### Clinical Performance Guideline

**Neonatal Resource Services**  
**Neonatal Abstinence Syndrome (NAS)**

**Purpose:** To provide guidelines for the monitoring and management of neonates with intrauterine exposure to illicit substance and for treatment of infants with neonatal abstinence syndrome (NAS).

**Target Client Population:** This guideline applies to the neonate who exhibits NAS from intrauterine exposure to illicit drugs or as a result of pain management during NICU hospitalization.

| Background | Neonatal abstinence syndrome has been described as a group of clinical findings associated with infant opioid withdrawal although signs of withdrawal can be also exhibited in infants exposed in utero to other substances such as benzodiazepines, barbiturates and alcohol. (AAP, 2012) The symptoms of NAS vary based on maternal and neonatal factors but may include irritability, lethargy, poor feeding, vomiting or diarrhea, hypertonicity, and occasionally seizures.

For infants with suspected or known substance exposure, observation and supportive care should be initially provided. Supportive care could include adjustment of the environment to decrease stimulation, swaddling of the infant, nutritional support and introduction of a pacifier for excessive sucking. Mild NAS symptoms may resolve within a few days without additional intervention.

Pharmacologic treatment may be necessary for infants exhibiting signs of moderate to severe withdrawal symptoms despite supportive care. Failure to provide the appropriate treatment for NAS may result in significant morbidity and mortality for the neonate. Preterm infants have a lesser risk of NAS and withdrawal symptoms than late preterm or term infants. Medical evidence has validated Finnegan scoring for term and late-preterm neonates. The use of Finnegan scoring in preterm infants may result in an inaccurate assessment of neonatal withdrawal status.

Maternal screening identifies substance use and assists in recognizing infants that are at risk for NAS. The management of NAS should be based on the symptoms of the infant and individualized for each neonate. Psychosocial assessment of applicable family members in the hospital followed by appropriate interventions based on that assessment is recommended.

| Treatment Criteria | Clinical evidence in the medical literature supports the following:

- Postnatal monitoring for withdrawal symptoms is indicated if there is a history of maternal substance use or enrollment in a methadone program, exposure to certain prescribed medications (benzodiazepines, barbiturates, etc.) or as part of a differential diagnosis when the infant has unexplained seizures, irritability or encephalopathy.

- In infants at high-risk for NAS, including those with mothers positive for substance use and those who exhibit signs/symptoms of withdrawal, the first urine and/or meconium specimen should be obtained for drug exposure screening. Urine specimens can detect recent substance exposure while... |
meconium screening can detect substance exposure from the time of gut development. Umbilical cord testing is an additional option. This screening must comply with state laws. (AAP, 2012; Montgomery, 2006)

- Infants presenting with signs of neonatal opioid withdrawal without history or suspicion of maternal substance abuse should have additional diagnostic testing performed to differentiate NAS from other conditions.

- Withdrawal symptoms occurring in the first 24 hours of life should prompt for history of maternal nicotine use as this may represent nicotine withdrawal as opposed to opiate withdrawal. (Garcia-Algar, 2008)

- Neonatal abstinence scoring using a tool such as the Finnegan NAS scoring system should be performed at least 2 hours after birth for infants with known or suspected substance exposure. This scoring includes clinical attributes or signs of withdrawal related to metabolic, gastrointestinal, neurological and respiratory status.

- Subsequent serial NAS scoring should occur 1/2 - 1 hour after each feeding. It is preferable to use the same reviewer/scorer each shift to minimize inter-rater variability and to give more reliable scores.

- Infants with Finnegan scores ≤ 7 require only observation and supportive care. For those infants not warranting treatment, an inpatient stay of 3 days is appropriate for newborn infants exposed to short-acting opiates and 5 days for newborn infants exposed to opiates with longer half-life (e.g., buprenorphine, methadone). (Hudak, 2012) For infants exposed to short-acting benzodiazepines (e.g., alprazolam), a 3 day observation period is appropriate with up to 5 days for exposure to longer-acting benzodiazepines (e.g., diazepam). Observation and NAS scoring can be performed in the normal newborn nursery or the mother’s room.

- Pharmacologic management may be initiated for an infant when 3 consecutive Finnegan scores are ≥ 8 or when 2 consecutive scores or the average of two scores are ≥ 12. It may also be warranted for infants with seizures, significant feeding intolerance (diarrhea, emesis) and weight loss or failure to gain weight, or unexplained fever and inability to sleep despite supportive measures. (Dow, 2012)

- Options for pharmacologic treatment of withdrawal symptoms may include morphine, methadone, and phenobarbital or combination therapy. The choice of drug should match the class of drug used by the mother, including the duration of action.
  
  - Morphine may be started at an initial dose of 0.04mg/kg PO administered with feedings every 3-4 hours. The dose may be increased depending on NAS scores by increments of 0.04 mg/kg/dose up to a maximum of 0.2 mg/kg per dose. (AAP, 2012)
  
  - Methadone, as an alternative to morphine, may be started at an initial dose of 0.05-0.1 mg/kg/dose PO administered with feedings every 6-24 hours. The dose may be increased depending on NAS scores by increments of 0.05 mg/kg/dose. (AAP, 2012)
  
  - Phenobarbital is a nonspecific central nervous system depressant used as an adjunct in opioid withdrawal in addition to treatment of non-opioid
withdrawal. Combination therapy utilizing morphine/phenobarbital may reduce not only the severity/duration of symptoms but also the length of hospital stay.

- Benzodiazepines are not recommended as first line or adjunct agents. Benzodiazepines have a synergistic effect with opioids leading to respiratory depression/hypotension and the neonate has a limited capacity to metabolize diazepam.

- Paregoric is a short-acting opiate that is no longer recommended for managing opiate withdrawal because it contains alcohol benzoic acid camphor, which can be neurotoxic. (Bio 2011)

- Tincture of opium is not recommended due to 25-fold higher concentration of morphine risking medication errors and morphine overdose. (Hudak, 2012)

- Although reports on the use of clonidine (an alpha 2-adrenergic receptor agonist), chlorpromazine, and buprenorphine in controlling NAS seem promising; further studies are needed before recommendation for widespread use of these agents is made (Agthe 2009, Kraft 2008, Broome 2011).

- Weaning should be initiated when the infant’s NAS scores consistently remain < 8 for 1-2 days. The dose should be decreased 10-20% from the highest total daily dose every 1-2 days for oral morphine and every 2-4 days for oral methadone based on symptoms.

- Morphine and methadone should be stopped when the dose reaches 10% of the highest dose for 24-48 hours.

- Discharge should occur within 2 days of stopping opiate therapy if all other discharge criteria are met and NAS scores do not meet criteria to reinstitute treatment.

- Select patients with optimal home environment and provider follow-up can successfully complete the NAS weaning process as an outpatient. (Backes, 2012; Smirk, 2014; Kelly, 2014)

- Due to its long half-life, phenobarbital adjuvant therapy can be weaned on an outpatient basis.

- For infants weaning from clonidine adjuvant therapy, data is lacking for support of a need to taper the medication. A reasonable time period to monitor for any cardiovascular changes is up to 48 hours after stopping the medication. (Agthe, 2009)

- Infants with NAS are in a hypermetabolic state. Their high caloric needs may warrant high caloric density formula or fortified human milk to prevent excessive weight loss and promote optimal weight gain.

- Women who are on methadone or buprenorphine maintenance and not abusing other drugs should be encouraged to breast-feed. Breastfeeding is associated with decreased severity and duration of NAS (McQueen 2011, D’Apolito 2013)
<table>
<thead>
<tr>
<th>Clinical Evidence</th>
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<tr>
<td>• In 2012 the American Academy of Pediatrics published an updated clinical report on Neonatal Drug Withdrawal. This report provides guidance on the identification and management of infants exposed to intrauterine substances in addition to the management of hospitalized neonates who need weaning from analgesics or sedatives.</td>
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<td>• A prospective multicenter cohort study by Wachman et al (2013) attempted to identify genetic factors that may influence the incidence and severity of neonatal abstinence syndrome (NAS). Participants from 5 tertiary care facilities included infants ≥ 36 weeks gestation who were being treated for NAS according to the institutions’ treatment protocols. Although there were limitations to this study, the authors concluded single-nucleotide polymorphisms in the OPRM1 and COMT genes were associated with NAS and resulted in reduced need for medical treatment and length of hospital stay for these infants. They also acknowledged these were preliminary findings and additional studies are needed in order to replicate these results.</td>
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<td>• A 2013 National Survey by Mehta et al outlined the variety of management strategies in neonatal abstinence syndrome. The authors concluded that increased prenatal counseling and home treatment programs could improve the care of these infants.</td>
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<td>• A 2013 Cochrane review by Minozzi et al compared maternal maintenance treatment programs. Based on the authors’ evaluations, maintenance treatment with buprenorphine appeared to result in less symptoms of substance withdrawal.</td>
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<td>• Review of data from a large multi-site randomized clinical trial was performed by Gaalema et al (2013). The authors compared the time to initiation of treatment for NAS between methadone- versus buprenorphine-exposed infants. The authors concluded that buprenorphine-exposed infants had less severe NAS than methadone-exposed neonates. However, the buprenorphine-exposed infants required treatment for NAS significantly later than the methadone-exposed neonates.</td>
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<td>• A 2012 retrospective descriptive study by Pritham et al determined that infants born to mothers undergoing methadone maintenance therapy had longer inpatient stays for NAS than infants with mothers involved in buprenorphine maintenance therapy. They also determined that breastfed neonates had shorter hospitalizations than formula-fed infants.</td>
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<td>• A prospective randomized clinical trial by Surran et al (2013) assessed the efficacy of adjunctive morphine sulfate treatment with clonidine versus phenobarbital for NAS. The authors found the addition of phenobarbital reduced the number of morphine treatment days as compared to clonidine. Adjunctive phenobarbital, however, resulted in an overall longer treatment time as compared to clonidine.</td>
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<td>• In 2012 Jansson and Velez provided a review on the clinical presentation and treatment of neonatal abstinence syndrome. This document addresses the difficulty with developing an optimal treatment strategy for affected infants due to the variability of symptoms and contributing factors. The authors</td>
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acknowledge the dearth of empirical evidence related to the management of infants with NAS and the need for more research in many related areas.

- A prospective cohort study by Cleary et al (2012) reached conclusions that maternal opiate, benzodiazepine or cocaine use result in a longer neonatal hospitalization for NAS than maternal methadone-only maintenance.

- Dow et al (2012) crafted a clinical practice guideline on neonatal abstinence syndrome in an effort to standardize the clinical management of the maternal dyad affected by substance abuse. The ultimate goal of the authors was to improve the outcomes of infants at risk for NAS. They felt that early identification of NAS with subsequent interventions could result in a shortened hospital stay. Recommendations for screening and scoring of NAS, pharmacological and non-pharmacological treatment, and discharge planning were included.

- A 2013 review by Logan et al describes the risk factors for NAS and the developmental outcomes of infants who were exposed in utero to opiates. Polysubstance exposure was discussed in addition to recommendations for pharmacologic management and breastfeeding.

- Wong et al (2011) published a clinical practice guideline for managing substance abuse in pregnancy. Based on fair evidence, their recommendations encouraged facilities to develop a protocol for assessment and management of infants exposed to intra-uterine opiates and advised that the risks and benefits of breastfeeding should be evaluated on an individual basis.

- In 2012, Kraft and van den Anker provided recommendations on the management of opioid neonatal abstinence syndrome. They indicated morphine is currently the standard opioid replacement although the use of buprenorphine and clonidine is emerging. The authors advised that although there is general lack of high quality clinical trial data to guide optimal NAS therapy, the currently available evidence supports the use of morphine therapy adjusted for symptom control with gradual weaning. Morphine dosing is addressed and the authors acknowledge there is not a generally accepted morphine maximum when treating NAS. This article indicated the use of phenobarbital appears to be particularly effective when used in infants with poly-drug exposure and is often used when maximum opioid replacement therapy is not effective or as an adjunct in combination therapy. Breastfeeding of NAS infants is promoted in women receiving methadone or buprenorphine maintenance. The authors concluded by addressing the need for improved pharmacologic treatment for infants with NAS which would not only result in decreased resource utilization but also improved psychosocial and developmental outcomes in these infants. The transition to outpatient therapy was noted as an emerging trend in NAS treatment.

- Bio et al (2011) provided an update on the pharmacologic management of infants with NAS. After their literature review, the authors concluded that paregoric is no longer recommended, oral morphine solutions appear to be the standard therapy for opiate withdrawal, methadone and buprenorphine are other potential therapies, and phenobarbital and clonidine can potentially be
Broome and Tsz-Yin (2011) discuss the signs and symptoms of NAS, scoring systems used in the assessment of NAS and treatment options for these infants. They focus on the utilization of clonidine and detail the studies that have evaluated its use. Although the authors conclude clonidine may be an alternative option for treatment of NAS, they also acknowledge the evidence is limited with no long-term outcomes available. They indicate additional studies are needed in support of the efficacy and safety of clonidine for treatment of NAS.

Montgomery et al (2006) evaluated the use of umbilical cord tissue in drug screening for fetal exposure to illicit drugs. Paired samples of both meconium and umbilical cord tissue were obtained from 118 patients who were suspected of using illicit drugs. Agreement between the two samples was found in 96.6% of the tests for amphetamines, 94.9% for opiates, 99.2% for cocaine and 90.7% for cannabinoids. The authors concluded that umbilical cord tissue could effectively be utilized in assessing fetal drug exposure with advantageous availability for immediate testing purposes.

Ebner et al (2007) compared the use of phenobarbital to morphine hydrochloride in the treatment of at-risk neonates whose mothers had been maintained on opioids. For those infants who required treatment for NAS, the authors found those that received morphine had a shorter mean duration of treatment versus those infants who were treated with phenobarbital.

Velez and Jansson (2008) discussed the non-pharmacologic management of infants with NAS and emphasized the importance of individualizing this care based on the needs of the infant in order to improve both the short- and long-term outcomes of these neonates. The authors indicate non-pharmacologic management should be the standard of care for all infants at risk for NAS even though it is not meant as a substitute for infants who require pharmacologic management based on their symptomatology.

An article by Burgos and Burke (2009) outlines the identification of, scoring systems for and medical treatment of neonatal abstinence syndrome. They discuss the recommended medications and associated weaning strategies for infants displaying signs of withdrawal.

Jansson et al (2009) discussed commonly used tools to assess NAS in addition to NAS management. They describe in detail how to use the most commonly referenced tool, the Finnegan Neonatal Abstinence Scoring System, including scoring, timing and management based on the severity of symptoms. The authors conclude a symptom-based treatment algorithm for affected NAS infants could result in less medication administration than a weight-based protocol. They also acknowledge additional research is needed to identify the optimal management of NAS infants.

Saiki et al (2010) evaluated the care of infants with NAS who were left with their mothers on the postnatal floor versus those who were cared for in the neonatal unit. Their results indicated those neonates who stayed with their mothers on the postnatal floor required less treatment for NAS, a shorter duration of treatment for NAS, and a shorter hospital stay than the group of infants who were left with their mothers.
neonates who were cared for in the neonatal unit.

- A Cochrane Review by Osborn et al (2010) evaluated the treatment of infants with NAS who were born to opiate dependent mothers. They attempted to evaluate the effectiveness and safety of using a sedative to treat opiate withdrawal symptoms. They concluded that infants with NAS secondary to opiate withdrawal should receive initial treatment with an opiate. They also indicated that in infants treated with an opiate, the addition of phenobarbitone or clonidine may reduce withdrawal severity.

- The 2009 clinical protocol from the Academy of Breastfeeding Medicine (ABM) makes recommendations for breastfeeding in drug-dependent women. These recommendations include the promotion of breastfeeding for women who: are participating in substance abuse treatment, are stable methadone-maintained, have 90 day abstinence prior to delivery, received consistent prenatal care, are taking no psychiatric medication contraindicated in lactation, and have no medical contraindication to breastfeeding.

- Keegan et al (2010) provides recommendations on the management of maternal and fetal withdrawal symptoms. They emphasize a multidisciplinary approach that should be individualized based on the substance in question and the needs of the patient.

- A review by Garcia-Algar (2008) outlined the symptoms of nicotine withdrawal in newborn infants. Based on the published literature, the authors concluded that newborn infants exposed in utero to maternal tobacco use could exhibit early onset nicotine withdrawal symptoms (within 12-24 hours after birth) if labor and delivery had interrupted the continuous exposure to nicotine. These symptoms were typically mild with a short duration and generally did not require treatment.

- A retrospective review by Backes et al (2012) sought to compare the safety and efficacy of a combined inpatient/outpatient approach in opioid treatment weaning for NAS to the traditional inpatient weaning strategy. The treatment cohort included 121 infants, 75 of which completed methadone treatment in the inpatient setting and 46 infants who were initially treated with methadone inpatient but completed the weaning process in the outpatient setting. Phenobarbital was added as an adjunctive agent in infants with an inadequate response to methadone. Twenty-four percent of infants in the inpatient cohort and 28% in the combined inpatient/outpatient cohort required adjunctive inpatient phenobarbital to control withdrawal symptoms. No difference in the total duration of phenobarbital treatment was identified between the two groups. The duration of methadone weaning in the inpatient/outpatient cohort was found to be longer. However, the cumulative methadone dosage was similar between the two groups. The readmission rate and number of emergency room visits for NAS-related symptoms was similar in both cohorts. No difference in the proportion of infants requiring a restart of inpatient medication for NAS symptoms was identified. The authors concluded that a combined inpatient/outpatient NAS treatment program utilizing community-based strategies would result in a shorter hospitalization with no increased risk of short-term adverse outcomes. It was noted that additional studies are warranted in order to evaluate the long-term benefits of combined inpatient
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assessment tools, weaning protocols and covariate adjustment. The authors indicated a need for additional high-quality randomized controlled trials to determine best practices in the pharmacologic management of NAS. Recommendations included the use of standard NAS protocols utilizing established assessment tools, accepted pharmacotherapy such as morphine and methadone and educational training for all staff involved in the care of NAS infants.

Specialty Society Guidelines:


Bibliography


Revision History
The following are approved changes incorporated into the revision numbers indicated below.

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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<tr>
<td>V1.0</td>
<td>05/16/2013</td>
<td>New clinical guideline (MB)</td>
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<tr>
<td>V2.0</td>
<td>06/04/2014</td>
<td>Job aid revised into medical necessity clinical guideline. (CE)</td>
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<tr>
<td>V3.0</td>
<td>06/03/2015</td>
<td>Annual review. (CE)</td>
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