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Meningococcal Groups C and Y and *Haemophilus b* Conjugate Vaccine

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Approximately 1,000 to 3,000 cases of meningococcal disease are diagnosed each year in the United States.^{1,2} Of the 13 identified meningococcal serogroups, only six (A, B, C, W, X, and Y) are known to produce invasive disease. Over the past decade, serogroups B, C, and Y have predominated in the United States. Although there is still not a vaccine for serogroup B, vaccines against serogroups A, C, W-135, and Y have been part of the routine adolescent immunization series since 1981.^{3,4}

While the immunization of adolescents has had a significant impact on the incidence of meningococcal disease, until recently there have been no options for protecting the patients at highest risk for infection, children younger than 1 year of age. Over a 10-year period from 1998 to 2007, the incidence of meningococcal disease in infants was 5.38 cases per 100,000 population in the United States.² In comparison, the incidence in adolescents and young adults (15-24 years of age) was only 0.78 per 100,000 population. Among the infants in this collaborative surveillance study, serogroup B was responsible for the greatest number of cases, 3.08 cases per 100,000 population, followed by serogroups C and Y, with 0.53 and 1.50 cases per 100,000 population respectively. The peak age of meningococcal infection has been suggested to be at 0-3 months for serogroup B, 4-5 months for serogroup C and 0-7 months for serogroup Y.^{2,3}

Invasive meningococcal disease is associated with significant morbidity and mortality in infants and young children. In a recent analysis using 2009 data, the adjusted mean length of stay for children with invasive meningococcal disease was 9 days with a cost per admission of \$36,454. The mortality rate among the infants in the analysis who developed meningococcal sepsis was 11.6%.⁴

The introduction of meningococcal conjugate vaccines, MenACWY-D (Menactra®) in 2005 and MenACWY-CRM (Menveo®) in 2010, was an important step in the development of vaccines that could provide effective seroconversion in infants and toddlers.⁵ While MenACWY-D is currently only approved by the Food and Drug Administration (FDA) for use in infants 9 months of age and older and MenACWY-CRM for patients 2 years of age and older, these vaccines have the potential to be of benefit in younger infants.

On June 14, 2012, the FDA approved the first combination meningococcal vaccine for use in infants and children from 6 weeks to 18 months of age.⁶ The *Haemophilus influenzae* type b (Hib) and meningococcal groups C and Y conjugate vaccine (HibMenCY-TT) is intended to be administered in a 4-dose series to be given at 2, 4, 6, and 12-15 months age. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) is expected to consider the inclusion of the HibMenCY-TT vaccine into the recommended childhood immunization schedule at their February 2013 meeting.

Vaccine Formulation

The HibMenCY-TT vaccine contains *Neisseria meningitidis* serogroup C and Y capsular polysaccharide antigens and *H. influenzae* type b capsular polysaccharide polyribosyl-ribitol-phosphate (PRP). Each component is covalently bound to inactivated tetanus toxoid. After purification, the conjugate is lyophilized with sucrose as a stabilizer. When prepared with the sterile saline diluent, each 0.5 mL dose of the vaccine contains 5 mcg of purified *N. meningitidis* C capsular polysaccharide, 5 mcg of *N. meningitidis* Y capsular polysaccharide, and 2.5 mcg of *H. influenzae* b capsular polysaccharide.⁶

Seroresponse

The safety and efficacy of HibMenCY-TT have been assessed in six premarketing clinical trials, with a total patient enrollment of 7,521 infants.⁶ In the June 2011 issue of *Pediatrics*, Bryant and colleagues published the results of a phase 3 randomized, single-blind study comparing HibMenCY-TT to a currently available Hib vaccine (ActHIB®).⁷ A total of 4,180 infants were enrolled at locations throughout the United States, Mexico, and Australia. Patients received study vaccine or Hib for either a four-dose series given at ages 2, 4, 6, and 12-15 months or a three-dose series given at ages 2, 4, and 6 months with PedvaxHIB® administered at 12-15 months.

Antibody production to HibMenCY-TT was assessed in 991 of the infants. Response to *H. influenzae* PRP (anti-PRP) was measured by enzyme-linked immunosorbent assay (ELISA). The percentage of children in the three-dose group with anti-PRP concentrations ≥ 1.0 mcg/mL was 96.3% (95% CI 94.3, 97.8) in the infants given HibMenCY-TT and 91.2% (95% CI 85.9, 95.0) in the infants given Hib. In the four-dose series, 99.2% of the infants in both groups had anti-PRP concentrations ≥ 1.0 mcg/mL (95% CI for HibMenCY-TT 97.6, 99.8 and 95% CI for Hib 95.7, 100), demonstrating non-inferiority of the Hib component of the HibMenCY-TT product.⁷

Response to the meningococcal C and Y components was measured by serum bactericidal assay using human complement (hSBA) titers. To meet acceptance criteria, the lower limit of the 95% confidence interval for the percentage of children with hSBA titers $\geq 1:8$ had to be greater than 90% one month after their final dose. Titers were evaluated in 491 infants given the three-dose series and 331 infants given the four-dose series. The percentage of patients in the three-dose group with hSBA $\geq 1:8$ was 98.8% (95% CI 97.4, 99.6) for serogroup C and 95.8% (95% CI 93.7, 97.4) for serogroup Y. In the four-dose group, the percentages for serogroups C and Y were 98.5% (95% CI 96.5, 99.5) and 98.8% (95% CI 97.0, 99.7), respectively.⁷

Nolan and colleagues published another phase 3 trial in the March 2011 issue of the *Pediatric Infectious Diseases Journal*.⁸ This study, conducted in Australia, randomized 1,104 infants to receive either HibMenCY-TT, a standard Hib vaccine with a meningococcal C conjugate vaccine already on the market in that country (Hib+MenC), or a Hib vaccine with no meningococcal vaccine at 2, 4, and 6 months of age. One month following the third dose, the percentage of infants with anti-PRP concentrations ≥ 1.0 mcg/mL was considered

within acceptable limits in all groups, with 96.2% (95% CI 93.2, 98.2) in the HibMenCY-TT group, 84.1% (95% CI 74.8, 91.0) in the Hib+MenC group, and 84.4% in the Hib without meningococcal vaccine group (95% CI 75.3, 91.2) achieving the target.

After three doses, the percentage of infants with a meningococcal serogroup C hSBA titer $\geq 1:8$ was 94.4% (95% CI 91.1, 96.8) in the HibMenCY-TT group, 96.0% (95% CI 90.0, 98.9) in the Hib+MenC group, and 0% in the Hib group. Serogroup Y titers were $\geq 1:8$ in 91.7% of HibMenCY-TT patients (95% CI 87.9, 94.6), but only 9.2% (95% CI 4.3, 16.7) in the MenC group and 5.2% (95% CI 1.7, 11.6) in the Hib group, as anticipated.⁸

Meningococcal seroresponse to HibMenCY-TT has also been compared to that produced by a quadrivalent meningococcal vaccine in older children.⁹ As part of a comparison trial of HibMenCY-TT and Hib vaccines given at 2, 4, and 6 months of age to 759 children in the United States, Marchant and colleagues compared the results in 205 HibMenCY-TT patients from that trial to a second control group of 142 children between 3 and 5 years of age given a single dose of a quadrivalent meningococcal polysaccharide vaccine (Menomune®). One month after immunization, the percentage of patients with hSBA titers $\geq 1:8$ was 95.9% for serogroup C and 89.4% for serogroup Y in the infants given HibMenCY-TT, significantly higher than the percentages for the children given the quadrivalent vaccine (30.2% and 47.5% for serogroups C and Y respectively, $p < 0.05$).

Administration of HibMenCY-TT with other vaccines at 2, 4, 6, and 12-15 months of age does not appear to adversely affect antibody production.⁷⁻¹¹ In 2010, Marshall and colleagues demonstrated no loss of seroresponse to 7-valent pneumococcal conjugate vaccine (Prevnar®) or the combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus vaccine (Pediarix®).¹⁰ A total of 606 infants were randomized in this study to receive either HibMenCY-TT or standard Hib vaccine at 2, 4, and 6 months of age, along with their standard immunizations. A subgroup of 366 infants was evaluated after a fourth dose at 12-15 months. One month after their final dose, at least 98.8% of the infants in both groups had antibody concentrations ≥ 0.2 mcg/mL for all pneumococcal serotypes. More than 99% of infants in both groups were seropositive for antibodies to all three pertussis antigens and more than 99.5% of subjects had seroprotective antibody levels against diphtheria and tetanus.

The anti-tetanus geometric mean antibody concentrations were significantly higher for the infants receiving HibMenCY-TT than those given the traditional series (GMC ratio 1.82, 95% CI 1.56, 2.12). More than 98.8% of all patients had seroprotective antibody titers against all three poliovirus types.¹⁰

There also appears to be no effect on immune response when the HibMenCY-TT vaccine is administered concomitantly with the measles-mumps-rubella and varicella vaccines at 12-15 months of age. In a study conducted by the manufacturer, antibody titers evaluated 6 weeks after immunization with these vaccines were within acceptable limits for all components using the following standards: anti-measles concentration ≥ 200 mIU/mL, anti-mumps concentration ≥ 51 ED₅₀, anti-rubella concentration ≥ 10 IU/mL, and anti-varicella titers $\geq 1:40$.⁶

Contraindications and Precautions

Hypersensitivity reactions, including anaphylaxis, have been reported after meningococcal, Hib, and tetanus toxoid immunization but appear to be rare. A severe allergic reaction to a previous dose of any of the components of the HibMenCY-TT vaccine is a contraindication to the use of the combination product. The HibMenCY-TT vaccine should be used with caution in any patient who has developed Guillian-Barré syndrome within 6 weeks of receiving a tetanus toxoid-containing vaccine. Use of HibMenCY-TT has not been studied in immunocompromised children or in those receiving immunosuppressive agents.⁶

Adverse Effects

The most commonly reported adverse effects within 4 days of HibMenCY-TT administration in pediatric clinical trials included pain (in 42-46% of patients), redness or swelling at the site of injection (14-35%), irritability (62-67%), drowsiness (48-62%), loss of appetite (30-33%), and fever greater than 100.4° F (11-26%).⁶ Fever greater than 104° F was present in only 0.1-0.3% of patients. In comparison studies, the incidence of adverse effects was approximately equal between infants receiving HibMenCY-TT and control infants receiving a standard Hib vaccine.⁷⁻¹⁰

Administration

The HibMenCY-TT vaccine is administered as a 0.5 mL intramuscular injection.⁶ It is supplied in a single dose vial of lyophilized vaccine that must be reconstituted with the saline diluent provided. The vaccine should be administered immediately after reconstitution. Vials of the lyophilized vaccine must be refrigerated and

protected from light until use. The saline diluent may be refrigerated or stored at room temperature. Neither the vaccine nor the diluent should be frozen. The product does not contain preservatives and the vial stopper does not contain latex.

The HibMenCY-TT vaccine may be administered concomitantly with the other vaccines routinely given during the 2, 4, 6, and 12-15 month visits. Separate injection sites should be used for HibMenCY-TT and other vaccines given at the same visit. It should not be mixed or diluted with another vaccine product. Parents should be aware that the HibMenCY-TT vaccine does not provide immunization against tetanus.⁶

Summary

The availability of conjugate meningococcal vaccines has created an opportunity for immunization of infants against a disease known to produce significant morbidity and mortality. The HibMenCY-TT vaccine provides protection against the two most prevalent meningococcal serogroups without adding more injections to the routine childhood immunization schedule. While high rates of seroconversion and a low incidence of adverse effects with HibMenCY-TT in premarketing clinical trials are encouraging, the benefits of early meningococcal immunization to the pediatric population must still be determined.

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Pharmacology Literature Review

Extended-Interval Gentamicin in Neonates

The authors of this prospective observational study evaluated an extended-interval gentamicin dosing strategy consisting of an initial 5 mg/kg dose with a dosing interval based on a single serum concentration drawn 22 hours later. Peak and trough serum concentrations were obtained after the second or third dose. Results from 104 neonates (23 weeks gestational age to term) were included. The mean peak and trough serum concentrations in the study population was 10.55 mcg/mL and 0.75 mcg/mL. All patients had trough concentrations less than 2.0 mcg/mL, and 82% of patients had peak concentrations that were within the authors' desired range of 5-12 mcg/mL. No patient had a peak concentration less than 5 mcg/mL. Based on their results, the authors concluded that their extended-interval gentamicin dosing strategy, using a single level at 22 hours to determine the dosing interval, produced appropriate serum concentrations in the neonates studied. Dersch-Miolls D, Akierman A, Alshaikh B, et al. Validation of a dosage individualization table for extended-interval gentamicin in neonates. ***Ann Pharmacother* 2012; 46:935-42.**

Kawasaki Disease Review

While traditional therapy with intravenous immune globulin with or without aspirin remains the cornerstone of treatment for Kawasaki disease, the authors of this review highlight new therapies that may be of benefit to patients with refractory disease. The article discusses the controversies surrounding the use of anticoagulants, as well as the potential role for immunosuppressive agents such as tumor necrosis factor-alpha (TNF- α) inhibitors. Luca NJC, Yeung RSM. *Epidemiology and management of Kawasaki disease.* ***Drugs* 2012;72:1029-38.**

Physiologically Based Modeling

This state-of-the-art review provides a concise discussion of physiologically based pharmacokinetic modeling (PBPK) and simulation in pediatric drug research. The authors address the benefits of models that integrate changes occurring during growth and development to predict pediatric pharmacokinetic parameters and guide the development of clinical studies. This methodology has already been incorporated into a number of different clinical research settings, including evaluation of dose-response relationships, correlation of dose and target organ toxicity, and drug-drug interactions. The authors suggest that the most critical use of PKPB will likely lie in first-time-in-pediatrics dose selection studies, where modeling has the potential to reduce the risks associated with traditional dose selection based on extrapolation or scaling of adult dosing. Barrett JS et al. Physiologically based pharmacokinetic (PBPK) modeling in children. ***Clin Pharmacol Ther* 2012;92:40-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their July meeting:

1. Generic dextroamphetamine sustained release 5 mg capsules and amphetamine-dextroamphetamine salt combination ER 5 mg capsules (equivalent to Adderall XR[®]) were added to the Formulary for the treatment of attention deficit-hyperactivity disorder.
2. Generic phenobarbital 32.4 mg tablets were added to the Formulary to replace 30 mg tablets, which are no longer being manufactured in the United States.
3. The restriction on the use of alprostadil (Prostin VR Pediatric[®]) was amended to include use in liver transplant patients.

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