

Vaccination of Preterm Infants

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Immunization of premature infants is usually recommended to occur at the chronological age comparable with term infants without correcting for gestational age following national infant vaccination programs. The main reason behind this recommendation is that preterm and low birth weight infants are at increased risk of infections in general and suffer from an increased frequency and severity of vaccine preventable infections. The need for timely vaccination of preterm infants is therefore great. However, vaccination is more likely to be delayed in preterm than in term infants [1,2].

Immune Response of Preterm Infants

At 8 weeks of age preterm infants have lower absolute counts of lymphocytes, T cells, B cells, and T helper cells and a lower CD4/CD8 ratio than term infants. By the age of 7 months B cell numbers in the preterm group have reached term equivalent, but the reduced absolute lymphocyte count, total T cell count, and T helper count persist [3]. During the third trimester of pregnancy an intense development of the B cell receptor repertoire actually occurs, thus, limiting the range of antigens recognised by preterm B cells compared to term infants. However, there is evidence that premature exposure to antigens can accelerate this development. This means that extremely low gestational age newborns may actually have a more diverse antibody repertoire by the time they reach the corrected age of 40 weeks than infants who are born at term [4], and this is an important argument against delayed immunisation of preterm infants.

The impaired functioning of immune defences to infection in especially preterm infants and their implication for vaccination have recently been reviewed in detail [5]. Shortly, external barrier functions potentially impact on immunization through the immunoregulatory functions of antimicrobial peptides and the impaired functions of the innate immune system through dendritic cells and macrophage dysfunction. The vaccine induced systemic protection involves B cells, cytotoxic T cells or T helper cells, or combined responses reflecting the interplay between the humoral and cell mediated immunity.

Effectiveness of Immunization in Preterm Infants

Vaccine responsiveness can be determined by either vaccine immunogenicity or efficacy studies. The latter is based on large numbers of individuals to demonstrate how much of a reduction in disease incidence occurs in vaccinated compared to unvaccinated persons. And this is the main problem for preterm infants: low frequency of diseases associated with low numbers of infants that would be required for such clinical trials. A systematic review was published recently determining vaccine responsiveness to tetanus, diphtheria, meningococcal C and pneumococcal conjugates, *Haemophilus influenzae* type B, polio and pertussis [6]. The focus of this review was to determine vaccine immunogenicity using immunological correlates of protection and to estimate whether an individual preterm infant was immune based on a "putative protective antibody level". Data showed that immunogenicity in premature infants was vaccine specific and whilst highly protective for the toxoid and inactivated preparations, responses to the subunit preparations were less optimal.

A physiological reason why premature infants may respond even better to vaccination than anticipated is the kinetics of trans-placental

transfer of maternal antibody. Maternofetal transport of immune globulin G starts around the 17th gestational week, is at equilibrium around the 33rd week, and reaches up to twofold higher values in the neonate at term. Thus, preterm infants, depending on their gestation, will have low or absent concentrations of maternal antibody. While this in part explains susceptibility to infections, it may provide an advantage in response to vaccines [1].

Adverse Events

A small number of infants may have apnoea with or without bradycardia temporally associated with immunization. Rates have been reported to range between 13 and 25% [7-9]. Resurgence or an increase of bradycardia and desaturation episodes or isolated desaturation episodes have been reported in 43% of infants immunized with a hexavalent vaccine [10]. Apneas, bradycardias and desaturations have been observed to occur more often in preterm infants with a chronological age below 67 to 70 days at the time of first immunization [11,12]. The risk factors for, and recurrence rate of apnoea with subsequent immunisations are unknown, which makes planning for subsequent immunizations for these highly vulnerable infants difficult. In a retrospective surveillance cohort analysis including all preterm infants with a cardiorespiratory event following first immunization 18% (95% confidence interval 6–31%) had recurrent apnoea with subsequent immunization [13]. Possible risk factors for recurrence included lower birth weight and ongoing hospitalization for complications relating to prematurity. No preterm infant with recurrent apnoea had a third episode of apnoea with subsequent immunization. For infants in the NICU without apnea during the 24 hours immediately before immunization, younger age, smaller size, and more severe illness at birth were reported to be important predictors of post-immunization apnea besides pre-immunization apnea being the most important one [12]. Thus, the American Academy of Pediatrics recommended immunization of preterm and low birth weight infants when they are medically stable [14], and the Committee for Infectious Diseases and Vaccination of the German Academy of Pediatrics and Adolescent Medicine [15] recommended very immature preterm infants (<28 weeks of gestational age) to be immunized during their first hospitalization irrespective of a history of cardiorespiratory events.

Conclusion

While absolute primary antibody responses might be lower

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in preterm infants immunized according to chronological age compared with term infants, the majority of preterm infants achieve concentrations generally accepted to be protective. In clinical practise the first vaccination (Diphtheria-tetanus-pertussis-polio-*Haemophilus influenzae* type B-hepatitis B and pneumococcal and meningococcal C conjugates) might be given following one to three days without a history of apneas/bradycardias during the first hospitalization with subsequent observation for cardiorespiratory events preferably when the preterm infant reached 67 to 70 days of life. In case of post-immunization cardiorespiratory events the subsequent vaccination should be administered under close monitoring during rehospitalisation for 48 to 72 hours.

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