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Issue No. 3, November 2005, is part of a 12-part CME activity (September 2005 – August 2006).

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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, 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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A Better Meningococcal Vaccine?

The high incidence rate and the risk of serious sequelae make adolescents and young adults a major target group for immunoprophylaxis. Meningococcal disease is the leading cause of meningitis and sepsis in this group, and it is associated with mortality rates exceeding 20%. The sporadic nature of this disease, as well as the propensity of this school-age population to function in close proximity with their peers, underscores the need for a vaccine prevention strategy. Much of the morbidity and mortality associated with meningococcal disease could be prevented if an effective vaccine, especially against serogroups A, C, Y and W135, were available.

The currently available quadrivalent meningococcal polysaccharide vaccine (PSV-4) does target these serogroups, but induces a T-cell-independent response that diminishes over time. As a result, PSV-4 is not recommended for routine immunization in the adolescent population. Previous studies of monovalent conjugated forms of meningococcal vaccines have demonstrated a T-cell-dependent antibody response allowing for better persistence, the development of immune memory, a reduction in carriage rates, and indirect or herd protection. A recently developed quadrivalent (A,C,Y, W135) polysaccharide-diphtheria toxoid conjugate vaccine (MCV-4) may show promise in this regard.

A recent study by Keyserling and colleagues compared the tolerability, immunogenicity, and immune memory of MCV-4 to

that of the currently available PSV-4 in a randomized double-blind trial involving 881 healthy 11- to 18-year olds from eleven clinical centers across the United States. Participants were randomized to vaccination with MCV-4 (n=440) or PSV-4 (n=441). Sera were collected both pre-and 28 days postvaccination. A subset of participants from each arm was given a booster of MCV-4 at the 3-year follow-up.

Both vaccines were well tolerated and most reactions reported by participants were mild. Patients vaccinated with MCV-4 reported more local reactions (72.3%) compared with those receiving PSV-4 (34.7%), with the most frequent complaint in both groups being pain

“Much of the morbidity and mortality associated with meningococcal disease could be prevented if an effective vaccine...were available.”

at the injection site. No significant complications of these local reactions were observed. The overall frequency of systemic reactions was similar in both groups (57.2% = MCV-4; 51.9% = PSV-4) with the most common being mild-to-moderate headaches. Seven episodes of serious adverse events were observed; all were considered unrelated to the vaccine.

The immunogenic potential of both vaccines was evident by comparable fourfold or greater postvaccination increases in serum bactericidal antibody geometric mean titers (SBA GMT) in both groups. The 3-year follow-

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Disclosures:

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A Better Meningococcal Vaccine?

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up showed a persistence of SBA and booster response to MCV-4 consistent with the presence of immune memory in those individuals previously vaccinated with MCV-4. This was not observed in those previously vaccinated with PSV-4.

In addition to tolerability and safety issues, this study demonstrated the ability of the MCV-4 vaccine to function effectively by eliciting both priming and booster responses, stimulating persistent protective antibody response, and excluding hyporesponsiveness following repeat vaccinations. These promising results may translate into the availability of a novel and effective vaccine against meningococcal disease for use in high-risk populations.

NOTE: In February 2005, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of adolescents (ages 11-12 years) at the preadolescent healthcare visit. For those who have not been vaccinated previously, ACIP recommends vaccination before high school

entry. Routine vaccination is also recommended for first-year college students living in dormitories. As of October 4, 2005, the Vaccine Adverse Event Reporting System (VAERS) received five reports of Guillain-Barré syndrome in persons after receipt of MCV-4. Since March 2005 approximately 2.5 million doses of MCV-4 have been distributed nationally. The number of administered doses and the precise incidence of Guillain-Barré syndrome are unknown. Presently there is insufficient evidence to conclude that MCV-4 causes Guillain-Barré syndrome. The Food and Drug Administration and the Centers for Disease Control are requesting that possible cases of Guillain-Barré syndrome occurring after MCV-4 be reported to VAERS (*MMWR*. Oct 14, 2005;54:1023-1025).

Keyserling H, Papa T, Koranyi K, et al. Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. *Arch Pediatr Adolesc Med*. 2005;159:907-913.

Passive Immunization Is Effective Against Congenital CMV Infection

Cytomegalovirus (CMV) infection of neonates can lead to serious neurologic complications and defects. Current estimates suggest that CMV infection is common, with approximately 1% of all neonates being infected. While the infection is symptomatic in only 10% of these cases, it is associated with clinically significant neurologic sequelae in almost half of symptomatic cases. Even in asymptomatic individuals, neurologic defects will develop in approximately 8% to 13% of cases. Furthermore, among women with a primary CMV infection during pregnancy, the rate of fetal infection is approximately 40%. Ideally, prenatal therapy would provide an obvious therapeutic option in the effort to reduce infection rates. Unfortunately, there is no prenatal therapy currently available. Nigro and colleagues recently published the results of their prospective study examining the ability of passive immunization with hyperimmune globulin

(HIG) to treat or prevent fetal CMV infection.

The study consisted of two groups: a therapy group composed of pregnant women whose amniotic fluid contained CMV virus or DNA and who received IV HIG at 200 U/Kg of maternal weight and a prevention group that consisted of women with a primary CMV infection who did not undergo amniocentesis and who received monthly IV HIG at 100 U/Kg of maternal weight. Monthly treatment was used in the prevention group because of the unknown infection status of the fetuses and the desire to sustain antibody concentrations up to delivery. Comparison groups were women who declined to receive IV HIG and had CMV-positive amniotic fluid, and women with primary CMV infection whose CMV amniotic infection status was unknown.

Within the therapy group (n=31), only 1 (3%) woman treated with HIG gave birth to an infant with CMV disease compared with 7 of 14 (50%) in the untreated group.

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“Unfortunately, there is no prenatal therapy for a primary CMV infection currently available.”

Passive Immunization Is Effective Against Congenital CMV Infection

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Treatment with HIG in the therapy group was associated with significantly lower risk of congenital CMV disease (adjusted odds ratio [OR] 0.02; 95% confidence interval [CI] $-\infty$ to 0.15; $P < 0.001$).

In the prevention group, 6 of 37 (16%) of the treated women had infants with congenital CMV infection compared with 19 of 47 (40%) of the untreated women. Within the prevention group, treatment with HIG was associated with a significantly lower risk of congenital CMV infection (adjusted OR, 0.32; 95% CI, 0.10 to 0.94; $P = 0.04$).

With respect to other variables, treatment with HIG significantly ($P < 0.001$) increased CMV-specific IgG concentrations and avidity and decreased the number and percentage of natural killer and *HLA-DR*⁺ cells. Whether the effects of HIG treatment are a result of the ability of HIG to inhibit CMV replication or a reduction of immune cells leading to a corresponding drop in production of cytokines (eg, tumor necrosis factor- α contributing to fetal damage) is

not clear. Hence, whether HIG reduces the pathogenic effects of CMV by neutralization or immune response modulation requires further investigation. Lastly, no adverse events were associated with HIG infusions in any of the groups.

The findings of this study give impetus for further examination through the initiation of randomized controlled trials, especially in locations where maternal CMV screening is not routine procedure, such as the United States. These results also should encourage evaluation of immunogenic, antibody-inducing CMV vaccines administered before or during pregnancy.

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

Nigro G, Adler SP, La Torre R, Best AM, for the Congenital Cytomegalovirus Collaborating Group. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med*. 2005;353:1350-1362.

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

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