Primary Care of the Premature Infant

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I must confess, I was born at a very early age.

—Groucho Marx

Learning Objectives:
1. Understand how the nutritional needs of the premature infant differ from those of term infants
2. Review projected growth and developmental trajectories for premature infants
3. Identify recommended screening evaluations and immunizations for premature infants

Primary Reference:
1. Andrews B, et al. NICU Follow-up: Medical and Developmental Management Age 0 to 3 Years
   http://neoreviews.aappublications.org/content/15/4/e123.full.pdf+html

CASE ONE:

You receive a call from the Newborn Intensive Care Unit (NICU) about an infant to be discharged to your practice. Barry Early is a 75-day-old, former 28-week gestation, 1080 gram infant born by Cesarean section for breech presentation and preterm labor. Pregnancy was otherwise uncomplicated. Barry was intubated in the delivery room and later diagnosed with respiratory distress syndrome. Currently, Barry is on room air but his chest X-ray is consistent with mild bronchopulmonary dysplasia. He is tolerating oral feedings and taking Neosure 22 kcal/oz, 45-50 mL every 3 hours. His head ultrasound showed a grade 2 intraventricular hemorrhage on the left. He was diagnosed with stage 2 retinopathy of prematurity that was resolving on his last examination, and ophthalmology follow-up is planned for 2 weeks. Hearing and car seat screenings were passed prior to discharge. He is on no medications other than multivitamin drops. Barry will be discharged today to his family that includes his parents and 4-year-old sister.

Two days later, Barry comes to your office with his parents and sister who report that things are going well since his discharge. He has gained 45 grams and is eating 60 mL every 3 hours.

1. Although this is a happy occasion, what social concerns specific to families leaving the NICU should you explore?

Life has been disrupted for this family since they have spent the last two and a half months with a child in an ICU. In addition to the typical infant concerns, they have faced additional, life-threatening medical issues. Providers should emphasize that it is typical for families to take time to adapt to the infant’s transition to home and that it is not uncommon for parents to suffer from an anticlimax, which may include grief and depression. Rates of post-partum depression and anxiety are higher among mothers and fathers of infants born <30 weeks gestational age compared to parents of healthy, full term infants. Parents should be reminded about postpartum visits and use of birth control since these issues may get overlooked during the whirlwind NICU experience. Medical providers should also assess support systems including access to a phone and referrals to visiting nurses and the state early intervention program.

Parents should be reminded that preterm infants may not follow typical visit schedules in the first year of life and may need interim visits for a variety of reasons. The role of the primary care provider in providing anticipatory guidance, developmental surveillance, vaccine administration, and care
coordination, should be reviewed, especially for children who will also be followed by multiple specialists.

2. Discuss the concept of “corrected age.” How does it apply to the different domains of health maintenance and surveillance (growth, development, etc.)?

Corrected age is calculated by subtracting the number of weeks the infant was born prematurely from his or her chronological age or, in other words, the age calculated from the original due date. It is important to review the importance of corrected age with families because it will provide them with a better benchmark for growth and developmental milestones than chronologic age.

Growth is corrected for prematurity until the patient reaches a corrected age of 2 years or plots solidly on standard growth curves. Growth charts for premature infants are available but the World Health Organization Fetal-Infant Growth Chart for Preterm Infants (“Fenton chart”) only goes up to 50 weeks gestational age (see Resources section) so typically, as an alternative, providers often use corrected ages when plotting growth on standard charts. Height, weight, head circumference, and growth velocity should be followed closely. When discussing growth expectations with parents, it is important to stress that the different growth parameters may achieve “catch up” at different times, with head circumference showing catch-up growth first (usually between 3-8 months after birth), followed by weight and finally length. It may be a cause for concern when catch-up growth for weight is not preceded by catch-up growth for head circumference.

Providers must remain aware that rapid head growth may represent a pathologic process (e.g., hydrocephalus) rather than normal catch-up growth. This distinction is often difficult but factors that suggest normal catch-up growth include: normal neurological examination (except for subtle variations in tone that are common in preterm infants - addressed below), appropriate developmental progress, and a head circumference that may be crossing percentiles but does not exceed the 97th percentile. Typically, serial head ultrasounds are obtained while the infant is in the NICU and results should be reviewed by the provider to determine whether the infant has a history of severe intraventricular hemorrhage and is therefore at risk for post hemorrhagic hydrocephalus.

Cranial imaging should be obtained in the child whose head circumference is growing more than 1.25 cm per week or who has a change in neurological status.

Weight gain greater than 40 grams per day should be investigated for possible adverse causes such as fluid retention or excessive feeding. Growth velocity can be affected by multiple factors including gestational age, birth weight, and NICU course including severity of illness and ongoing illnesses/conditions.

The achievement of developmental milestones and the provision of anticipatory guidance should also be geared towards corrected age. Corrected age should be used to predict when a child will be developmentally ready to sleep through the night, develop colic, experience tooth eruption, and so on. Typically, the more preterm an infant, the longer it will take the child to approximate the developmental trajectory of a term infant. Also, just like catch-up growth, not all areas of development will mature at the same rate. There is some debate as to how long to correct development for prematurity, although 2 - 2 ½ years is common.

The immunization schedule is a notable exception to the use of corrected age when caring for premature infants. Immunization administration should follow chronological age.

3. Does breastmilk provide adequate nutrition for preterm infants? When should formula-fed preterm infants be switched to term formula?

The nutritional needs of the preterm infant exceed those of the full term infant during the first few months of life and the appropriate feeding choice is important. In addition to increased caloric requirements, these infants miss the significant amount of mineral deposition that occurs during the third trimester, so have increased mineral requirements. Preterm infant formulas and breast milk fortifiers are specifically designed to address these nutritional requirements.

Breast milk is always recommended for the preterm infant. Human milk fortifier (HMF) added to the breast milk is recommended for infants weighing less than 2 kilograms at birth to not only increase
caloric content but also to supplement protein, vitamin, and mineral intake while in the NICU. Preterm formulas (e.g., Enfamil Premature, Similac Special Care High Protein, Good Start Premature 24) and/or breast milk with human milk fortifier each provide 24 calories/ounce, and should be continued until the infant weighs 2.2 kilograms, or achieves 36 weeks corrected age, or is being prepared for discharge. At that time, the infant should be switched to a transitional formula such as Neosure or Enfacare, which provide 22 calories/ounce and have higher concentrations of protein, calcium, phosphorus, vitamins and other minerals than term formulas. Prior to discharge, infants receiving breast milk fortified with HMF should be transitioned to breast milk fortified with Neosure or Enfacare powder to increase the caloric and mineral content of the breast milk (1 tsp Neosure or Enfacare powder: 130 cc breast milk = 22 cal/oz; 1 tsp Neosure or Enfacare powder: 70 cc breast milk = 24 cal/oz). As they transition to direct breastfeeding they should continue to receive fortified breast milk or transitional formula when not fed at the breast. Some infants with predisposing conditions such as severe bronchopulmonary dysplasia (BPD) may require higher caloric concentrations.

Infants receiving transitional formula require multivitamin drops until they are consuming approximately 800 cc per day. Breast fed infants should receive multivitamin drops with iron until 12 months of age. As per AAP recommendations, soy milk formulas should NOT be given to preterm infants because they do not support appropriate growth.

It is important to consider the patient’s NICU course, growth velocity and feeding tolerance when deciding when to transition a preterm infant from transitional formulas to a standard formula. There is no standard timeline, however it is common to continue transitional formula until an infant is gaining weight steadily, taking oral feedings well, and self-regulating intake. Typically this occurs around 4 to 9 months of age. Some providers with continue their use until the infant has reached at least the 50th percentile weight for corrected age.

CASE continued:

You review the vaccine record from the NICU and note that Barry received DTap, IPV, Hib, hepatitis B, and Pneumococcal 13-valent conjugate vaccines at 2 months of age. You notice that he did not receive a rotavirus vaccine.

4. Why did he not get the rotavirus vaccine while in the NICU? Will you offer any vaccines today? What other alterations from the standard childhood vaccination schedule will you consider?

The rotavirus vaccine is a live vaccine and contraindicated for hospitalized patients due to concern for shedding virus and spreading infection. It should not be administered in the hospital outside of clinical trials designed to assess its safety. The CDC’s Advisory Committee on Immunization Practices supports rotavirus vaccination if patients meet age criteria for the first dose of the vaccine, are clinically stable, and are discharged from the hospital. A history of necrotizing enterocolitis is not an exclusion criterion. Accordingly, assuming Barry is in stable condition, he should receive the rotavirus vaccine today.

The concept of “cocooning” is very important for preterm infants and their families. Parents, siblings and other close contacts (e.g., grandparents, babysitters) who have not previously received Tdap should receive a single dose of Tdap to protect the infant from pertussis. Tdap can be given no matter when the last Td was administered. Also, these close contacts should receive influenza vaccine during the appropriate season. Other infection control practices, such as strict hand hygiene, avoidance of sick contacts and cigarette smoke, and restricting public exposures should be reviewed.

This patient has already received his other 2-month vaccines and can continue with the standard vaccine schedules according to chronologic (not corrected) age. In addition, palivizumab (Synagis) should be offered when appropriate. Palivizumab is a humanized murine monoclonal anti-F glycoprotein immunoglobulin with neutralizing and fusion inhibitory activity against RSV. It has been shown to reduce the incidence of RSV-associated hospitalization in at-risk populations, and guidelines are provided by the AAP for eligibility, initiation, and length of treatment. The RSV season typically runs from November through March in North America, although it can vary based on actual location. Palivizumab is given as an intramuscular injection monthly for up to a maximum of 5 doses. Eligibility
is based on gestational age at birth, age at the start of the season, and other predisposing conditions including chronic lung disease and congenital heart disease.

Infants should be screened for palivizumab eligibility well in advance of the anticipated administration date because insurance preauthorization may result in delays. Infants should continue to receive palivizumab after a documented RSV infection since there are multiple strains of the virus.

Moderators should review current palivizumab recommendations that are available at the link provided in the Resources section.

CASE continued:

Barry returns for his well child check and 4 month vaccinations. When you saw him at 2 weeks post-discharge he was doing well and there were no concerns. He has gained 35 grams/day since his last appointment. Mrs. Early reports that he is still doing well overall but is concerned that “he has developed asthma.” He was in the Emergency Department last week for wheezing associated with an upper respiratory infection and was sent home with albuterol. He has returned to baseline and has not needed albuterol for the past 5 days.

5. How does the history of respiratory distress syndrome and bronchopulmonary dysplasia factor into the recent respiratory difficulties?

Infants with mild BPD may develop bronchospasm associated with upper respiratory infections. Clinically they appear like children with asthma and are treated with the same maintenance and rescue medications as are asthmatics. Respiratory difficulties typically resolve by 1-2 years of age. In infants with more severe BPD, it is not uncommon for abnormal lung function to persist into adolescence. Since this is Barry’s first episode, reassurance is appropriate, with careful instruction to contact you if he develops additional episodes of wheezing. Inhaled corticosteroids (ICS) should be instituted following National Asthma Education and Prevention Program guidelines. If symptoms are not controlled with standard doses of ICS, the child should be referred to a pulmonary specialist.

6. What anticipatory guidance will you provide related to introduction of solid foods at this 4-month visit?

Introduction of solids should follow the same developmental readiness cues that one would use for term infants. Given that developmental age must be corrected for degree of prematurity, most preterm infants are not ready for solids until 4 to 6 months corrected age. As such, Barry is unlikely to be developmentally ready for solids since his corrected age is still only 1 month. At 6 months of age, infants who receive WIC supplements may be eligible for cereals and potentially other semisolid foods; the local WIC office will likely request medical authorization to do this in the case of a very preterm infant. Families should be reminded regularly about growth and developmental expectations specific to their infants.

CASE continued:

Barry continues with regular follow-up at your office and with the state early intervention program. At 8 months of age, he is starting to sit with support, is rolling both ways well, and is babbling and cooing. You notice some increased tone in his heel cords and hips, and his reflexes are mildly brisk.

7. How concerned are you about these findings?

Preterm infants, especially those born at less than 1500 grams, may have abnormal findings on muscular and neurologic exam for the first 12-18 months. Initially, passive tone is extensor but as the preterm infant matures, passive flexor tone gradually overcomes passive extensor tone. Typical findings also include jittery movements that may cause the infant to startle, thereby initiating a pattern of cyclic jitter/startle. Providers can demonstrate how supportive positioning techniques
including midline orientation, hand-to-mouth activity, and passive flexor patterns will diminish this cycle and help the infant come to a calm, sometimes alert state. Primitive reflexes should be monitored based on corrected age.

Generalized hypotonia with head lag is common. As infants get older, hypertonicity of the heel cords and hips with decreased truncal tone is typical, usually within the first several months after discharge. If a child does not follow the typical progression of developmental skills (i.e., a parent says the child is not yet sitting but “loves to stand”), this should serve as a red flag for abnormal tone. Preterm infants with abnormal tone are typically late walkers and will often have a certain degree of toe walking which, as long as the foot can flatten when the child is standing, is usually not of concern. The majority of tone issues resolve, usually by 12 months corrected age, but it is difficult to predict in whom. Some professionals will argue against therapy since these tone patterns do disappear in the majority of children; early intervention is recommended in any case to minimize the effects of the abnormal patterning on the normal progression of development. Parents of children with extensor posturing or hypertonia should be advised to not use walkers, standers, or jumpers since they encourage extensor posture.

It is important to not only confirm that the state early intervention program is seeing the child but also to clarify what type of services they are providing. If a patient with neuromuscular abnormalities is simply being monitored with sequential screening tests and has not received a full assessment, medical providers should contact the state program requesting that a physical therapist see the child. In a child with more significant tone issues, a referral to a pediatric rehabilitation specialist to supplement the state services may be warranted.

As with other children, development should be monitored throughout childhood. A study of former preterm infants, less than 28 weeks gestation and less than 1000 grams, noted that approximately three quarters had cognitive, educational, or behavioral difficulties at nine years of age, with half of those having multiple areas of concern.

8. What additional screening will you consider with a preterm infant?

Hearing: In accordance with the 2007 Position Statement of the Joint Committee on Infant Hearing, all infants who received care in a NICU for more than 5 days should be referred for diagnostic audiological assessment at least once by 24-30 months of age even if they passed their discharge hearing screening.

Vision: The primary care provider should have a clear understanding about the desired timing of ophthalmologic follow-up on a case-by-case basis. Although the majority of retinopathy of prematurity (ROP) resolves, it has been reported that infants diagnosed with ROP have up to 10 times the risk for refractive errors than their same gestational age peers. In addition, there is a higher incidence of other visual disorders including strabismus, amblyopia, and cataracts in preterm infants. The AAP 2018 Policy Statement on ROP recommends ophthalmology examination 4-6 months after discharge.

Blood pressure: All premature infants should have a blood pressure obtained at their initial visit because they are at risk for neonatal hypertension due to a variety of complications of prematurity and interventions used in the NICU (e.g., BPD, umbilical artery catheterization, methylxanthine use). Infants with BPD who require diuretics, home oxygen therapy, or bronchodilators should have a blood pressure obtained at each well child visit. It is important to use appropriate cuff size and obtain values in non-crying infants when possible.

Anemia: Iron deficiency is common in premature infants. As previously noted, breast fed infants should receive multivitamin drops with iron until they are on solids as at least 2 mg/kg/day of elemental iron is recommended through the first year of life. Providers should confirm that Hgb, Hct, and reticulocytes were obtained within the two weeks prior to discharge. If not, they should be obtained at the initial visit. In addition, providers should follow the AAP routine health maintenance guidelines regarding anemia prevention and screening.

Newborn screening: Newborn screening may have to be repeated in infants who were transfused prior to their final screen. Recommendations are state specific and typically range from two to three months after the final transfusion.
**Additional References:**

**Resources:**
1. AAP 2014 recommendations for use of palivizumab in high-risk infants, young children. http://pediatrics.aappublications.org/content/134/2/415

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