

Anaphylaxis Complicating Routine Childhood Immunization: *Hemophilus Influenza* b Conjugated Vaccine

MICHAEL R. NELSON, M.D.,^{1,2} HOWARD OAKS, M.D.,³ LAURIE J. SMITH, M.D.,^{1,2}
and RENATA J.M. ENGLER, M.D.^{1,2}

ABSTRACT

Increasing numbers of vaccines are being introduced into the infant and childhood immunization schedules. Immediate hypersensitivity reactions to include anaphylaxis can occur during the immunization visit. Determining the cause of a vaccine-associated immediate hypersensitivity reaction may require multiple specific skin test and challenge procedures. We report the case of a 4-month-old Caucasian male who developed an urticarial rash within 10 minutes of receiving his 4-month immunizations, diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio (IPV), and the diphtheria mutant protein (CRM¹⁹⁷) conjugated *Hemophilus influenzae* type b (HbOC). The child was referred for an allergy-immunology consultation in order to determine the cause of the reaction and a future vaccine management strategy. Negative prick skin tests were obtained with full-strength vaccine and subsequent dose challenges with DTaP and IPV vaccines were tolerated without reaction. Prick skin testing with full-strength HbOC was negative, but dose challenge with 0.05 mL resulted in an anaphylactic reaction within 10 minutes of the first challenge dose. The reaction included generalized hives, nasal congestion and diffuse wheezing. Subsequent intradermal skin testing with four different *Hemophilus influenzae* type b (Hib) vaccines at 1:100 dilution revealed isolated skin test reactivity to HbOC but not the other protein conjugated Hib vaccines. Skin testing with CRM¹⁹⁷ alone (the protein conjugate in HbOC) was positive, confirming the source of the reaction. The patient tolerated subsequent Hib immunization with a CRM-free preparation without complications. Our case report suggests that the mutant diphtheria protein CRM¹⁹⁷ may be an allergenic protein in some patients who develop anaphylaxis to the HbOC vaccine. The availability of vaccines with different protein conjugates provides an alternative vaccination strategy for those patients with specific sensitization. The

¹Allergy-Immunology Department, Walter Reed Army Medical Center, Washington, D.C.

²Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine, Bethesda, Maryland.

³Womack Army Medical Center, Fort Bragg, North Carolina.

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question of cross-reactions and risk for anaphylaxis with other vaccines containing the CRM¹⁹⁷ remains to be determined. The new pneumococcal vaccine (Prevnar™) contains CRM¹⁹⁷. (Pediatr Asthma Allergy Immunol 2000;14[4]:316–321.)

INTRODUCTION

THE CHILDHOOD IMMUNIZATION SCHEDULE has expanded in complexity and consistently requires more than one type of vaccine to be administered during each of the traditional well-baby evaluations during the first year of life.⁽¹⁾ Hypersensitivity reactions are rare and have been primarily reported in conjunction with tetanus, influenza, measles and pertussis.⁽²⁾ Although the incidence of allergic reactions after diphtheria-tetanus-acellular pertussis (DTaP) is unknown, the rate of anaphylaxis to diphtheria-tetanus-pertussis (DTP) is estimated to be approximately 2 cases per 100,000 injections with severe anaphylactic reactions being very rare.⁽³⁾ There have been no documented case reports of anaphylaxis in association with the *Hemophilus influenza* type b polysaccharide-conjugated vaccine since its introduction in this country in 1988. The 2000 Red Book specifically states that, “when conjugate vaccines are administered during the same visit that diphtheria and tetanus toxoid and acellular pertussis vaccine is given, the rates of systemic reactions do not differ from those observed when only DTaP vaccine is administered.”⁽³⁾ We report the case of a child who developed anaphylactic hypersensitivity to a specific protein-conjugated *Hemophilus influenza* type b (Hib) vaccine with no cross-reactive sensitivity to other (CRM¹⁹⁷ free) conjugated Hib vaccines.

CASE REPORT

A 4-month-old Caucasian male presenting for his routine childhood immunizations developed a generalized urticarial rash within 10 minutes of receiving DTaP, inactivated polio (IPV), and diphtheria mutant protein (CRM¹⁹⁷) conjugated *Haemophilus influenzae* type b (HbOC) injections. There were no respiratory or cardiovascular symptoms and the rash resolved without treatment within 45 minutes. The patient was an otherwise healthy infant with normal growth and development after 35 weeks gestation and spontaneous vaginal delivery with a birth weight of 3.4 kgs. There was no history of atopic disease or asthma. The history of prior vaccine exposure and specific vaccine preparations received at 4 months are detailed in

TABLE 1. IMMUNIZATION HISTORY OF CHILD WITH AN IMMEDIATE HYPERSENSITIVITY REACTION

<i>Vaccine</i>	<i>Trade name</i>	<i>Manufacturer</i>	<i>Preservatives, adjuvants, antibiotics</i>	<i>Dates received</i>
HBV	Engerix	Smith, Kline Beechum	Thimerosal Aluminum hydroxide	Birth & 2 months
DTaP	Acel-Immune	Wyeth-Lederle	Thimerosal Aluminum hydroxide	2 & 4 months
IPV	IPOL	Pasteur-Merieux Connaught	Formaldehyde, neomycin, streptomycin, polymixin B	2 & 4 months
Hib conjugate	Hib-TITER	Wyeth-Lederle	Thimerosal ^a Mutant diphtheria toxin protein carrier CRM ¹⁹⁷	2 & 4 months

^aMultidose vial.

DTaP, diphtheria-tetanus-acellular pertussis; HBV, hepatitis B vaccine; IPV, inactivated polio vaccine; Hib, *Hemophilus influenzae* type b.

TABLE 2. VACCINE SKIN TESTING AND CHALLENGE RESULTS

Vaccine	Trade name	Skin prick test		Intradermal skin test @ 1:100		Dose challenge results
		Wheal	Flare	Wheal	Flare	
		mm	mm	mm	mm	
DTaP	Acel-Immune	0 × 0	0 × 0	0 × 0	0 × 0	Tolerated full dose
IPV	Ipol	0 × 0	0 × 0	0 × 0	0 × 0	Tolerated full dose
HbOC	Hib-TITER	0 × 0	0 × 0	See Table 3		Systemic reaction within 5 minutes of 0.05 mL IM
Histamine		4 × 4	8 × 8	8 × 8	20 × 30	
Saline		0 × 0	0 × 0	0 × 0	0 × 0	

DTaP, diphtheria-tetanus-acellular pertussis; IPV, inactivated polio; HbOC, *Hemophilus influenzae* type b; IM, intramuscularly.

Table 1. The patient was referred to Walter Reed Allergy-Immunology Department at 8 months of age with the request that he be evaluated for continuation of his immunizations to include the third dose of DTaP, a protein-conjugated Hib, IPV, and hepatitis B vaccine (HBV).

The benefit-risk ratio of avoidance of immunizations versus attempting to define the culprit to allow safe continuation of the vaccination program was reviewed with the parents and informed consent was obtained for skin testing and progressive dose challenge with the required vaccines. Skin testing was performed by the prick method to the full-strength vaccines only, because no data are currently available regarding the predictive value of intradermal skin testing with these vaccines. For a progressive dose challenge, it was planned to administer 0.05 mL of vaccine. If this was tolerated, the child was then to receive 0.1, 0.15, and 0.2 mL of vaccine given every 30 minutes with careful observation. Each vaccine skin test and challenge were performed on a different day. First, DTaP was tested and after a negative prick test the dose challenge was administered without difficulty. On another day, the child underwent a skin test to HbOC. After a negative prick test, 0.05 mL of vaccine was given intramuscularly. Within 10 minutes the patient developed scattered urticarial lesions over the trunk and face, nasal congestion, and expiratory wheezing. Both epinephrine (0.1 mL of 1:1000) and nebulized albuterol were required to resolve the reaction completely. There was no late-phase reaction and systemic corticosteroids were not utilized. On the next visit, the child underwent both prick and intradermal skin testing to IPV. These tests were negative and a dose challenge was tolerated without reaction. Later, intradermal skin testing with 1:100 strength of DTaP and HbOC were performed. Table 2 outlines the results of the vaccine skin tests and progressive dose challenges performed on this infant. At the end of the testing period, the child also successfully received the third HBV.

Having identified HbOC as the vaccine causing the adverse event, we elected to pursue further testing to identify what part of the vaccine was responsible for the reaction, because the child would still benefit from further Hib immunization. Because prick skin testing had been negative to the HbOC vaccine, it was elected to perform both prick and intradermal skin testing to all the conjugated hemophilus vaccines and the protein conjugate, CRM¹⁹⁷ that was kindly supplied by Wyeth-Lederle (Lederle Laboratories; marketed by Wyeth-Lederle Vaccines, Wyeth-Ayerst Laboratories, Philadelphia, PA). Full-strength vaccine and CRM¹⁹⁷ were used for prick testing and a 1:100 dilution (in sterile, buffered normal saline) of each Hib capsular polysaccharide vaccine and the CRM¹⁹⁷ protein were used for intradermal testing. The prick skin tests were all negative, as were all the intradermal tests except HbOC, which contains CRM¹⁹⁷ and the CRM¹⁹⁷ alone (Table 3). Three volunteer staff physicians were tested to the CRM¹⁹⁷ protein by prick and intradermal methods with no reactivity. The patient subsequently received a full dose of the ActHIB (Pasteur Mérieux Serums & Vaccines SA, Lyon, France; distributed by Connaught Laboratories, Swiftwater, PA) preparation without any adverse reactions. The parents were advised regarding the potential risks of future vaccines containing the CRM¹⁹⁷ protein as a conjugate.

TABLE 3. SKIN TESTING WITH *HEMOPHILUS INFLUENZAE* TYPE b CONJUGATE VACCINES AND CRM¹⁹⁷

Trade name & Manufacturer	Abbreviation	Skin prick test		Intradermal skin test @ 1:100	
		Wheal mm	Flare mm	Wheal mm	Flare mm
HibTITER Wyeth-Lederle Vaccines, PA	HbOC	0 × 0	0 × 0	4 × 4	20 × 10
PedvaxHIB Merck & Co, PA	PRP-OMP	0 × 0	0 × 0	0 × 0	0 × 0
ActHIB Pasteur Merieux Connaught, PA	PRP-T	0 × 0	0 × 0	0 × 0	0 × 0
ProHIBiT Pasteur Merieux Connaught, PA	PRP-D	0 × 0	0 × 0	0 × 0	0 × 0
Wyeth-Lederle special product	CRM ¹⁹⁷	0 × 0	0 × 0	6 × 6	10 × 10
Histamine		4 × 4	8 × 8	8 × 8	20 × 30
Saline		0 × 0	0 × 0	0 × 0	0 × 0

DISCUSSION

Because of the importance of completing this patient's immunization series, we elected to attempt skin testing with the vaccines that were given during the initial event to ascertain which vaccine might be implicated in causing the problem. It has been suggested that intradermal skin testing does not add to the process, and so we initially tested only with the prick test method.^(4,5) After a negative skin test our plan was to dose challenge with each vaccine on a separate day. This was done because there are few data in the literature about the negative predictive value of vaccine skin testing and we did not feel comfortable giving a full immunizing dose after a negative prick skin test.⁽⁶⁾ With measles-mumps-rubella (MMR), which has the most literature, there are several reported cases of children reacting to MMR vaccine with negative prick skin tests to the vaccine.^(5,7,8) When the infant reacted to the HbOC vaccine at 0.05 mL intramuscularly, we realized that in this case the negative prick skin test failed to predict a reaction. Therefore, as we pursued the evaluation of the reaction, we added intradermal skin testing with all the vaccines at a concentration of 1:100 to further elucidate his sensitivity. Because all the other vaccines had negative intradermal tests and the HbOC was positive, we conclude that in this case adding the intradermal testing to the prick test provided additional information.

All package inserts for vaccines contain a warning regarding continued immunization in the context of a history of a hypersensitivity reaction to any component of a vaccine. But similar to adverse drug reactions, there are clinical scenarios where the benefit of a specific drug or vaccine outweighs the risk of attempting to modify the strategy for administering the drug in a controlled and safer way. Strategies used to manage patients with an adverse drug reaction history when the drug is an essential part of good medical treatment include using an immunologically unique preparation or one with different preservatives or constituents from those suspected to be the cause of the reaction. If the drug is necessary, with no alternatives, desensitization may be undertaken. However, in situations where it is not clear which drug is responsible for the reaction and skin tests are not helpful, a gradual dose challenge technique has been utilized.^(9,10)

In a 1-year-old child, such as the case presented, the benefit of Hib immunization to prevent invasive disease prior to 24 months of age has been well established. Prior to the availability of effective vaccines, *Hemophilus influenzae* type b was the leading cause of invasive bacterial disease among children, with 1

in 200 children developing invasive disease by age 5 years and 60% of these children having meningitis. With a 3% to 6% mortality and permanent sequelae, ranging from mild hearing loss to mental retardation, affecting another 15% to 30% of meningitis survivors, the dramatic benefits of effective immunization in the first 2 years of life is one of the success stories of preventive medicine and immunizations.⁽¹¹⁾ By 1997, invasive *Haemophilus influenzae* type b invasive disease had declined by 99% because the conjugate vaccines were first licensed for children aged 18 to 59 months in 1988 and in 1990 when its use was extended to infants.⁽¹²⁾

Each of the four available *Hemophilus influenza* type b vaccines contains the bacteria's capsular polysaccharide, polyribosylribitolphosphate (PRP) or PRP oligomers conjugated to a carrier protein to enhance immunogenicity. They are immunogenically unique with different protein conjugates, different size polysaccharides and the variable presence of a spacer linkage as outlined in Table 4. The protein conjugate in HbOC is CRM¹⁹⁷, (cross-reacting molecule 197), a nontoxic mutant of diphtheria toxin isolated from cultures of *C. diphtheria* C7 (197). Of the four Hib vaccines, HbOC utilizes the smallest PRP polymers, approximately 20 repeat units in length. The PRP-protein carrier conjugation in HbOC is the only one that does not utilize a spacer molecule between the two major components. The fact that our patient reacted only to this formulation of protein-conjugated Hib vaccine raised the question of which component was causing the reproducible anaphylaxis. The positive intradermal skin test to the CRM¹⁹⁷ protein alone suggests that the allergic sensitization was specific to this protein rather than the preservative or a unique antigenic determinant created by the covalent conjugation process between PRP and CRM¹⁹⁷.

Before the introduction of the *Hemophilus influenza* type b vaccine conjugates, there was an unconjugated polysaccharide vaccine licensed for use in this country. In a postmarketing study the first year after its widespread use in this country, with 4.5 million doses sold, there were reports of two definite anaphylactic reactions.⁽¹³⁾ These patients both had hypotension and dyspnea and were treated with epinephrine. There were also seven reports of syncope, three of which required epinephrine and/or benadryl. Six of the seven reactions occurred within 2 hours of the vaccine administration. With the advent of the conjugate vaccine, there has been only one case report in the literature of an urticarial reaction to *Hemophilus influenza* type b vaccine conjugated with tetanus (ActHIB). This was reported in a letter to the editor.⁽¹⁴⁾ This case presented a 2-year-old boy who developed an urticarial rash 9 days after the vaccination. In the letter, the author mentions that the Committee on Safety of Medicines in Great Britain had received 84 reports of urticaria and 19 of angioedema after the administration of Hib vaccine since 1992. As with many of the earlier reports, these are symptoms temporally associated with the administration of the vaccine and reported, but not published in a detailed report, with no definitive evaluation of the episodes. The package inserts for the conjugate *Hemophilus influenza* type b vaccines mention rash as a side effect but do not report any anaphylactic symptoms. Our case appears to be the first report that demonstrates an anaphylactic event to HbOC vaccine, implicating the CRM¹⁹⁷ conjugate and proving it with skin testing and challenge.

Of particular interest is the fact that a newly licensed heptavalent pneumococcal conjugate vaccine (Prevnar™, Lederle Laboratories, Pearl River, NY) is recommended for universal use in children 23 months and younger,

TABLE 4. *HEMOPHILUS INFLUENZAE* TYPE b PROTEIN CONJUGATE VACCINES: DISTINCT STRUCTURES

Vaccine Type	Carrier	Linkage	Polysaccharide
HbOC	CRM ¹⁹⁷ (nontoxic mutant diphtheria toxin)	No spacer	Small
PRP-OMP	OMP (outer membrane protein of <i>Neisseria meningitidis</i>)	Spacer	Medium
PRP-T	Tetanus toxoid	Spacer	Large
PRP-D	Diphtheria toxoid	Spacer	Medium

to be given concurrently with other recommended childhood vaccines at 2, 4, 6, and 12 to 15 months of age.⁽¹⁵⁾ This vaccine utilizes the same protein conjugate as the HbOC vaccine, CRM¹⁹⁷. Prevnar™ contains polysaccharides of pneumococcal serotype 4, 6B, 9V, 14, 19F, 23F, and oligosaccharide of serotype 18C which are conjugated to CRM¹⁹⁷. Each serotype is conjugated as a monovalent preparation before compounding as a multivalent vaccine. Preliminary studies of vaccine safety report no difference between Prevnar™ and controls for allergic reaction/hives, asthma, or shortness of breath but larger postmarketing studies will be needed to define the incidence of anaphylaxis with this vaccine.⁽¹⁶⁾ However, any patient with immediate hypersensitivity to HbOC should be considered at risk for anaphylaxis with this new vaccine because the reaction may be due to the conjugate protein.

Anaphylaxis to routine pediatric immunizations is a rare event. The allergist can play an important role in discerning which of several vaccines might be the inciting agent. Skin testing with both prick and intradermal methods with the vaccine, as well as dose challenges may help elucidate the etiology of the reaction. It is important to note that although the *Haemophilus influenza* type b vaccines are considered generically similar, they have important differences in their constituents which may be critical in the production of allergic reactions.

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Address reprint requests to:

Michael R. Nelson, M.D.

Allergy-Immunology Department

Walter Reed Army Medical Center

6900 Georgia Avenue, N.W.

Washington, D.C. 20307-5001

E-mail: Michael.nelson@amedd.army.mil

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