

Enterococcal Endocarditis Carries Good Prognosis

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WASHINGTON — Enterococcal native valve endocarditis has a clinical picture distinct from that of other types of endocarditis and is generally associated with a better prognosis, Jay R. McDonald, M.D., reported in a poster presentation at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Enterococci account for 5%-20% of all

episodes of infective endocarditis, but most descriptions of the condition in the literature have been limited to small sample sizes in just one or two centers and have not included useful comparison groups.

Now, for the first time, a merged database of the International Collaboration on Endocarditis has allowed for an examination of prospectively collected data on cases of infective endocarditis reported during 1970-1999 from seven sites in

five countries (France, the United Kingdom, Spain, Sweden, and the United States.)

"The aging population and emerging antimicrobial resistance among enterococci make this a pathogen of increasing importance," said Dr. McDonald of Duke University, Durham, N.C.

Of 1,285 patients aged 18 or older with left-sided native valve endocarditis (NVE), there were 107 infected with enterococcus, 314 with *Staphylococcus aureus*, 666 with

streptococci, and 198 with other pathogens.

Another 296 patients had prosthetic valve endocarditis (PVE), of whom 45 had enterococcus.

The 512 patients from the database with right-sided NVE were excluded from this analysis because such patients have a distinct natural history and epidemiology (young IV drug users), he explained at the conference, sponsored by the American Society for Microbiology.

In-hospital mortality was significantly lower among patients with left-sided NVE due to enterococcus than among those with disease due to *S. aureus* (11.2% vs. 26.5%), despite the fact that the enterococcus group was older (66.4 vs. 60 years) and had similar rates of both heart failure (45.8% vs. 43.6%) and nosocomial acquisition (15.3% vs. 19.4%).

Moreover, the 11.2% rate of in-hospital mortality for the enterococcus group



Antimicrobial resistance makes enterococci pathogen-5 of increasing importance.

DR. McDONALD

was similar to the 10.2% rate among those with streptococcal NVE, even though the latter were younger (57.8 vs. 66.4 years), had less disease associated with the aortic valve (28.6% vs. 44.4%), and were less likely to have heart failure (35.1% vs. 45.8%).

Compared with patients who had enterococcal prosthetic valve endocarditis, those with enterococcal NVE had significantly more new valve regurgitation (45.6% vs. 12.8%), fewer abscesses (6.3% vs. 20.1%), and similar rates of in-hospital mortality (12.6%/14.8%) and early surgery (31.1%/31.7%), Dr. McDonald reported.

In a multivariate analysis of all patients with left-sided NVE, factors that significantly increased the risk for in-hospital mortality included age in 10-year intervals, systemic embolization, infection with *S. aureus*, intracardiac abscess, and heart failure. In contrast, infection with either viridans streptococci or enterococcus increased the chance of survival.

Interestingly, unlike early studies of enterococcal endocarditis, the disease was rarely seen among young women. Of the total 107 with enterococcal NVE, women accounted for just 27%.

Of those 29 women, all but two were aged 50 and older, whereas 10 of the 78 men were under age 50 (including 3 in their 20s). This difference may be explained by improved antibiotic prophylaxis for gynecologic procedures, which was the major risk factor for enterococcal endocarditis among young women in the early studies, Dr. McDonald told this newspaper.

The International Collaboration on Endocarditis is planning a larger prospective study to better characterize the disorder, he said.

Table 1: Summary of Solicited Events Observed within 10 Days after Each Dose for Vaccine and Placebo Recipients, Healthy Children 60-71 Months of Age

| Event | Post-Dose One | | Post-Dose Two | |
|-----------------------------|-----------------|----------------|-----------------|----------------|
| | FluMist 214* | Placebo 95* | FluMist 161* | Placebo 75* |
| Any event | 65.4 | 61.4 | 66.5 | 53.3 |
| Cough | 26.8 | 32.7 | 38.5 | 30.7 |
| Runny Nose/Nasal Congestion | 48.1 | 44.2 | 46.0 | 32.0 |
| Sore Throat | 12.6 | 19.8 | 9.3 | 16.0 |
| Irritability | 19.5 | 16.8 | 9.9 | 9.3 |
| Headache | 17.8 | 11.6 | 6.8 | 16.0 |
| Chills | 6.1 | 5.3 | 2.5 | 4.0 |
| Vomiting | 4.7 | 3.2 | 2.5 | 1.0 |
| Muscle Aches | 6.1 | 4.2 | 5.0 | 4.0 |
| Decreased Activity | 14.0 | 12.6 | 10.6 | 13.3 |
| Fever†: | | | | |
| Temp 1 | 9.5 | 9.9 | 4.3 | 4.0 |
| Temp 2 | 2.2 | 2.0 | 0.6 | 1.3 |
| Temp 3 | 0.0 | 0.0 | 0.0 | 0.0 |

Note: There were no statistically significant differences in any of these events (p-value >0.05); Fisher's exact method.
* Number of evaluable subjects (those who returned diary cards) for each event.
† Fever:
Temp 1: Oral >100°F, rectal or axillary >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or axillary >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or axillary >104.6°F, or axillary >103.6°F.

For the cohort of 128 children who received FluMist® (Influenza Virus Vaccine Live, Intranasal) across three consecutive years, rates of solicited adverse events were not significantly increased when compared to placebo recipients.

Medically Attended Events in Children and Adolescents: A large randomized, double-blind, placebo-controlled trial in healthy children 1 through 17 years of age was conducted at 31 clinics in the Northern California Kaiser-Permanente Health Maintenance Organization (HMO) to assess the rate of medically attended events (MAEs) within 42 days of vaccination. Participants were randomized 2:1 (vaccine:placebo). A total of 6657 evaluable children 5-17 years of age were enrolled, including 3244 boys and 3413 girls. Of these 6657 children, 2606 were 5-8 years of age and 4051 were 9-17 years of age. Dose two for children less than nine years of age was to be administered 28 to 42 days after Dose One.

Data regarding MAEs were obtained from the Kaiser-Permanente computerized health care utilization databases for hospitalizations, emergency department visits and clinical visits. MAEs were analyzed individually and within four pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these four pre-specified grouped diagnoses, no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses, and age groups. Selected respiratory tract illnesses of special interest (pneumonia, bronchitis, bronchiolitis, and croup) were included in acute respiratory tract events and were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist recipients, an increased risk was not observed for rare events that have been reported with naturally occurring influenza virus infection, including seizures, febrile seizures, and epilepsy. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or myocarditis (influenza-associated rare disorders) were reported in this study.

In this study, in individuals 5-17 years of age, four individual MAEs were significantly increased and 11 were significantly decreased. Of the four individual MAEs associated with increased risk, a biological association with FluMist is plausible for one: abdominal pain. Of the 11 individual MAEs associated with decreased risk, a biologically plausible association with FluMist exists for seven: asthma, conjunctivitis, cough, viral syndrome, otitis media, and wheezing/shortness of breath. However, in the same study, a statistically significant increase in asthma or reactive airways disease was observed for children 12-59 months of age following Dose One (Relative Risk 3.53, 90% CI: 1.1, 15.7). As a result of this finding, FluMist is not indicated for children <60 months of age.

Solicited Adverse Events in Adults: In the placebo-controlled Adult Effectiveness Study, the rate of solicited adverse events in the subset of healthy adults 18-49 years of age are shown in Table 2. Statistically significant differences were observed for any event, cough, runny nose, sore throat, chills, and tiredness/weakness. Fever >100°F was similar in FluMist and placebo recipients after a single dose. There was no significant increase in ILI as defined by the CDC in the FluMist group compared to the placebo group.

Table 2: Summary of Solicited Events Observed within 7 Days after Each Dose for Vaccine and Placebo Recipients, Healthy Adults 18-49 Years of Age

| Event | FluMist N=2548* | Placebo N=1290* |
|--------------------|--------------------|--------------------|
| | (%) | (%) |
| Any event | 71.9* | 62.6 |
| Cough | 13.9* | 10.8 |
| Runny Nose | 44.5* | 27.1 |
| Sore Throat | 4.8* | 1.1 |
| Headache | 40.4 | 38.4 |
| Chills | 8.6* | 6.0 |
| Muscle Aches | 16.7 | 14.6 |
| Tiredness/Weakness | 25.7* | 21.6 |
| Fever†: | | |
| Oral Temp >100°F | 1.5 | 1.3 |
| Oral Temp >101°F | 0.5 | 0.7 |
| Oral Temp >102°F | 0.1 | 0.2 |
| Oral Temp >103°F | 0.0 | 0.0 |

* Denotes statistically significant p-value <0.05; no adjustments for multiple comparisons; Fisher's exact method.

† Number of evaluable subjects (those who returned diary cards), [97.9% of FluMist recipients and 97.9% of placebo recipients.]

Other Adverse Events in Children and Adults: In addition to the solicited events, parents of subjects in the Pediatric Efficacy Trial also reported other adverse events that occurred during the course of the trial. Among healthy children age 60-71 months, the events that occurred in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (3.7% FluMist vs 0% placebo), otitis media (1.4% FluMist vs 0% placebo), accidental injury (2.3% FluMist vs 2.1% placebo), diarrhea (3.7% FluMist vs 1.1% placebo), following Dose One and otitis media (3.1% FluMist vs 1.3% placebo) following Dose Two. None of these differences were statistically significant.

In addition to the solicited events, adults who participated in the Adult Effectiveness Study also reported other adverse events that occurred during the course of the clinical trial. For adults 18-49 years of age in the Adult Effectiveness Study, nasal congestion (9.2% FluMist vs 2.2% placebo), rhinitis (6.3% FluMist vs 3.1% placebo), and sinusitis (4.1% FluMist vs 2.2% placebo) were reported significantly more often than FluMist recipients compared to placebo recipients.

Adverse events reported post-licensure have included nausea, rash, hypersensitivity reactions (including anaphylaxis, facial edema, and urticaria). These events occurred at similar rates in FluMist versus placebo recipients in pre-licensure studies.

Annually, 20-40 cases of Guillain-Barré syndrome (GBS) that occur within 42 days of administration of inactivated influenza vaccine are reported to VAERS. In 2003-2004, one case of GBS with temporal association with FluMist was reported. Evidence of a causal relationship between influenza vaccines, including FluMist, has not been established.

ADVERSE EVENT REPORTING

Reporting by vaccine recipients or the parents/guardians of vaccinees and health care providers of all adverse events occurring after vaccine administration is encouraged. The U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the FDA Web site at: <http://www.vaers.org>.

DOSAGE AND ADMINISTRATION FOR NASAL USE ONLY DO NOT ADMINISTER PARENTERALLY. FluMist® should be administered according to the following schedule:

| Age Group | Vaccination Status | Dosage Schedule |
|--|--|---|
| Children age 5 years through 8 years | Not previously vaccinated with FluMist | 2 doses (0.5 mL each, 60 days apart ± 14 days) for initial season |
| Children age 5 years through 8 years | Previously vaccinated with FluMist | 1 dose (0.5 mL) per season |
| Children and Adults age 9 through 49 years | Not applicable | 1 dose (0.5 mL) per season |

For healthy children age 5 years through 8 years who have not previously received FluMist vaccine, the recommended dosage schedule for nasal administration is one 0.5 mL dose followed by a second 0.5 mL dose given at least 6 weeks later. Only limited data are available on the degree of protection in children who receive one dose.

For all other healthy individuals, including children age 5-8 years who have previously received at least one dose of FluMist, the recommended schedule is one dose. FluMist should be administered prior to exposure to influenza. The peak of influenza activity is variable from year to year, but generally occurs in the U.S. between late December and early March. Because the duration of protection induced by FluMist is not known and yearly antigenic variation in the influenza strains is possible, annual revaccination may increase the likelihood of protection.

Based on FluMist Prescribing Information dated September 2004.



2004-2005 Formula
FOR NASAL ADMINISTRATION ONLY
Rx only
Brief summary of Prescribing Information

INDICATIONS AND USAGE

FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age.

FluMist is not indicated for immunization of individuals less than 5 years of age, or 50 years of age and older, or for therapy of influenza, nor will it protect against infections and illness caused by infectious agents other than influenza A or B viruses.

CONTRAINDICATIONS

Under no circumstances should FluMist® be administered parenterally.

Individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of FluMist, including eggs or egg products, should not receive FluMist.

FluMist is contraindicated in children and adolescents (5-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye syndrome with aspirin and wild-type influenza infection.

FluMist should not be administered to individuals who have a history of Guillain-Barré syndrome.

As with other live virus vaccines, FluMist should not be administered to individuals with known or suspected immune deficiency diseases such as combined immunodeficiency, agammaglobulinemia, and thymic abnormalities and conditions such as human immunodeficiency virus infection, malignancy, leukemia, or lymphoma. FluMist is also contraindicated in patients who may be immunosuppressed or have altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

WARNINGS

The safety of FluMist in individuals with asthma or reactive airways disease has not been established. In a large safety study in children 1-17 years of age, children <5 years of age who received FluMist were found to have an increased rate of asthma within 42 days of vaccination when compared to placebo recipients (see ADVERSE REACTIONS). FluMist should not be administered to individuals with a history of asthma or reactive airways disease.

The safety of FluMist in individuals with underlying medical conditions that may predispose them to severe disease following wild-type influenza infection has not been established. FluMist is not indicated for these individuals. High-risk individuals include, but are not limited to, adults and children with chronic disorders of the cardiovascular and pulmonary systems, including asthma; pregnant women, adults and children who require regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes), renal dysfunction, or hemoglobinopathies; and adults and children with congenital or acquired immunosuppression caused by underlying disease or immunosuppressive therapy (see CONTRAINDICATIONS). Intramuscularly administered inactivated influenza vaccines are available to immunize high-risk individuals.

As with any vaccine, FluMist may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

General: CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT. Prior to administration of FluMist, individuals or their parent/guardian should be asked about their current health status and their personal medical history, including immune status, to determine the existence of any contraindications (see CONTRAINDICATIONS and WARNINGS) to immunization with FluMist. FluMist recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. EPINEPHRINE INJECTION (1:1000) OR COMPARABLE TREATMENT MUST BE READILY AVAILABLE IN THE EVENT OF AN ACUTE ANAPHYLACTIC REACTION FOLLOWING VACCINATION. The health care provider should ensure prevention of any allergic or other adverse reactions by reviewing the individual's history for possible sensitivity to influenza vaccine components, including eggs and egg products. Administration of FluMist should be postponed until after the acute phase (at least 72 hours) of febrile and/or respiratory illnesses.

Information for Vaccine Recipients or Parents/Guardians: Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of FluMist, and the need for two doses for the first use of FluMist in 5-8 year olds. Due to the possible transmission of vaccine virus, vaccine recipients or their parents/guardians should be advised to avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered (see ADVERSE EVENT REPORTING).

Drug Interactions: Children or adolescents who are receiving therapy or aspirin-containing therapy should not receive FluMist (see CONTRAINDICATIONS). FluMist should not be administered to persons on immunosuppressive therapy. The concurrent use of FluMist with antiviral compounds that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for interference between such compounds and FluMist, it is advisable not to administer FluMist until 48 hours after the cessation of antiviral therapy and that antiviral agents not be administered until two weeks after administration of FluMist unless medically indicated.

There are no data regarding co-administration of FluMist with other intranasal preparations, including steroids.

Concurrent Administration with Other Vaccines: The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been determined. Therefore, FluMist should not be administered concurrently with other vaccines. Studies of FluMist in healthy individuals excluded subjects who received any live virus vaccine within one month of enrollment and any inactivated or subunit vaccine within two weeks of enrollment; therefore, health care providers should adhere to these intervals when administering FluMist.

Laboratory Interactions: Data related to the length of time that FluMist can be recovered from nasal specimens of children and adults are limited. Nasopharyngeal secretions or swabs collected from vaccinees may test positive for influenza virus up to three weeks.

Carcinogenesis, Mutagenesis, Impairment of Fertility: FluMist has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

Pregnancy (Category C): Animal reproduction studies have not been conducted with FluMist. It is also not known whether FluMist can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Therefore, FluMist should not be administered to pregnant women.

Nursing Mothers: It is not known whether FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if FluMist is administered to nursing mothers.

Pediatric Use: The safety of FluMist in infants and children <60 months of age has not been established.

Geriatric Use: Clinical studies with FluMist did not include sufficient numbers of adults age 65 years and older to determine if they respond differently from younger individuals. The safe use of FluMist in persons 65 years and older has not been established.

ADVERSE REACTIONS

Serious Adverse Events: Across all clinical trials, serious adverse events (SAEs) were monitored after vaccination for 42 days in children and for 28 days in adults. SAEs occurred at a similar rate (<1%) in FluMist and placebo recipients for both healthy children and healthy adults.

Overall, across the placebo-controlled trials in adults and children, the incidence of selected adverse reactions that may be complications of influenza (such as pneumonia, bronchitis, bronchiolitis, or central nervous system events) was similar in FluMist and placebo groups.

Adverse Events in Placebo-Controlled Trials: In all placebo-controlled studies, allantoic fluid from uninfected eggs was used as the placebo. In randomized, placebo-controlled trials, 4719 healthy children 5-17 years of age and 2864 healthy adults 18-49 years of age received FluMist and 2327 healthy children and 1454 healthy adults received the placebo. In placebo-controlled clinical trials conducted in healthy populations, solicited adverse events and daily temperatures were collected on diary cards. These solicited events included runny nose/nasal congestion, sore throat, cough, irritability, headache, chills, vomiting, muscle aches, and decreased activity and a feeling of tiredness/weakness.

Solicited Adverse Events in Children: Table 1 shows an analysis of solicited events for the Pediatric Efficacy Study in the subset of healthy children 60-71 months of age. The largest absolute differences between FluMist and placebo after Dose One were observed in the incidences of headache and runny nose/nasal congestion. No differences were observed for fever (>100°F oral). Following Dose Two, the largest absolute differences between FluMist and placebo were runny nose/nasal congestion and cough. There was no significant increase in influenza-like illness (ILI) as defined by the CDC in the FluMist group compared to the placebo group. CDC has defined CDC-ILI as having fever (temperature ≥100°F oral) plus either cough or sore throat on the same day or on consecutive days.

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