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 (NAS) 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) NAS occurs more frequently in infants exposed to long-acting and maintenance opioids than in those exposed to short-acting opioids. (Patrick, 2015) The incidence and duration of NAS may be decreased in pregnant women treated with buprenorphine and naloxone compared to methadone. (Nanda, 2015; Wiegand, 2015) The symptoms of NAS vary based on maternal and neonatal factors but may include irritability, lethargy, poor feeding, vomiting or diarrhea, hypertonicity, excessive sucking, sweating, jitteriness, tremors and occasionally seizures.

For infants with suspected or known substance exposure, observation and supportive care should be initially provided. Early ongoing engagement with the primary caregiver is preferable. 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. (Ordean, 2015)

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 30-60 minutes 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).
  - Infants with known antenatal exposure to both opioids and benzodiazepines can be observed in the hospital for 4 to 7 days duration based on short vs. long half-life of the drug exposure. (Hudak, 2012)
  - 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)

- NAS standardized treatment protocol and staff education are effective strategies to reduce hospital length of stay (Asti, 2015; Hall, 2014; Hall, 2015)

- 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, compared to morphine, has the potential to shorten the length of NAS treatment. (Brown, 2015) Methadone 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)

- Buprenorphine shows promise as an alternate agent to treat NAS with a shortened length of stay. (Hall, 2015)

- 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 and can lead to life threatening respiratory depression/hypotension. 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)

- Clonidine (an alpha 2-adrenergic receptor agonist) has been reported as both a first-line and adjunctive agent for NAS. (Agthe, 2009; Kraft, 2008; Broome, 2011; Bada, 2015)

- 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 weaning should be based on dose and not interval due to its short half-life.

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

- Discharge should occur within two days of stopping opiate therapy if all other discharge criteria are met and NAS scores do not meet criteria to reinstitute treatment. Hospital stay should not be extended if subsequent scores following this 48 hour observation period do not meet criteria to restart pharmacologic management.

- 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; Hall, 2015; Lee, 2015)

- 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 over a period more than 48 hours. 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>Brown et al (2015) conducted a prospective, double-blind randomized trial comparing the treatment duration of methadone and morphine for neonatal abstinence syndrome. Thirty-one methadone- and buprenorphine-exposed infants met the authors’ inclusion criteria after maternal consent. Randomization placed 15 infants in the methadone treatment cohort and 16 in the morphine treatment group. The median length of methadone treatment (14 days) was identified as significantly shorter than that of morphine treatment (21 days). The authors noted the need for a larger multicenter trial to confirm their findings.</td>
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<tr>
<td>A retrospective cohort analysis by Hall et al (2015) compared the duration of NAS treatment between buprenorphine and methadone. The authors indicated that a formalized treatment protocol had demonstrated improved short-term outcomes for infants with NAS but no consensus had been reached on the optimal pharmacologic regimen. The study enrollment included 38 infants treated with buprenorphine and 163 infants who were given methadone to treat NAS symptoms as a result of exposure to short-acting opioids or buprenorphine. The buprenorphine treatment cohort demonstrated a shorter adjusted treatment duration (9.4 days) and length of stay (16.3 days) than the methadone treatment group (14 days and 20.7 days respectively).</td>
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<td>Patrick et al (2015) performed a retrospective cohort study with the goal to identify neonatal complications resulting from antenatal opioid pain reliever use. The study demonstrated NAS occurred more frequently in infants exposed to long-acting and maintenance opioids than in those exposed to short-acting opioids. Infants diagnosed with NAS were identified as more likely to be born preterm with a low birth weight, face feeding difficulties, have a respiratory diagnosis and experience seizures. The authors found wide variability in the risk for neonatal withdrawal symptoms based on opioid type and dose, SSRI utilization and amount of cigarette use by the mother.</td>
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<td>A retrospective study by Wiegand et al (2015) compared the characteristics and prevalence of NAS between infants whose mothers were treated with methadone versus buprenorphine and naloxone in pregnancy. The number of</td>
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infants diagnosed with NAS in the buprenorphine and naloxone cohort was approximately 50% less than those diagnosed with NAS in the methadone-exposed group. The infants exposed to buprenorphine and naloxone also demonstrated lower peak NAS scores with a shorter overall hospitalization.

- A randomized prospective study by Bada et al (2015) compared the effects of clonidine versus morphine treatment for NAS on neurobehavioral performance. Dosing protocols for each were established and following control of symptoms, the dose was tapered by 10% every other day. The duration of morphine treatment was identified as significantly longer than the clonidine treatment. The NICU Network Neurobehavioral Scale (NNNS) was administered at 1 week and again at 2-4 weeks after initiation of treatment. The Bayley Scales II and Preschool Language Scale IV were administered at 1-year adjusted age. At one year of age no significant differences were noted between the two cohorts. However, the NNNS scores improved with clonidine but not with morphine. The authors acknowledge the need for a multicenter randomized trial comparing these two NAS treatments.

- A quality improvement project was conducted by Asti et al (2015) with the intent to reduce length of stay for infants with NAS. Accurate monitoring of NAS symptoms, use of a standardized treatment protocol, education of hospital personnel and multi-disciplinary collaboration were identified as key drivers. This project successfully reduced hospital days from 36 to 18 days by the end of the study period. No infants were readmitted within 30 days due to NAS symptoms. Standard treatment protocol and staff education on NAS were found to be the two most effective strategies for reducing length of hospitalization.

- A multicenter retrospective cohort study by Hall et al (2015) evaluated the effects of a standardized weaning protocol on the length of hospital stay and duration of opioid treatment in NAS treatment. Adoption of a protocol-driven weaning process for NAS was reported to significantly decrease the NAS treatment duration and amount of adjunctive treatment required. As a result, the infant’s length of inpatient stay was also reduced. The authors noted that reduced length of stay through home opioid weaning, however, may contribute to an overall longer duration of opioid treatment for the infant.

- A retrospective analysis by Lee et al (2015) noted that the number of NAS cases identified in this study increased steadily from 2007 to 2013. Infants who began methadone treatment inpatient and were discharged to complete treatment on an outpatient basis demonstrated a 55% reduction in length of stay over infants who received their full methadone treatment as an inpatient. Out of 139 NAS cases included in this study, one infant was readmitted for NAS symptoms secondary to maternal inability to obtain the required methadone to complete outpatient therapy. The authors indicated a combined inpatient/outpatient methadone treatment protocol for NAS can reduce an infant’s length of stay and associated health care expenditures without increasing unfavorable events.

- Nanda et al (2015) analyzed data from infants admitted to West Virginia University Hospital’s NICU due to maternal drug exposure from 2009 to 2011. The number of cases related to buprenorphine exposure increased from one case in 2009 to 25 cases in 2011. The number of infants admitted with
methadone exposure did not change significantly over this three-year period. For infants who required pharmacological treatment, morphine was the drug of choice used to treat NAS in both of these cohorts. No significant difference in length of stay or length of treatment was identified between infants with buprenorphine versus methadone exposure. The authors noted that although the incidence of infants with buprenorphine exposure increased during the study period, only one-fourth of these infants required pharmacological treatment.

- Ordean et al (2015) reported on the results of multisite cohort study evaluating neonatal outcomes from a group of 94 methadone-maintained pregnancies from 1997 to 2009. The mean gestational age from this cohort was identified as 38 weeks and the mean birth weight was 2856 grams. Sixty-nine infants required NICU admission but only 27% of these infants required pharmacological therapy for NAS. Non-pharmacological interventions such as skin-to-skin contact and breastfeeding were identified as factors associated with a decreased severity of NAS and thus a reduced need for NAS medications.

- 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 five 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 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 utilized as adjunctive treatment.

- 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...
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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.

  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 and outpatient methadone treatment.

- Smirk et al (2014) performed a retrospective review to evaluate and compare a home-based detoxification program for NAS with traditional inpatient management. Out of 118 infants treated for NAS, 38 were managed at home. The authors identified a shorter hospital stay, similar total NAS treatment duration and an increased rate of breastfeeding in the infants managed with home-based detoxification. The authors acknowledged the paucity of current literature on outpatient NAS therapy and emphasized the impact of patient selection on the safety of home-based detoxification.

- A retrospective cohort study by Kelly et al (2014) evaluated the safety and efficacy of at-home oral morphine weaning for NAS. Fifty-two out of 80 neonates treated for NAS completed their morphine weaning after they were discharged from the hospital. These infants received a longer duration of morphine therapy but demonstrated significantly less returns to the hospital for continued withdrawal treatment (1/52 home-based weaned infants versus 4/28 inpatient weaned infants). The authors concluded that in select cases, at-home morphine weaning may be considered a safe and cost-effective NAS management strategy.

- In 2014, Hall et al performed a retrospective cohort analysis of term and late preterm neonates who had received pharmacologic treatment for neonatal abstinence syndrome (NAS) in the hospital setting. This study analyzed the length of hospital stay and total duration of opioid treatment related to various pharmacologic treatment strategies. The included cohort of 547 infants contained 130 who were managed without an NAS weaning protocol and 417 who were managed with an established NAS weaning protocol. After accounting for hospital variation, the authors identified a significantly shorter duration of opioid treatment and hospital stay in the infants who received protocol-based weaning regardless of the treatment opioid utilized.

- A single-center prospective study by Bada et al (2015) compared morphine versus clonidine treatment for NAS. Thirty-one infants were randomized to receive morphine or clonidine in eight divided doses. Protocol allowed a 25% dose escalation every 24 hours for continued symptoms and a tapered dose
by 10% every other day after control of symptoms. Blinded researchers assessed the infants with the NNNS, Bayley Scales III and Preschool Language Scale IV. Infants treated with clonidine demonstrated a lower height of arousal and excitability with a shorter duration of treatment. Twelve-month motor, cognitive and language scores were similar between the two groups. The authors concluded that clonidine could be considered a favorable single-drug alternative to morphine but additional multicenter randomized trials are needed.

- Bagley et al (2014) performed a systematic review on the assessment and management of neonatal abstinence syndrome. The authors addressed studies related to NAS assessment tools, nonpharmacologic interventions and pharmacotherapy. The need for standardized NAS scoring among healthcare providers was emphasized. The limited evidence related to nonpharmacologic treatment suggested these interventions may be effective in reducing clinical symptoms and subsequently the need for medication. Studies pertaining to NAS pharmacotherapy were noted as small and inconsistent in terms of 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


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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>
</tr>
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<tbody>
<tr>
<td>V1.0</td>
<td>05/16/2013</td>
<td>New clinical guideline (MB)</td>
</tr>
<tr>
<td>V2.0</td>
<td>06/04/2014</td>
<td>Job aid revised into medical necessity clinical guideline. (CE)</td>
</tr>
<tr>
<td>V3.0</td>
<td>06/03/2015</td>
<td>Annual review with update by RS. (CE)</td>
</tr>
<tr>
<td>V4.0</td>
<td>05/05/2016</td>
<td>Annual review with revisions performed by RS. Information on NAS standardized protocols, buprenorphine, clonidine, and morphine weaning added. (CE)</td>
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