Neonatal Abstinence Syndrome: Evaluation and Management

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Objectives

• Explain the scope/incidence of Neonatal Abstinence Syndrome.

• Discuss identification of Neonatal Abstinence Syndrome.

• Discuss the appropriate monitoring – abstinence scales.

• Explain appropriate management of Neonatal Abstinence Syndrome.
On the rise

- ~4.5% of pregnant women 15-44 years old report recent use of illicit drugs*
- Increase in number of infants coded at discharge with neonatal withdrawal increased from 7653 in 1995 to 11,937 in 2008
- SSM Saint Mary’s is experiencing ~ a 2-3x the number of babies it did compared to 2—3.

Cost of NAS

- Average hospitalization for an infant was $53,400.
- Medicaid is primary payer ~ 78%.
- Does not include the “hidden costs” of addiction.
- Could costs be reduced by standardization of care as well as care management changes?

Neonatal Abstinence Syndrome

- Result of fetal exposure to illicit or prescription drug use by the mother prenatally.
- Results in transient neonatal signs consistent with withdrawal or acute toxicity.
- May cause sustained/permanent signs as a result of the drug effect.
Withdrawal vs Acute toxicity vs Permanent Drug effect

• Some drugs cause *acute toxicity*. Signs and symptoms abate with drug elimination (time). Most commonly seen in neonates exposed to SSRIs.

• Signs and symptoms of *withdrawal* worsen with drug elimination (time).

• Some signs and symptoms are the result of a permanent drug effect eg. fetal alcohol syndrome.
Most common drugs causing withdrawal symptoms in neonates today…
Nicotine Withdrawal in the Neonate

- 10% of pregnant women use tobacco.
- Dose dependent. Occurs during 12-36 hol.
- Sx/Sx: hypertonicity, irritability, tremors and sleep disturbances.
- Using Finnegan scoring tool infants may exhibit Sx/Sx resulting in a scores of 4.
- Often infants will be withdrawing from nicotine and opioids simultaneously.


Cocaine

- Sx/Sx likely related to drug effect/toxicity
- Difficult to assess since many of these infants had polysubstance exposure
- Signs and symptoms:
  - Controversial if there are any at all.
  - Some report irritability, hyperactivity, tremors, high-pitched cry and excessive sucking.
  - Heavy exposure: infants more excitable and had poorer state regulation.
Cocaine

- Peak effects around day 2-3
- No recommended pharmacologic treatment.
Methamphetamine

• Another potent sympathomimetic similar to cocaine.
• Contributes to risk of placental abruption, preterm delivery, fetal distress and intrauterine growth restriction.
Methamphetamine

- Few infants demonstrate withdrawal symptoms
- Again difficult to assess cause and effect as many infants are polysubstance exposed.
- Long-term effects: possibly neurotoxic affecting cognitive and behavioral skills and physical dexterity.
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Most frequently prescribed drugs to treat depression in women. ~6% of all pregnancies.
- Third trimester use linked to several signs and symptoms in about 30% of pregnancies: jitteriness, continuous crying, irritability, restlessness, tremors, fever, hypertonia, respiratory distress, tachypnea, feeding difficulty, sleep disturbances, seizures and hypoglycemia.
- Onset of Sx/Sx from several hours to several days.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Is the “syndrome” as a result of too much serotonin (acute toxicity) or too little (withdrawal)?
SSRI toxicity vs Withdrawal

- **Toxicity:** Agitation, autonomic hyperactivity such as fever, tachypnea, tachycardia, and neuromuscular abnormalities such as tremor and hypertonia

  Vs

- **Withdrawal:** anxiety, headache, sluggishness, fatigue and occasionally dystonia.
Currently, cognitive development seems normal, while behavioral abnormalities may be increased\(^1\):

- In boys, prenatal exposure to SSRIs may increase susceptibility to ASD or DD. Findings from published studies on SSRIs and ASD continue to be inconsistent. Potential recall bias and residual confounding by indication are concerns. Larger samples are needed to replicate DD results. Because maternal depression itself carries risks for the fetus, the benefits of prenatal SSRI use should be carefully weighed against potential harms\(^2\).

- Prolonged use of SSRI during pregnancy was associated with lower language competence in children by age three independently of depression\(^3\).


Opioids

• Mechanism of action: activate the μ-opioid receptor in the CNS acutely inhibiting the release of noradrenaline at synaptic terminals.

• Natural, endogenous and synthetic available

• Side-effects: sedation, euphoria, miosis, respiratory depression and decreased GI motility.
Opioids

• With chronic exposure, tolerance develops.
• With abrupt cessation, supranormal amounts of noradrenaline are released producing the characteristic symptoms of withdrawal.
Opioid Use/Abuse in Pregnancy

- Opioids are lipophilic and easily cross the placenta
- Detoxification is associated with increased risk of fetal distress or loss.
Goal of methadone treatment in Pregnancy

• Can sustain opioid concentrations in the mother or fetus that minimize cravings;
• Suppress abstinence symptoms
• Block heroin-induced euphoria
• Prevents fetal distress
• Optimize prenatal care and general maternal health
• Help with anticipation of neonatal withdrawal
Disadvantages of methadone treatment during pregnancy

• Extremely unlikely successful detoxification after delivery;
• More severe and prolonged course of NAS compared with heroin exposure.
Role of Buprenorphine in treatment of opioid dependence during pregnancy.

- Synthetic partial µ-opioid agonist
- Not approved by the FDA for use in pregnancy
  - Class C pregnancy drugs
- May be used alone or in combination with naloxone (opiod antagonist)
- “Ceiling effect”
Advantages of Buprenorphine Treatment regimens

• Infants had shorter hospital stays (10 vs 17.5 days)
• Shorter treatment durations for NAS (4.1 vs 9.9 days)
• Lower cumulative doses of morphine (1.1 mg vs 10.4 mg)

... compared to infants whose mothers were treated with methadone.

Clinical presentation of NAS

- Varies based on:
  - The opioid
  - Maternal drug history eg timing of most recent use
  - Maternal metabolism
  - Net transfer of drug across the placenta
  - Placental metabolism
  - Infant metabolism and excretion
  - Other concomitant drug use such as cigarettes, etc.
NAS

• Onset:
  – heroin use ~ 24 hours
  – for Methadone/Buprenorphine use usually 48-72 hours but may be up to 5-7 days
  – Depends on half life of drug used

• Incidence and severity greater with methadone exposure vs buprenorphine or heroin exposed infants.
# NAS – signs and symptoms

## Neurologic signs
- Irritability
- Increased wakefulness
- High-pitched cry
- Tremor
- Increased muscle tone
- Frequent yawning and sneezing
- Seizures (2–11%)

## Gastrointestinal
- Vomiting/diarrhea
- Dehydration
- Poor weight gain
- Poor feeding
- Uncoordinated and constant sucking

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NAS – signs and symptoms

Autonomic

– Diaphoresis
– Nasal stuffiness
– Fever
– Mottling
– Temperature instability
– Piloerection
– Mild elevations in respiratory rate and blood pressure

Diagnosis of NAS

- Rule out other possibilities such as sepsis, hypoglycemia, hypocalcemia and trauma.
- Detailed maternal history
- Clinical symptoms
Diagnosis of NAS - Drug screen

Which is “best”?
Meconium

– Preferred over urine for testing of neonates.
– Highly specific (~95%)
– Documents drug use over an extended period of time, covering at least the last trimester of pregnancy
– Meconium is easier to obtain than urine (combining all meconium voids can be helpful if sample size is small. Need at least 4 grams.)
Urine testing indicates drug use only over the last 1–10 days
Umbilical Cord Tissue

- Preferred specimen for assessing in utero exposure of the neonate to maternal drug use when meconium is not available
- Deposition of drugs in umbilical cord tissue is not well studied, but window of detection appears similar to meconium
Diagnosis of NAS - Drug screen

Which is “best”? 
Tools for Assessing NAS

- Quantify severity
- Assist with determination of initiation of therapy and titrations of therapy
- Scores calculated at regular intervals to assess severity of withdrawal
Tools for Assessing NAS

• It allows us to evaluate the onset and progression of these symptoms, and assess the response to detoxification management strategies.

• Treatment threshold is specific to each tool
Tools for Assessing NAS

• Finnegan scoring system
• Lipsitz Tool
• Neonatal Narcotic Withdrawal Index
• Ostrea System
• Neonatal Withdrawal Inventory
Tools for Assessing NAS

- **Stick with one across your practice** so everyone is speaking the same language.
- Permits standardization and consistency of management.
- Nursing staff must be proficient in the use and application of this tool.
- Must have interobserver reliability.
Non-pharmacologic Treatment

• *Should be Standardized.*
• Should start immediately after birth.
• Used as *adjunct* therapy to medical treatment.
• Must educate families with specific details and demonstrations.
Non-pharmacologic Treatment

- Swaddling
- Rocking
- Minimal sensory and environmental stimulation
- Maintain temperature stability
Non-pharmacologic Treatment

- Consider use of weighted blankets or gentle firm pressure
- Promote skin to skin contact
- Minimize interruptions
  - Cluster care
  - Allow infant to demand feed
- OT/PT or infant massage if available
Non-pharmacologic Treatment

- Pacifier for excessive sucking
- Rooming in with mom if safe.
- Frequent diaper changes for loose and frequent stools
- May benefit from higher calorie formula to assist with higher metabolic demands of withdrawal (150-250 kcal/kg/d).
- Frequent smaller volume feeds.
Breast-feeding on Methadone

- Breast milk feedings did significantly reduce the need for withdrawal pharmacotherapy compared with formula-fed infants (53% vs 79%, P<0.001)
- Reduced length of hospital stay by an average of 5 days.

However...

Breast-feeding on Methadone

• Not a good idea for moms who are not participating in a drug rehab program.
• Polysubstance abuse also an exclusion criteria.
• CDC states mothers with Hepatitis B and C are not contraindications to breast-feeding.
• HIV or other co-morbid diseases are a contraindication to breast-feeding.
Preserving the Maternal-Infant Dyad

• Antenatal consults and ongoing education of parents to discuss what to expect with Social work involvement as well as drug counselor if available.

• Allow infants to room with mom*:
  – a decreased use of morphine
  – Improved weight gain
  – More babies went home with their mothers

Culture Change

• Nursing and physician education to help change in attitudes.
• Addiction is a disease.
• The drugs change addicts brains interfering with normal mother-baby bonding.
• Must support mom before, during and after hospitalization.

Preserving the Maternal-Infant Dyad

• Encourage mom to enter rehab
• Encourage participation in a support group
• Offer a support group.
• Know your local resources to support moms eg rehab facilities, counselors, subsidized housing or homes for moms and their babies.

Pharmacologic Management of NAS

“Opiates compared to supportive care may reduce time to regain birth weight and duration of supportive care but increase duration of hospital stay. “

That being said…
AAP guidelines for Pharmacologic Treatment

“Drug therapy is indicated to relieve moderate to severe signs of NAS and to prevent complications such as fever, weight loss, and seizures if an infant does not respond to a committed program of nonpharmacologic support.”
Morpine vs Methadone

- ½ life ~ 4.5-13.3 hrs
- Dosage 0.02-0.05 mg/kg per dose q3-4hrs
- Ethanol content: Zero
- Bioavailability: variable but <40%
- More up/down drug levels until steady state reached.

- ½ life ~ 4-62 hrs
- Dosage 0.05-0.1 mg/kg per dose q6 hrs initially. May wean to q12.
- Ethanol content: 8%
- Bioavailability: 36-100%
- Longer half-life results in less ups and downs.
Morphine vs Methadone

- Requires more frequent dosing q3-4 vs q6-12hr
- Higher risk of drug accumulation and resultant toxicity
  - Less nimble to wean.
  - More ethanol
Indications for Starting Pharmacologic Therapy

- Depends on NAS scoring tool
- Typically with modified Finnegan scores: 3 (2) scores 8 or greater, 2 scores greater >9 are indications for treatment.
- Transfer to Special Care Nursery or NICU for close monitoring.
Pharmacologic management of NAS – morphine dosing

Two options

- Symptom-based: Individualizes treatment with presumed goal of more rapidly reducing NAS signs and symptoms.
Weight-based Dosing

• Standard dosing of medication for neonates with risk of over-treatment of SGA/growth-restricted infants.
• Dose escalated for continued elevated scores >8-10.
• For example…
Weight-based Dosing

- 3 kg infant admitted to NICU/Special care nursery for NAS scores of 12, 13.
- Started on oral morphine solution with a dose of 0.02 mg/kg/d.
- Scored q2hrs per modified Finnegan. Still 10 at 2 hrs after initial dose → Given morphine 0.04mg/kg PO.
- Scored again 2 hrs later and score 9. Given morphine 0.06 mg/kg PO x1.
Symptom-based Scoring

- Assumes infants are >37 weeks
- Assumes not significantly growth restricted.
- Starting dose depends on initial scores eg.
- Why dose according to symptoms?
  - Spectrum of physiologic and behavioral Sx is more variable than infant birthweights
  - As are the frequent changes in infant withdrawal status
  - Dosing by weight assumes some correlation with plasma levels, but there is not a demonstrable relationship between plasma drug levels and NAS Sx

Morphine dosing according to Categories of scores

<table>
<thead>
<tr>
<th>Categories</th>
<th>Score</th>
<th>Morphine dose (oral solution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-8</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>9-12</td>
<td>0.04 mg</td>
</tr>
<tr>
<td>II</td>
<td>13-16</td>
<td>0.08 mg</td>
</tr>
<tr>
<td>III</td>
<td>17-20</td>
<td>0.12 mg</td>
</tr>
<tr>
<td>IV</td>
<td>21-24</td>
<td>0.16 mg</td>
</tr>
<tr>
<td>V</td>
<td>&gt;25</td>
<td>0.20 mg</td>
</tr>
</tbody>
</table>

Maximum dose of morphine?

- Not really
- Dose should be titrated up according to continuing NAS scores >8.

However, if infant symptoms are still not controlled on 1 mg/kg/d of morphine and/or there are complications/unacceptable side effects of morphine use, consider changing to methadone or adding clonidine.
Weaning

• When NAS scores <8 for 48 hours and in the presence of adequate weight gain, consider weaning by 0.02 mg/dose (0.05 ml).

• Do not wean faster than q24-48 hours.

• It is recommended to wean the dose by 0.02 mg (0.05 ml) until the starting dose is reached.
Weaning

• Once the starting dose has been reached, the frequency of the medication can be adjusted.

• Recommended interval changes are every 4 hours, to every 6 hours, and then to every 8 hours.

• If the baby had difficulty on a q 8 hour interval, consider weaning to q12 hours.
Role of clonidine in NAS

- Alpha$_2$-adrenergic receptor agonist used to ameliorate opiate withdrawal symptoms.
- Prevents hyperactivity and autonomic instability to promote normal patterns of sleeping, feeding and weight gain.
- Must be weaned off over a week.
- Likely a role but not recommended or widely used yet

Weaning

Once tolerating q8-12 hours for 24-48 hours, stop the morphine and observe for at least 24 - 48 hours prior to discharge.
Weaning: Need for reescalation

- If two or more scores are >9, treatment should be reescalated.
- Go back to last dose or interval when scores were <8 consistently.
- Wait another 24-48 hours before weaning if needed to reescalate dose.
Questions?
References

- ARUP Consult: the physician’s guide to laboratory test selection and interpretation web site: topic “Newborn Drug Screening - Meconium and Umbilical Cord”.
- Modified Finnegan Scoring Tool.
References