different than the live intranasal influenza vaccine used in the United States) showed a strong association with Bell's palsy.[44] This vaccine is no longer in clinical use in Switzerland and was never licensed in the United States, but this association has prompted concern about intranasal vaccines, and both live and inactivated influenza vaccines.

Composition. The influenza vaccine actually is a combination vaccine that protects against three viruses: two influenza A and one influenza B subtype. The exact strains used in the United States' vaccine vary from year to year, depending on a scientific prediction of which influenza viruses will circulate here in the following winter. This prediction is based on careful monitoring of circulating strains in Asia. Asia is an important site for influenza surveillance because historically it is in this region that new strains of influenza virus have originated in fowl and pigs, and passed to humans living in close contact with these animals. After the new strain passes from animal to human, it then spreads around the globe from person to person.

The effectiveness of influenza vaccine depends both on how accurately scientists predict which influenza virus strain will circulate in the United States and on host factors such as the age of the recipient. If there is a poor match between the influenza viruses chosen for the vaccine and those that actually make their way to America, the vaccine may not be very effective. Fortunately, the influenza experts from WHO and CDC usually have been successful in predicting which strain will come each year.

Each year, antigenically equivalent strains are used in all U.S. influenza vaccine types and brands.[45]

Timing of Vaccination. Antibodies reach protective levels approximately two weeks after vaccination.[46,47] For optimal protection during influenza season, vaccination has been recommended in October or November. For travelers to the southern hemisphere, it may be advisable to protect patients during April through September. The first year a child younger than age 9 receives influenza vaccine, he or she should receive two doses separated by at least 4 weeks (injectable) or 6 weeks (intranasal spray); the first dose is only a primer. All other eligible people should receive one dose per year.

There are two chief reasons why annual revaccination is necessary for protection. First, immunity from the vaccine wanes after vaccination and may fall below the protective level within a year, or even within a few months in the elderly.[48] Secondly, the predominant virus usually changes from year to year.

Who Should Receive Influenza Vaccine? For the 2004-2005 influenza vaccination season, the United States Public Health service initially recommended influenza vaccine for four chief categories of people:[7] certain age groups (all persons older than 50 years and healthy children ages 6-23 months), all individuals 6 months of age or older with chronic diseases (including residents of nursing homes), women who expected to be pregnant during influenza season, as well as close contacts (e.g., health care workers, household members) of chronically ill patients and contacts of infants and toddlers 0-23 months of age. The vaccine also was recommended for some international travelers. Because of a severe and acute vaccine shortage (See the section "The

2004 influenza vaccine shortage" below), these recommendations were changed slightly. This year, healthy people 50-64 years of age and contacts of healthy children 6-23 months of age were removed from the recommended list.[49]

It is important to note that health care workers with direct patient contact remain on the list of individuals for whom the influenza vaccine is recommended. Because influenza viruses easily are transmitted, health care workers are urged to receive the influenza vaccine so they will not put patients, themselves, their families, and others at risk.[50]

New Recommendations for Pediatric Vaccination. In light of the potential severity of influenza among otherwise healthy infants and toddlers,[51-53] and the availability of a safe and efficacious vaccine,[29] in 2004 the American Academy of Pediatrics (AAP)[54] and the Advisory Committee on Immunization Practices (ACIP) issued a new recommendation broadening the pool of children who routinely should be vaccinated. Under the new guideline, healthy children ages 6-23 months routinely should be vaccinated (the previous recommendation was merely that these children be vaccinated "when feasible").[55]

Widespread implementation of the expanded recommendation is expected to reduce the number of healthy young children infected and consequently hospitalized with influenza-related illness. The new recommendation, by increasing herd immunity, also would provide greater protection to high-risk individuals such as children and adults with chronic medical conditions and the elderly. General use of the vaccine among children 6-23 months of age probably also would decrease some families' medical bills and lost days of school and work.

However, significant practical obstacles to implementation exist, even in a year when there was no vaccine shortage. A very large number of U.S. children are in the target age group,[56] and the window of opportunity for vaccination is relatively brief. This problem is compounded for the group who are receiving the influenza vaccine for the first time and so must receive a second dose (and so a second visit)[57] at least four weeks after the first to achieve full immunity. For these reasons, successful implementation of the new guidelines will require a carefully planned campaign in primary care offices.[58]

Who Should Not Receive the Influenza Vaccine?[15] Several contraindications and precautions to vaccination are common to both the injectable and the intranasal influenza vaccines. These vaccines should not be given to a person if he or she:

• had a hypersensitivity reaction to a prior dose of influenza vaccine or to any vaccine component including eggs. Appropriate allergy evaluation and desensitization is in order if the person is at risk for influenza complications.

• has a moderate to severe illness. If this is the case, the person may receive the vaccine when feeling better.

• is outside the age range for which the vaccine is licensed for use. The appropriate ages for the two injectable influenza vaccine brands are 6 months of age or older for Fluzone (Aventis Pasteur) and 4 years of age or older for Fluvirin (Chiron, not available for the 2004-2005 season). The intranasal influenza vaccine, FluMist made by MedImmune, is licensed for persons 5-49 years of age.

The live intranasal influenza vaccine has several more contraindications to its use. Additional groups of people who should not be given the spray include:

• All patients with a chronic illness;

• Pediatric patients on chronic aspirin therapy. Since the nasal spray influenza vaccine is an attenuated live virus, children who take aspirin should not receive this vaccine because of the potential for inducing Reye's syndrome;

• Persons with a personal past medical history of GBS;

• Pregnant women; and

• Health care workers and other close contacts of patients who are in a protected environment because of severe immunosuppression (e.g., receiving a bone marrow transplant). This limitation is because of the remote risk for transmission of the vaccine-strain virus.

Can Influenza Vaccine Give You the Flu? Many patients and health care providers alike believe that influenza vaccine causes influenza disease. There are no live viruses in the injectable flu vaccine, so influenza infection resulting from the injectable vaccine is not possible. Recipients may mistake minor side effects such as fever and muscle aches as influenza. Patients also should be aware that, because the vaccine does not work for about two weeks after it is given, vaccinees may get influenza infection if they are infected before being vaccinated. Finally, the vaccine does not protect against many other viruses that prompt influenza-like symptoms (e.g., adenovirus, respiratory syncytial virus, rhinovirus, and parainfluenza viruses).

The 2004 Influenza Vaccine Shortage. In years prior to 2004 there have been shortages of influenza vaccine, but few in the recent past were as severe or as unexpected as the influenza vaccine shortage of fall 2004. After weeks of announcements regarding possible contamination of some lots of influenza vaccine, on Oct. 5, 2004, Chiron, the leading manufacturer of influenza vaccine for use in the United States, notified the CDC that none of its influenza vaccine for the 2004-2005 influenza season would be available for distribution in the United States. Because of the withdrawal of a previous manufacturer from the influenza vaccine market, Chiron's announcement left only one injectable influenza vaccine manufacturer (Aventis Pasteur) in the market for this year. MedImmune, the only company with an intranasal spray vaccine licensed for use here, had planned to produce just over 1 million doses. Because of the long vaccine production cycle for both injectable and intranasal influenza vaccine, a rapid, extensive expansion of production was not possible. Ironically, the season of this tremendous vaccine shortage was also the first season in which there was a full recommendation to expand influenza vaccination to healthy children 6-23 months of age. (Please see the section "New recommendations for pediatric vaccination" above.)

Because of the shortage, state and local health departments have worked in coordination to develop influenza vaccine distribution plans that guarantee vaccination of the most vulnerable populations. Most states, to support physician adherence to the triage system, have announced sanctions against health care professionals who knowingly give influenza vaccine to persons not included in the interim recommendations.[59]

The Role of Emergency Departments and Hospitals in Vaccinating Patients. Although not standard, there have been EDs that have vaccinated patients against influenza since 1992. A sample of ED visits obtained from National Hospital Ambulatory Medical Care Survey data indicated that, during the nine-year period from 1992-2000, approximately 247,000 influenza vaccinations were administered in the ED setting. In 77% of these cases, patients requested vaccination as their chief complaint. Clearly, because of the large number of chronically ill patients who seek care in the emergency setting, there is room for expansion of vaccination programs if resources permit.[60] The new pediatric recommendation raises the possibility of offering influenza vaccine within the context of pediatric emergency medicine settings as well.[61] Interesting, paramedics have implemented influenza immunization programs in a host of settings such as retail stores, community events, EMS stations, churches, and senior citizen complexes.[62]

Appropriate hospital inpatients also are expected to receive influenza vaccine prior to discharge during the flu season. This expectation is part of the JCAHO core measures and the CMS quality hospital initiative. Hospitals that do not comply with this quality requirement may be subject to decreases in Medicare reimbursement in the future.

Pandemic Influenza

There have been influenza pandemics in 1889, 1918-1919, 1957, 1968-1969, and 1977. In the 1918-1919 pandemic, approximately 21 million people died worldwide, with 549,000 deaths in the United States. Unlike the typical recent influenza epidemics, the Spanish Flu mainly killed young adults. This disease singlehandedly decreased life expectancy by 10 years. Pandemics such as those listed above follow antigenic shifts. New antigenic strains appear, against which the population has no immunity. The next pandemic is thought by many experts to be inevitable and overdue.

In August 1997, a young boy in Hong Kong died of a strain of influenza that previously had infected only birds. By December, 18 people in the region were directly infected with an avian influenza virus and, of these, 6 died.[63] The source of the outbreak was infected fowl. Epidemiologists feared that if this new influenza were to spread, not just from bird to human, but from human to human, a massive pandemic could follow. Attempts to produce a vaccine failed; the viruses killed the very cells in which scientists tried to grow them. Finally, not sure if the intervention would work, officials in Hong Kong ordered the slaughter and disposal of 1.5 million chickens. No cases of this strain of influenza have been identified since then, but there are no guarantees that it will not re-emerge.[64]

The WHO Influenza Surveillance Network serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. Since 1952, the WHO has maintained a network of centers worldwide—currently 112 such institutions in 83 countries. These centers submit new influenza isolates to four WHO collaborating centers, located in Australia, Japan, the United Kingdom, and the United States. One goal of the network is to detect new emerging influenza strains rapidly and alert public health officials if there is pandemic potential.[65]

Much attention has gone into the development of a detailed U.S. pandemic influenza plan, which has three main goals: 1) to limit the burden of disease; 2) to minimize social disruption (e.g., sick leave, hospitalization, and death); and 3) to reduce economic losses attributable to the pandemic. All communities would need to be involved in a coordinated response in the event of a pandemic.[66] To achieve these goals, priority areas to be addressed include:

- global and national influenza surveillance;
- vaccine development and production;
- vaccine use and coverage;
- chemoprophylaxis and therapy;
- guidelines for clinical care and health resources management;
- emergency preparedness; and
- research.

Conclusions

Influenza, a highly communicable infectious disease , is caused by influenza viruses. These viruses will never be eradicated because humans become susceptible again each time the viruses undergo an antigenic change. Influenza takes an enormous toll on humanity with respect to mortality, hospitalization, and medically attended illness. Despite the licensure of antiviral medications, immunization is the best control measure of influenza.

Many experts believe another pandemic is quite possible if antigenic shift occurs and entire populations are without immunity to the new strain. A concerted worldwide effort to detect new strains as soon as they arise is in place, but at present there is no mechanism for the rapid mass production of relevant vaccine. Until difficulties in vaccine development and manufacturing can be solved, pandemics of influenza will be a threat as long as there are humans to serve as virus incubators and launch pads. Even during typical yearly epidemics, the impact of influenza is not inconsequential. The drama of pandemics should not lead us to underestimate the destructive power influenza exhibits year after year in this country and throughout the world.

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Physician CME Questions

1. Which of the following is true regarding influenza epidemiology?
   A. The vast majority of deaths attributed to influenza and pneumonia occur in infants.
   B. Rates of hospitalization depend upon the predominating influenza virus strain, as well as host factors such as age, the presence of underlying medical conditions, and socioeconomic status.
   C. Seniors (persons 65 years of age or older) are the only age group with markedly elevated rates of influenza-associated hospitalization.
   D. For children, influenza is an uncommon cause of fevers, ear infections, and other upper respiratory infections that lead to medical visits.

2. Which of the following is true regarding influenza geographic and temporal distribution?
   A. Influenza epidemics are an annual event and only one influenza virus can predominate each year.
   B. Influenza does not circulate in warm tropical regions.
   C. In the United States, peak influenza activity is from November through April, with the most frequent peaks occurring in January and February.
   D. Because no peaks have been documented in March and April, the Advisory Committee on Immunization Practices recommends discontinuing vaccination efforts in December.

3. Which of the following is true regarding influenza viruses and their transmission?

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

A. There are three types of influenza viruses, A, B, and C, but A and B are the two types that cause epidemics in humans.
B. Influenza A, but not B, is known to have two surface glycoproteins that are important for immune recognition and categorization.
C. The segmented nature of the influenza genome allows for the frequent genetic reassortment that is considered the basis for the emergence of new subtypes, a process called antigenic drift.
D. The virus is shed in the stool and respiratory secretions of an infected person.

4. Which of the following is true regarding influenza disease and its complications?
   A. As with hepatitis B, the incubation phase from exposure to shedding is 45 to 60 days.
   B. A simple case of influenza has a slow, gradual onset and can include fever, headache, muscle aches, exhaustion, sore throat, runny or stuffy nose, and dry cough.
   C. GI upset (nausea and vomiting) leading to dehydration is the chief complication of influenza.
   D. Influenza has been implicated in cardiac disease and in neurologic symptoms including acute viral encephalitis, Reye's syndrome, and Guillain-Barré syndrome.

5. Which of the following is true regarding influenza diagnostic tests?
   A. The purpose of making an early diagnosis of influenza is to prevent unnecessary use of bacterial antibiotics and maintain the option for use of antiviral therapy.
   B. Samples should be collected within the first 14 days of illness.
   C. Viral cultures are of very little value because current rapid antigen tests are more sensitive than culture.
   D. All rapid antigen tests can detect influenza A and B viruses within 30 minutes to 1 hour.

In Future Issues: ***Anticoagulation Therapy***

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

6. Which of the following is true regarding influenza antivirals?
   A. Two influenza antiviral medications are licensed for use in children younger than 1 year old.
   B. To date, no strains of influenza virus have mutated enough to be resistant to any of the antiviral drugs.
   C. Two of the antiviral medications, amantadine and rimantadine, are effective against influenza A and B.
   D. Zanamivir and oseltamivir are both approved for treatment of influenza, and oseltamivir also is approved for prophylaxis in adults.

7. Which of the following is true regarding influenza vaccination?
   A. For both inactivated and live influenza vaccines, anaphylactic-type allergic reaction to chicken eggs is a true contraindication to influenza vaccination.
   B. For both inactivated and live influenza vaccines, pregnancy is a true contraindication to influenza vaccination.
   C. After influenza vaccination, antibodies reach protective levels in approximately 3-5 days.
   D. The most common side effect of influenza vaccination is influenza infection.

CME Answer Key

1. B; 2. C; 3. A; 4. D; 5. A; 6. D; 7. A

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.