Progeny HEALTH®

Best Practices

for Management of Infants with Neonatal Opioid Withdrawal Syndrome

Background

Neonatal drug withdrawal can occur when newborn infants are exposed to medications or addictive substances in utero or following prolonged postnatal exposure. This condition has traditionally been called Neonatal Abstinence Syndrome (NAS). Neonatal Opioid Withdrawal Syndrome (NOWS) is a withdrawal syndrome specifically due to in utero opioid exposure (Patrick 2020). NAS and NOWS are withdrawal syndromes characterized by dysfunction in respiratory, gastrointestinal, and/or nervous system regulation. The diagnosis is dependent on symptoms of withdrawal and not necessarily the need for pharmacologic therapy (Devlin 2018).

In the early 2000s, opioid pain relief prescription sales quadrupled which resulted in a significant increase in opioid addiction and deaths (Patrick 2020). By 2016, the number of infants diagnosed with NOWS grew nearly 8-fold which resulted in 1 infant being diagnosed every 15 minutes and continues to be of concern (Patrick 2021). Between 2010 and 2017, estimated rates of neonatal drug withdrawal and maternal opioid-related diagnoses significantly increased with notable state-level variation (Hirai 2020).

The growing number of opioids prescribed for women of child-bearing age, such as hydrocodone and oxycodone, as well as a resurgence in heroin use has made maternal opioid use a growing concern in the neonatal population (Epstein 2013 and Kellog 2011). Use of buprenorphine and methadone to combat maternal opioid use disorder has also led to neonatal withdrawal (Jones 2012). In 2019, one in five women who used prescription opioids during their pregnancy reported misuse of the medication (Devlin 2021).

1 in 5

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Few standard, evidence-based approaches for managing NOWS have been universally adopted, resulting in significant variation in care and a general lack of high-quality data to inform clinical practice (Devlin 2021). A large cross-sectional study was done to look at the site-to-site variation in several domains which further emphasized the lack of consistency. Due to the significant variation, infants may not be receiving efficient and effective care for withdrawal (Young 2020). The Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Collaborative as part of the National Institutes of Health HEAL Initiative was developed to conduct evidence-based research to help standardize clinical care of infants with withdrawal (Devlin 2021).

Differential Diagnosis

Most cases of neonatal drug withdrawal are associated with opioids, sedatives, and hypnotics. Other psychoactive drugs used during pregnancy including antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), antipsychotics and nicotine, can produce “withdrawal-like” symptoms in the newborn infant. These symptoms should be treated with supportive care. Drug effects can be seen in infant’s exposed to central nervous system stimulants such as cocaine and methamphetamine. Effects from these drugs are usually immediate, but typically do not require pharmacological intervention (Smith 2003 and Kocherlakota 2014). Polypharmacy brings added challenges to managing these infants.

According to the 2012 American Academy of Pediatrics (AAP) clinical report on Neonatal Drug Withdrawal, each nursery that cares for infants should develop a protocol that defines indications and procedures for screening for intrauterine drug exposure and a protocol that identifies and screens babies showing signs of withdrawal (Hudek 2012). A standardized plan should be utilized for the evaluation and comprehensive treatment of infants at risk for, or showing signs of withdrawal.

Laboratory screening for opioid exposure is accomplished by using neonatal urine, umbilical cord, and/or meconium specimens. A urine sample must be collected as soon as possible after birth because many drugs are rapidly metabolized and eliminated. Meconium testing can reflect exposure as early as 20 weeks gestation. Meconium must be collected before stools have transitioned and collection can be labor-intensive.

Testing of umbilical cord tissue by using drug class-specific immunoassays has been shown to be in concordance with testing of paired meconium specimens and has a faster turn-around time of 48 to 72 hours (Patrick 2020). Since signs of NOWS are similar to sepsis, hypoglycemia, hypocalcemia, hyperthyroidism, hyperviscosity syndrome, and neurological issues, it is important to carefully review the maternal and neonatal medical histories. Basic laboratory tests, such as an electrolyte panel including glucose, calcium, and a complete blood cell count, should be considered, even if there is a compelling history for NOWS (Chasnoff 2003).

Signs and Symptoms

Because opioid receptors are concentrated in the central nervous system and the gastrointestinal tract, the predominant clinical signs reflect these systems (Patrick 2020). Signs and symptoms of NOWS and/or drug withdrawal are characterized by neurologic excitability and gastrointestinal, autonomic, and respiratory dysfunction (Kocherlakota 2014) such as:

- **Neurologic:** restlessness, high-pitched cry, tremors, sleep disturbances, seizures, irritability, hypertonicity, hyperactivity, clonus, or nystagmus.
- **Gastrointestinal:** poor feeding, discoordinated feedings, vomiting, loose stools, or increased sucking.
- **Respiratory:** rapid respirations, respiratory distress.
- **Autonomic:** sneezing, fist-sucking, excessive yawning, sweating, flushing of skin, fever, nasal stuffiness, and skin abrasions.

Premature infants are often less affected by in-utero drug exposure. This is likely due to less in-utero exposure, decreased CNS maturity, and/or lower birth weight resulting in lower stores of fat-soluble opioids. Premature infants tend to have less severe symptoms, are less likely to require pharmacological treatment, and have shorter treatment courses when they do require treatment (Lainwala 2005 and Dysart 2007). In addition, there is no consistent correlation between maternal drug doses and neonatal symptoms in either term or preterm babies (Dodds 2019).

Assessment and Nonpharmacological Treatment

Infants at risk for NOWS should be carefully monitored in the hospital for the development of signs and symptoms consistent with withdrawal. Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal and staff should be trained in the correct use of an abstinence assessment tool (Hudek 2012). The most commonly used tool is the Modified Finnegan scoring system (Kocherlakota 2014). This tool evaluates twenty of the most common symptoms of NOWS in an infant and associates a score with each item which reflects the severity of the symptom.

A total score of eight or greater is considered high. Trending scores over time is important to determine if supportive and/or pharmacologic treatment will be necessary. It is important that all staff members who use a withdrawal scoring tool be instructed in its use so that scoring is uniform from one staff member to the next. It is also important for staff members to understand that increased scores can be achieved by a normal newborn that has not been exposed to any drugs in utero.

Modified Finnegan Neonatal Abstinence Score Sheet[1]

System	Signs and Symptoms	Score	AM						PM						Comments
Central Nervous System Disturbances	Excessive high-pitched (or other) cry < 5 mins	2													
	Continuous high-pitched (or other) cry > 5 mins	3													
	Sleeps < 1 hour after feeding	3													
	Sleeps < 2 hours after feeding	2													
	Sleeps < 3 hours after feeding	1													
	Hyperactive Moro reflex	2													
	Markedly hyperactive Moro reflex	3													
	Mild tremors when disturbed	1													
	Moderate-severe tremors when disturbed	2													
	Mild tremors when undisturbed	3													
	Moderate-severe tremors when undisturbed	4													
	Increased muscle tone	1													
	Excoriation (chin, knees, elbow, toes, nose)	1													
	Myoclonic jerks (twitching/jerking of limbs)	3													
	Generalised convulsions	5													
Metabolic/ Vasomotor/ Respiratory Disturbances	Sweating	1													
	Hyperthermia 37.2-38.3C	1													
	Hyperthermia > 38.4C	2													
	Frequent yawning (> 3-4 times/ scoring interval)	1													
	Mottling	1													
	Nasal stuffiness	1													
	Sneezing (> 3-4 times/scoring interval)	1													
	Nasal flaring	2													
	Respiratory rate > 60/min	1													
	Respiratory rate > 60/min with retractions	2													
Gastrointestinal Disturbances	Excessive sucking	1													
	Poor feeding (infrequent/uncoordinated suck)	2													
	Regurgitation (≥ 2 times during/post feeding)	2													
	Projectile vomiting	3													
	Loose stools (curds/seedy appearance)	2													
	Watery stools (water ring on nappy around stool)	3													
	Total Score														
	Date/Time														
	Initials of Scorer														

A newer scoring system that is utilized is the Eat, Sleep, Console (ESC) framework. This approach focuses on how withdrawal is impacting the infant's ability to function. The parameters in this framework are:

- E – Eat (can an infant eat one or more ounces per feeding or breastfeed well)
- S – Sleep (can an infant sleep for an hour or longer undisturbed)
- C – Console (can an infant be consoled in 10 minutes or less)

Maximizing the newborn's nesting time with his or her mother, focusing on non-pharmacologic treatment, and giving as needed doses of morphine should the infant's withdrawal symptoms fail to be reduced, is the essence of ESC. A steady morphine dose should be considered if as needed doses are being used with an increasing frequency without adequate symptom control (Grossman 2017 and Gross man 2018). Some studies have shown that implementation of the ESC model results in decreased length of stay and decreased medication use (Dodds 2019), but it is still unclear if decreased length of stays are attributable to the ESC approach or if these facilities are adhering better to nonpharmacologic approaches which can also reduce length of stay (Patrick 2020). Ongoing studies are being performed to validate previous results and to compare against traditional management if these infants (Devlin 2021).

An infant born to a mother taking a short-acting release opioid, such as hydrocodone which has an average half-life of four hours, may be safely discharged by three days of age if there are no signs of withdrawal. An infant born to a mother taking a long-acting opioid such as buprenorphine and methadone should be observed for five days (Hudek 2012) and safely discharged if the infant's withdrawal scores are stable, a home situation is arranged, and appropriate follow-up is scheduled (Patrick 2020).

Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli, both light and sound, by placing the infant in a dark, quiet environment. It also is necessary to avoid auto-stimulation by carefully swaddling an infant and responding early to an infant's signals of discomfort.

Adopting appropriate infant positioning and comforting techniques, such as swaying and rocking, and providing frequent small volumes of a formula or preparation of breast milk with an increased caloric density to minimize hunger while allowing for adequate growth, will help to control the symptoms of withdrawal. Caloric needs may be as high as 150 to 250 kcal/kg/day because of increased energy expenditure and loss of calories from regurgitation, vomiting, and/or loose stools. The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment (Hudek 2012).

When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed, provided that the infant continues to gain weight (American Academy of Pediatrics 2012, American College of Obstetricians and Gynecologists 2012, and Abdel-Latif 2006). Breastfeeding has been shown to mitigate NOWS symptoms and shorten length of stay (Isemann 2011, Pritham 2013, and Sarker 2006).

Appropriate psychosocial support should be provided for infants and their mothers with involvement of county and/or state agencies when necessary. Identification of supportive family members or guardians may be necessary to support the maternal-infant dyad upon discharge from the hospital.

Pharmacologic Treatment

Drug therapy is indicated to relieve moderate to severe signs of drug withdrawal caused by prenatal and/or postnatal opioid exposure and to prevent complications such as fever, weight loss, and seizures if an infant is still having marked withdrawal symptoms despite a committed program of non-pharmacologic support (Hudek 2012).

Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal infant bonding. Clinicians have historically treated drug withdrawal with a variety of drug preparations, including opioids (morphine, methadone, or buprenorphine), barbiturates (phenobarbital), benzodiazepines (diazepam, lorazepam), paregoric and clonidine. However, opioids should be used as the initial medication when pharmacologic treatment is indicated for opioid withdrawal.

Morphine is the most commonly used drug because its shorter half-life makes weaning easier. Methadone may be the preferred drug if the goal is to discharge the infant while receiving medication and continue weaning as an outpatient. Studies have shown that Methadone was associated with a significantly shorter length of stay (14%) and shorter length of treatment time (16%) compared to morphine (Davis 2018). One should consider getting an electrocardiogram (ECG) when starting an infant on methadone due to the risk of a prolonged QT interval (Siu 2014 and Dodds 2019).

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Paregoric is not recommended because it contains variable concentrations of other opioids, as well as toxic ingredients such as camphor, anise oil, alcohol, and benzoic acid (Siu 2014). The use of diazepam has also fallen out of favor.

Clonidine and phenobarbital have been used in combination with an opioid or other drug in some infants to reduce withdrawal symptoms. Phenobarbital may be preferred if infant is having more central nervous symptom symptoms due to its pharmacokinetics (Broome 2011). There have been studies showing the efficacy of clonidine as first-line therapy for withdrawal, though it is used extensively as a second-line medication. Literature is emerging, but studies show infants treated with phenobarbital had a shorter length of hospital stay and shorter morphine treatment duration than infants treated with clonidine (Merhar 2021 and Brusseau 2020).

Buprenorphine is a new treatment option and has been shown to reduce length of treatment in a large meta-analysis, but there were limitations in these studies, such as bias, variations in opioid exposures, and variations in treatment protocols. There is ongoing research to determine protocols and optimized dosing (Disher 2019). Often buprenorphine is used if the mothers were receiving buprenorphine prenatally (Kocherlakota 2014).

Typically, pharmacologic treatment is initiated when there are three consecutive Finnegan scores of eight or greater, or two consecutive scores of 12 or greater (Jansson 2009). Neonatal medication reference manuals should be consulted prior to the onset of pharmacotherapy in order to identify the most updated recommended dosages. Protocols vary among institutions for pharmacologic therapy with Eat, Sleep, Console scoring but if nonpharmacological measures are not sufficient, infants are typically treated with an as needed dose of Morphine. If infants continue to need frequent doses, consideration should be made to schedule morphine.

In general, the initial dose of the drug used for therapy is adjusted, per nursery protocol, until the symptoms are controlled, and then maintained for 48-72 hours until the daily average Modified Finnegan score is less than or equal to 8. Based upon the withdrawal scores and other assessments, including weight and physical examination, the initial drug dosage is then decreased at an appropriate interval with the goal of maintaining a daily average Modified Finnegan score of less than or equal to eight. Morphine is typically discontinued when a total daily dosage of approximately 0.12 mg/kg/day divided every three to four hours is reached and daily average scores remain less than or equal to eight for 24 hours. Because of the short half-life of morphine, weaning the dose to an interval of greater than every 4 hours (i.e. every 12 hours) is not necessary and not recommended based on the pharmacokinetics of morphine (Women and Newborn Health Service 2006). Once the dose has been weaned to 0.12 mg/kg/day and daily average scores are less than or equal to eight, morphine can be discontinued (Jansson 2019).

While many NICU's have adopted this minimum dosage as the level that triggers discontinuation, there are occasional infants who have a history of difficult or failed weaning who may require weaning to even lower doses of morphine before ending treatment. There is a lack of literature showing comparative studies that examine superiority of various regimens for these treatments resulting in heterogeneity at different hospital facilities. Thus, there is no standard accepted regimen (Mangat 2019).

The infant should be monitored for 24 to 48 hours after last dose of morphine to ensure no additional treatment is required before being discharged to home. Continued hospitalization for an infant prescribed a prolonged sub-therapeutic dose of morphine may present a greater risk to the infant, as it leads to ongoing separation of the infant from their family and increased risk of hospital acquired morbidity.

It should be noted that the Modified Finnegan scoring system was validated in term newborns but is commonly used for all NOWS-affected infants. Scoring infants over 28 days of age should include adjustments for maturational aspects seen in some score elements.

For infants who are receiving the maximum dose of oral opioid and continue to have consistent scores greater than eight, phenobarbital or clonidine can be added as a second medication (Jansson 2018). Phenobarbital and clonidine can then be continued at a therapeutic dose while the opioid is being weaned. Once opioid therapy has been discontinued, the infant can be discharged on phenobarbital, which can be weaned by the pediatrician or primary care doctor in the outpatient setting. Due to the potential for rebound effects, clonidine is not typically managed or discontinued in the outpatient setting.

Common Treatment Regimens *Specific regimens and doses may vary between hospital protocols

Medication	Mechanism of Action	Starting Dose	Increase	Weaning & Discontinuation
Morphine	A short-acting opioid that binds to opiate receptors in CNS causing CNS depression.	0.04-0.05 mg/kg/dose Q3-4 hours	0.04-0.05 mg/kg/dose to max 0.2 mg/kg/dose (maximum daily dose 1 mg/kg/d)	Wean by 10% of peak dose Q24-48 hours as scores allow. Discontinue when <0.12 mg/kg/d.
Methadone	A long-acting opioid that binds to opiate receptors in CNS causing CNS depression. **Benefit:** longer half-life so less flux between peak and trough levels and ease of administration due to less frequent dosing intervals.	0.05-0.1 mg/kg/dose Q6-12 hours	0.05 mg/kg/dose to a maximum daily dose 1 mg/kg/d	Wean by 10% of peak dose Q24-48 hours as scores allow. Discontinue when dose reaches 0.05 mg/kg/d. * May also discharge home and complete outpatient wean.
Phenobarbital	Binds to CNS receptors. **Benefit:** CNS depression so helpful if infant is having more CNS symptoms.	**Loading dose:** 16 mg/kg **Maintenance dose:** 1-4 mg/kg/dose Q12 hours	Maximum dose 1.25 mcg/kg Q3 hours	Wean by 10-20% Q24 hours. Discontinue once reaches <2 mg/kg/d or if serum level <15 mcg/ml. *May also discharge home and complete outpatient wean.
Clonidine	Central-acting alpha 2 adrenergic receptor agonist which reduces sympathetic outflow. Abrupt discontinuation can lead to rapid increase in blood pressure and sympathetic overactivity.	0.5-1 mcg/kg Q3-6 hours	Maximum dose 1.25 mcg/kg Q3 hours	Decrease by 50% per day over 2 days then stop.
Buprenorphine	Long-acting partial opioid receptor agonist. **Benefit:** improved safety particularly with respiratory depression.	4.405.3 mcg/kg per dose under tongue Q8 hours	Maximum dose 1.25 mcg/kg Q3 hours	Decrease by 50% per day over 2 days then stop.

Discharge Planning

Timing of discharge depends upon the infant's symptoms, if any, and the last known date of intrauterine drug exposure. Untreated infants who are below the treatment threshold based on the unit's scoring protocol may be considered for discharge.

Some physicians may consider discharging an infant receiving treatment with methadone or phenobarbital after stabilization of scores for several days and allow for weaning as an outpatient, provided that very close follow-up care with an outpatient practitioner can be arranged on a regular basis (Schwartz 2021).

The following are criteria for discharge for infants who were medically treated for withdrawal (Hudek 2012):

- The infant should be clinically stable with good weight gain and adequate oral feeding. A formula or preparation of breast milk with an increased caloric density may be needed to meet the increased energy requirements of these newborns.
- Co-morbidities have been treated or controlled such that outpatient care would be appropriate.
- The infant remains below treatment threshold after discontinuation of drug for at least 24 to 48 hours.
- If the infant is to be discharged on continued drug therapy, withdrawal scores are less than eight for 48-72 hours and the home environment has been assessed for safety.

The following are special discharge planning considerations (Hudek 2012):

- Assessment of the family and home environment has taken place.
- Notification of Child Protective Services, or the equivalent in each State, should take place in a timely fashion, as required by law or hospital policy, to avoid delays in discharge, if the infant is otherwise stable.
- Alternate living arrangements have been made for the infant if the home environment has been determined to be unsafe.
- Parents who have a need for family support and home nursing visits have had these services arranged.
- Mother has been referred for participation in a drug/alcohol treatment program, if not already participating in one.
- Support agencies have received referrals when appropriate.
- Any legal requirements for reporting have been met.
- Care providers have been identified or the need for foster placement has been evaluated.
- Caregivers have received education on symptoms of withdrawal and administration of medications.
- Caregivers understand that the infant may continue to be irritable at home and have been educated on the signs of recurrence of withdrawal such as poor sleeping, loose stools, and weight loss.
- An outpatient follow-up appointment has been made for 24-48 hours after discharge.
- All regular discharge planning activities have been completed.

Outpatient Management of Neonatal Abstinence Syndrome

Outpatient management of NOWS may be an opportunity for a select group of infants. Access to appropriate support and close follow-up must be arranged prior to discharge from the hospital. Outpatient pharmacies should be identified that will dispense the medication appropriately. During the discharge process, consider having the family fill their infant's prescription in advance of discharge and present the outpatient medication to the nursing staff to verify proper dosing. The infant should be discharged under the care of a physician who is comfortable and experienced with NOWS (Badas 2015 and Grossman 2017).

Infants eligible for outpatient management must be receiving a stable or decreasing dose of medication, be able to tolerate oral feedings with consistent weight gain and be medically stable. In addition, their families and/or guardians must demonstrate a supportive and safe home environment. Frequent and attentive visitation, ability to administer the medication and obtain weekly refills from the pharmacy, commitment to follow-up with the primary care provider within days of discharge and weekly thereafter, acceptance of home nursing visitation and competence with newborn care skills are essential requirements for the infant's caretakers.

An office visit with the pediatrician or primary care provider comfortable with caring for babies with NOWS should be scheduled to occur within 1-2 days of discharge, and then at frequent intervals determined by the pediatrician to promote compliance and consistency in the assessments. Readmission to the hospital may be necessary if there is non-compliance with the home management program or if outpatient medical management is unsuccessful.

Compared to outpatient weaning, the use of inpatient pharmacologic treatment is consistently reported as being associated with longer lengths of hospitalization, but shorter total duration of treatment (Murphy-Oikonen 2018).

Long-Term Consequences Of Prenatal Exposure To Opioids

There are only several recent prospective studies that looked at long-term neurodevelopmental consequences of prenatal opioid exposure. One study showed lower IQ scores in exposed boys at 8.5 years old. In another study, exposed children had average cognitive scores, but their scores were significantly lower than unexposed peers. Retrospective chart reviews showed children diagnosed with NOWS showed an increased risk for behavioral and academic problems (Conradt 2019).

Other studies show that there were no neurologic differences between children at 12 months of age and seven years of age, suggesting the early neurological signs seen in opioid-exposed infants are transient and short-lived. Studies did show some potential for growth failure that increases progressively over time. In addition, children were seen to have a higher incidence of behavioral problems over time, as well as lower cognitive scores (Bauer 2020). However, it is not clear if the effects seen in studies are due to socio-demographic and environmental factors such as poverty.

Infants born to mothers using opioids during pregnancy are at risk of a range of visual problems, the underlying causes of which are not clear. Infants who received pharmaceutical treatment due to withdrawal after birth may be at particular risk of developing nystagmus (Hamilton 2010). Infants who have a history of NOWS have a higher rate of language delays (Miller 2020). A recent meta-analysis of association between prenatal opioid exposure and attention-deficit hyperactivity disorder shows an increased risk of ADHD symptoms in school-aged children. It is difficult to know if this is due to biological, social, and environmental risks, as well (Schwartz 2021).

Regular visits with the pediatrician should occur more frequently to assess for developmental concerns (especially language) and for any family needs.

Depending on the infant's individual needs, follow up could include:

- Neurodevelopmental assessments to identify motor deficits, cognitive delays, performed by Early Intervention programs.
- Psycho-behavioral assessments to identify hyperactivity, impulsivity, and attention-deficit in preschool-aged children, as well as school absence, school failure, and other behavioral problems in school-aged children.
- Ophthalmologic assessment due to an increased incidence of nystagmus and strabismus.
- Awareness of the increased risk of ear infections
- Development of a crying plan with parents to avoid Shaken Baby Syndrome
- Awareness of the increased risk for SIDS and appropriate parental education.

Early Intervention clinics can be a great resource for these parents and do not require a physician referral. There are some post-hospital discharge programs that are designed specifically for infants who have experienced withdrawal after birth. For example, Johns Hopkins has a Neonatal Abstinence Syndrome Clinic where infants see a physician, occupational therapist, neurodevelopmental psychologist, and a feeding specialist within two to four weeks after hospital discharge. The infants then have planned follow-up with the various practitioners at this clinic.

Psychosocial support in the community can also be achieved with the assistance of a social worker or case manager who can coordinate discharge planning activities and referrals to external agencies as needed. ProgenyHealth's Case Managers collaborate closely with these mothers with the main goal of keeping them connected to their Primary Care Practitioner and being able to recognize early on any red flags for the infant or mother.

Conclusion

Neonatal abstinence syndrome has become a major health problem in the United States. It is recommended that taking a team-based approach to the management of these at-risk infants will lead to improved health outcomes.

ProgenyHealth's NOWS Best Practice can be used as a resource for NICUs, to assist in the creation of internal guidelines and/or protocols for management of these cases. Having such a guideline is a crucial first step in achieving successful clinical outcomes, while also assuring a safe and comprehensive discharge plan is in place for these infants and their families.

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