

Literature Review: Antiviral Use for Influenza

City of Milwaukee Health Department

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The following articles may be of interest to physicians and other clinicians who may manage patients of, or contacts to, either seasonal or pandemic influenza.

Stiver, H. G. (2007). *Use of vaccines and antiviral drugs in the next influenza pandemic. BC Medical Journal*; 49(5):249-253.

<http://www.bcmj.org/use-vaccines-and-antiviral-drugs-next-influenza-pandemic>

Summary:

This outstanding overview offers advice on how “to optimize the use of vaccines and antiviral agents, and to employ effective clinical management of patients in the event of a pandemic.”

Influenza A strains are of concern during a pandemic, not B strains. As of June 2007, there have been 269 confirmed cases of H5N1 avian influenza and “the disease has been very severe with a 60% mortality rate in the recognized reported cases.”

Amantadine resistance has increased to the point that “more than 90% of people are resistant and its no longer recommended for treatment or prophylaxis.” Thankfully “almost all the strains tested have been susceptible to oseltamivir” (although oseltamivir is not recommended for infants less than a year old).

The suggested dose of oseltamivir, 75 mg taken twice a day for five days, appears to be well tolerated, although “nausea and vomiting occur in 7% of persons.” “Oseltamivir given within 12 hours of symptom onset rather than 48 hours has resulted in 3 fewer days of symptoms.”

An additional article from the same journal may also be of interest, *Pandemic influenza - A primer for physicians* (Skowronski DM, Kendall P) <http://www.bcmj.org/pandemic-influenza-primer-physicians>

Centers for Disease Control and Prevention. (2008). *Influenza-testing and antiviral-agent prescribing practices-Connecticut, Minnesota, New Mexico, and New York, 2006-07 influenza season. Morbidity and Mortality Weekly Report*; 57(3):61-64.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5703a1.htm>

Summary:

Approximately 36,000 people die of influenza each flu season. If antiviral therapy is initiated within 48 hours of onset of influenza like illness, the duration of the illness may be lessened. Antivirals can also be used prophylactically for influenza. *However, physician practice regarding influenza testing and use of antivirals appears to be suboptimal. Additional*

educational measures may be needed to ensure physicians are knowledgeable about current prescribing practices.

The CDC surveyed 2679 physicians, and 1262 responded. After excluding subspecialists, the results showed influenza-related practices of family physicians (268), internists (213), pediatricians (204), and ob/gyns (45).

In regard to influenza testing, 88% ordered rapid antigen testing, 19% ordered viral culture, and 6% ordered serology. Use of rapid testing varied by region of the country, and those in practice longer (≥ 10 years) were less likely to order tests than those who entered practice more recently. The CDC cautions that rapid antigen testing “produce incorrect results for 25-30% of persons with influenza.”

In regard to influenza treatment, 54% prescribed antiviral agents to at least some patients with influenza like illness. Of prescribers, 87% prescribed oseltamivir, 18% amantadine, 9% rimantadine, and 5% zanamivir. However, amantadine and rimantadine have not been recommended since January 2006 because they have a “high rate of resistance among circulating influenza A strains” Side effects for oseltamivir including hallucinations, delirium, and abnormal behavior in children for the duration of the treatment. Zanamivir should not be prescribed to patients with respiratory diseases because it can cause bronchospasm.

Fiore, A. E., Shay, D. K., Haber, P., Iskander, J. K., Uyeki, T. M., Mootrey, G., Bresee, J. S., & Cox. N. J. (2007). Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. Morbidity and Mortality Weekly Report; 56:RR-6.

<http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf>

Summary:

This 60-page report provides detail on almost all aspects of influenza. The 2008 version is expected during the summer months of 2008.

In terms of antiviral medications, this report states that they can be useful both as a prophylactic and as a treatment for influenza. Rapid development of high levels of resistance to both amantadine and rimantadine has been documented for influenza A. Oseltamivir is approved for treatment or prophylaxis of people aged one year old or older. Zanamivir can be used for treatment of anyone seven years old or older, and for prophylaxis for patients five years old or older. Resistance to zanamivir and oseltamivir has been documented as well but the resistance “does not appear to be frequent.”

For “outpatients with uncomplicated influenza”, the CDC recommends “initiation of antiviral treatment within 2 days of illness onset...although the benefit of treatment is greater as the time after illness onset is reduced.” “When administered within 2 days of illness onset to otherwise healthy children or adults, zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day.” Treatment with either recommended antiviral should continue for five days, but “minimal to no benefit is reported when antiviral treatment is initiated >2 days after onset of uncomplicated influenza.”

Stiver, G. (2003). *The treatment of influenza with antivirals. Canadian Medical Association Journal*, 168(1):49-57.

<http://www.cma.ca/cgi/reprint/168/1/49>

Summary:

This article, while slightly dated, provides a clear, basic overview of use of antivirals for both seasonal and pandemic influenza. Studies of antivirals have shown significant reductions in "feverishness, cough, nasal obstruction, sore throat, myalgias, headache and fatigue ... of between 1 and 2.5 days, depending on the subgroup analyzed, compared with placebo.... Secondary benefits included 50%-70% fewer complications, 30%-50% fewer courses of antibiotics compared with placebo and earlier return to normal activities by 1-3 days."

Antivirals should not be prescribed without a positive diagnosis, and should be limited to febrile patients early in their disease. "Most of the benefit occurs when drug therapy is started earlier than 30 hours after onset of symptoms."

Bartlett, J. G. (2006). Planning for avian influenza. *Annals of Internal Medicine*; 145:141-144.

<http://www.annals.org/cgi/reprint/145/2/141.pdf>

Summary:

H5N1 has three of the four "properties necessary to cause a serious pandemic: It can infect people, nearly all people are immunologically naïve, and it is highly lethal." The only missing component "is the lack of sustained human-human transmission." Based on the 1918 influenza pandemic, we can expect that in a pandemic now:

- 1) the attack rate in the United States would be 30% causing 90 million cases;
- 2) of those infected, about 50% would seek medical care;
- 3) the excess mortality would be 209,000 to 1,903,000 deaths; and
- 4) the outbreak in a community ... is likely to be over in 3-4 months."

There are three major weapons that will be used to fight this pandemic: "vaccines, antiviral agents, and social distancing."

Vaccine: Bartlett calls for a vaccine for H5N1 and "a substantial increase in our vaccine production capacity." As of the date of this article, "worldwide production capacity for this vaccine would be enough to vaccinate a total of 75 million people, which is about one fourth of the U.S. population or 1.25% of the world population."

Social Distancing: "Social distancing appears to be paramount"

Antivirals: "Oseltamivir and zanamivir are about 60% effective in preventing seasonal influenza, but their effectiveness for preventing pandemic influenza is unknown." Further, the "largest risk is having a household member with influenza, and one of the most effective containment strategies is early antiviral treatment of the index case and confinement to the home."

Based on the 1918 experience, a pandemic now would require "197% of hospital beds, 461% of intensive care unit beds, and 198% of all available respirators." The "greatest need will be providers skilled in primary care, infection control, emergency medicine, pulmonary-critical

care, and infectious diseases; nurses, respiratory therapists; pharmacists; and support personnel.”

“The American Medical Association Code of Medical Ethics states ‘that a duty to serve overrides autonomy rights in societal emergencies, even in cases that involve personal risk to physicians.’” Nonetheless, there is a “reciprocal obligation for institutions to provide maximum available protection, including antiviral agents, vaccines, personal protective equipment, and liability protection.”

Halloran, M. E., Hayden, F. G., Yang, Y., Logini, Jr., I. M., Monto, A. S. (2007). Antiviral effects on influenza transmission and pathogenicity: Observations from household-based trials. American Journal of Epidemiology; 165:212-221.

<http://aje.oxfordjournals.org/cgi/reprint/165/2/212>

Summary:

This meta-analysis of four studies on the efficacy of antivirals in post exposure prophylaxis to preventing influenza infection in household contacts shows that “substantial protection of household contacts against influenza illness [is provided] with postexposure prophylaxis by either zanamivir or oseltamivir.”

Protection against infection is lower than protection against illness. In fact, “(p)rophylactic protection of both zanamivir and oseltamivir against symptomatic influenza is quite good, about 75-85 percent ... [but the] efficacy in reducing pathogenicity is in the 45-60 percent range.”

Hammond, G. W. (2002). Strategies for the control of influenza infections. The Canadian Journal of CME, 141-147.

<http://www.stacommunications.com/journals/cme/2002/02-Feb/cmefeb02Influenza.pdf>

Summary:

In addition to an overview of seasonal influenza and its control strategies, the author points out that “up to one-third of infected individuals may be asymptomatic, but can transmit infection” and that “it is common for approximately 15%-20% of a population to be infected annually...usually within two months in a single community.”