Progeny HEALTH®

Best Practices

for Management of Infants with Neonatal Abstinence Syndrome

BACKGROUND

Neonatal drug withdrawal can occur when newborn infants are exposed to medications or addictive substances in-utero, or can occur following prolonged postnatal exposure. This condition, known as Neonatal Abstinence Syndrome (NAS), also sometimes called Neonatal Opioid Withdrawal Syndrome (NOWS), refers to a constellation of signs and symptoms resulting from opioid withdrawal after cessation of maternal drug supply at the time of delivery. NAS is characterized by dysfunction in respiratory, gastrointestinal, and/or nervous system regulation. Opioid use in women of child-bearing age is a growing concern and between 800,000 and 1 million infants are born annually to women who used a variety of drugs during pregnancy.[1] Recent studies have shown that 1 in 9 infants are exposed to alcohol, 1 in 5 are exposed to nicotine, and 1 in 20 are exposed to illicit drugs.[1] 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.[2,3]

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.

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 one that identifies and screens babies showing signs of NAS.[4] A standardized plan should be utilized for the evaluation and comprehensive treatment of infants at risk for, or showing signs of, withdrawal. Laboratory screening is most commonly accomplished by using neonatal urine and/or meconium specimens. A urine sample must be collected as soon as possible after birth because many drugs are rapidly metabolized and eliminated.[5,6,8] Meconium must be collected before it is contaminated by transitional, human milk, or formula stools, since the assay may not be valid, or the reference laboratory may reject the sample.[9,10] 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.[11] Since signs of NAS are similar to sepsis; hypoglycemia, hypocalcemia, hyperthyroidism and hyperviscosity syndrome, 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 NAS.[5,12]

SIGNS AND SYMPTOMS

Signs and symptoms of NAS and/or drug withdrawal are characterized by neurologic excitability and gastrointestinal, autonomic, and respiratory dysfunction such as:[13]

- Neurologic: restlessness, high-pitched cry, tremors, sleep disturbances, seizures, irritability, hypertonicity, hyperactivity, clonus, or nystagmus.

- Gastrointestinal: poor feeding, 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.

Increasing gestational age at birth correlates directly with increasing severity of drug withdrawal symptoms. This is likely due to longer in-utero exposure and/or higher birth weight resulting in greater stores of fat-soluble opioids.[14,15] Premature infants are often less affected by in-utero drug exposure. They tend to have less severe symptoms, are less likely to require pharmacological treatment, and have shorter treatment courses when they do require treatment.[16] In addition, there is no consistent correlation between maternal drug doses and neonatal symptoms in either term or preterm babies.[17]

ASSESSMENT AND NONPHARMACOLOGICAL TREATMENT

Infants at risk for NAS 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.[4] The most commonly used tool is the Finnegan scoring system.[18,19] This tool evaluates twenty of the most common symptoms of NAS in an infant and associates a score with each item which reflects the severity of the symptom. A total score of 8 or greater is considered high and may warrant further treatment. It is important that all staff members who use an NAS 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.

A newer scoring system that is showing promise is the Eating, Sleeping, Consoling (ESC) framework. In a 2017 study of 50 infants at Yale University, Finnegan scoring would have led to starting morphine therapy in 30 patients (60%). Morphine was started on only 6 patients (12%) using the ESC framework. Average length of stay was reduced from 22.5 days to 5.9 days with no readmissions or adverse events.[41]

The parameters in this framework are defined by:
- E – Eat (can an infant eat one or more ounces per feeding or breastfeed well)
- S – Sleeping (sleep for an hour or longer undisturbed)
- C – Console (be consoled in 10 minutes or less)

Maximizing the newborn's nesting time with their mother, focusing on non-pharmacologic treatment, and giving as-needed doses of morphine, should the infant's withdrawal symptoms fail to be adequately 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.[41,42]

An infant born to a mother on a low-dose prescription opioid with a short half-life, such as hydrocodone which has an average half-life of 4 hours, may be safely discharged by 3 days of age if there are no signs of withdrawal. An infant born to a mother taking an opioid with a prolonged half-life, such as methadone or buprenorphine, should be observed for 5 to 7 days.[4] Neonates with in-utero exposure to methadone who did not exhibit symptoms of NAS in the first 3 days of life are unlikely to require pharmacological treatment.[20] 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.[4]

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.[21,22,23] Breastfeeding has

been shown to mitigate NAS symptoms and shorten length of stay.[24,25,26]

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 NAS 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.[4] Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal-infant bonding. Clinicians have treated NAS with a variety of drug preparations, including opioids (morphine, methadone or buprenorphine), barbiturates (phenobarbital), benzodiazepines (diazepam, lorazepam), and clonidine. However, morphine or methadone should be used as the initial medication when pharmacologic treatment is indicated for opioid withdrawal.[4]

Eighty-three percent of clinicians in the United States use an opioid (morphine or methadone) as the drug of first choice.[27] 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.[49] One should consider getting an electrocardiogram (ECG) when starting an infant on methadone due to the risk of a prolonged QT interval.[47,48]

Phenobarbital is used by the majority of practitioners as an adjunctive treatment if an opioid does not adequately control withdrawal symptoms.[4,27,28] 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.[29] The use of diazepam has also fallen into disfavor.[18,30,31] Clonidine has been used in combination with an opioid or other drug in some infants to reduce withdrawal symptoms.[33] Buprenorphine has been studied as a potential agent to treat NAS.[34,35,43] While

Table 1

NAS Treatment Regimens

Medication	Starting	Increase	Weaning	Discontinuation
Morphine	0.04 - 0.05 mg/kg/dose q 3–4 hours[4,19]	0.04 - 0.05 mg/kg/dose to a maximum of 0.2 mg/kg/dose (maximum daily dosage of 1 mg/kg/day)[4,19]	Wean by 10% of peak dose q 24-48 hours as scores allow	Discontinue once dose reaches ~0.12 mg/kg/day
Methadone	0.05 - 0.1 mg/kg/dose q 6-12 hours[4,19]	0.05 mg/kg/dose to a maximum of 1 mg/kg/day	Dosing interval may be increased to q 12-24 hours after stabilization. Then wean by 10% of peak dose q 24-48 hours as scores allow Consider an EKG on the infant due to risks of long QT[47,48]	Discontinue once dose reaches 0.05 mg/kg/day or 10% of peak dose[15] Alternatively, may discharge home on methadone once NAS stable and complete outpatient wean
Phenobarbital	Loading dose: 16 mg/kg Maintenance dose: 1-4 mg/kg/dose q 12 hours[19,36]	Increase as needed per symptoms. One may target a serum level of 15-30 mcg/mL[36]	Wean by 10-20% q 24 hours	Discontinue once dose reaches <2 mg/kg/day or serum level < 15 mcg/mL The infant may be discharged on phenobarbital and weaned as an outpatient.
Clonidine	0.5 -1 mcg/kg q 3-6 hours [19,33,36,37,40,44,45,46]	Maximum dose 1.25 mcg/kg q 3 hours[44,45,46]	Decrease by 50% per day over two days, then stop[33,44,45,46]	

morphine or methadone are often the initial medications used to manage infants with NAS withdrawing from opioids, conclusive data are lacking to suggest the optimal strategy for treatment of poly-substance withdrawal, or withdrawal from benzodiazepines or other sedatives.

Typically, pharmacologic treatment is initiated when there are three consecutive Finnegan scores of 8 or greater, or two consecutive scores of 12 or greater.[19] Neonatal medication reference manuals should be consulted prior to the onset of pharmacotherapy in order to identify the most updated recommended dosages.

Table 1 shows treatment regimens for medications commonly used to treat NAS secondary to opioid withdrawal.

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 Finnegan score is less than or equal to 8. Based upon the NAS scores and other assessments, including weight and physical examination, the drug dosage is then decreased by 10% every 24-48 hours, with the goal of maintaining a daily average Finnegan score of less than or equal to 8. Our experience working with neonatologists throughout the country reveals that morphine is typically discontinued when a total daily dosage of 0.12 mg/kg/day is reached and daily average scores remain less than or equal to 8 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.[19,38] Once the dose has been weaned to 0.12 mg/kg/day divided every 3-4 hours and daily average scores are less than or equal to 8, morphine can be discontinued.[39,44,45,46] While many NICU's have adopted this minimum dosage as the level that triggers discontinuation, there are occasional infants who may require weaning to even lower doses of morphine before ending treatment.

The infant should be monitored for 24 to 48 hours after discontinuation of morphine before being discharged to home. Continued hospitalization for an infant prescribed a 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 Finnegan scoring system was validated in term newborns, but is commonly used for all NAS-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 scores greater than 8, phenobarbital or clonidine can be added as a second medication.[4,27,28,44,45,46] Phenobarbital 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.

Clonidine, a centrally acting α-adrenergic receptor agonist, has been studied as a single replacement therapy or adjunct therapy. There have been studies showing the efficacy of clonidine as first-line therapy for NAS, though it is used extensively as a second-line medication.[40,44,45,46] Due to the potential for rebound effects, clonidine is not typically managed or discontinued in the outpatient setting.

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 after five days of life, may be considered for discharge. Continued hospitalization for an infant exposed to methadone or buprenorphine whose scores are increasing, or close outpatient follow-up for an infant with low scores, will be necessary for 5-7 days because of the long half-life of methadone. Some physicians may consider discharging an infant receiving treatment with methadone 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.[49]

The following are criteria for discharge for infants who were medically treated for NAS:[4]

- 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, NAS scores are less than 8 for 48-72 hours and the home environment has been assessed for safety.

The following are special discharge planning considerations:[4]

- 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[40,41]

Outpatient management of NAS 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 NAS.

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.

Weaning of medication may continue as it had while hospitalized, approximately 10% every 24-48 hours for neonatal morphine solution or oral methadone solution, by weaning the dose using a consistent interval. Alternatively, as the infant gains weight he/she will wean on a per kilogram basis. Morphine therapy is often stopped when the total daily dose is less than 0.12 mg/kg/day, and phenobarbital may be stopped when the total daily dose is less than 2 mg/kg/day.

An office visit with the pediatrician or primary care provider comfortable with caring for babies with NAS should occur within a few days of discharge, and then weekly 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.

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.

Depending on the infant's individual needs, this 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 for SIDS and appropriate parental education.

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 NAS 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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