



Release Date: September 2005

Valid Until: February 2007

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Issue No. 4, December 2005, is part of a 12-part CME activity (September 2005 – August 2006).

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Applicants will receive a certificate of participation from PPS by return mail within 6 to 8 weeks of the date of receipt of the completed evaluation/registration form.

Learning Objectives

After studying the literature presented in this Pediatric Respiratory Care™ series, participants will be able to:

- Identify respiratory disorders in pediatric patients
- Summarize risk factors for respiratory disorders in pediatric patients
- Select an appropriate therapeutic regimen for patients with pediatric respiratory disorders

Target Audience

This educational activity is designed for pediatricians, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, primary care physicians, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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This CME activity is supported by an unrestricted educational grant from MedImmune, Inc.

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Clinical Insights® in

PEDIATRIC RESPIRATORY CARE

VOLUME 1, NUMBER 4 • DECEMBER 2005

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The Coming Pandemic?

Growing concerns of a coming influenza pandemic are best exemplified by the cases in Vietnam, in which the highly pathogenic avian influenza A (H5N1) virus has crossed the species barrier, resulting in human fatalities. Recently, the geographic distribution of H5N1 has been expanding, and greater numbers of the human population are at risk. In May, international influenza experts gathered in Hanoi to discuss the emerging threat. A review describing the H5N1 strain and recommendations for its prevention and case management has been published. Even with limited data available, the highly pathogenic avian H5N1 influenza virus infecting humans differs from human influenza A viruses in several ways.

Viral isolation and the detection of H5-specific RNA have been used to diagnose H5N1 influenza. In contrast with human influenza A, infection with H5N1 may be associated with a higher frequency of viral detection and higher viral RNA levels in pharyngeal rather than nasal samples. Commercially available rapid antigen tests have proved less sensitive than reverse transcriptase-polymerase chain reaction assays, and results from such test kits should be regarded with caution.

Occurrence of human influenza (H5N1) has paralleled the outbreaks of the highly pathogenic avian influenza (H5N1), yet reports of human disease have been rare. The relatively low frequency of H5N1 illness

in humans suggests that the virus must cross a substantial species barrier. In most cases of human H5N1, direct contact with infected poultry appears to be necessary for transmission. Reports of H5N1 human-to-human transmission have been sparse. This scenario is in contrast with human influenza, which is transmitted by inhalation of infectious droplets, direct human contact, or fomites.

“Even with limited data available, the highly pathogenic avian H5N1 influenza virus infecting humans differs from human influenza viruses in numerous ways.”

Clinical description of human H5N1 disease is limited to hospitalized patients. Differences between the human and avian influenza lie in the clinical severity of the latter. The incubation period of H5N1, (2–4 days, range ≥8 days), appears longer than for other known human influenzas. Upper respiratory tract symptoms are only occasionally present. Most patients present with high fever and lower respiratory tract symptoms. Some patients infected with H5N1 exhibit a watery diarrhea without blood that may precede respiratory manifestations by ≥1 week. Pleural effusions are uncommon; multifocal lung consolidation involving at least two zones appears common.

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Disclosures:

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The Coming Pandemic?

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The pneumonic process appears to be of a viral etiology rather than a bacterial superinfection. Progression from the early stages of infection to respiratory failure has been associated with bilateral ground-glass infiltrates and manifestations of acute respiratory distress syndrome. Multiorgan failure is common and the fatality rate is high.

Reports indicate that early treatment can provide the greatest benefit. Patients with suspected or proven H5N1 infection should be hospitalized in isolation for monitoring, diagnostic testing, and antiviral therapy. Neuraminidase inhibitors should be administered as early as possible, even if diagnostic laboratory results are pending. Inhaled zanamivir has not been studied in cases of human influenza A (H5N1). Recently, mouse studies with influenza A (H5N1) isolated in 2004 required oseltamivir doses twice as high with more prolonged administration (8 days) to result in good survival. Mutants expressing antiviral resistance to oseltamivir can arise; yet they appear to exhibit reduced pathogenicity. Unfortunately, no H5N1-specific vaccines currently are available for human use.

Studies of various H5N1 isolates suggest that these viruses continue to evolve with

(1) changes in antigenicity and internal gene constellations, (2) expanding avian species host ranges, (3) enhanced pathogenicity in various animal models leading to systemic infections, and (4) increased environmental stability. Recently H5N1 infections have caused high rates of mortality among infants and young children, in contrast to earlier H5N1 outbreaks with more frequent deaths among patients >13 years of age.

The avian influenza H5N1 strain exhibits several important differences from the human influenzas: in routes of transmission, clinical severity, pathogenesis, and even responses to treatment. Regardless of recent progress, knowledge of the epidemiology, natural history, and management of H5N1 disease in humans is far from complete, and more clinical and epidemiologic studies are needed.

NOTE: the FDA has not approved the discussed use of the drug in this study.

Writing Committee of the World Health Organization Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med.* 2005;353:1374-1385.

Effective Use of Stockpiled Neuraminidase Inhibitors During a Pandemic

The spread of highly pathogenic strains of avian influenza (H5N1) has ignited concern about the potential for a pandemic. Two groups of antivirals are available as treatments and prophylaxis for influenza. The adamantanes (amantadine and rimantadine) might be effective against pandemic strains; however, there are questions regarding adverse reactions and the development of antiviral resistance. The neuraminidase inhibitors (oseltamivir and zanamivir) reduce the period of symptomatic illness for both the A and B forms of influenza viruses. Antiviral resistance to these agents can occur, yet resistant strains appear to become pathogenically weakened. Hence, the neuraminidase inhibitors are considered a key therapeutic option during the early phases of a

pandemic. Many countries have considered stockpiling these agents as a precautionary measure. Yet it is still unknown how much drug to accumulate and how best to use the available stockpiles for maximal benefit. To answer these questions, Gani and colleagues modeled different scenarios to derive estimates of the effect of various stockpile sizes on hospitalization rates.

The baseline scenario utilized WHO data to assume a clinical attack rate of 25% of the population, in a single wave, with no interventions attempted. The investigators first estimated the effect of different-sized antiviral stockpiles on the overall clinical attack rate. Using this baseline scenario, the estimated impact of clinical attack rates from 20% to 40% was modeled. The findings

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Effective Use of Stockpiled Neuraminidase Inhibitors During a Pandemic

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demonstrated that a stockpile of only 12% was sufficient to treat all patients even if the clinical attack rate was 25%. In addition to clinical attack rate, the authors modeled the impact of stockpile size on hospitalizations based on treating four groups: (1) all patients, (2) at-risk groups, (3) children and the elderly (1–14; ≥65 years of age), and (4) the working population (15–64 years of age). If a large enough stockpile were available, the best option to minimize hospitalizations would be to treat all patients. In this case, a 12% stockpile would decrease hospitalizations by 77%. Treating the working population would require the same size stockpile, but hospitalization would only be reduced by 40%. With stockpile sizes ≥7%, the best strategy was to treat the at-risk groups, demonstrating a 45% reduction in hospitalization. For stockpile sizes between 7% and 10%, treating the children and the elderly was the best strategy. At stockpiles >10% everyone could be treated.

These results suggested that the optimal strategy was dependent on treating persons at highest risk for hospitalization.

Since the age-specific clinical attack rate has varied between pandemics, the analyses were repeated using the previous rates (1918, 1957, and 1968). In all cases, the most beneficial use of smaller stockpiles (<10%) was to target treatment to highest risk populations. Treating the young and the elderly was only slightly less effective. Treatment of the working population generally is not the best strategy, but treating this demographic group may have benefits (eg, reduced absenteeism) beyond reducing hospitalization. NOTE: When stockpiles are large (20%–25%), treatment of all patients is consistently the best strategy. This report did not model for groups with higher transmission rates. Targeting such groups would result in greater reduction in transmission than reported in this article.

NOTE: the FDA has not approved the discussed use of the drug in this study.

Gani R, Hughes H, Fleming D, Griffin T, Medlock J, Leach S. Potential impact of antiviral drug use during influenza pandemic. *Emerg Infect Dis.* 2005;11:1355-1362.

PRCI™ MISSION STATEMENT

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Clinical Insights in Pediatric Respiratory Care is edited by PRCI™ faculty member Pedro A. Piedra, MD.

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EM-T304-PHYCME-1205-13K