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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, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other health-care professionals involved in the care and management of pediatric respiratory patients.

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Oseltamivir for Treating Influenza A and B: A Comparative Study

Oseltamivir functions as a neuraminidase inhibitor and is frequently prescribed in Japan for the treatment of influenza.

Well-documented use of this medication, as well as data from clinical trials, have established oseltamivir as an effective treatment against type A influenza, but little is known about its effects on type B influenza. This lack of information prompted investigators to conduct a prospective, multicenter study on the duration of fever in patients diagnosed with influenza during the 2003–2004 and 2004–2005 influenza seasons.

Family doctors, pediatricians, and physicians at 36 clinics in Japan, belonging to the Influenza Study Group of the Japan Physicians Association, helped to assemble patient data between December 6, 2003 and April 11, 2005. Patients with a body temperature of 37.5°C (99.5°F) or higher, presenting with systemic and upper respiratory tract symptoms were considered eligible for enrollment. These patients were tested for influenza using commercial antigen detection tests. The decision on whether to administer oseltamivir was at the discretion of the physician.

A total of 3,351 patients were enrolled in the study; 1,818 patients with type A influenza and 1,485 patients with type B influenza received treatment with oseltamivir, and 21 patients with

type A influenza and 27 patients with type B influenza did not receive treatment with an anti-influenza medication. The treatment regimen was administered orally twice a day for 5 days (75 mg for adults and children weighing 37.5 kg [83.4 lb] or greater; and 2 mg/kg for children weighing less than 37.5 kg [83.4 lb]).

Physicians recorded the age and gender of each patient, along with the number of vaccinations received (≥ 0), and the results of the antigen detection test kit. In addition, the dates and times of the first fever (37.5°C [99.5°F] or higher) and dose of oseltamivir, and the last fever were captured and reported electronically to a central facility. Patients were asked to measure and record body temperature at least three times a day.

An analysis of the data collected established that, regardless of virus type, the duration of fever in patients treated with the oseltamivir was shorter than in those patients who did not receive anti-influenza medication (patients with type A influenza: 47.9 h \pm 26.0 h compared with 82.4 h \pm 36.0 h, respectively [$P < 0.001$]; patients with type B influenza: 65.4 h \pm 32.8 h compared with 78.3 h \pm 41.9 h, respectively [$P < 0.001$]). In addition, patients with type B influenza receiving treatment with oseltamivir maintained a lower fever temperature for a longer time (38.8°C [101.8°F] \pm 0.6°C for a duration of 65.4 h \pm 32.8 h) as com-

Duration of fever was significantly shorter in patients who received treatment 12 hours or less after onset of symptoms as compared with those who received their first dose of oseltamivir at 13 to 24 hours, 25 to 36 hours, or 37 to 48 hours after onset.

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Disclosures:

- * Dr Piedra is professor of molecular virology and microbiology, and pediatrics at Baylor College of Medicine. He has indicated relevant financial relationships as noted: he receives grant/research support from MedImmune, Inc.; is a speaker for MedImmune, Inc.; is an expert witness for Sanofi-Pasteur; and is an ad hoc consultant for GlaxoSmithKline, MedImmune, Inc., and Sanofi-Pasteur.
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Osetamivir for Treating Influenza A and B *(Continued)*

pared with patients with type A influenza (39.0°C [102°F] ± 0.7°C for a duration of 47.9 h ± 26.0 h [$P < 0.001$]).

Further analysis led researchers to divide the participants receiving osetamivir into eight additional categories. Four categories were based on the time from onset of fever until the hour of first administration of the study drug (0–12 h, 13–24 h, 25–36 h, 37–48 h); and four categories were based on age (0–6, 7–15, 16–64, and those older than 64 years of age). An evaluation of data using this alternative format confirmed that the duration of fever was significantly longer for patients with type B influenza as compared with patients with type A influenza, regardless of the time of onset, first administration of osetamivir, or age ($P < 0.001$).

Detailed analysis revealed the total duration of fever was significantly shorter in patients who received treatment 12 hours or less after onset of symptoms (type A influenza: 37.6 h ± 25.9 h; type B influenza: 53.1 h ± 31.2 h) as compared with those who received their first dose of osetamivir at 13 to 24 hours, 25 to 36 hours, or 37 to 48 hours after onset ($P < 0.001$). In addition, fever symptoms were consistently of a shorter duration in patients aged 7 to 15 years diagnosed with either type of influenza as compared with those patients aged 6 years or younger, 16 to 64 years, and those older than 64 years.

Investigators conducted further analysis in an attempt to isolate the virus in patients previously treated with osetamivir. Again, the rapid antigen detection kits and additional testing verified the findings. Type A influenza was isolated in 15.9% of patients tested and type B influenza was isolated in 51.6% of patients tested. These results proved that the type B influenza virus endured treatment with osetamivir at a higher rate than the type A influenza virus, as observed 4 to 6 days after treatment was initiated.

At the conclusion of this research, it became evident that type B influenza was not as susceptible to treatment with osetamivir as was type A influenza. Fever symptoms lasted longer in patients with type B influenza regardless of gender, age, or time of first treatment. However, it is important to note that all patients receiving treatment with osetamivir experienced a quicker recovery than those patients who chose not to receive an anti-influenza medication.

Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of osetamivir for the treatment of influenza A and influenza B: A Japanese multicenter study of the 2003–2004 and 2004–2005 influenza seasons. *Clin Infect Dis*. 2006;43:439–444.

COMMENTARY

H. CODY MEISSNER, MD, Professor of Pediatrics, Tufts University School of Medicine, Chief, Pediatric Infectious Disease, Tufts-New England Medical Center, Boston, Massachusetts.

Influenza immunization with either a killed, inactivated vaccine or with the live-attenuated vaccine is the mainstay of disease prevention. For individuals who develop disease, chemotherapy with an anti-viral agent is likely to modestly reduce the duration of illness if therapy can be initiated within the first 24 to 48 hours of symptom onset. Choices among anti-viral agents were reduced during the 2005–2006 respiratory virus season to neuraminidase inhibitors (oseltamivir and zanamivir) because of the appearance of resistance to M2 inhibitors (the adamantanes, amantadine and rimantadine) among significant numbers of type A influenza isolates. The report by Kawai et al provides evidence that, although osetamivir is useful in reducing the duration of symptoms in infections caused by both type A and type B influenza, the drug's effect on temperature reduction is greater in patients with type A disease than in patients with type B disease. High-level resistance to neuraminidase inhibitors fortunately remains an uncommon occurrence. Nonetheless, the need for adherence to Centers for Disease Control and Prevention guidelines for appropriate use of anti-viral agents is clear in order to reduce the risk of new patterns of resistance.

Detecting Influenza Viruses Resistant to Neuraminidase Inhibitors

Influenza is a treatable and potentially preventable virus, yet morbidity and mortality rates remain unabated throughout the world. Reports of the highly pathogenic type A (H5N1) avian flu affecting human populations surfaced for the first time in 1997 and then again in 2003 and 2004 prompting researchers to focus attention on improving the most frequently employed treatment and prevention options available.

Recently, influenza A/H3N2 and some of the highly pathogenic H5N1 viruses were shown to

be resistant to M2 protein inhibitors (adamantanes) such as amantadine and rimantadine. M2 inhibitors have no activity against type B influenza strains. In addition, treatment of type A influenza with M2 inhibitors promotes the development of mutant strains of the virus which are resistant to treatment. These resistant strains are contagious and will cause disease.

The majority of type A and type B influenza isolates are susceptible to neuraminidase inhibitors (NAIs), such as zanamivir and osetamivir,

Continued



A/NI and B type viruses are more susceptible to treatment with zanamivir; and oseltamivir is more effective for the treatment of A/N2 type viruses.

Detecting Influenza Viruses *(Continued)*

which have been found to be effective treatment against influenza if started within 48 hours of onset of disease and emergence of resistance patterns are infrequent. This makes NAIs a more sensible choice for treatment.

The Neuraminidase Inhibitor Susceptibility Network (NISN) was founded in 1999 to monitor the use of NAIs for the treatment of influenza and to assess the long-term impact of its increased usage on society. The NISN began this investigation by reviewing more than 1,000 clinical specimens collected during the 3 years before NAIs were used anywhere in the world (1996–1999). Samples were routinely collected and subsequently selected for submission by the World Health Organization (WHO) collaborating centers, which are strategically located in Atlanta, Georgia, United States; London, United Kingdom; Melbourne, Australia; and Tokyo, Japan.

Another 2,287 isolates, from the 3 years after zanamivir and oseltamivir became licensed and available in some areas of the world, were chosen by the WHO collaborating centers for the purposes of this research. All specimens were categorized according to isolate type and subtype as follows: 882 type A (H3N2), 743 type B, 622 type A (H1N1), and 40 type A (H1N2).

To determine virus susceptibility to treatment with oseltamivir and zanamivir, a chemiluminescent enzyme inhibition assay was performed and the 50% mean inhibitory concentrations (IC₅₀s) were calculated electronically. In general, resistant variations of viruses will have an IC₅₀ value which is at least 10-fold greater than that of the parent virus. For the purposes of this research, all strains tested that showed IC₅₀ values at least 10-fold greater than the mean value of all the viruses from that year combined were determined to not be susceptible to treatment, or an extreme outlier.

The IC₅₀ values remain stable during the

study period and all findings were consistent with previously published data. A/NI and B type viruses are more susceptible to treatment with zanamivir; and oseltamivir is more effective for the treatment of A/N2 type viruses. Previously documented research indicates that mutant variations of viruses emerging in patients treated with NAIs have proven to be weak and less transmissible.

After the 3-year study period, a total of eight extreme outliers were revealed, and the results were as follows: 1 of 465 viruses tested (0.22%) from the 1999–2000 season; 3 of 842 viruses tested (0.36%) from the 2000–2001 season; and 4 of 980 viruses tested (0.41%) from the 2001–2002 season. No antiviral use could be associated with these extreme outliers. These results include the analysis of isolates collected from Japan and the United States, where NAIs are used more frequently. It is also relevant to note that there were no extreme outliers discovered in the 1,054 viruses (1996–1999) used as a baseline for this study.

Researchers continue surveillance for emergence of resistance and their analyses of extreme outliers to determine which mechanism may be responsible for causing the mutant variations to emerge as viruses less susceptible to treatment with NAIs. It is important to recognize the potential for a pandemic with the emergence of type A (H5N1) avian viruses. Currently, NAIs are the major treatment option for this strain and more research is needed to further establish the long-term effects, safety, and efficacy of this particular treatment.

Monto AS, McKimm-Breschkin JL, Macken C, et al. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother.* 2006;50:2395-2402.

PRCI MISSION STATEMENT

The PRCI is a multicomponent educational program on pediatric respiratory disorders designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients. PRCI programs address issues concerning asthma, respiratory syncytial virus, and other respiratory tract infections and disorders. Methods to prevent, control, and treat respiratory illnesses in children are also evaluated.

Clinical Insights® in Pediatric Respiratory Care Post-test

- Which of the following statements is *false* regarding treatment with oseltamivir?
 - Regardless of virus type, fever duration in patients treated with oseltamivir was shorter than it was in those patients who did not receive treatment.
 - Patients with type B influenza receiving oseltamivir maintained a lower fever temperature for a longer time as compared with patients with type A influenza.
 - Duration of fever was significantly shorter for patients with type B influenza as compared with patients with type A influenza, regardless of the time of onset, first administration of oseltamivir, or age.
 - Influenza B type virus endured treatment with oseltamivir at a higher rate than the type A influenza virus, as observed 4 to 6 days after treatment was initiated.
- A/NI and B type viruses are more susceptible to treatment with:
 - Oseltamivir
 - Zanamivir
 - Amantadine
 - All of the above

1. Duration of fever was significantly longer for patients with type B influenza as compared with patients with type A influenza, regardless of the time of onset, first administration of oseltamivir, or age.
2. A/NI and B type viruses are more susceptible to treatment with zanamivir; oseltamivir is more effective for the treatment of A/N2 type viruses.

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