Influenza: Prevention and Therapy

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Subtypes of Influenza

The influenza virus is an RNA-containing enveloped virus. The envelope is covered with spikes of two types: hemagglutinin (H) and neuraminidase (N). There are at least three subtypes of influenza: influenza A, B, and C. Influenza C, which accounts for a small proportion of common cold illnesses, will not be discussed further here. Alterations in the antigenic structure of the influenza viruses can lead to infection with variant strains of virus. As a result, infection with these variants may occur because of limited resistance to these new strains in the population at risk.

There are two kinds of antigenic variation: antigenic drift and antigenic shift. Antigenic drift, which occurs with both influenza A and B viruses, involves relatively minor changes within the subtype in either the H or N as a result of permutations. For example, antigenic drift is responsible for the H3N2 variants of influenza A virus: A/England/72, A/Port Chalmers/73, A/Scotland/74, A/Victoria/75, and A/Texas/77. Because of the absence of antibody in the population at risk, immunologic selection can take place, and modified strains of virus can be transmitted from person to person.

Antigenic shift refers to major changes of the entire surface protein, either H or N or both. The new H or N is renumbered to distinguish it from other types of influenza A (ie, H0N1, H1N1, H2N2, etc.). Antigenic shift, which is caused by genetic recombination or reassortment, is thought to be responsible for the periodic pandemics or widespread disease with influenza that occurs about every ten years.

Prevention of Influenza

Vaccines for influenza are between 70% and 85% effective in reducing attack rates (1). In general, influenza vaccine should be given in the fall of each year before influenza first appears during the winter season. The vaccine is recommended for those at high risk for influenza infection and its complications. High-risk persons include individuals over the age of 60 and patients with chronic underlying diseases of any type such as diabetes, obstructive lung disease, chronic renal disease, malignancy, or heart disease of any etiology (2).

Persons who provide essential community services such as health care workers should also be vaccinated (3).

The vaccine formulation is usually bivalent, containing antigens against two subtypes of influenza A virus. Recently, the vaccine has become trivalent, containing antigens for two types of influenza A and one of influenza B. The vaccine formulation is generally changed from year to year because of the antigenic shift of the influenza virus.

The vaccine is relatively benign in terms of side effects. The major side effect is soreness at the injection site, which occurs in about 25% of those receiving the vaccine. A much smaller number will have fever, myalgias, or other constitutional symptoms lasting only a few days. The Guillain-Barré syndrome, which was seen during the national immunization program for swine flu, has not been seen with subsequent vaccine formulations. An unwarranted fear of the Guillain-Barré syndrome has made it difficult for many vaccine programs to be carried out, especially among health care workers. Recommendations for influenza vaccine are published yearly by the Centers for Disease Control in their Morbidity and Mortality Weekly Reports (2).

Amantadine hydrochloride (Symmetrel) is also used as preventive therapy for influenza. This antiviral agent is effective in preventing up to 90% of influenza A, but not influenza B virus infections (4). Amantadine may be used alone without vaccine during an influenza epidemic, or it may be used in combination with influenza vaccine. If used alone, the drug should be continued for the duration of the outbreak of influenza, usually five to six weeks. If used in combination with influenza vaccine, it is usually given for two weeks while waiting for a protective antibody titer to develop from vaccination. Some patients may have mild, reversible central nervous system (CNS) side effects such as nervousness, insomnia, difficulty concentrating or, rarely, nightmares and hallucinations. Gastrointestinal symptoms...
also occur. Our experience with amantadine has shown that compliance often is poor because of the gastrointestinal or other side effects. Therefore, the drug should probably be used in combination with the vaccine so that it can be given for as short a time as possible. The recommended dose for adults (200mg/day) should be taken in the morning in order to avoid any CNS side effects that might interfere with sleep if the drug were given in the evening.

In general, the best preventive therapy for influenza remains vaccination, either alone in the fall or in combination with amantadine if preventive measures are initiated after an outbreak of influenza occurs in the community.

Recently, rimantadine hydrochloride, an amantadine analog, has been reported to be more active than amantadine against influenza A virus in vitro and against experimentally-induced influenza A infection in laboratory animals (5). In another study, rimantadine used prophylactically was associated with significantly fewer CNS side effects; this finding suggests that rimantadine would be a reasonable alternative to amantadine once it has been approved by the Food and Drug Administration (6).

### Treatment

Amantadine probably has its greatest utility in the therapy of established infections with influenza virus. The drug, which is specific for influenza A viruses but not for influenza B viruses, results in more rapid defervescence and more rapid diminution in systemic and respiratory symptoms (7). For maximum benefit, amantadine should be initiated within 48 hours of the onset of the symptoms of influenza A. The drug is probably underused because most physicians are not familiar with it, and they are not familiar with the fact that the drug is licensed by the Food and Drug Administration both to treat and prevent influenza A infections. Our experience has been that compliance with amantadine is better when it is used for treatment rather than prophylaxis since patients may be more motivated to take the drug when they are ill.

One problem with initiating amantadine therapy is recognizing the syndrome. In many places, virus isolation facilities are not readily available, and when they are, the results of virus isolation may take up to a week or more. Therefore, the physician must be able to recognize the symptoms of influenza infection and initiate therapy based on clinical impression. When it is established that influenza A virus is prevalent in the community, most persons with acute febrile respiratory or acute febrile undifferentiated illness can be assumed to have influenza A virus infection. It is important to remember that influenza is a disease primarily of the respiratory tract and not of the gastrointestinal tract. Gastrointestinal symptoms without respiratory symptoms are rarely due to influenza virus.

This is the era of antiviral chemotherapy. Many antiviral compounds are currently on the market and more are being developed. As rapid viral diagnostic techniques become available, the decision-making process used for bacterial infections will also be applied to viral infections. The physician should be aware of this new direction in virology and become familiar with these antiviral compounds and their use.

### References