Influenza Update 2000

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Between 30,000-40,000 Americans die annually as a result of influenza epidemics. Spread primarily through the respiratory tract, influenza's classic signs and symptoms are the abrupt onset of fever, myalgia, headache, sore throat, malaise, and nonproductive cough. The elderly and patients with underlying medical illnesses may be at risk for secondary complications. Influenza is caused by an RNA myxovirus that exists in types A, B, and C; however, the A and B types are responsible for most human illness. The Centers for Disease Control and Prevention tracks the viruses' regular pathway through the US each year as they emerge first in Alaska and spread through the lower 48 states, peaking in activity during the winter months. Influenza is preventable by vaccination (efficacy 70%, depending on individual immune status) and is recommended for everyone at increased risk of complications from influenza between 6 months and 50 years of age, and universally for those over the age of 50. The composition of the vaccine has been changed for 2000-2001 to include two new type-A strains and one new type-B. Currently four drugs are available for the treatment of influenza. Early diagnosis can help reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. Bacterial infections can have similar symptoms or be complications of influenza and should be suspected and treated appropriately if present.

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The 1999-2000 influenza season has been heralded as the worst in recent times. Fact or fiction? It appears that earlier reports suggesting a worse year may have been exaggerated according to the Centers for Disease Control and Prevention. The intensity of the infection patterns was consistent with levels reported over the past 5 years suggesting that last year's flu season was not unusually severe (1). Unfortunately, 30,000-40,000 Americans die annually as a result of seasonal influenza epidemics.

Classic signs and symptoms are the abrupt onset of fever, myalgia, headache, sore throat, malaise, and nonproductive cough. Most cases resolve over 1-2 weeks; however, there may be secondary infectious complications in patients with underlying medical illnesses such as bacterial pneumonia, sinusitis, and bronchitis. The elderly are also at risk for noninfectious complications such as congestive heart failure and arrhythmia. More than 90% of pneumonia and influenza deaths occur in the elderly.

Pathogenesis of Influenza

Influenza is caused by an RNA myxovirus that exists in three types (A, B or C); however, the A and B types are responsible for most human illness. The virus contains neuraminidase and hemagglutinin surface antigens (surface spike glycoproteins), undergoes continual antigenic changes (i.e. antigen drift), and can cause epidemics. Influenza A, in contrast to influenza B, contains a unique M_2 protein on the outer surface of the virus. Influenza A generally causes more severe illness, undergoes antigenic drifts more rapidly than influenza B, and has caused the recent pandemics. Most deaths are due to type A (subtype H3N2) strains, such as A/Sydney. The vast majority of the isolates of the 1999-2000 season were type A (H3N2) strains antigenically similar to the vaccine strain A/Sydney/05/97. New strains often emerge from Mainland China, where ducks, pigs, and people live in close proximity.

Influenza causes epidemics of disease and mortality virtually every year but is seasonal in activity, peaking in the winter months. The virus spreads primarily through the respiratory tract, entering the lining of the nasopharynx where the hemagglutinin on the virus binds to the host cell's sialic acid residue. The virus enters the host cell and releases viral RNA, which replicates in the cell nucleus. New copies of the virus are released and spread within the mucosal lining of the respiratory tract only after surface neuraminidases have cleaved the sialic acid binding sites of the new progeny virus, allowing the release from the originally infected cell to spread to adjacent cells.

Prevention

The virus follows a regular pathway each year. In North America, the first cases are found in Alaska and subsequently spread to the lower 48 states usually by late November. The CDC influenza surveillance program (888 232-3228; www.cdc.gov/ncidod/diseases/flu) provides weekly laboratory, mortality, and state-specific epidemiological reports. The CDC uses four kinds of surveillance data to estimate the severity of influenza epidemics:

1. A sentinel physician surveillance network
2. Reports from state and territorial epidemiologists
3. World Health Organization and collaborating influenza virus laboratories
4. A 122-city mortality reporting system

Influenza is preventable by vaccination. The efficacy of the vaccine is 70%, depending on the patient's immune status and the accuracy of the predictions of public health authorities regarding the epidemics that may emerge each year, and is more effective in healthy, young persons. Two weeks are needed to develop protective immunity after vaccine administration. Persons who receive the vaccine and still get the flu generally have milder disease. The CDC Advisory Committee on Immunization Practices has issued updated recommendations for the prevention and control of influenza using the influenza vaccine (Table 1) and antiviral agents. The vaccine is recommended for anyone over 6 months of age at increased risk of complications from influenza. The age recommendation for universal vaccination has been changed to 50 (decreased from 65) (2).

The composition of the vaccine itself will also be changed for 2000-2001. It will include two new type A strains (A/Moscow and A/New Caledonia). These strains, first identified in 1999, will replace the A/Beijing and A/Sydney strains included in last year's vaccine. The B/Beijing strain will also be included (2).

Table 1: Recommendations concerning specific target groups for vaccination (3).

- Persons 50 years of age or older
- Residents of nursing homes and other chronic care facilities housing persons of any age who have chronic medical conditions
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including, asthma
- Adults and children who required regular medical follow-up or hospitalization during the preceding year due to chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- Children and teenagers (6 months to 18 years) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye's syndrome after influenza infection
- Women who will be in the second or third trimester of pregnancy during the influenza seasons

The CDC published a notice in the summer of 2000 that the supply of influenza vaccine was delayed and modified the recommendations for its use. Briefly, the advisory stated that organized influenza vaccination campaigns would be delayed but that persons at high risk of influenza complications and their close contacts should proceed routinely during regular healthcare visits (3).

The early diagnosis of influenza can help reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, since bacterial infections can have symptoms similar to influenza or be a complication of influenza, they should be suspected and appropriately treated if present. There are new commercially available rapid diagnostic tests for influenza. Generally, these tests do not distinguish between types A and B and detect only the presence of viral neuraminidase. Despite the availability of these limited rapid tests, viral culture collection and surveillance by state and local health departments and the CDC are still considered important as these isolates can

Table 2: Comparison of Influenza Therapy.

	amantadine	rimatadine	oseltamivir	zanamivir
Indication	Influenza A Prophylaxis	Influenza A Prophylaxis	Influenza A and B	Influenza A and B
Dose	100 mg bid x 7 days*	100 mg bid x 7 days	75 mg bid x 5 days	2 inhalations bid x 5 days
Adverse events	CNS (13% vs. 4% placebo)	CNS (6% vs. 4% placebo)	Nausea (9.9% vs. 5.5% placebo	Potential bronchospasm
Average Wholesale Treatment Cost	$13.05	$26.41	$53.00	$44.40

* Lower dose is recommended in renal impairment (Cr Cl < 30 mL/min)

provide the specific information on circulating subtypes and strains.

Treatments

Four drugs are now available for the treatment of influenza (Table 2). Early treatment (within 48 hours of onset) has been shown to be most effective. Amantadine (Symmetrel®) was the first agent approved for the treatment and prevention of influenza. Its primary mechanism of action is to block the ion channel M_2 protein on the surface of influenza A and interrupt hemagglutinin binding. Rimantadine (Flumadine®) is also available for both treatment and prevention and has a similar mechanism of action. These drugs can decrease the mean duration of illness when used within 48 hours of symptom onset in influenza A infection. However, a major limitation of use is the presence of adverse central nervous system effects including confusion, disorientation, depression, nervousness, and insomnia. As shown in Table 2, adverse events are less common with rimatadine than amantadine (6% vs. 13% vs. 4% for placebo).

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are neuraminidase inhibitors approved for use by the FDA in 1999 for the treatment of uncomplicated influenza infections, but neither has been approved for prophylaxis. These newer agents are active against both influenza A and B and have a unique action mechanism. They inhibit influenza surface neuraminidase, preventing cleavage of the sialic acid residues and viral release from the host cell, interrupting the virus's spread to other cells. As with the older drugs, oseltamivir and zanamivir should be used within 48 hours of symptom onset.

Zanamivir is available as a dry mist powder delivered via an inhalation device and can be used for treatment for persons >7 years of age. In a multicenter, double blind, placebo-controlled trial, zanamivir decreased the medial duration of illness by 1.5 days (4). A subanalysis in this trial showed high-risk patients had fewer influenza complications and less antibiotic therapy for associated complications. Caution is recommended in patients with asthma or other underlying lung diseases due to a risk of bronchospasm. The FDA has received reports of deteriorated respiratory function following the inhalation of the drug in these populations.

Oseltamivir is an orally administered neuraminidase inhibitor that has demonstrated a modest benefit by reducing the median time to symptom improvement by 1.3 days. It is approved for the treatment of persons ≥18 years. The most common adverse effects include nausea, vomiting, bronchitis, difficulty sleeping, and dizziness. Patients with creatinine clearance of <30 mL/min should receive a reduced dosage (5,6).

Prophylaxis with these antiviral agents is not a substitute for vaccination. However, since mass vaccination will be delayed this year, they may be considered for the prevention and control of influenza in certain scenarios (Table 3) (2). Both amantadine and rimatadine are indicated for the prophylaxis of influenza A (effectiveness 70-90%) (7-10) but are ineffective against influenza

Table 3: Indications for Prophylaxis.

- Persons at high risk who are vaccinated after influenza activity has begun
- Persons who provide care to those at high risk
- Persons who have immune deficiency
- Control in institutions such as nursing homes, or other chronic settings

B. For effective prophylaxis, they must be taken each day for the duration of influenza activity in the community beginning during the peak of influenza activity in the specific patient's community. Zanamivir and oseltamivir have not been approved for prophylaxis, but recent studies suggest that both are similarly effective for influenza prevention (11-13).

Conclusion

So why all the flu hype? Likely, the development of new influenza diagnostic tests and the two new anti-viral drugs, complete with direct-to-consumer advertising for the newer influenza drugs, caught the attention of the media. Hopefully, the widespread heightened awareness, regardless of fact or fiction, will prompt both at-risk and healthy people to get our best weapon—Vaccination.

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