Perspectives on Influenza Virus Infection

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Influenza virus is one of the most severe respiratory tract pathogens, annually causing substantial morbidity, mortality, and economic loss. Influenza virus infection is usually self-limited in most instances, but it also causes several severe complications such as primary viral pneumonia, secondary bacterial pneumonia, myocarditis, and central nervous system complications. These complications may be life-threatening and/or result in major sequelae, especially in the elderly, the immunocompromised hosts, and the patients with chronic illness.

Currently, two classes of antiviral agents, the M2 ion channel inhibitors and neuraminidase (NA) inhibitors, have been used to treat influenza. The first class, adamantanes (amantadine and rimantadine), targets the proton ion channel formed by the viral M2 protein. Because this protein is absent in influenza B viruses, adamantanes have antiviral activity against influenza A viruses only. The NA inhibitors, including oseltamivir, are the only drugs possessing activity against both influenza A and influenza B viruses. These drugs are recommended to be used early in the disease course, usually no later than 2 days after the symptom onset. A recent report suggested antiviral therapy is beneficial for hospitalized patients even if being used after 2 days of symptom onset. Therefore, making a definite diagnosis of influenza virus infection is more important. In addition to viral culture, several rapid diagnostic tests have been developed. Reverse transcription polymerase chain reaction (RT-PCR) is preferred due to its speed, sensitivity, and specificity, but it is not widely available to most clinicians.

Enzyme immunoassay (EIA) rapid antigen detection is commercially available and is now used in some hospitals. The use of EIA is hindered by its low sensitivity. The sensitivity of EIA is only 50–70% compared with that of viral culture, and the specificity is close to 95%. Overall, a satisfactory rapid diagnostic test to confirm influenza is still lacking.

Along with the increasing use of anti-influenza virus agents, the resistance to adamantanes and NA inhibitors has become a rising concern in recent years. In a global surveillance study, a significant increase in adamantane resistance was noted, from 0.4% in 1994–1995 to 12.3% in 2003–2004. In the study, 84% of resistant viruses were obtained since the 2003 influenza season and, of those, 61% were collected from people in Asia. There was a substantial increase during 2002 to 2004 in China, Hong Kong, South Korea, and Taiwan. The rates of resistance were less than 10% before 2002 in these areas. Alarmingly, the frequencies of adamantane resistance after 2003 rose to 73.8% in China, 69.6% in Hong Kong, 15.1% in South Korea, and 22.7% in Taiwan. In another worldwide study surveying influenza A viruses isolated during 2004 to 2006, the overall resistance was 90.6% in H3N2 and 15.6% in H1N1. The rapid spread of adamantane resistance significantly diminishes its role in the treatment of influenza diseases. The resistance rate to NA inhibitors, oseltamivir and zanamivir, were reported to be low (0.33% for oseltamivir) in the 1999 to 2002. In another study conducted in France, resistance to oseltamivir and/or zanamivir remained low at 1% during 2005 and 2006. However, the rate of
oseltamivir resistance in the influenza A (H1N1) virus increased significantly from less than 1% before 2007 to 8.6% during 2007 to 2008 in United States.9 The recent growing resistance raises public health concerns and necessitates close monitoring of resistance to NA inhibitors. During this flu season (2008–2009) in United States, the resistance rates of influenza A (H1N1) were 98.2% (162/165) to oseltamivir, 0% to zanamivir, and 1.2% (2/165) to adamantanes.10 In contrast, the resistance rates of influenza A (H3N2) were 0% both to oseltamivir and zanamivir, but was 100% (37/37) to adamantanes. In influenza B, the NA inhibitor resistance remained 0% (0/67). Therefore, the CDC of the United States issued interim recommendations for the use of antiviral agents in the 2008–2009 flu season.11 When influenza A (H1N1) virus infection or exposure is suspected, zanamivir or a combination of oseltamivir and rimantadine are more appropriate options than oseltamivir alone. This reinforced the importance of laboratory testing and local influenza surveillance, which can help with physician decision-making regarding the choice of antiviral agents for their patients. During this flu season in Taiwan, the major type was influenza A virus, while H1N1 and H3N2 were co-circulating during 2008–2009. The oseltamivir resistance rate of influenza A (H1N1) in Taiwan is also nearly 100%.12

In this issue of journal, Wang et al reported that 51% of the influenza-like illness (ILI) patients were culture-confirmed influenza during the 2006–2007 flu season.13 The high culture positive rate reported in this issue is remarkable. This indicates that in the influenza seasons or in an influenza epidemic, sudden onset fever with the acute respiratory infection symptoms in subjects younger than 18 years old is predictive of influenza virus infection. In Wang’s report, influenza B virus contributed 86.1% of the culture-confirmed influenza infection. This reflected the fact that there was an influenza B virus outbreak during 2006–2007 flu season in Taiwan. Wang et al also analyzed data that showed that leukopenia was found in 56.1% of children with influenza B virus infection in whom a blood test was performed. In those children infected with influenza B virus who had blood creatinine kinase (CK) tested, 56.5% had elevated CK and associated myalgia. In general, these findings are consistent with previous reports. Shen et al analyzed 274 influenza A and influenza B virus infected patients during 2005 to 2007. Children with influenza B infection tended to have lower leukocytes counts and higher serum CK than those with influenza A infection.14 Influenza associated myositis (IAM) occurs mostly in influenza B infection.15,16 Hu et al reported the rates of IAM were 5.5% and 33.9% in influenza A and influenza B infections respectively. The proposed mechanism of IAM was direct muscle invasion by influenza virus, which was supported by the fact that the influenza virus was isolated from the muscle biopsy specimen from patients with IAM.17,18 However, the differences in the capabilities of influenza A and influenza B viruses to cause IAM remain unexplained. A glycoprotein (NB) encoded by RNA segment 6 is unique to the influenza B virus. The NB protein is an integral component of the membrane of influenza B virion. This unique NB protein may render influenza B virus more myotropic than influenza A virus. However, this hypothesis awaits further experimental confirmation.

References