Immunizations in the Nursery

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Overview

Immunization is one of the most important tools of pediatric preventative care. However, a tremendous number of infants are at risk of not being up-to-date on their vaccines at the time of nursery discharge. For well newborns, approximately 30–40% do not receive their birth dose of hepatitis B vaccine [1]. Under-immunization is even more common among preterm infants discharged from the neonatal intensive care unit (NICU); studies estimate that up to 50% of preterm infants are missing ≥1 immunization [2, 3].

Under-immunization in the nursery is problematic for several reasons:

1. Missed opportunity to prevent vertical transmission (hepatitis B).
2. Missed opportunity to prevent healthcare-associated infection (pertussis, influenza).
3. Restrictions on live virus vaccines may prevent infant from ever receiving rotavirus vaccine.
4. Time delay between hospital discharge and first well-child visit as outpatient increases the time window during which the infant is at risk for preventable infections.
5. Not giving immunizations on time in the nursery may "normalize" under-immunization to the family.

This chapter describes administration strategies for all routine childhood vaccines. In general, vaccines should be given at the normal chronologic ages to all

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J. B. Cantey (ed.), *Neonatal Infections*, https://doi.org/10.1007/978-3-319-90038-4_28

infants (i.e., not corrected [post-menstrual] age). A 2-month-old former 23-week infant who is now 32 weeks corrected is due for the 2-month immunizations!

Hepatitis B Vaccine

Approximately 1000 new cases of perinatal hepatitis B virus (HBV) infection are diagnosed each year in the United States [4]. For neonates infected perinatally with HBV, more than 90% will become chronically infected, and >25% will develop hepatocellular carcinoma or liver cirrhosis [5]. In order to prevent perinatal infection, all pregnant women should be screened for the presence of hepatitis B surface antigen (HBsAg) in their blood prior to delivery (see chapter "Hepatitis B in the Perinatal Period").

The hepatitis B vaccine is approximately 85–95% effective when given in the first 12 h of life [6]. In addition, hepatitis B immune globulin (HBIG) provides passive immunoprophylaxis to infants with known perinatal exposure to HBV. The administration of hepatitis B vaccine, with or without HBIG, is determined by the infant's weight and HBV exposure status. In general, all infants should receive hepatitis B vaccine as soon as possible after delivery (Table 1). Prompt immunization is key to prevent vertical transmission from HBV-infected mothers and will also help protect infants born to mothers whose HBV status is either unknown or falsely negative. However, infants <2 kg born to HBsAg-negative mothers should be immunized at age 1 month—or at the time of discharge—in order to improve their immune response to immunization.

In addition to immunization, infants born to HBV-positive mothers should undergo confirmatory testing between ages 9 and 12 months, after completion of their three-dose hepatitis B vaccine series (at birth as well as ages 2 and 6 months). Providers should obtain HBsAg and anti-HBs to ensure that the infant is not infected (negative HBsAg) and has mounted a protective immune response. If the anti-HBs level is <10 mIU/mL, the infant is not considered protected and should receive additional dose(s) [7].

Table 1 Hepatitis B vaccine and immune globulin administration strategies

Maternal HBsAg status at delivery	Hepatitis B vaccine	Hepatitis B immune globulin
Positive	Within 12 h	Within 12 h
Negative	*≥2 kg*: Within 24 h	Not indicated
	<2 kg: At 1 month of age or discharge, whichever comes first	
Unknown/ pending	Within 12 h	*≥2 kg*: If mother's HBsAg test is positive *OR* at age 7 days or hospital discharge if mother's HBsAg status still unknown
		<2 kg: Within 12 h unless mother's HBsAg testing is negative by then

2-, 4-, and 6-Month Vaccines

The collection of vaccines due at ages 2, 4, and 6 months accounts for the majority of immunizations administered in the NICU, and are second only to the hepatitis B vaccine in terms of total doses administered in US nurseries. These vaccines include diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio virus (IPV), *Haemophilus influenzae* type b (Hib), and 13-valent pneumococcal vaccine (PCV-13). Rotavirus is included in the 2-4-6-month schedule but is discussed separately below.

Delay or absence of these 2-4-6-month vaccines accounts for a substantial fraction of nursery under-immunization [3]. Providers are often concerned about the increased frequency of apneas and bradycardia surrounding immunizations. Randomized controlled trials have confirmed that immunization is associated with an increase in inflammation, including C-reactive protein and prostaglandins, which can trigger apnea, bradycardia, respiratory decompensation, and other signs of clinical instability [8–10]. Unsurprisingly, the incidence of sepsis evaluations (e.g., cultures and empiric antibiotic administration) more than triples in the 3 days following immunization as a result [10]. Therefore, providers may delay immunizations until the infants are older, larger, or closer to discharge. However, vaccine-preventable illnesses—most notably pertussis—are capable of causing fatal nosocomial infections [11]. In addition, immunization near the time of discharge can still cause transient inflammation, which is associated with discharge delays and readmission for apneic events [12]. Additionally, infants who are immunized late may acquire vaccine-preventable infections after discharge, but before they have mounted a protective antibody response [13].

In general, 2-4-6-month immunizations should be administered promptly (Box 1). Rare exceptions can be made for infants being supported with noninvasive ventilation with tenuous respiratory status, who may require re-intubation with further respiratory decompensation. However, these infants should be immunized as soon as is feasible. Of note, active or recent administration of glucocorticoids does not seem to meaningfully affect vaccine response and is not a reason to delay immunization [14, 15]. Routine administration of antipyretics (e.g., ibuprofen, acetaminophen) has been associated with decreased antibody response to immunizations in infants and should be avoided in general [16].

Box 1 Approach to 2-, 4-, and 6-Month Vaccines in Preterm Infants

Immunizations should be given promptly at age 2, 4, and 6 months for all preterm infants

- Active or recent corticosteroid use *does not* meaningfully affect vaccine response
- Routine use of acetaminophen or ibuprofen post-immunization can reduce vaccine response and should be avoided

- Combination vaccines (e.g., DTaP/IPV/hepatitis B) have similar safety profiles to individual vaccines and can be used to minimize required injections
- Live-attenuated oral rotavirus vaccine should be included in the 2-4-6-month schedule

Absolute contraindications:

- Anaphylaxis to a vaccine component (not reported in preterm infants)
- History of intussusception (rotavirus)

Post-immunization monitoring

- Vaccine-associated events[a] occur within 72 h of immunization
- Sepsis evaluations—but not sepsis risk—increased within 72 h of immunization
- Discharge <72 h post-immunization associated with increased risk for readmission

[a]Apnea, bradycardia, desaturation, respiratory decompensation, temperature instability, feeding intolerance

Rotavirus Vaccine

Rotavirus vaccine, a live-attenuated virus vaccine, is indicated at ages 2, 4, and 6 months. Since live-attenuated viruses can be transmitted horizontally, and because wild-type rotavirus is associated with necrotizing enterocolitis and other intra-abdominal pathology among neonates [17, 18], the majority of neonatal providers historically have been hesitant to adopt routine administration of this vaccine in the nursery [19]. Unfortunately, the first dose of rotavirus vaccine must be administered by age 104 days (<15 weeks), and therefore many infants are too old for rotavirus immunization by the time of NICU discharge [20]. This is concerning, as preterm infants have a higher risk of hospitalization and death from wild-type rotavirus infection than term infants [21]. Infants with congenital gastrointestinal pathology or short-gut syndrome are also especially vulnerable to rotavirus [22]. Fortunately, safety data for the rotavirus immunization in the NICU continues to grow.

Safety Profile

Current studies suggest that there is no increased risk for feeding intolerance, necrotizing enterocolitis, or poor weight gain following rotavirus immunization

[23, 24]. This remains true for infants with congenital gastrointestinal anomalies or short-gut syndrome [25, 26]. A history of intussusception is an absolute contraindication to rotavirus vaccine for all infants, but rotavirus vaccine-associated intussusception has not been reported in preterm infants.

Shedding

Immunized infants begin shedding vaccine-strain rotavirus within 24 h of immunization. Shedding lasts for up to 2 weeks, with a median of 8 days with the first dose of rotavirus vaccine and 5 days after the second [27]. With proper handwashing hygiene, transmission between immunized and unimmunized infants should not occur [27]. In a study of preterm twins, in which one twin was immunized with rotavirus and the other was not, 29% of the unvaccinated twins acquired rotavirus immunity, but none had clinical signs of infection [28]. Illness from horizontal transmission of the vaccine strain has not been reported in the nursery setting and is extremely rare in older children [29].

In conclusion, the limited available evidence supports routine rotavirus immunization in the NICU setting. Standard precautions, including close attention to handwashing hygiene, are sufficient; contact precautions are not necessary post-immunization.

Influenza Vaccine

Infants Age ≥6 Months

Influenza immunization should be given for all infants age ≥6 months. As with any infant, preterm infants receiving their first dose of influenza vaccine should receive a second dose 1 month later [30]. The same risk exists for post-vaccine events following influenza vaccine as after 2-4-6 month vaccines.

Infants Younger Than Age 6 Months

Although there is no formal recommendation to administer influenza vaccine to infants age <6 months, there are units that will selectively administer influenza vaccine to high-risk infants (e.g., those with severe bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency) before discharge, even if age <6 months; this approach has not been rigorously studied [31]. A more proven approach to infants age <6 months is passive protection from maternally derived antibody. Immunization of pregnant women against influenza prevents more than 50% of influenza-associated morbidity among their infants during the first 6 months of life [32].

Palivizumab Prophylaxis

Palivizumab (Synagis®) provides passive protection against lower respiratory tract infections caused by respiratory syncytial virus (RSV). Palivizumab is a monoclonal antibody against a surface glycoprotein on RSV that causes fusion with respiratory epithelial cells [33]. By blocking the F (fusion) protein, palivizumab can prevent infection with RSV. However, once RSV infection is acquired, the virus can spread cell to cell without relying on the F protein, so palivizumab is minimally effective for treatment of RSV infection.

Palivizumab is given as monthly 15 mg/kg intramuscular injections during RSV season. This regimen reduces RSV-related hospitalizations by >50% and clinic visits by >80% [34, 35]. However, due to the cost of palivizumab (approximately $9000 per patient per season) and the relatively mild benefit seen in larger preterm infants, the most recent recommendations from the American Academy of Pediatrics narrowed the range of infants for whom palivizumab is recommended [36]. The current recommendations are summarized in Table 2.

At present, palivizumab is not recommended for prevention of hospital-acquired RSV and therefore is not recommended for infants with ongoing NICU admission. Many NICUs will administer the first dose of palivizumab near the time of hospital discharge; however, evidence supporting NICU administration of the first dose rather than outpatient administration is limited [37]. In contrast to vaccines, palivizumab administration does not seem to be associated with a subsequent increase in cardiopulmonary events.

Table 2 Recommendations for palivizumab prophylaxis in the first 2 years of life, adapted from reference 36

Indication	First year of life	Second year of life
Gestational age ≤28 weeks	Yes	Yes, if BPD still being treated[a]
Gestational age 29–31 weeks with BPD[b]	Yes	Yes, if BPD still being treated
Gestational age 29–31 weeks without BPD	No	No
Gestational age ≥32 weeks	No	No
Hemodynamically significant congenital heart disease[c]	Yes	No
Severe pulmonary or neuromuscular disease that impairs airway clearance	Yes	No
Profound immunocompromise[d]	Yes	Yes

BPD bronchopulmonary dysplasia

[a]Ongoing treatment including systemic corticosteroids, supplemental oxygen, or bronchodilators within 6 months of the start of RSV season (which is generally November in the United States)

[b]BPD defined as requirement for supplemental oxygen ≥28 days after birth

[c]Includes acyanotic heart disease requiring medication and/or surgical correction, moderate to severe pulmonary hypertension, and cyanotic heart disease. Does not include hemodynamically insignificant acyanotic heart disease or lesions that have been successfully surgically corrected

[d]No standard definition; generally includes severe combined immunodeficiency, DiGeorge syndrome, etc. Best determined in consultation with pediatric immunology providers

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