Discharge of Medically Complex Infants and Developmental Follow-up

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INTRODUCING OUR NEW CHRONIC CONDITIONS FEATURE

Just before morning sign-in rounds began the other day I quickly perused the list of children admitted to the hospital and noted recurrent themes of indwelling catheters, gastrostomy tubes, tracheostomies, and ileostomies. For some individuals, diagnoses were many, the number of which was surpassed by the medications ordered. What happened to the child admitted for a single reason, whose care seemed simple in comparison to today? When did hospital length of stay become inversely proportional to the complexity of care? Yes, General Pediatrics has changed for the better; our children are surviving significant morbidities. Yet our outpatient care is becoming ever more complicated. We now care for patients in our clinics whom we used to care for in our hospitals.

“Discharge of Medically Complex Infants and Developmental Follow-Up” is the first of two articles in 2021 to kick off our new Chronic Conditions feature, which will be a quarterly feature in 2022 and beyond. Pediatrics in Review strongly believes it is time to regularly address the care of the infant, child, and adolescent with complex, chronic disease(s). We hope you agree.

Dr. Joseph Zenel
Editor in Chief, Pediatrics in Review

ABSTRACT

At the time of discharge from the NICU, many infants have ongoing complex medical issues that will require coordinated, multispecialty follow-up. Discharge planning and transfer of care for infants with medical complexity require a multidisciplinary team effort that begins early during the NICU hospitalization. It is critical that the primary care physician is involved in this process because he or she will serve as the chief communicator and coordinator of care after discharge. Although some infants with medical complexity may be followed in specialized multidisciplinary NICU follow-up clinics, these are not universally available. The responsibility then falls to the primary care physician to coordinate with different subspecialties based on the infant’s needs. Many infants with medical complexity are technology-dependent at the time of discharge and may require home oxygen, ventilators, monitors, or tube feeding. Prematurity, critical illness, and prolonged NICU hospitalization that lead to

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ABBREVIATIONS

AAP American Academy of Pediatrics
ADHD attention-deficit/hyperactivity disorder
AKI acute kidney injury
BPD bronchopulmonary dysplasia
CDC Centers for Disease Control and Prevention
CHD congenital heart disease
ECMO extracorporeal membrane oxygenation
GER gastroesophageal reflux
GT gastrostomy tube
HIE hypoxic ischemic encephalopathy
IVH intraventricular hemorrhage
MBDP metabolic bone disease of prematurity
NEC necrotizing enterocolitis
NICHD NRN Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network
PCP primary care physician
PDA patent ductus arteriosus
PMA postmenstrual age
PN parenteral nutrition
ROP retinopathy of prematurity
RSV respiratory syncytial virus
VLBW very low-birthweight
medical complexity also increase the risk of neurodevelopmental delay or impairment. As such, these infants will not only require routine developmental surveillance and screening by the primary care physician but also should be followed longitudinally by a neurodevelopmental specialist, either a developmental-behavioral pediatrician or a neonatologist with experience in neurodevelopmental assessment.

INTRODUCTION

Survival of infants born preterm or critically ill has increased over time due to improvements in evidence-based care of mothers and infants and advanced technologies available in the NICU. These infants often have complex medical issues that remain active at the time of NICU discharge and require ongoing coordinated follow-up. Many infants may be technology-dependent, requiring respiratory support, vital sign monitoring, or tube feeding. They also require close monitoring for the development of additional medical problems that may arise as a result of exposures during their NICU hospitalization, such as hypertension after acute kidney injury (AKI) in the neonatal period. Discharge planning for infants with medical complexity requires a multidisciplinary team effort; neonatologists, subspecialists, the general pediatrician or family physician who will provide primary care for the infant, social workers, respiratory therapists, physical and occupational therapists, speech-language pathologists and feeding therapists, nutritionists, and, most importantly, the baby’s family must work together for this process to be successful and to ensure a safe discharge from the NICU (Fig).

Preterm and very low-birthweight (VLBW) infants compose a significant proportion of medically complex infants discharged from the NICU. Since 2014, the rate of preterm birth has been increasing, and in 2018, deliveries before 37 weeks’ gestation accounted for 10% of all births in the United States. (1) Despite the increased preterm birth rate and survival of preterm infants, there has not been an increase in major prematurity-associated complications over time. According to the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) data from nearly 35,000 infants born at less than 29 weeks’ gestation, rates of necrotizing enterocolitis (NEC), late-onset sepsis, severe intracranial hemorrhage, and retinopathy of prematurity (ROP) decreased by 2012. (2) Rates of bronchopulmonary dysplasia (BPD), however, have increased over time. Similar outcomes have been noted in the International Network for Evaluation of Outcomes cohort. (3)

Other medically complex infants who benefit from comprehensive, coordinated follow-up include those with congenital anomalies, genetic syndromes, complex congenital heart disease (CHD), or inborn errors of
metabolism; infants with a history of meningitis or neonatal encephalopathy, including hypoxic ischemic encephalopathy (HIE); and infants treated with extracorporeal membrane oxygenation (ECMO) (Table).

The process of discharge and care transition planning ideally begins early during the NICU course. The ultimate goal is to optimize health, neurodevelopment, and function while minimizing exacerbations of chronic medical conditions after NICU discharge. (4) It is imperative that the NICU care team partners with the infant’s family to determine when, where, and how this goal is met. Timing of discharge may be difficult to predict, and criteria for discharge readiness must be tailored to each patient. There must also be contingency planning. For example, one criterion for discharge of a preterm infant typically includes the ability to take all enteral feeds by mouth while also demonstrating adequate growth. (5) Although some infants achieve this before reaching term equivalent (37 weeks’ postmenstrual age [PMA]), others may require partial tube feeding beyond their due date. For the latter group, the team must decide between continued NICU hospitalization, discharge home with partial tube feeding if the family is amenable and able, or transfer to acute or subacute rehabilitation, if available, for intensive feeding therapy. A significant time investment is required when implementing technology-dependent care in the home, both to obtain needed supplies and also to allow for parental education and acquisition of required skills. Placement in pediatric rehabilitation or long-term care facilities may take time if there is limited bed availability and may not even be an option in some communities across the United States. Because of this, the team must periodically assess and revise discharge plans and criteria. For technology-dependent infants, assessing stability for discharge home can be difficult because there is not a standard definition of “stable.” The American Academy of Pediatrics (AAP) Council on Children with Disabilities recommends that “the child’s care needs should be stable and predictable before discharge, with ‘no major changes made to the medical regimen for at least several days.” (4)

Infants with medical complexity or who require prolonged NICU hospitalizations are at greater risk for developmental

### Table. Common Neonatal and Infant Diagnoses Requiring Coordinated Follow-up After NICU Discharge

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<th>CATEGORY</th>
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<td>General</td>
<td>Prematurity</td>
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<td>Genetic syndromes</td>
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<td>Neonatal abstinence syndrome</td>
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<td>Pulmonary</td>
<td>Bronchopulmonary dysplasia</td>
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<td>Congenital lung anomalies (congenital diaphragmatic hernia, congenital pulmonary airway malformation)</td>
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<td>Meconium aspiration syndrome</td>
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<td>Cardiovascular</td>
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<td>Infectious disease</td>
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<td>Recurrent infections</td>
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<td>Perinatal HIV exposure</td>
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<td>Perinatal hepatitis B/C exposure</td>
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<td>Gastrointestinal</td>
<td>Congenital anomalies (gastroschisis, atresias, duplications)</td>
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<td>Short gut syndrome</td>
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<td>Renal</td>
<td>Congenital renal anomalies (multicystic dysplastic kidney)</td>
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<td>Acute kidney injury</td>
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<td>Genitourinary</td>
<td>Congenital GU anomalies (posterior urethral valves, hypospadias)</td>
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<td>Vesicoureteral reflux</td>
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<td>Metabolic</td>
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Any congenital or acquired condition or complication that may impact long-term health, function, and/or neurodevelopment adds to medical complexity.

CNS=central nervous system, ECMO=extracorporeal membrane oxygenation, ENT=ear, nose, throat, GU=genitourinary, HIV=human immunodeficiency virus, PDA=patent ductus arteriosus.
delays and neurodevelopmental impairment, particularly if they experienced perinatal or postnatal brain injury: ischemic injury; intracranial, parenchymal, and/or cerebellar hemorrhage; hydrocephalus; stroke; or brain atrophy. (6) In addition to the routine surveillance and screening that are performed during health supervision visits with the primary care physician (PCP), they require additional close follow-up with a neurodevelopmental specialist, either a developmental-behavioral pediatrician or a neonatologist with experience in neurodevelopmental assessment. Many of these infants also benefit from services provided by early intervention programs, and they are often referred to these programs before discharge from the NICU. (7)

For this review, we have taken a systems-based approach to coordination of care on discharge from the NICU. Although most infants do not require follow-up of every organ system, those who have had particularly complicated courses will require care from multiple subspecialists. In these cases, the PCP’s role as coordinator and communicator is particularly highlighted.

General Considerations
The AAP has championed the medical home model for care of all infants, children, and adolescents. (8) Care in this setting should be “accessible, continuous, comprehensive, family centered,” and coordinated across care settings and disciplines. For medically complex infants, it is essential that a medical home is established as part of the discharge process. In some regions of the country, infants with medical complexity may receive their primary care in multidisciplinary NICU follow-up clinics or specialized clinics for infants and children with medical complexity where they are able to see both their PCP and subspecialty pediatricians in one location. Some clinics have additional resources available, such as social work or case management. Unfortunately, these clinics are not widely available, and many medically complex infants are managed by their PCPs in a general practice environment. The PCP must serve as the lead communicator and coordinator and provide family-centered care. He or she must coordinate appropriate follow-up of each medical issue, make referrals as new issues arise, supervise medication adherence, and work with insurers and durable medical equipment supply companies to ensure that families have needed supplies. Periodic assessment of the family’s support system and available resources is important because issues relating to food insecurity, housing, environmental exposures, utilities, parental employment, or access to public assistance can further impact child health, well-being, and family functioning. In one cohort of preterm infants born at less than 35 weeks’ gestation, nearly half did not receive care in a medical home model. (9) These families were more likely to be of a lower socioeconomic status and to have a lower educational level. In addition, the high-risk infants who did not receive care in a medical home were more likely to have language delay diagnosed on neurodevelopmental screening. In contrast, medically complex infants who received their care in a comprehensive, multidisciplinary medical home had decreased emergency department visits and hospitalizations over time. (10) To promote health and optimize outcomes, continuity and coordination of care are critical.

Over the course of the infant’s NICU stay, it is important to serially assess the parents’ well-being, family strengths and resiliency factors, available support, and resource needs. Family circumstances often change during long hospitalizations. NICU mothers and fathers are more vulnerable to depression and anxiety and often experience symptoms of posttraumatic stress disorder. (11) The incidence of postpartum depression is higher for mothers of infants admitted to the NICU compared with mothers of healthy newborns. (12) Although postpartum depression screening is recommended at the 1-, 2-, 4-, and 6-month health supervision visits, mothers of medically complex infants who require prolonged hospitalizations miss out on these screening opportunities. (13) NICU mothers and fathers should be screened for depression, anxiety, and posttraumatic stress symptoms during and after hospitalization because symptoms may persist even after the infant comes home, but evidence regarding timing and frequency of screening is lacking.

Comprehensive discharge planning is particularly important for technology-dependent infants. The family must identify at least 2 caregivers to receive teaching and training on all aspects of care. (5) Caregiver education should begin as early as is feasible and continue until competency and comfort are demonstrated. The family should be counseled on smoking cessation and minimization of second-hand smoke exposure. Safety of the home environment, notably stable access to electricity, water, and telephone, must be evaluated. The NICU team also needs to determine what other family and community resources may be available, coordinate home nursing services, and work with durable medical equipment companies to obtain needed supplies and establish contingencies and troubleshooting protocols should equipment fail. (4) After discharge, as the needs of medically complex infants evolve, repeated psychosocial assessments must be performed in the family-centered medical home to ensure that the health and well-being of the infant and family are being supported. (14)
Some medically complex infants are diagnosed as having life-limiting disorders prenatally or during their NICU hospitalization. Examples include genetic syndromes and chromosomal abnormalities such as trisomy 18, severe inborn errors of metabolism, central nervous system malformations, and severe HIE. (15) Home palliative care is often considered for these infants. The goals of discharge planning in these cases transition from optimization of health and neurodevelopment to maximizing quality family time and managing uncomfortable or distressing symptoms. (5) In addition to establishing a medical home, coordinating home nursing care, and arranging for needed equipment, because these infants are often technology-dependent, the discharging team must also clarify goals of care, put in place “do not resuscitate” or “do not intubate” advanced directives per the wishes of the family, and begin to provide bereavement support and resources.

Medically complex infants should also undergo routine newborn screenings and receive required immunizations before discharge. Hearing should be assessed by auditory brainstem response because otoacoustic emissions testing may miss an auditory neuropathy. If this cannot be performed in the NICU, an outpatient referral to audiology should be made. High-risk infants, including those who required ECMO, have an increased risk of late-onset sensorineural hearing loss even if they passed their first screen and require repeated screening between 24 and 30 months. (16) Infant car seat tolerance testing should be performed for infants born at less than 37 weeks gestation and those at risk for apnea, bradycardia, or oxygen desaturation using their own car seat that is appropriate for their weight. (17) Any pending newborn metabolic screens should be followed up to ensure that additional laboratory tests or evaluations are not needed.

**PULMONARY**

**Bronchopulmonary Dysplasia**

BPD is one of the most common morbidities in preterm infants, and its incidence has been increasing over time. (2)(3) BPD is diagnosed when an infant requires more than 21% oxygen for at least 28 days. (18) Severity is then assessed at 36 weeks’ PMA; BPD is classified as mild, moderate, or severe if the infant is breathing room air, requires less than 30% oxygen, or requires at least 30% oxygen or positive pressure ventilation, respectively. By definition, patients with moderate or severe BPD still require respiratory support when the focus is shifting to discharge planning. In addition to oxygen and ventilator support, infants with BPD may also be treated with diuretics, inhaled steroids, bronchodilators, and, less frequently, periodic courses of systemic corticosteroids. (19) Infants with moderate to severe BPD are monitored serially with echocardiography for possible development of pulmonary hypertension and pulmonary vein stenosis, sequelae that increase the risk of complications and death.

On discharge, infants with BPD require coordinated care from the PCP, a pediatric pulmonologist, a pediatric cardiologist, and/or a neonatologist. BPD clinics allow for comprehensive care from all of the subspecialties in one location, although these clinics are not accessible to all infants. These infants must be followed longitudinally because they are at risk for impaired pulmonary function, reactive airway disease, and hospitalization due to severe respiratory illnesses. Patients with BPD with atrial septal defects, pulmonary hypertension, or pulmonary vein stenosis must be followed very closely because they are at particularly high risk for poor long-term outcomes, including developmental delay and impairment. Infants with BPD require close neurodevelopmental follow-up.

Many patients with BPD are treated with long-term diuretic therapy, although this practice is not evidence-based and is not associated with improved long-term outcomes. (19)(20) If treatment continues beyond discharge, monitoring for adverse effects must also continue. Electrolyte derangements are common, and many infants receive electrolyte supplementation. There is no evidence to guide frequency of laboratory monitoring, but periodic basic metabolic panels should be followed, particularly if medication dosage has been adjusted. Evidence regarding duration of treatment and process of weaning is also lacking, but the decision to reduce or discontinue therapy should be made with input from all care team members.

In the NICHD NRN cohort, 58% of extremely preterm infants (<27 weeks’ gestational age) with moderate or severe BPD were discharged home on oxygen. (21) Their BPD was more severe, and they required prolonged ventilation compared with BPD infants who were discharged on room air. Infants discharged on home oxygen had higher health-care costs and utilization and more frequent hospitalizations, with a trend toward improved growth compared with infants with similar severity of illness but who were discharged home without oxygen. (21) There was no difference in survival or neurodevelopmental outcomes. There is wide variation in whether an infant with BPD is discharged on home oxygen. Among NICUs participating in the California Perinatal Quality Care Collaborative, 9% to 95% of infants with BPD were discharged on oxygen. (22) The patients who had the highest odds of home oxygen use were those at earlier PMA who...
presumably met all other criteria for discharge and were not kept in the NICU for further oxygen weaning attempts and those at later PMA who may have been sicker or failed attempts at weaning oxygen.

There is also wide variation in the criteria for and process of weaning oxygen at home. (20) Evidence-based protocols are lacking, and care is often dictated by local practice. Although some clinicians will wean these patients clinically, others will perform polysomnography before weaning or discontinuing oxygen. In addition, many parents discontinue oxygen at home without guidance from the medical team.

A subset of infants with severe BPD will require tracheostomy for the provision of long-term ventilator support or because of airway complications. Discharge planning for these patients becomes even more complex. A determination has to be made among the NICU team and the patient’s family whether the infant is a candidate for long-term invasive ventilation at home or requires out-of-home care in an acute rehabilitation or skilled nursing facility, if available. (4) The Pediatric Assembly of the American Thoracic Society has established recommendations and guidelines for children requiring long-term ventilator support. (23) Critical to the success and safety of home ventilation are a medical home that can provide comprehensive, coordinated, family-centered care; a family that is willing and able to provide care with a minimum of 2 trained caregivers, 1 of whom is awake and at home at all times; and a close relationship with the durable medical equipment company to ensure that the family has adequate supplies with backup at home and a plan for regular maintenance and troubleshooting, if needed.

The process of weaning, discontinuing ventilator support, and, ultimately, decannulation may take several years. The PCP, pediatric pulmonologist, otolaryngologist, and/or neonatologist must work in concert. When tracheostomy and ventilator-dependent infants discharged from the NICU are cared for in a medical home, there is higher likelihood of being weaned from the ventilator, reduced hospital admission rates, and reduced mortality. (24)

Other Pulmonary Diagnoses
Just as with BPD, infants with other pulmonary disorders should be treated in a multidisciplinary, coordinated fashion, with close neurodevelopmental follow-up. Other disorders include meconium aspiration coincident with persistent pulmonary hypertension of the newborn and/or HIE, congenital diaphragmatic hernia, and other congenital lung malformations. A subset of infants with congenital diaphragmatic hernia, meconium aspiration syndrome, or persistent pulmonary hypertension of the newborn are treated with ECMO; they require coordinated follow-up after discharge because they are at higher risk for poor oral feeding, neurologic complications, developmental delay, and long-term neurodevelopmental impairment. (25)

CARDIOVASCULAR

Congenital Heart Disease
Infants with CHD, including those with structural heart disease, cardiomyopathy, arrhythmias and conduction abnormalities, are a heterogeneous group with complex needs that require a coordinated and comprehensive effort in discharge planning and postdischarge care. Some infants with CHD require home oxygen and oxygen saturation monitoring. Many are discharged on medications, such as antiarrhythmics or diuretics for heart failure, and require close monitoring of progression of symptoms and adverse medication effects. Some infants with CHD have higher baseline metabolic demands that they are unable to meet with oral feeding alone; they often require home tube feedings and calorie-dense formulas to optimize intake and promote adequate growth in preparation for future surgical repair. The most medically complex of infants with critical CHD who require surgical intervention during the first year of life may require transitional out-of-home care if they are not stable for the home environment. This determination must be a joint effort of the NICU team, pediatric cardiology, cardiothoracic surgery, and the infant’s family and should be reassessed during the NICU hospitalization and after discharge as the infant’s clinical status evolves.

In addition to subspecialty follow-up, infants with critical CHD need close surveillance and monitoring of their neurodevelopment. Infants with complex lesions and those who require early surgical repair or palliation with cardiopulmonary bypass are particularly at risk for developmental delay. (26)

Other Cardiovascular Diagnoses
It is common for a preterm infant to undergo echocardiographic evaluation in the NICU for a murmur noted on examination or to confirm the presence of a patent ductus arteriosus (PDA). If a PDA is still patent at the time of discharge, continued pediatric cardiology follow-up is required to determine the need for surgical PDA closure if spontaneous closure does not occur. Transcatheter PDA closure is being performed with increasing frequency in...
smaller infants born at earlier gestational ages. (27) After discharge, these infants will also require close outpatient follow-up with serial echocardiography and endocarditis prophylaxis for 6 months after the procedure. (28) Infants with atrial septal defects or ventricular septal defects often require pediatric cardiology follow-up based on the defect size and location and the direction of blood flow. Infants with large ventricular septal defects will require close monitoring for the development of heart failure signs and symptoms.

Neonatal hypertension is diagnosed in 0.2% to 3% of infants admitted to the NICU. (29) Its etiology is often multifactorial, and causes include prematurity, BPD, aortic coarctation, renal parenchymal disease, history of umbilical arterial catheter placement, or other renovascular disease. After discharge, particularly for infants requiring treatment for hypertension, blood pressure should be measured at health supervision visits, and pediatric cardiology follow-up should be considered.

FEEDING AND NUTRITION

Human Milk and Formula Fortification

Mothers’ own breast milk is the optimal nutrition for all infants, and the benefits of human milk in preterm infants have been well-characterized. Human milk requires fortification in the NICU because it does not meet the caloric, macronutrient and mineral needs of the preterm infant. The evidence on whether and how to fortify human milk on discharge is mixed. Some infants fed fortified human milk after discharge did not have improved growth compared with infants fed unfortified human milk. (30) Other studies have shown that infants fed fortified human milk after discharge do have improved growth and higher mineral intake, and the improvement was sustained at 1-year follow-up. (31) (32) Fortification was also associated with improved lung function and should be considered in the BPD population. (33) Fortification has not been shown to impact neurodevelopment. (34) In light of this, type and duration of fortification is often dictated by local practice.

In 2006, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition recommended that infants with appropriate weight for PMA be discharged on unfortified human milk or standard formula, and infants with suboptimal growth (<10th percentile for PMA) receive fortification or supplementation with transitional formula, providing 22 to 26 kcal/oz, through 40 to 52 weeks’ PMA. (35) According to the European Milk Bank Association there may be benefits to fortification for all preterm infants without having negative effects on human milk feeding. (36) The decision to fortify human milk on discharge should be individualized to each patient. Infants feeding more than 170 to 180 mL/kg per day may not require fortification. For preterm infants born weighing less than 1,250 g or any infant with intrauterine or postnatal growth restriction, fortification should be considered and continued for at least 12 weeks past term age (3 months’ corrected age). (37) Fortification should also be tailored to meet mothers’ breastfeeding goals. For mothers who want to exclusively nurse at the breast, on-demand breastfeeding may be supplemented with an additional 1 or 2 formula feeds per day. For mothers who would rather express their milk and feed by bottle, formula may be added directly to expressed human milk. Once the infant has achieved steady growth, between the 25th and 50th percentile for corrected age, decreasing or discontinuing fortification may be considered. As infants grow and mature, their metabolic and mineral requirements decrease. Periodic monitoring of calcium and phosphorus should be performed to avoid excess intake.

Oral feeding requires significant energy expenditure and coordination, and infants may exhibit poor feeding efficiency or endurance due to immaturity or illness. To support feeding efficacy, parents and caregivers are typically taught infant-driven or cue-based feeding techniques. Infants should not be allowed to feed for more than 20 to 25 minutes without a rest period. They should be observed for signs of fatigue and loss of coordination because these increase the risk of poor growth, choking, and cyanotic and apneic events.

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is defined by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition in the 2018 clinical guidelines update as passage of gastric contents into the esophagus with or without regurgitation or vomiting. (38) It is a common occurrence in preterm infants due to transient lower esophageal sphincter relaxation, presence of a feeding tube that prevents complete sphincter closure, supine positioning during or after feeding, and other factors. (39) Crying, fussiness, arching of the back, and apneic events are commonly reported behaviors thought to result from GER, but studies have failed to demonstrate that they are temporally related to reflux events. Despite this, many infants are diagnosed clinically as having GER and are treated with acid suppression or prokinetic agents. (38) (39) Not only is there no evidence to support the use of pharmacotherapy in preterm infants, there is also significant risk of adverse drug effects such as infection and NEC.
The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends no diagnostic testing or treatment for infants with GER. (38) If GER leads to “troublesome” signs and symptoms, such as weight loss; forceful, bilious, or bloody emesis; or diarrhea, that affect daily functioning or lead to complications (GER disease), nonpharmacologic management is recommended first, including avoidance of overfeeding with smaller-volume frequent feeds and adding thickening agents to formula. Continued breastfeeding should be encouraged. Although right and left side-lying positioning has been associated with improved gastric emptying and fewer episodes of lower esophageal sphincter relaxation, respectively, this should be discouraged in promotion of safe-sleep supine positioning to minimize risk of sudden infant death syndrome. (39)

Tube Feeding
Although some preterm infants achieve full oral feeding before 37 weeks’ PMA, others remain in the NICU beyond their due date for partial tube feeding. This commonly delays discharge from the NICU. In addition, medically complex infants with neurologic conditions or congenital anomalies may be unable to fully feed by mouth. The NICU team must determine whether these infants are stable for discharge home or require transitional care, and whether they can be discharged home on a combination of oral and nasogastric tube feeding or require gastrostomy tube (GT) placement. Both forms of tube feeding carry risks of complications in the community setting. In one level IV NICU’s experience, sicker and more medically complex infants were more likely to be discharged with a GT and had more emergency department visits for GT malfunction or complications. (40) Of infants who were discharged with nasogastric tube feeds, more than 60% achieved full oral feeding within 2 months of discharge, and only 21% subsequently required GT placement. The NICU team, working collaboratively with speech-language pathologists and feeding therapists, otorhinolaryngologists, pediatric neurology if the infant has significant neurologic dysfunction, the infant’s family, and the PCP, must consider the likelihood that the infant will achieve full oral feeding after 2 to 3 months of supplemental nasogastric tube feeds. If this is unlikely, a GT should be placed.

Intestinal Failure and Parenteral Nutrition
Gastrointestinal complications commonly add to the medical complexity of infants in the NICU. These complications include NEC, congenital anomalies such as gastroschisis, intestinal atresias, malrotation with midgut volvulus, and others. The incidence of NEC in preterm and VLBW infants during the past 2 to 3 decades is estimated to be approximately 13%, but the incidence has been decreasing with time and varies by institution. (2)(41) Infants with gastrointestinal issues often have prolonged, complicated hospitalizations that place them at risk for ongoing surgical and feeding issues and neurodevelopmental delay or impairment. (41) Those with stage III NEC requiring peritoneal drainage or bowel resection are at the highest risk for poor long-term outcomes.

A subset of these infants will be diagnosed with intestinal failure and will require prolonged parenteral nutrition (PN). In one cohort, 35% of infants with surgical NEC required more than 90 days of PN. (42) Bowel resection over peritoneal drain placement, resection of the ileocecal valve, and amount and proportion of bowel resection were predictive of intestinal failure. Discharge planning for these infants requires extensive coordination and collaboration. The care team, in conjunction with practitioners who specialize in intestinal failure, including pediatric gastroenterologists, nutritionists, PN pharmacists, and social workers, must identify which infants are candidates for home PN and which will require inpatient intestinal rehabilitation. (43) If PN-dependent infants are to be cared for at home, the family must undergo extensive teaching and training, nursing home care must be established, and close outpatient follow-up in a medical home model must be coordinated. Nutrition, including enteral and oral feeding, should be optimized while attempting to limit PN-associated toxicities such as worsening cholestasis. Growth must be followed closely, and PN and enteral feeds should be increased as the infant grows to ensure adequate caloric intake. Periodic laboratory monitoring of serum electrolytes, liver function, trace elements, fat-soluble vitamins, and urinary sodium should also be performed, and supplementation should be prescribed as needed. Consideration should also be given to close neurodevelopmental follow-up and referral to early intervention services to closely monitor for delays and intervene with physical, occupational, and speech therapy if indicated.

Metabolic Bone Disease of Prematurity
Preterm and VLBW infants are at risk for metabolic bone disease of prematurity (MBDP) because they miss out on much of the calcium accrual that occurs during the third trimester of gestation. Up to 20% of extremely low-birthweight infants born weighing less than 1,000 g may have
radiographically apparent MBDP, but this is certainly an underestimation of the problem. (44) Incidence has decreased as fortification of breast milk has become the standard of care. In a survey of US neonatologists, treatment of MBDP included human milk fortification followed by vitamin D and direct calcium and phosphorus supplementation. (45) Discontinuation of treatment was dictated by alkaline phosphatase levels. Three-quarters of the responding neonatologists reported that MBDP should be managed by the PCP after discharge. The AAP Committee on Nutrition recommends that all VLBW infants receive at least 400 IU of vitamin D daily. (44) Alkaline phosphatase levels should be measured 2 to 4 weeks after discharge in VLBW infants discharged on an unfortified exclusive human milk diet. For alkaline phosphatase levels greater than 800 IU/L (13.4 μkat/L), supplementation with transitional formula should be considered. If alkaline phosphatase levels exceed 1,000 IU/L (16.7 μkat/L), calcium and phosphorus supplementation should be prescribed.

**RENTAL**

**Acute Kidney Injury**

AKI is increasingly recognized as a common occurrence in the NICU, although it continues to be underdiagnosed. (46) The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study reported an incidence of 30% in critically ill infants, and it was inversely proportional to gestational age. (47) AKI is associated with poor long-term health outcomes, including chronic kidney disease and hypertension. (48)

The AAP recommends that blood pressure should be measured annually at health supervision visits starting at age 3 years. (49) For infants and children at higher risk for hypertension, blood pressure should be measured before 3 years of age, although exact timing and frequency remain unclear. Infants with medical complexity and multiple risk factors for hypertension, such as prematurity, BPD, episodes of AKI, history of umbilical arterial catheter placement, and history of urinary tract infection, perhaps should have their blood pressures monitored earlier and more frequently with an appropriately sized blood pressure cuff.

**Other Renal Diagnoses**

In addition to AKI, infants with congenital renal or genito-urinary anomalies should have close outpatient follow-up with pediatric nephrology and urology, if applicable. They may require urinary tract infection prophylaxis and should also undergo routine blood pressure screening at all health supervision visits.

**HEMATOLOGIC**

Anemia of prematurity is one of the most common hematologic diagnoses encountered in the NICU. Preterm infants are at risk for anemia because they miss out on much of the iron accrual that occurs during the third trimester of gestation. (37) In addition, the red blood cell life span in preterm infants is nearly half that of term infants’ red blood cells. Preterm infants have a blunted response to erythropoietin, and they experience iatrogenic blood loss due to frequent phlebotomy. It is recommended that preterm infants receive at least 2 mg/kg per day of iron until 12 months of age. Although a diet of standard infant formula typically provides the recommended daily intake of iron, breastfed infants or those with poor growth will likely require additional supplementation. Evidence regarding the need for or frequency of hematocrit monitoring is lacking, but the PCP may consider following levels more closely in infants whose predischarge hematocrit level was low, who required multiple packed red blood cell transfusions while in the NICU, or who are slow to gain weight.

**INFECTIOUS DISEASE**

Timely vaccination is critical in high-risk and medically complex infants, who may be at even higher risk for vaccine-preventable illnesses. In one level IV NICU, only 56% of patients were fully vaccinated based on chronological age at the time of discharge or transfer. (50) According to the Centers for Disease Control and Prevention (CDC) Committee on Immunization Practices, preterm infants should be vaccinated according to chronological age regardless of gestational age at birth. (51) Hepatitis B vaccine should be given at 30 days of age, once the infant weighs more than 2 kg, or at discharge, whichever is sooner. If a preterm infant received the hepatitis B vaccine at birth due to positive or unknown maternal status, he or she will require 3 additional doses. Two-month vaccines can be given as early as 6 weeks of age, but the appropriate interval (4 weeks) between the first and second hepatitis B vaccine must be maintained.

High-risk infants are also candidates for respiratory syncytial virus (RSV) prophylaxis. (52) Exact criteria for candidacy may change from year to year, but generally very preterm infants less than 29 weeks’ gestation at birth, preterm infants with BPD, and infants with some forms of CHD, other pulmonary abnormalities, or...
neuromuscular disease should receive prophylaxis during their first RSV season. Infants younger than 24 months with BPD that required medical treatment in the previous 6 months or those with hemodynamically significant CHD should also receive prophylaxis. Depending on the region of the country, RSV season generally begins October to January and ends March to May. Local health department data may help guide timing of administration. Infants should receive up to 5 doses of palivizumab, a monoclonal antibody that binds to fusion protein on the surface of the virus to prevent entry into respiratory epithelial cells, via intramuscular injection every 30 days. Discharging NICU teams and PCPs must be cognizant that infants discharged during late spring and summer will still be candidates for prophylaxis for the upcoming RSV season.

**OPHTHALMOLOGIC**

**Retinopathy of Prematurity**

ROP is due to abnormal retinal vessel growth that in its severest forms leads to blindness. The incidence of ROP has been decreasing over time due to more judicious use of supplemental oxygen in the early neonatal period, and the incidence of ROP increases as gestational age at birth decreases. (2)(3) VLBW and preterm infants born at less than 31 weeks’ gestation are typically screened for ROP starting at 31 to 32 weeks’ PMA or 4 weeks’ chronologic age, whichever is later. Serial examinations based on findings are performed every 1 to 3 weeks until the retina is fully vascularized. Many high-risk infants, particularly those who required laser treatment or intravitreal antivascular endothelial growth factor injections, will require close follow-up with pediatric ophthalmology after discharge. In addition, preterm infants are at risk for myopia, amblyopia, and strabismus later in infancy and childhood and should be followed longitudinally.

Other Ophthalmologic Diagnoses

Infants with congenital eye disorders (such as glaucoma or cataracts) or systemic illness with eye involvement (such as cytomegalovirus infection with chorioretinitis) should have close outpatient follow-up with a pediatric ophthalmologist.

**NEUROLOGIC**

**Intracranial Hemorrhage**

Preterm infants are at risk for intraventricular hemorrhage (IVH), and the incidence of IVH is inversely proportional to gestational age at birth. IVH results from bleeding in the germinal matrix, a primitive vascular structure located in the caudothalamic groove that is larger in very preterm infants but involutes as gestation progresses, and hemorrhage may extend into the ventricular system. (53) IVH can also occur in infants born closer to term; these hemorrhages are frequently associated with underlying intracranial bleeding or infarction. Over time, rates of severe IVH in preterm infants have been decreasing. (2)(4) Although most IVHs occur during the first week of life, they have long-term neurodevelopmental implications. In the severest forms of IVH (grade 4), obstruction of venous flow in the periventricular white matter leads to infarction and varying degrees of intraparenchymal bleeding. (53) Periventricular leukomalacia describes the white matter damage and volume loss that occurs as a result of cerebral hemorrhage and hypoperfusion; it may be cystic in the setting of parenchymal bleeding or more diffuse. (54) Grade 4 IVH and periventricular leukomalacia are associated with poorer neurodevelopmental outcomes.

Subdural and subarachnoid hemorrhages also occur during the neonatal period in term and preterm infants. Incidence is unclear as small hemorrhages are often asymptomatic and difficult to identify on ultrasonography. (53) Large, catastrophic hemorrhages result in brain compression and hemodynamic instability and are associated with poor outcomes.

Neonatal strokes are more common in term infants, and seizures are often the presenting sign. (53) Strokes resulting from arterial infarction are more frequent on the left side and typically involve the middle cerebral artery, although infarctions at other and multiple sites can also occur. Cerebral arterial infarction can also occur in utero, and the fetus may develop a porencephalic cyst in the affected region that is noted on prenatal imaging. Neonatal stroke may also arise from sinusvenous thrombosis. Sinusvenous thrombosis is associated with HIE, sepsis, and underlying clotting disorders, and there is much debate on whether to treat these patients with anticoagulation therapy. Infants with neonatal strokes are at high risk for neurodevelopmental impairment, particularly cerebral palsy, and must be followed closely by pediatric neurology and neurodevelopmental specialists.

Hydrocephalus and Diverting Shunts

Hydrocephalus may be congenital, as seen in infants with congenital aqueductal stenosis or Chiari II malformation, or may occur as a complication of intracranial hemorrhage or infection. Infants with severe or rapidly progressive hydrocephalus require cerebrospinal fluid diversion. Most
commonly, a ventriculoperitoneal shunt is placed. (55) However, preterm infants with posthemorrhagic hydrocephalus as a complication of IVH may be too small to undergo shunt placement and may require a temporary ventricular access device or reservoir. Other medically complex infants with gastrointestinal complications may not be candidates for ventriculoperitoneal shunt placement and instead may require ventriculoatrial, ventriculooctrial, or ventriculopersidgaleal shunts. Not only are infants with shunts at risk for poorer neurodevelopmental outcomes, they must also be monitored closely for shunt complications, including malfunction and infection, and frequently require shunt revisions. (55)(56)

Apnea of Prematurity

Apnea of prematurity is a common diagnosis in the NICU, and its incidence increases with decreasing gestational age. (57) Preterm infants display central nervous system respiratory center immaturity when they have pauses during spontaneous respiration greater than 10 to 20 seconds, often with an associated decrease in heart rate and/or oxygen saturation. There may also be a component of airway obstruction that contributes to apnea of prematurity. Apnea of prematurity typically resolves by 37 weeks’ PMA, although it can persist to 44 weeks’ PMA in infants born at earlier gestational ages or in infants with BPD.

Apnea of prematurity is treated with caffeine. Because of caffeine’s long half-life, infants have traditionally been monitored for recurrence of apnea for 5 to 7 days once the medication is discontinued. This practice has evolved into a discharge criterion in many NICUs; an infant is ready for discharge home when they have gone 5 to 7 days without an apneic, bradycardic, and/or desaturation event. (57) With every event, discharge is delayed another 5 to 7 days. However, even in infants who pass the observation period without having any events, apnea, bradycardia, and desaturation events have been noted to continue after discharge. (58)

If an infant has otherwise met the discharge criteria but continues to have apneic events, he or she may be discharged on home oxygen saturation monitoring with or without continued caffeine treatment. In one large level III NICU, 54% of preterm infants were discharged on home monitoring and 17% were discharged on caffeine. (59) Standardizing definitions of clinically significant events and establishing unit protocols for monitoring led to a reduction in home monitoring and caffeine use on discharge. For infants discharged on home monitoring, there are no evidence-based guidelines regarding duration or criteria for discontinuation. In addition, there is a lack of evidence demonstrating improved outcomes with home monitoring. In light of this, the PCP, in conjunction with a neonatologist or pediatric pulmonologist, must decide when and how monitoring is discontinued based on experience and local practice.

Other Neurologic Diagnoses

Seizures are a common presenting sign of underlying central nervous system or systemic disorders. These disorders include structural malformations, infection, HIE, metabolic derangements, genetic syndromes, or inborn errors of metabolism. Many infants who experience seizures during their NICU stay continue receiving antiepileptic medications after discharge. They require close follow-up with pediatric neurology to follow drug levels and monitor for adverse drug effects.

In addition, infants with central nervous system malformations, such as myelomeningocele, or neuromuscular disorders require coordinated care, close follow-up with pediatric neurology and other pediatric subspecialties, and close monitoring of their neurodevelopment to optimize long-term outcomes.

NEURODEVELOPMENT

Virtually all the medically complex infants described in the previous sections are at risk for neurodevelopmental impairment and require close, coordinated follow-up with serial neurodevelopmental assessments and the provision of physical, occupational, and speech therapy, if indicated, to optimize long-term health outcomes and function. (6) Neurodevelopmental impairment includes developmental delays in all domains: motor, coordination, or tone abnormalities; cerebral palsy; vision and hearing deficits; cognitive impairment; problems with sensory processing, communication, behavior, and more. Local practice dictates which infants with medical complexity meet the criteria for assessment in specialized NICU follow-up clinics, if available. Infants below specified birthweights and gestational ages typically qualify, in addition to those with HIE, complex CHD, or those treated with ECMO.

Assessment of neurodevelopment begins before NICU discharge. Brain magnetic resonance imaging is being used with increased frequency in preterm infants who have reached term-corrected age. Magnetic resonance imaging allows for detection of subtle findings that may not be clearly seen on cranial ultrasonography, including diffuse periventricular leukomalacia and signs of cerebellar
hemorrhage, and helps to identify infants at higher risk for cerebral palsy and cognitive impairment. (6)(60) The General Movements Assessment is a clinical assessment that also can be performed before discharge and is then repeated at 1 and 3 months’ corrected age. (6)(60)(61) The General Movements Assessment is highly sensitive and specific for predicting spastic cerebral palsy. Together, this information assists NICU teams and PCPs when discussing long-term prognosis with parents of medically complex infants.

As part of the discharge planning process, medically complex infants should be referred for early intervention services. (7) Criteria vary by state; some infants may meet the criteria for developmental screening, and others will automatically be eligible for physical, occupational, or speech therapy services. Additional information is available at the CDC website (www.cdc.gov/ncbddd/actearly/parents/states.html). In addition, the AAP recommends that medically complex infants with suspicion for a motor disorder, even in the absence of a diagnosis, should be followed in a medical home environment with close developmental surveillance. (62)

The AAP recommends that routine developmental surveillance should be performed by the PCP at all health supervision visits for all infants, and formal assessment tools should be used at 9, 18, and 30 months. (63) Developmental assessments should take degree of prematurity into account, and preterm infants should be assessed according to corrected age (age from term equivalent), not chronological age, until 2 years of age. Also, screening for autism should be performed at 18 and 24 months. High-risk infants with medical complexity will require screening and assessment above and beyond what is routine.

Timing of neurodevelopmental follow-up and assessment varies and is often dictated by the practice environment. Medically complex infants who establish their medical home in a multidisciplinary NICU follow-up clinic may have an earlier assessment by a neonatologist or other developmental specialist. Other infants may have their first formal assessment at 3 to 4 months’ corrected age. (6) Neurodevelopmental assessments include a full physical examination with complete neurologic examination and age-appropriate screening tools. Repeated assessments are performed at 8 to 12 months and then again at 18 to 24 months, at which time transient neurodevelopmental issues would be expected to have resolved. Medically complex infants with suspected delays or diagnoses may be followed more closely and have more frequent evaluations. Cognitive testing may be performed after 3 years of age. Repeated evaluations throughout childhood are often helpful, particularly if impairment is identified, because performance at 8 years of age is predictive of academic performance later in childhood and adolescence.

Preterm and medically complex infants may be at higher risk for autism and attention-deficit/hyperactivity disorder (ADHD) than the general population. Infants born preterm are more likely to have an abnormal autism screen. (6)(64) In some cases, it is challenging to discern whether there is truly an abnormality in sensory processing or whether the screening test is confounded by coexisting neurodevelopmental impairment. Screening for ADHD is similarly challenging. According to the AAP, there is insufficient evidence supporting screening and diagnosis in children younger than 4 years. (65) When these children are old enough to undergo screening, they are 3 to 4 times more likely to screen positive for ADHD. (6) Underlying cognitive impairment may exacerbate ADHD symptoms, and inattention or hyperactivity may contribute to poor cognitive performance.

Summary

- Medically complex infants have multiple medical issues, many of which have not yet resolved at the time of NICU discharge, which will require close and coordinated multispecialty follow-up.
- Based on some research evidence as well as consensus, a multidisciplinary medical home is the ideal care environment for many medically complex infants, if available. (9)(10)
- The primary care physician is the chief communicator and coordinator of a medically complex infant’s care.
- Many medically complex infants are discharged from the NICU with technology requirements, such as oxygen, ventilators, monitors, and feeding tubes.
- Medically complex infants require not only treatment and management of their current medical problems but also close monitoring for the development of new problems that may arise as a result of exposures in the NICU.
- Based on strong research evidence, prematurity and critical illness in the neonatal period increase the risk
of developmental delay and neurodevelopmental impairment. (6)(21)(25)(26)(41)

- Based on some research evidence as well as consensus, the PCP plays an important role in developmental surveillance and screening of all infants, but medically complex infants with a higher risk of impairment should be followed longitudinally by a developmental specialist. (5)(63)(66)

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Jillian Connors, Tomas Havranek and Deborah Campbell
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