Interleukin-6, C-Reactive Protein, and Abnormal Cardiorespiratory Responses to Immunization in Premature Infants

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ABSTRACT. *Objective.* **We report our experience with routine immunization of 89 premature infants in the neonatal intensive care unit because 1) a substantial number of them developed abnormal clinical signs, and 2) all but one of those who received diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine responded with elevations of interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations that are otherwise characteristic of bacterial disease.**

Methodology. **We hypothesized that the elevated IL-6 and CRP levels were solely a response to immunization and that treatment with antibiotics was not necessary. We performed this study in two consecutive parts. In part 1, we prospectively evaluated 79 consecutive premature infants who were immunized with DTwP, *Haemophilus* b conjugate vaccine, hepatitis B vaccine, and inactivated polio vaccine, (Hib, HBV, and IPV). IL-6 and CRP were determined before immunization and every 12 hours on three occasions after immunization. In part 2, we studied an additional 10 infants who received acellular pertussis vaccine (DTaP) and who, 2 days later, received Hib, HBV, and IPV immunization simultaneously. We followed the same schedule of IL-6 and CRP determinations as in part 1.**

Results. **In part 1, 24 infants (30%) developed abnormal cardiorespiratory signs within 24 hours after immunization. CRP and IL-6 values rose to abnormal levels after immunization in all but one infant; that infant was later shown to have a T-cell abnormality. In part 2, 3 infants had abnormal cardiorespiratory signs after simultaneous immunization with Hib, HBV, and IPV, but not after DTaP. IL-6 and CRP levels remained normal in all 10 infants.**

Conclusions. **Part 1 demonstrates clearly the temporal relationship between IL-6 and CRP increments after DTwP, Hib, HBV, and IPV vaccines. In part 2 (DTaP was substituted for DTwP), there were no elevations of IL-6 or CRP, thus indicating that whole-cell pertussis component of DTwP was responsible for IL-6 and CRP elevations. Abnormal cardiorespiratory signs occurred frequently after immunizations in part 1, but they were unrelated to the magnitude of IL-6 and CRP elevations. The frequency of cardiorespiratory difficulty and its occasional severity suggest a need to monitor premature infants for ~48 hours after routine immunization.** *Pediatrics* **1998;101(3). URL: http://www.pediatrics.org/cgi/content/full/101/3/e3;** ***immunization, C-reactive protein, Interleukin-6, premature, bronchopulmonary dysplasia.***

ABBREVIATIONS. IL-6, interleukin-6; CRP, C-reactive protein; WBC, white blood cell; DTwP, diphtheria–tetanus–whole-cell pertussis; HBV, hepatitis B vaccine; DTaP, diphtheria–tetanus–acellular pertussis; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenzae* conjugate type b; BPD, bronchopulmonary dysplasia; HIV, human immunodeficiency virus.

In 1982, the American Academy of Pediatrics recommended routine immunization of premature or low birth weight infants at 2 months' postnatal age.[1] Later, a survey showed that only 56% of pediatricians and 34% of family physicians were in compliance with the American Academy of Pediatrics recommendation.[2] Some cautiously used a vaccine dose smaller than recommended or arbitrarily designated various weights at which immunizations were initiated.[2–4] However, clinical trials have shown that decreased doses of vaccine result in ineffective immunologic responses to pertussis vaccine,[4,5] and that the risk of neurologic signs was no higher in premature than in full-term infants.[4,5] Routine immunization of preterm infants beginning at the second postnatal month is now a pervasive practice in the physician's office and in the neonatal intensive care unit as well. During the course of administering these routine immunizations, we observed that a substantial number of premature infants developed abnormal cardiorespiratory signs soon after immunization, often necessitating evaluations for septicemia and therapy with antibiotics. Blood culture results were regularly negative in these infants, but our routine studies showed that C-reactive protein (CRP) values were always elevated. Therefore, we prospectively studied interleukin-6 (IL-6) and CRP responses to immunization, seeking to demonstrate that immunization itself stimulates increases in blood IL-6 and CRP levels, and that usually there is no need for antibiotic therapy.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the University of Tennessee, Memphis, and was performed at the Regional Medical Center at Memphis from January 1996 to July 1997. Subjects for this study were recruited from premature infants at ~2 months of postnatal age who qualified for routine immunizations as recommended.[6] Infants with acute illness or deteriorating conditions were not immunized.

Immunization was ordered by the attending physician after parental consent. IL-6, CRP levels, and white blood cell (WBC)

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indices were determined before immunization. If CRP values were normal and there was no indication of an acute disorder, immunization was initiated. Within 12 hours after the immunization, IL-6, CRP, and WBC indices were determined and then repeated three times at 12-hour intervals. If CRP values were abnormal, IL-6, CRP, and WBC indices were determined daily until all values returned to normal. IL-6 results did not influence clinical decisions. Serum concentrations of CRP were measured by rate immunonephelometry using automated instrumentation (Automated Immunochemistry System, Beckman Instruments Inc, Fullerton, CA). The level of detection was 0.4 mg/dL. Plasma IL-6 was measured by a sandwich enzyme-linked immunosorbent assay technique (Endogen Inc, Woburn, MA). The level of detection was 1.0 pg/mL.

In part 1, we studied consecutively infants who received one set of vaccines. A set of immunizations included diphtheria toxoid, tetanus toxoid, pertussis vaccine adsorbed, plus *Haemophilus* b conjugate vaccine (Tetramune, Lederle Laboratories, Wayne, NJ) and hepatitis B vaccine (HBV) (Recombivax HB, Merck, Sharp & Dohme, West Point, PA). Infants also received inactivated poliovirus vaccine (IPOL, Connaught Laboratories Inc, Swiftwater, PA) unless they were anticipated to be discharged within a few days.

In part 2, infants were consecutively added to the study, when acellular pertussis vaccine was approved for primary immunization. Tripedia (diphtheria–tetanus–acellular pertussis [DTaP], Connaught Laboratories) was first administered to each infant. Two days later, HBV, inactivated poliovirus vaccine (IPV), and Hib (*Haemophilus* b conjugate vaccine) (HibTITER, Lederle Laboratories, Pearl River, NY) were administered simultaneously. IL-6, CRP levels, and WBC indices were determined before immunization as in part 1. Three determinations of IL-6 and CRP were performed every 12 hours after Tripedia and again after the immunizations that were given 2 days later. As to method of administration of vaccine, diphtheria–tetanus–pertussis, Hib, and HBV were given intramuscularly and IPV, subcutaneously, on the anterolateral aspect of the left or right thigh using a 5/8-inch long, 25-gauge needle.

All infants were monitored with pulse oximetry set to alarm at $< 85\%$ O_2 saturation, and with cardiorespiratory monitors set at a respiratory pause of > 20 seconds and a heart rate < 80 beats per minute. Vital signs were documented by staff nurses. All infants received acetaminophen, 10 mg/kg, orally before immunization, and then every 6 hours for 24 hours after immunization. The appropriateness of an evaluation for septicemia and for antibiotic therapy was at the discretion of attending physicians. For analysis, infants were placed in one of four groups based on the presence or absence of abnormal cardiorespiratory signs 3 days before and 3 days after immunization. Group 1 consisted of infants who had no abnormal signs either before or after immunization. Group 2 consisted of infants whose episodes began after immunization; they needed intervention. Group 3 consisted of infants who had occasional cardiorespiratory signs before immunization that increased in frequency after immunization; this group also needed intervention. Group 4 consisted of infants who had occasional cardiorespiratory signs before immunization that were unchanged afterward; this group did not need intervention.

Statistical Methods

Means, SD units, frequencies, and proportions were determined. Variables in the four groups of infants were compared using both parametric and nonparametric methods. Multivariate analysis of variance was used to analyze continuous data such as birth weight, gestational age, and highest CRP, followed by multiple comparisons using Tukey's method if the F value was significant at $P < .05$. Because of the wide variation in the postnatal age of the infants at immunization, the data were analyzed using nonparametric method, the Kruskal–Wallis test. Categorical data were compared among groups using χ^2 analysis. A P value of $<.05$ was considered statistically significant.

RESULTS

In part 1, 79 premature infants received their first set of immunization (diphtheria–tetanus–whole-cell pertussis [DTwP], Hib, HBV, and IPV), and 2 infants received their second set of immunization. Thirty-six infants received IPV, and the remaining infants were given oral poliovirus vaccine at the time of discharge. Their mean birth weight was 870 ± 270 g (490 to 2040 g); 63 infants (80%) were <1000 g. Mean gestational age was 28 ± 2 weeks (24 to 33 weeks). Of these infants, 77% were black and 39% were male. The mean postnatal age at the time of first immunization was 72 ± 17 days (51 to 129 days). Mean weight at the time of immunization was 2050 ± 430 g (1180 to 3170 g). Postimmunization determinations of IL-6, CRP, and WBC indices were made at means of 8 ± 3 hours, 19 ± 4 hours, and 32 ± 6 hours.

IL-6 was obtained in the first 30 infants. The mean preimmunization value was 2 ± 2 pg/mL (1.0 to 6.0 pg/mL). Values increased to a mean of 130 ± 90 pg/mL, 70 ± 70 pg/mL, and 15 ± 15 pg/mL, respectively, at first, second, and third postimmunization determinations. Peak IL-6 values appeared between 3 and 14 hours after immunization (Fig 1).

All infants in part 1 had preimmunization CRP values of <1.0 mg/dL. After immunization, the first CRP was elevated (>1.0 mg/dL) in 9 infants. The second CRP was elevated in 63 infants, and the third was increased in 78 of the 79 infants. The first abnormal CRP levels occurred at a mean of 20 ± 5 hours after immunization (11 to 34 hours), with a mean value of 3.0 ± 1.5 mg/dL (1.5 to 9.5 mg/dL). Peak CRP values (4.0 ± 2.0 mg/dL) occurred in samples collected at a mean of 32 ± 9 hours (19 to 71 hours) after immunization. In 25 infants, the highest CRP was 5.0 to 10.0 mg/dL. CRP values returned to normal (<1.0 mg/dL) at a mean of 82 ± 27 hours (39 to 181 hours) after immunization (Fig 1).

In part 1, 3 infants were extremely irritable and 24 infants (30%) had abnormal cardiorespiratory signs that increased in frequency or appeared for the first time. These signs included apnea, bradycardia, and oxygen desaturation that required vigorous stimulation, initiation, or increase in oxygen supplementation. One of these infants required continuous positive airway pressure, and 2 others needed intermittent positive pressure ventilation. Cardiorespiratory signs first appeared within 12 to 24 hours of immunization and usually disappeared 48 hours later; however, in a few infants the abnormal clinical signs persisted for 4 days. Two infants received antibiotics; their blood cultures tested negative. Table 1 compares four groups of infants in part 1 based on the presence or absence of cardiorespiratory signs during 3 days before and 3 days after immunization. The four groups were significantly different as to postnatal age at immunization. However, infants in groups 2 and 3 (those who required intervention because of worsening symptoms or new symptoms) were older than infants in group 4, in whom symptoms were unchanged. There was no apparent relation between abnormal clinical signs and the IL-6 and CRP responses.

Table 2 lists the clinical characteristics of the four groups. A total of 74 infants had apnea of prematurity, bronchopulmonary dysplasia (BPD), or both. Apnea of prematurity was defined as a respiratory pause ≥20 seconds, usually associated with heart rates <80 beats per minute, for which no other cause could be identified.[7] BPD was defined as a persistent

TABLE 1. Comparison of Different Groups of Infants Based on Presence or Absence of Cardiorespiratory Symptoms (Part 1)*

	Group 1 (n = 47)	Group 2 (n = 18)	Group 3 (n = 6)	Group 4 (n = 9)
	Mean ± SD (Range)			
Birth weight (g)	890 ± 230 (490–1440)	740 ± 140 (470–950)	810 ± 190 (560–1130)	910 ± 340 (600–1580)
Gestational age (weeks)	28 ± 2 (24–33)	27 ± 2 (24–30)	27 ± 2 (24–29)	28 ± 2 (25–32)
Immunization age (days)†	72 ± 19 (54–138)	80 ± 19 (60–120)	73 ± 6 (65–76)	62 ± 5 (56–68)
Immunization weight (g)	2120 ± 580 (1180–4480)	2040 ± 340 (1560–3070)	2020 ± 400 (1470–2660)	2110 ± 600 (1580–3170)
Maximum CRP response (mg/dL)	4.6 ± 1.9 (1.5–9.5)	3.5 ± 1.7 (1.3–6.3)	3.4 ± 1.0 (2.3–4.7)	4.4 ± 3.6 (1.4–10.0)

* Group 1 consisted of infants who had no abnormal signs either before or after immunization. Group 2 consisted of infants whose episodes began after immunization; they needed intervention. Group 3 consisted of infants who had occasional cardiorespiratory signs before immunization, but the frequency increased after immunization; this group needed intervention. Group 4 consisted of infants who had occasional cardiorespiratory signs before immunization and whose episodes were unchanged afterward; this group did not need intervention. One infant who showed no CRP response to immunization is presented in the text only.
† $P < .05$ (group 4 vs groups 2 and 3).

TABLE 2. Characteristics of Different Groups of Infants Based on Presence or Absence of Cardiorespiratory Symptoms (Part 1)*

	Group 1 (n = 47)	Group 2 (n = 18)	Group 3 (n = 6)	Group 4 (n = 9)
Asphyxia	1/47	1/18	0/6	2/9
Maternal substance abuse	3/47	0/18	1/6	1/9
Apnea of prematurity	30/47	10/18	5/6	5/9
Bronchopulmonary dysplasia	34/47	17/18	4/6	8/9
Xanthine	4/47	2/18	2/6	3/9
Diuretics	6/47	3/18	1/6	0/9
Steroids	2/47	2/18	1/6	0/9
Oxygen	12/47	5/18	2/6	5/9
Apnea monitor	4/47	3/18	1/6	0/9

* See text for group descriptions; one infant who showed no CRP response to immunization is presented in the text only.

requirement for oxygen supplementation beyond 28 postnatal days plus abnormal pulmonary radiographic findings.[8] A total of 35 infants were receiving medication for apnea of prematurity or BPD at the time of immunization. Clinical characteristics were not significantly different among groups.

In part 2, 10 infants were immunized. Their mean birth weight was 850 ± 300 (470 to 1370 g). Mean gestational age was 27 ± 2 weeks (24 to 32 weeks). Seven infants were black, and 4 were male. The mean postnatal age at the time of immunization was 62 ± 6 days (54 to 74 days); mean weight was 1850 ± 550 g (1230 to 2640 g). Two infants had occasional cardiorespiratory signs before immunization, and these episodes were unchanged afterward. In 3 infants, however, cardiorespiratory signs began or increased in frequency after the simultaneous immunizations with Hib, HBV, and IPV. Each of these infants required vigorous stimulation, initiation, or increase in oxygen supplementation or bag/mask. IL-6 and CRP levels were not elevated after any of the immunizations. Six infants had apnea of prematurity; 8 infants had BPD. Two infants were receiving theophylline, and 5 infants were on oxygen supplementation at the time of immunization.

The only infant (in part 1) for which IL-6 and CRP levels did not increase after immunization with DTwP was a 74-day-old white female in whom truncus arteriosus was identified in utero. She was extremely irritable after immunization. She had previously required six evaluations for infection during her nursery stay, and in none were IL-6 and CRP levels elevated; however, on separate occasions these evaluations yielded blood cultures positive for *Escherichia coli*, *Staphylococcus aureus*, and group D *Enterococcus*. At 5 months of age, results of an immunocompetence profile demonstrated reversal of the CD4:CD8 ratio (0.26) and a decreased response to pokeweed mitogen (<10% of control). Human immunodeficiency virus (HIV) culture and HIV-p24 antigen results were negative at 7 months of age. Candida and cytomegalovirus infections were identified at 8 months of age, and the infant showed signs of rejection of a surgical conduit that was placed for correction of her truncus arteriosus. These findings are consistent with DiGeorge anomaly.

DISCUSSION

This study of immunized premature infants revealed that 1) cardiorespiratory symptoms occur in a substantial number (30%) of infants; 2) immunization with whole-cell pertussis vaccine triggers production of IL-6 and therefore CRP in virtually all infants; and 3) a lack of CRP response after immunization (DTwP) occurred in only one infant, in whom a T-cell deficiency was later demonstrated.

In part 1, a substantial number of our premature infants had significant cardiorespiratory signs. Apneic episodes often required vigorous stimulation; oxygen supplementation was enhanced, and occasionally positive pressure ventilation was initiated. Cardiorespiratory signs after immunization have been reported by others,[9–12] but most of the premature infants in our study had chronic lung disease, which may have predisposed them to the abnormal clinical responses we observed. Close monitoring for ~48 hours after immunization would be advisable.[6,10]

Complications have been reported to occur more frequently after immunization with DTP vaccine

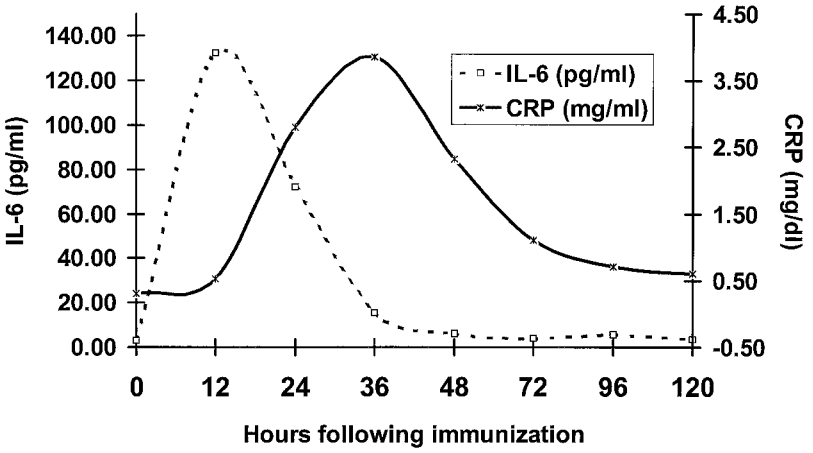

Fig 1. Time course for plasma IL-6 (n = 30) and serum CRP (n = 81) responses to immunization. The x-axis represents time period (hours), the y-axis represents mean concentration of IL-6 (pg/mL) and CRP (mg/dL).

than with DT vaccine and are most likely caused by the pertussis component.[13] We used the whole-cell pertussis vaccine in our first 79 infants (part 1); 30% showed cardiorespiratory signs. However, although there were no cardiorespiratory signs in 10 infants after they received the acellular form of pertussis vaccine in part 2, there were moderately severe signs of cardiorespiratory disturbance in 3 infants after immunizations with Hib, HBV, and IPV together.

In part 1 of this study, the rise in IL-6 and CRP levels apparently was stimulated by immunization with whole-cell pertussis (DTwP), because such a response was not seen after the acellular form (DTaP) nor after administration of the other vaccines 2 days later (part 2 of the study).

DTwP vaccines are prepared from inactivated *Bordetella pertussis*, which includes multiple antigens. On the other hand, DTaP contains several purified antigens, and the number of antigens varies according to the manufacturer. DTaP (Tripedia) vaccine contains inactivated toxoid and filamentous hemagglutinin, two of the five purified antigens derived from *B pertussis*.[14] Purified lipid A, derived from *B pertussis* endotoxin, does not induce IL-1 responses in human monocytes.[15] Thus, failure to stimulate IL-1 production may have resulted in absence of IL-6 and CRP elevations.

CRP is one of the acute phase reactants produced by hepatocytes in response to stimulation by cytokines,[16] primarily IL-6. CRP is a reliable marker of bacterial sepsis.[17–19] However, CRP also increases after surgical interventions, in meconium aspiration pneumonitis, and in necrotizing enterocolitis[18,19] in infants without sepsis. Abnormal CRP response to immunization as an incidental finding has been reported.[20] Our study (part 1) is the first to demonstrate systematically IL-6 and CRP increase after routine immunization with whole-cell pertussis vaccine. With knowledge of the precise time of stimulation (immunization) and without the influence of antibiotic therapy, we could demonstrate timed responses and peaks of IL-6 and CRP. The lag time for CRP response in rabbits after injection with *E coli* lipopolysaccharide was 4 to 12 hours.[21] As defined by the schedule of blood collections, we observed a lag period of 12 to 29 hours. CRP increased in all but one infant; however, 69% were asymptomatic. The incidence and severity of cardiorespiratory signs were not related to the magnitude of IL-6 and CRP elevations. In one infant, CRP rose to 10.0 mg/dL, yet there were no new abnormal clinical signs after immunization. Two infants were treated with antibiotics, and results of their blood cultures were negative. In part 2, with total absence of abnormally high CRP and IL-6 values, cardiorespiratory difficulties were apparent in three infants after the Hib, HBV, and IPV set of immunizations.

We evaluated the IL-6 responses to immunization in the first 30 infants (in part 1), and all 10 infants in part 2. IL-6 is an important mediator of inflammatory response.[22,23] It is synthesized and released by monocytes, macrophages, lymphocytes, endothelial cells, fibroblasts, and many other cells.[23] IL-6 acts as a messenger between damaged tissues and hepatocytes; it is the major inducer of acute phase protein synthesis, including CRP.[16] In a study of adult volunteers,[24] peak IL-6 plasma levels were observed 2 to 4 hours after endotoxin injection, followed by a peak CRP level at 20 hours. Within limits imposed by our sampling schedule, we observed peak IL-6 responses at a mean of 8 $\pm$ 5 hours, followed by peak CRP responses at 32 $\pm$ 8 hours after immunization.

In part 1, lack of CRP and IL-6 responses to immunization in one infant may be significant. This infant was later found to have T-cell deficiency (low CD4:CD8 ratio). An abnormal CD4:CD8 ratio is common in AIDS patients. Children with symptomatic HIV infection usually do not respond adequately to immunization.[25] Their CRP responses are unknown. Immunocompromised patients with leukemia (B-cell deficiency) who do not have T-cell deficiency respond normally to tissue inflammation and generate CRP.[26] Absence of a CRP response after immunization (whole-cell pertussis) may be an easily demonstrated sign of an underlying T-cell deficiency.

In conclusion, this study demonstrates that abnormal cardiorespiratory signs occur in a substantial number of premature infants after routine immunization, and that the frequency of abnormal clinical responses and their occasional severity indicate a need for cardiorespiratory monitoring for ~48 hours after administration of vaccine. For infants already discharged, caretakers should be made aware of the possibility of adverse reactions, either as a new

symptom or increasing episodes of symptoms. Also, they need to be advised to contact the primary care physician immediately when these symptoms occur.

Furthermore, unrelated to abnormal clinical signs, DTwP vaccine elicits elevated IL-6 and CRP responses in virtually all infants studied. These increases in IL-6 and CRP do not suggest septicemia; workup and antibiotic therapy would not be indicated.

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