Influenza

Will New Diagnostic Tests and Antiviral Drugs Make a Difference?

Each year with the onset of the influenza "season," we are reminded of our inability to provide long-term protection against the suffering and excess mortality associated with this disease. Prevention of severe influenza requires annual vaccination of populations at risk with hemagglutinin protein of epidemic viral strains. Currently influenza A subtypes H1N1 and H3N2 and influenza B are used. In recent years, vaccination of individuals > 65 years old has increased from < 25% to as much as 70%, but as late as 1997, < 30% of high-risk individuals < 65 years old were being vaccinated annually.1,2

To provide an effective vaccine each year requires not only good science, but also good luck. Influenza viruses change genetically over time, and before vaccine production can begin, isolates that show antigenic "drift" must be located, characterized, and tested for their ability to grow well in vitro. A large amount of vaccine must then be produced rapidly to meet immunization deadlines. If there are problems in production, shortages will develop, as is the case for the present year.

In the event of a major genetic change in influenza, ie, an antigenic "shift" or reassortment of genes between wild viruses, which can result in the emergence of a pandemic strain, time becomes even more important. The health consequences of a delay in this case are potentially catastrophic. The uncertainties of this situation are exemplified by the swine influenza scare of 1976.3

There are several ongoing initiatives to improve influenza vaccines, including the use of a live attenuated vaccine administered by nasal spray. The latter is nearing clinical availability.4,5 Complete control of influenza and its complications by vaccination, however, remains problematic.

Given the limitations of vaccination for control of influenza in the immediate future, experience with antiviral drugs and especially with the new neuraminidase inhibitors, zanamivir and oseltamivir, is of interest.6,7 These new drugs, although more expensive, are active against both A and B influenza viruses, whereas amantadine and rimantadine affect only influenza A.

The development in recent years of very rapid diagnostic tests for influenza, including direct enzyme immunoassay (Directigen BD Diagnostic Systems; Sparks, MD) and an endogenous viral-encoded enzyme assay (ZstatFlu ZymeTx; Oklahoma City, OK), is important because rapid diagnosis is essential for optimum use of antiviral drugs. All currently available drugs for influenza should be started within 2 days of symptoms to be most effective.3 Viral culture or viral detection with fluorescent-labeled

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11 O'Donnell DE. Assessment of bronchodilator efficacy in symptomatic COPD: is spirometry useful? Chest 2000; 117(suppl):42S–47S
antibodies or the polymerase chain reaction are less rapid than the cited tests and not as widely available.\(^9\)

In this issue of CHEST, Oliveira and Marik (see page 1717) discuss their experience with the use of rapid diagnostic tests and antiviral drug treatment of 139 patients admitted to a large metropolitan hospital from December 1999 to February 2000 with upper or lower respiratory symptoms. Their results, in a representative group of patients with acute respiratory infection, reveal several potential problems in rapid diagnosis and treatment of influenza.

Of the 139 patients screened with Directigen (A virus) or ZstatFlu (A or B virus) in the study, 35 tested positive for influenza A. Most (88%) had serious comorbid illnesses. Seventeen patients developed pneumonia, while 18 patients had only upper respiratory infection (URI) with influenza. Of note, the number of cases of influenza diagnosed in their study was fourfold to sevenfold greater than had been seen in any of the preceding 5 years. Although the authors do not indicate how influenza was diagnosed previously, it seems most likely the increase was due to routine diagnostic testing, as part of the study. The specificity of their results was evaluated by viral cultures in only five patients, but the diagnostic tests they used have shown high specificity (>90%) in other studies.\(^2,8,9\)

Ideally, cultures would have been obtained in all patients because these rapid diagnostic tests are less sensitive, particularly in adults. However, as the present study indicates, routine viral cultures may not be available, even in some large metropolitan hospitals. Because the rapid diagnostic tests are readily available and can provide a timely diagnosis in at least a small majority of patients with influenza,\(^2,8,9\) they appear likely to be used without culture in a variety of clinical settings.

The timing of antiviral therapy in the study of Oliveira and Marik provides insight into problems other clinicians may encounter in the routine treatment of influenza with antiviral drugs. Many patients in the present study did not receive antiviral treatment within 2 days after the onset of symptoms, as needed for best results. Only 4 of 14 patients with influenza and pneumonia, who received antiviral therapy, were treated within 2 days of the onset of illness; on average, they were started on antiviral drugs at about 4 days of illness. Although the mean duration of symptoms before hospital admission in this group was just 2 days, the range was 1 to 7 days, so outpatient diagnosis and treatment would have been required for therapeutic efficacy in some patients. Similarly, patients who had only URI with influenza were ill an average of 3.3 days before they were admitted to the hospital and received treatment. For many patients, best management may require etiologic diagnosis and initiation of treatment in the outpatient department by generalists.\(^10\)

Perhaps the most important question facing physicians currently is whether the antiviral drugs now available are good enough to justify a concerted effort at routine etiologic diagnosis and treatment of influenza. Health-care providers are very familiar with amantadine and rimantadine for antiviral prophylaxis, but early diagnosis and routine treatment with antiviral drugs is a newer concept. In the end, physicians must depend on their own perceptions of the safety and efficacy of the antiviral drugs in determining their clinical approach.

Existing information shows that all four of the available antiviral drugs are safe when properly used and have mild-to-moderate side effects.\(^2,5\) In clinical trials with zanamivir and oseltamivir, symptoms of influenza have usually abated 1 to 1.5 days earlier with treatment than with placebo. Greater benefit has been reported in some severely ill patients or those treated on the first day of symptoms.\(^5\) Although all four antiviral drugs are approved for therapy of uncomplicated, acute influenza in healthy individuals, efficacy with influenza in high-risk patients, as mentioned by Oliveira and Marik, remains to be established. Prophylaxis is approved for amantadine and rimantadine, and is pending for oseltamivir and zanamivir.

In recent reviews,\(^2,5\) it is recommended that high-risk individuals with influenza and all individuals with severe influenza be treated with antiviral drugs. It is also recommended that treatment be considered in healthy individuals with influenza where shortening of the illness might be important to the patient. Prophylaxis should be provided for unvaccinated people at high risk in an epidemic, for as long as needed to develop protective antibodies. Prophylaxis is also suggested during an outbreak for unvaccinated persons caring for or living with people at high risk, and all staff and patients in long-term care institutions that house patients at high risk.

It seems clear that to offer prophylaxis or treatment in a timely manner, there must be provision for rapid diagnosis, whether in the inpatient or outpatient setting. The cost of rapid diagnostic testing and treatment (usually a 5-day course) would be expected to run at least $100. Longer-term treatment or prophylaxis, especially with zanamivir or oseltamivir, would be proportionally more expensive.

Although it is too early to conclude that widespread prophylaxis and treatment with existing antiviral drugs will have a profound clinical impact on the severity of illness and excess mortality from influenza, it seems important to explore the potential
of antiviral treatment concurrent with efforts to control influenza with vaccination.

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The Effect of Right Ventricular Dysfunction on Left Ventricular Form and Function

I t is a platitude known to all second-year medical students that the most common cause of right ventricular failure is left ventricular failure. It is decidedly less well known that right ventricular dysfunction has an effect on left ventricular form and function. In 1910, the French physiologist P. I. Bernheim postulated an interaction between the left and right ventricles such that an alteration in the function of one ventricle led to an alteration in the function of the other ventricle. He specifically proposed that left ventricular dilatation or hypertrophy would cause the right ventricle to be compressed with a resultant decrease in right ventricular function. Today, we know what Bernheim did not know, that decreased right ventricular function secondary to left ventricular dilatation/hypertrophy is the result of increased right ventricular afterload secondary to passive pulmonary hypertension (elevated left ventricular filling pressure leads to increased pulmonary arterial diastolic and systolic pressures).

In recent years, it has been clearly documented in experimental animal models and in patients that right ventricular dilatation and hypertrophy shift the interventricular septum leftward, thereby causing decreased left ventricular cavity size, contractility, compliance, and ejection fraction as well as increased left ventricular diastolic pressure. This phenomenon has been coyly described as “the reverse Bernheim phenomenon,” even though Bernheim never actually suggested such a term. The physiologic terms most commonly employed to describe this phenomenon are “ventricular interaction or ventricular interdependence.” The observed changes in left ventricular function can occur in normal hearts or in those of patients with cardiac disease. The reverse Bernheim phenomenon has been noted in patients with both volume and pressure overload of the right ventricle.

The restraining pericardium plays an important role in furthering ventricular interaction secondary to acute changes in right ventricular volume/function, since pericardial stretch cannot occur acutely. The restraining influence of the pericardium ensures that a sudden increase in right ventricular volume occurs at the expense of left ventricular volume as a result of the leftward shift of the septum. Even in chronically dilated right ventricles, pericardial restraint ensures that the interventricular septum will shift to the left, thereby decreasing left ventricular volumes and altering systolic and diastolic function.

In patients with right ventricular pressure overload, such as the patients described by Marcus et al in this issue of CHEST (see page 1761), there is a second potential mechanism for altering left ventricular function: the myocardial hypertrophic process that is affecting the right ventricle produces concomitant hypertrophy of the interventricular septum. Left ventricular compliance is altered by the septal hypertrophy. Both mechanisms probably play a role in changing left ventricular diastolic function.

Marcus et al used nuclear MRI to study left and right ventricular volumes and filling rates as well as septal curvature, and pulmonary arterial flow curves in 12 patients with rather severe primary pulmonary hypertension. Their work confirms and extends previous studies in this area. Marcus et al noted that the