Neonatal Abstinence Syndrome Inpatient Management Quality Improvement Toolkit

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OVERVIEW

The purpose of this toolkit is to provide a practical guide for optimal inpatient management of substance-exposed newborns (SENs) at risk for neonatal abstinence syndrome (NAS), leading to standardization of care for all birthing hospitals in Massachusetts with improved outcomes. The toolkit is meant to be a summary of potentially best practices for the assessment and management of infants with NAS. It aims to provide inpatient teams with sample guidelines and protocols, as well as links to literature references and websites on each topic for additional information. The practices promoted in this toolkit are based on an extensive literature review, and consultation with lead NAS centers in the area.

PRENATAL CONSULTATION

We recommend that all pregnant women with known opioid use disorder have a prenatal counselling as early on as feasible after the pregnancy has been diagnosed, providing the mothers to be an opportunity to decrease adverse pregnancy outcomes. This consultation should be performed by both the Obstetric as well as Pediatric teams to address both maternal as well as neonatal care provisions. The goals of the consultation are:

1) To prepare the family for a healthy pregnancy resulting in a term birth.
    a. Discuss the need for continued sobriety for the best outcomes for the infant and be eligible to breastfeed their infant
    b. Discuss the impact of tobacco, marijuana as well prescribed psychiatric medications on infants
    c. Help create a pregnancy plan with core care providers identified early in pregnancy for provision of consistent education and care
    d. Discuss what goals they need to achieve to successfully transition their infants from hospital to home with support of DCF
2) To discuss signs and symptoms of NAS
3) To discuss non-pharmacologic and pharmacologic management of NAS
    a. Non-pharmacologic care as first-line treatment
    b. What % of infants require medication, which medications are used at your institution, and how will medication choice decisions be made
4) To discuss breastfeeding in the setting of maternal opioid use disorder
    a. Review hospital guidelines and eligibility criteria
5) To prepare the family for the hospitalization of infant for NAS monitoring.
    a. Discuss length of inpatient monitoring for 4-7 days for opioid-exposed infants
    b. Discuss location of care
    c. If baby requires pharmacologic treatment, anticipated length of hospitalization
    d. Making arrangements to be present during the hospitalization including speaking to residential treatment programs, methadone guest dosing near the hospital, childcare preparations, and transportation considerations
    e. Getting a support person to assist the mother during the hospitalization
6) To discuss the process of mandatory 51A / DCF screening and toxicology screening

A sample prenatal consultation note template is provided as ***Appendix A.*** A parent handbook and/or handouts summarizing the above information are helpful. Examples are provided in ***Appendix B.***

INPATIENT MONITORING

The American Academy of Pediatrics recommends inpatient monitoring for **4-7 days** for SENs for signs of NAS.[1] Approximately 40-70% of SENs require pharmacologic treatment for NAS despite optimal non-pharmacologic first-line treatment. Most SENs will exhibit signs and symptoms within 48-72 hours of birth after in-utero opioid exposure. Recent data from Boston Medical Center (BMC) over a 5 year period (n=550 infants) indicated that 95% of infants who required pharmacotherapy were identified by day 4, and >99% by day 7. A 2014 meta-analysis indicated a lower risk for NAS requiring pharmacotherapy (RR=0.90) and shorter hospitalizations by 7 days in buprenorphine versus methadone exposed infants, however there is significant confounding by indication.[2] Infants exposed to short-acting opioids such as oxycodone have a reported lower risk for NAS requiring pharmacotherapy.[3] We recommend that infants exposed to short acting opioids be observed for a minimum of 4-5 days for signs of withdrawal.

Co-exposure to nicotine and psychiatric medications increase the risk for NAS requiring pharmacotherapy due to an overlap of withdrawal symptoms from these medications with opioid withdrawal, and drug interactions.[4–6] Careful consideration of the symptom profile (primary neurologic symptoms) and timing of symptoms (< 24 hours of life) can help to distinguish between opioid and co-exposure withdrawal.

Department of Children and Families (DCF)

A copy of the MA DCF guidelines for perinatal substance use is provided in ***Appendix C.*** Key recommendations are:

- Physicians, nurses and social workers are all mandated reporters for any concerns related to abuse or neglect of children.
- Hospitals should have a written policy for reporting positive tests and other concerns to DCF.
- A mandated reporter must file a 51A report with DCF for all infants with neonatal drug withdrawal as well as any infants born to mothers on opioid agonist treatment (methadone and buprenorphine).
- If the mother was only on prescribed methadone, buprenorphine, or other appropriately prescribed medications, the case may be screened out by DCF after filing.
- A social work consultation should be obtained shortly after delivery to facilitate 51A filing and DCF evaluation.
- A DCF decision must be obtained before the infant is discharged home.

DCF website: http://www.mass.gov/eohhs/gov/departments/dcf/
51A filing website: http://www.mass.gov/eopss/docs/msp/missing/51a.pdf

TOXICOLOGY SCREENING

Screening for substance use in pregnancy and use of toxicology testing should be based on your individual hospital's policies. Some general recommendations for toxicology testing consideration include:[7]

1) Known or suspected substance use disorder during the current pregnancy, including women stable on methadone and/or buprenorphine agonist therapy
2) Minimal or no prenatal care
3) Infants with signs/symptoms of NAS where substance exposure is suspected
4) Placental abruption
5) Unexplained intrauterine growth restriction
6) Unexplained neonatal seizures or apnea in a term infant

Maternal Urine Toxicology: A witnessed maternal urine is recommended on admission to Labor & Delivery (L&D). This will detect drugs that have been used within the previous 48-72 hours. THC may be present in the urine for one month following marijuana use. At minimum, a basic urine panel containing cocaine, amphetamines, benzodiazepines, and opiates should be sent.[8] If available, an expanded opioid panel should be sent from the urine, which will specify methadone, buprenorphine, oxycodone, opiate, and/or fentanyl exposure.[9]

Infant Urine Toxicology: Attempt to collect the infant's first void for testing as this will have the highest concentration of substances. Infant urine toxicology results reflect exposure in the preceding 3 days, however cocaine metabolites may be present for 4-5 days. Marijuana may be detected in the urine for weeks after last maternal use; hospitals should consider the utility of urine marijuana screening. Qualitative urine screening should be confirmed with quantitative screening due to risk of false positives.

Meconium Toxicology: Includes enzyme-linked immunosorbent assay (ELISA) testing typically for amphetamines, barbituates, cannabinoids, cocaine/metabolites, opioids, and PCP. Meconium testing in term infants reflects exposure during the second half of gestation. Meconium has a high sensitivity for testing for opiates and cocaine, thus is recommended for perinatal drug testing.[9]

Umbilical cord Testing: Umbilical cord segment testing at the time of birth for toxicology has a more rapid turn-around time than meconium and has been shown to be >90% sensitive and specific for most drugs of abuse including opiates and cocaine, similar to meconium. Cord testing detects more prolonged period of in-utero exposure similar to meconium testing.[10]

Consent: Verbal and/or written consent for maternal and infant toxicology screen should be per hospital policy.

NAS SCORING & ASSESSMENT TOOLS

All infants with in-utero opioid exposure should be assessed every 3-4 hours, timed around cares and feedings, for signs and symptoms of NAS. Key principles of scoring include:

1) The infant should be kept in the room with the mother for scoring if possible
2) The score encompasses the entire 3-4 hour period, not one point in time
3) The infant should be scored after feeding to ensure hunger is not contributing

The most commonly used NAS scoring tool is the **Finnegan Neonatal Abstinence Scoring Tool** (FNAST).(***Appendix D).*** The FNAST is a 21 item scoring system created in the 1970's, characterizing all possible withdrawal signs and symptoms an infant may exhibit, divided into neurologic, autonomic, gastrointestinal categories. It was demonstrated to have a high inter-rater reliability coefficient of 0.82 when first developed.[11,12] Typically scores $\geq$8 are used to determine the need for pharmacotherapy. Using a standardized scoring method such as that available for the FNAST through **Neoadvances** (http://neoadvances.com) in which all providers are trained has been shown to improve NAS outcomes.[13]

Recently, some have come to question the Finnegan as leading to over medication due to overlap of symptoms with other normal infant behavior, and lack of validation for determining what cut off scores should be used to guide pharmacotherapy. A recent study found that the Finnegan had poor psychometric properties and poor internal consistency.[14] Careful provider score interpretation of the Finnegan with prioritization of the physiologic functioning of the infant (e.g., ability to **eat, sleep, and console**) to determine need for pharmacotherapy is an alternative approach that has been associated with a decreased use of medication in preliminary studies.[15–20](***Appendix I – Boston Medical Center Guidelines)***

NON-PHARMACOLOGIC CARE

First-line treatment for infants at risk for NAS is non-pharmacologic care with engagement of the mother as the primary caretaker.[1] Proper use of non-pharmacologic care as first-line treatment has been shown to reduce the need for pharmacologic management by 30-50%.[12,19,21–23] A recent meta-analysis demonstrated a 60% reduction in need for pharmacologic treatment length of stay with rooming-in models of care.[24,25] Essentials of non-pharmacologic care include:

1) Rooming-in model of care: *This can include rooming-in on a postpartum ward, private room NICU, or pediatric inpatient ward.*
2) Skin-to-skin contact
3) Infant holding / gentle rocking / swaying
4) Breastfeeding promotion for eligible mothers
5) Clustering of infant care / allowing for uninterrupted periods of sleep
6) Swaddling
7) Pacifiers
8) Decreasing environmental stimuli to noise and light
9) Feeding on demand
10) Engagement of the mother as the primary caregiver of her infant, with active participation and presence at the bedside throughout the hospitalization

Sample **NAS symptom parent diaries** and **non-pharmacologic care handouts** are provided in ***Appendix E and F.*** All infants should also receive an **occupational / physical therapy consultation**.

BREASTFEEDING

Breastfeeding is recommended by the Academy of Breastfeeding Medicine (ABM), American Academy of Pediatrics (AAP), and the American College of Obstetrics & Gynecology (ACOG) in "stable" women with opioid use disorders on maintenance medications.[26–28] Methadone and buprenorphine are both lactation category 2 medications, with extremely low levels in infant plasma not expected to influence withdrawal severity.[29–31] Breastfeeding in the setting of oxycodone and other short-acting opioids commonly prescribed to postpartum women after C-section are generally safe for lactation except at higher doses due to risk for infant sedation.[29]

Breastfeeding decreases the severity of NAS and need for pharmacotherapy by 30-50%, with associated shorter hospitalizations by 1-2 weeks.[12] "Stability" is defined most explicitly by the ABM as engaged in prenatal care, engaged in substance abuse treatment, a postpartum recovery plan in place, and no relapses in the prior 30 days.[26] Careful consideration should be taken to cases where the mother has sought out care late in the pregnancy, with relapses in the 30-90 days prior to delivery.[26] Sample institutional breastfeeding guidelines are provided in ***Appendix G.***

Formula feeding and supplemental feedings:

There is no current evidence to support one formula supplement vs another for improving NAS outcomes, or proactively starting increased calorie feedings in infants when no other medical indication is present. Babies should be fed on demand and until content. If a baby has excessive weight loss or poor weight gain, a feeding assessment should occur to ensure efficacy and sufficient frequency of feedings. Babies may require more frequent feedings or higher volumes of feeding when withdrawal symptoms are present especially symptoms likely to be associated with increased energy expenditure (e.g., undisturbed tremors, excessive crying) or increased losses (e.g., vomiting, diarrhea). We recommend use of higher calorie (24kcal/oz) breastmilk or formula when excessive weight loss or poor weight gain are present despite optimization of feedings, which is supported by a recent randomized controlled trial.[32]

Hepatitis C and breastfeeding:
Hepatitis C infection in the mother is not a contraindication for breastfeeding. The American Academy of Pediatrics recommends to discuss with mothers that transmission of hepatitis C virus to infants through breastfeeding has not been documented, but to briefly abstain if nipples or surrounding skin are bleeding or cracked.[33]

Marijuana and breastfeeding:
Marijuana use is estimated to impact 10-15% of pregnant women. There is concern for maternal impairment after using marijuana while caring for her infant. Due to its lipophilic nature, THC, the active substance in marijuana, accumulates in the breast milk with potential risk for neurodevelopment impairment.[26–29,34–36] Long-term follow-up data on infants exposed to varying amounts of marijuana via the breast milk are currently lacking. Marijuana is currently classified as a lactation category E medication based on its illicit drug status in many states.[29]

Breastfeeding recommendations should be per hospital policy. General recommendations are:

- Screen all pregnant women for marijuana use starting early in pregnancy and upon admission to L&D.
- Educate about potential harm and recommend abstinence while breastfeeding and caring for her infant.
- In mothers who admit to daily or frequent use, breastfeeding is not recommended.
- Breastfeeding in occasional marijuana users is not an absolute contraindication; focus should be on maternal education about the potential harm and about safe breastfeeding
- Sample marijuana breastfeeding guidelines are provided in ***Appendix H.***

PHARMACOLOGIC MANAGEMENT

Pharmacotherapy is typically initiated for 2 or 3 consecutive Finnegan scores ≥8 or 1 or 2 consecutive scores ≥12. If using a function based scoring system, medication is indicated if the baby is unable to eat / sleep / console effectively with non-pharmacologic measures, and/or if significant autonomic instability is present (e.g., tachypnea, respiratory distress) and felt related to NAS.

First-line Pharmacotherapy Options:
Morphine and Methadone:
Both morphine and methadone are approved by the AAP as appropriate choices for first-line pharmacologic agents.[1,12,25] Morphine is the most commonly used medication, chosen by 50-70% of nurseries in the U.S. Morphine is typically dosed every 3−4 hours with dose ranges of 0.3−1.0 mg/kg/day and most commonly weaned in the inpatient setting. Methadone is used by 20−25% of hospitals with dose ranges of 0.2−0.9 mg/kg, typically with less frequent dosing every 6−12 hours, with recent pharmacokinetic data suggesting every 6 hour dosing may be optimal during the capture phase, with subsequent spacing to q12 hour dosing.[37] A 2014 retrospective cohort study which included data from 14 Children's Hospitals in the U.S. found that methadone was associated with shorter length of opioid therapy and shorter hospitalizations.[38] A single center randomized control trial of 31 methadone or buprenorphine exposed infants found that methadone had the advantage with 7 fewer days of opioid treatment in comparison with morphine.[39] One benefit of morphine is its short half-life, with frequent dosing making tailoring of dose to symptoms potentially easier. The advantages of methadone are that is can be dosed less frequently with a longer half-life which may be better for cases of more severe withdrawal. Less frequent dosing also makes methadone a more feasible option for outpatient dosing which is increasing utilized in other states.[40,41] Regardless of choice of primary agent, a standardized weaning protocol has been associated with improved outcomes.[42] Typically opioids are weaned by 10% daily until reaching 20% of the maximum dose then discontinued. ***See appendix I*** for sample protocols.

Buprenorphine: Sublingual buprenorphine is also being trialed as a first line agent with promising results from studies to date.[25] Dosing used in prior studies are 13-39 micrograms per kg per day in 3 divided doses.[18] Prior randomized trials comparing buprenorphine to neonatal opium solution, morphine, or methadone indicated shorter duration of treatment in the buprenorphine on the range of 4-15 days.[18,43,44] Buprenorphine may be more beneficial for buprenorphine- exposed infants.

Adjunctive Therapy Options:

Phenobarbital: Phenobarbital is the most commonly used second-line agent.[1] Typically phenobarbital is started as a rescue agent at daily dosing of 5-8mg/kg/day in 1-2 divided doses after an initial load. Phenobarbital requires the monitoring of serum levels, with a goal level of 20-30 for NAS. There is no standard recommendation for phenobarbital weaning. We recommend starting the phenobarbital wean 48-72 hours after the infant has completed the wean off of morphine or methadone. Phenobarbital can be weaned as an outpatient by 20% every 3-5 days. Phenobarbital may be better for polypharmacy exposed infants, and those with severe neurologic symptoms.[45] There is concern that prolonged use of phenobarbital in neonates may put infants at risk for future neurodevelopmental delays based on the seizure literature.[46] Sample phenobarbital protocols are provided in ***Appendix I.***

Clonidine: Clonidine is an *α*2-adrenergic receptor agonist which has been used to treat opioid withdrawal in older children and adults, and is being used increasingly in neonates with NAS.[47–49] Clonidine has been used primarily as an adjunctive agent, either started at the same time as the opioid or as rescue therapy, though has also been trialed as a primary agent.[25,47–49] Typically dosing of clonidine is 6 micrograms per kg per day divided every 4-6 hours. Blood pressure and heart rate monitoring is necessary during clonidine treatment and weaning due to potential adverse effects as arrhythmias and rebound hypertension. Though an RCT demonstrated no increased risk for these when weaning is done in a step wise manner.[48] Clonidine is typically weaned in the inpatient setting after the opioid has been discontinued by decreasing the dose in as stepwise manner, such as by increasing the interval. See sample clonidine protocol in ***Appendix I.***

In a randomized study comparing phenobarbital versus clonidine as adjunctive therapy started at the same time as morphine sulfate, though the phenobarbital group had shorter inpatient days of treatment but a much higher outpatient treatment profile.[48]

DISCHARGE PLANNING

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Criteria for discharge include inpatient monitoring for 4-7 days for infants who do not meet criteria for pharmacotherapy, and 24-48 hours off of opioid replacement therapy for pharmacologically treated infants. [1] Stable weight and adequate oral intake should be observed prior to discharge. Essential considerations for discharge planning include ensuring a safe home environment (including a safe sleep space separate from the parents' bed) and early infant follow-up.

Infants with prenatal opioid exposure are at higher risk for failure to thrive, behavioral and developmental delays which are multifactorial in nature.[50–52] They are also at higher risk for eye abnormalities, particularly strabismus.[51,53] Lastly, they are at risk for perinatal hepatitis C virus (HCV) transmission, with 58% of women with opioid use disorders in a Boston Medical Center cohort from 2006-2015 found to be HCV-exposed, and a documented 4-8% transmission rate in HIV-negative women with chronic hepatitis C, although many infants do spontaneously clear the virus.[33,54–56]

Specific recommendations for follow-up include:

1) Safe sleep promotion

2) Verbal hand off with outpatient pediatrician discussing relevant medical and social issues during hospital course including:
    - Documentation of phenobarbital weaning plan, if indicated
    - Custody status of infant
    - Maternal substance use disorder treatment status
    - Any parenting behaviors of concern, if observed prior to discharge
3) Primary care follow-up within 1-2 days of discharge
4) Visiting nurse assessment including weight check within first 1-3 days following discharge
5) Early Intervention referral for all substance exposed newborns: http://www.mass.gov/eohhs/gov/departments/dph/programs/family-health/early-intervention/
6) High risk infant follow-up clinic starting at 6-8 weeks of life
7) Pediatric infectious diseases outpatient appointment for Hepatitis C exposed infants: https://www.bmc.org/pediatrics-infectious-disease
    a. Recommended laboratory testing includes:[33,53–56]
        1. Antibody testing at 15-18 months, as maternal antibody can take up to 15-18 months to clear
        2. If a diagnosis is desired sooner for parental anxiety or clinical suspicion, RNA testing can also be done starting as early as 2-6 months (earlier is not recommended because of more frequent false positive results).
    b. Recommended Approach:
        1. If feasible, pediatric infectious diseases outpatient referral, with initial apt at age 2-6 months for testing and counselling
        2. If preference to follow infant in primary care, send serum *quantitative* HCV RNA every 6 months, starting at age 3-6 months, along with HCV Antibody starting at 15 months of age. Two negative HCV RNAs (on separate occasions) or any negative antibody are considered sufficient to exclude chronic HCV infection. For any positive tests, refer to pediatric infectious diseases.
8) Ophthalmology follow-up at 4-6 months of age to look for refractive errors and strabismus.[51,53]

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