**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.

### 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. (This screening must comply with state laws, AAP 2012)
• 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.

• 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 follow ½ -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. An inpatient stay of 3-7 days for observation of neonatal abstinence syndrome is warranted for asymptomatic at-risk infants although the duration of monitoring is variable based on the maternal drug history. 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 average ≥ 8 or when 2 consecutive 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 provides short-acting control of withdrawal symptoms and is the preferred agent over the longer-acting methadone for opioid withdrawal. (Kraft, 2012; Bio, 2011)
  
  • 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 a second line alternative to morphine, may be started at an initial dose of 0.05-0.1 mg/kg/dose PO administered with feedings every 6 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)
### Treatment Criteria (continued)

- 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% of the initial total daily dose every 1-2 days for oral morphine and every week for oral methadone based on symptoms.

- Babies with NAS are in a hypermetabolic state. Their high caloric needs (up to 250cal/kg/day) may require high caloric density formula or fortified breast 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).

### Clinical Evidence

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.
• 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 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 indicate morphine is currently the standard opioid replacement although the use of buprenorphine and clonidine is emerging. The authors advise 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 indicates 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 conclude 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.

• 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 utilized as adjunctive treatment.
**Clinical Evidence (continued)**

- 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.

- 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 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.
Bibliography


Fig2-2.


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

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<thead>
<tr>
<th>Revision</th>
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<th>Description of Change</th>
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