Neonatal Abstinence Syndrome
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Disclosures
I have no financial disclosures

Objectives
- Identify the substances associated with neonatal abstinence syndrome (NAS)
- Discuss the pathophysiology of NAS
- Understand the symptoms/clinical manifestations of NAS
- Discuss the evaluation of NAS via scoring systems
- Understand the treatment options available and which patients qualify for treatment
  - Understand criteria for escalation/weaning of pharmacologic therapies
- Discuss discharge criteria, follow-up needs, and outcomes of NAS
What is Neonatal Abstinence Syndrome?

“Neonatal abstinence syndrome (NAS) is a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy”

- Chronic fetal exposure to substances
- Multisystem disorder – primarily affects CNS, autonomic nervous system, and GI tract
- NAS is rarely fatal, but may cause significant illness/symptoms and can result in prolonged hospital stays

Substances Associated with NAS

- Alcohol
- Antidepressants – SSRIs, SNRIs, TCAs
- Barbiturates
- Benzodiazepines
- Caffeine
- Inhalants
- Marijuana
- Opiates
- Tobacco/nicotine
- Stimulants – cocaine, methamphetamines

A Look to the Past – History of NAS
A Look to the Past – History of NAS

- Opium use dates back to ancient civilizations
- Opium addiction first recorded at end of 18th century
- Congenital morphinism (opiate withdrawal following birth) first diagnosed in 1875
  - Most of the infants with this diagnosis died
  - 1903 – first case of infant surviving after treatment with morphine
  - 1947 – first successful treatment of secondary seizures
- Subsequently renamed Neonatal Abstinence Syndrome

Opiate Use in Reproductive Age Women

- CDC 2015
- Epidemiology
  - Maternal opioid use is increasing
    - Increased from 1.2 to 5.6 mothers per 1000 live births from 2000-2009
    - 6% of mothers used opioids for more than a month during pregnancy
    - Rise in methadone maintenance treatment accounts, in part, for increased incidence of NAS
  - The incidence of NAS has been increasing in the US
    - Incidence of NAS increased from 1.2 to 5.8 per 1000 hospital births per year from 2000-2012
NICU Admissions for NAS

Evolution of NAS
- Prior to 1970, NAS generally secondary to morphine or heroin use
- Today NAS may be secondary to use of morphine, heroin, methadone, buprenorphine, prescription opiates, antidepressants, anxiolytics, and other substances
- NAS has become more complex and severe
  - Increased use of opiates
  - Complicated by simultaneous use of multiple substances (including illicit drugs)

Opioid Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (μ)</td>
<td>Brain, spinal cord, peripheral sensory neurons, intestinal tract</td>
<td>Analgesia, physical dependence, respiratory depression, euphoria, reduced GI motility, physical dependence</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Brain, spinal cord, peripheral sensory neurons</td>
<td>Analgesia, anti-convulsant effects, hallucinogenic effects, drowsiness, euphoria, sedation</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Brain, peripheral sensory neurons</td>
<td>Analgesia, antidepressant effects, constipating effects, physical dependence</td>
</tr>
</tbody>
</table>
Pathophysiology

- Pathophysiology poorly understood
- Many factors affect the accumulation of opioids in the fetus.
  - Opiates have low molecular weights, are water soluble and lipophilic thus they are easily transferred to the fetus from the placenta
    - This process increases with increasing gestational age
  - Synthetic opiates cross the placenta more readily than semi-synthetic opiates
  - Combination of cocaine or heroin with methadone increases permeability of methadone across the placenta
  - Drugs can readily cross the blood brain barrier of the fetus
  - Prolonged half life common in the fetus

Pathophysiology

Opiate withdrawal is a complex phenomenon

- Cellular and molecular mechanism is poorly understood, even in adults
- More complicated in neonates given immature neurologic development

Locus Coeruleus of the Pons is the most important center of activity in opioid withdrawal

- Lack of opiates causes increased production of norepinephrine – which is responsible for most of the signs of NAS

No relationship between maternal opioid dose and NAS
**Pathophysiology**

- SSRIs/SNRIs cause withdrawal symptoms due to excess serotonin and norepinephrine
- TCA's cause a cholinergic rebound
- Benzodiazepine withdrawal probably cause increased GABA release
- Methamphetamine withdrawal may be secondary to decrease in dopamine and serotonin
- Inhalant withdrawal involves dopamine, glutamate, and GABA pathways

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**Risk Factors for Development/Severity of NAS**

**TABLE 2 Risk factors for increasing severity and/or intensity of NAS**

<table>
<thead>
<tr>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term&lt;0399</td>
<td>Male gender&lt;0399</td>
</tr>
<tr>
<td>Low birth weight&lt;2500</td>
<td>Methadone&lt;0399</td>
</tr>
<tr>
<td>Polydrug abuse&lt;0399</td>
<td>Smoking&lt;0399</td>
</tr>
<tr>
<td>Combination with benzodiazepines&lt;0399</td>
<td>Combination with SSRIs&lt;0399</td>
</tr>
<tr>
<td>μ-opioid receptor (OPRM1) 118 Arg/Asp&lt;0399</td>
<td>Combination with SSRI's&lt;0399</td>
</tr>
<tr>
<td>Catechol-O-methyltransferase (COMT) 158 Ala/pro&lt;0399</td>
<td></td>
</tr>
</tbody>
</table>

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**Symptoms/Clinical Manifestations**

Dysfunction in 4 domains (state control and attention, motor and tone control, sensory integration, and autonomic functioning) cause the characteristic signs of NAS

- High pitched cry/irritability
- Sleep/wake disturbances
- Alterations in tone or movement (hyperactive primitive reflexes, hypertonicity, and tremors)
- Feeding difficulties
- GI disturbances (vomiting and loose stools)
- Autonomic dysfunction (sweating, sneezing, mottling, fever, nasal stuffiness, and yawning)
- Failure to thrive (may require more than 150 kcal/kg/day)
Clinical Manifestations
- Seizures reported in 2-11% of infants with NAS
  - May be caused by different drugs, including opiates, barbiturates, alcohol, and sedative-hypnotics
  - Cause of seizures unknown, abnormal EEG changes can be seen in >30% of neonates withdrawing from opiates
  - Naloxone use must be avoided in cases of chronic maternal opioid use as it can precipitate seizures
- SGA (birth weight less than 10th percentile)
- Respiratory complications (tachypnea and apnea)

Prematurity and NAS
Incidence and severity of NAS less extensive in preterm neonates
- Decreased cumulative exposure
- Decreased transmission across placenta in earlier gestations
- Decreased drug clearance
- Decreased excretion due to renal and hepatic maturity
- Decreased receptor development and sensitivity
Assessment of symptoms can be difficult as scoring systems are not intended for premature neonates

Timing of Withdrawal
- Signs may be present at birth and not reach peak until 3-4 days of life
- May not appear until 10-14 days of life
- Subacute withdrawal may persist for 4-6 months
- Neurologic irritability (abnormal Moro reflex) noted to last up to 7-8 months of age
Timing of Withdrawal

**Clinical Report: Neonatal Drug Withdrawal 2012**

### Laboratory Testing
- NAS is a clinical diagnosis, but toxicological confirmation is necessary to identify the substance(s) mother was using or abusing.
- Urine testing has low sensitivity and high false negative rate – only infants with recent exposure will have a positive test.
- Mecinum analysis is sensitive and specific:
  - Drugs excreted into either hepatobiliary system or amniotic fluid via renal excretion.
  - Reflects drug exposure in second and third trimesters.
  - Testing often performed offsite and results may take days to weeks.
  - Mecinum passage may be delayed, may have already occurred in utero, and must be collected before contaminated with transitional stools.
  - Mecinum is light and temperature sensitive so proper storage is important.

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset, h</th>
<th>Frequency, %</th>
<th>Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>24-48</td>
<td>45-86%</td>
<td>5-10</td>
</tr>
<tr>
<td>Methadone</td>
<td>48-72</td>
<td>12-54%</td>
<td>Up to 30</td>
</tr>
<tr>
<td>Naloxone</td>
<td>24-48</td>
<td>25-50%</td>
<td>1-3</td>
</tr>
<tr>
<td>Methadone (oral)</td>
<td>24-48</td>
<td>25-50%</td>
<td>1-3</td>
</tr>
<tr>
<td>Methadone (nasal)</td>
<td>24-48</td>
<td>25-50%</td>
<td>1-3</td>
</tr>
<tr>
<td>Methadone (intravenous)</td>
<td>24-48</td>
<td>25-50%</td>
<td>1-3</td>
</tr>
<tr>
<td>Methadone (sublingual)</td>
<td>24-48</td>
<td>25-50%</td>
<td>1-3</td>
</tr>
</tbody>
</table>

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**Lawrence: Neonatal Abstinence Syndrome**
Laboratory Testing

- Umbilical cord testing using immunoassays is a promising method of testing, but currently the utility in medical management is limited.
- Testing of neonatal hair is challenging and often culturally unacceptable so medical management is limited.
- A combination of maternal urine and neonatal meconium usually yields the best results.
- Need for consent for testing varies among states.
- Each hospital should adopt a policy for maternal and newborn screening that complies with laws and avoids discriminatory practices.

Comorbidities

- Sexually transmitted infections
  - Syphilis
  - Chlamydia and gonorrhea
  - Hepatitis C
  - HIV
- Maternal polydrug use
- Psychiatric comorbidity common in substance abusing women.
NAS Scoring

• Several scoring systems have been developed and verified to evaluate withdrawal symptoms
  • Finnegan NAS scoring system
  • Lipsitz tool
  • All scoring systems are subject to interobserver variability
  • Tools measure the severity of symptoms and are used to initiate, escalate, and wean pharmacologic therapies
  • In each birth center caring for infants with NAS, a scoring system should be adopted
  • Management protocols should be developed using the scoring systems
    • Decreases duration of opioid exposure and length of stay

NAS Scoring

• Finnegan Scoring system and its modified versions are designed for term neonates
  • It is the most widely used scoring method
  • Major limitation is non-applicability to <37 weeks GA, and babies older than 30 days
  • NAS scoring should begin at birth and ongoing assessments should be performed every 3-4 hours (after feeds) during hospital stay
  • Score should represent status of infant at the time of feeds and in the preceding interval
Finnegan Scoring System

CNS Disturbance
- Excessive high pitched cry (2)
- Continuous high pitched cry (3)
- Sleeps <1 hr after feeding (3)
- Sleeps <2 hrs after feeding (2)
- Sleeps <3 hrs after feeding (1)
- Hyperactive Moro Reflex (2)
- Markedly Hyperactive Moro reflex (3)
- Mild tremors: Disturbed (1)
- Mod-Severe tremors: Disturbed (2)
- Mild tremors: Undisturbed (3)
- Mod-Severe tremors: Undisturbed (4)
- Myoclonic Jerks (3)
- Generalized Convulsions (5)

Finnegan Scoring System

Metabolic/Vasomotor/Respiratory Disturbances
- Sweating (1)
- Fever 100°F-101°F/38.3°C-38.9°C (1)
- Fever >101°F/38.9°C (2)
- Frequent Yawning [>3-4x/interval] (1)
- Mottling (1)
- Nasal Stuffiness (1)
- Sneezing [>3-4x/interval] (1)
- Nasal Flaring (2)
- Respiratory Rate >60/min (1)
- Respiratory rate >60/min with retractions (2)

Finnegan Scoring System

GI Disturbance
- Excessive sucking (1)
- Poor feeding (2)
- Regurgitation (2)
- Projectile vomiting (3)
- Loose Stools (2)
- Watery Stools (3)
Supportive Care
- Should be performed in ALL neonates, may help to avoid pharmacologic treatment, and lead to earlier discharge
- Decrease stimuli – quiet, dark environment
- Avoid overheating
- Gentle handling
- Swaddling
- Encourage skin to skin contact
- Feed on demand
- Consider need for higher caloric density formula/fortified breast milk to supplement increased caloric needs
- Rooming in with mother and baby also decreases the severity of withdrawal

Breastfeeding
- Multiple studies have shown that breast milk contains only minimal quantities of methadone and buprenorphine
  - The amount of methadone or buprenorphine in breast milk is too small to treat NAS
- Sudden discontinuation of breast milk is not associated with the worsening of NAS
  - However, gradual weaning from breastfeeding is advised
  - Breastfeeding increases mother-infant bonding, enhances maternal confidence, and encourages active maternal participation in the management of the infant
  - Breastfeeding may decrease the incidence of NAS, the need for pharmacological treatment, and the length of the hospital stay
- Breastfeeding is contraindicated only if the mother is taking illicit drugs, has polydrug abuse, or is infected with HIV

Pharmacologic Treatment
- Required in 27.91% of neonates with NAS
- Aimed to improve short-term clinical symptoms
- Given complex nature of withdrawal and unknown effects of various drugs, currently data is limited regarding optimal pharmacologic agents for treatment of NAS
  - Opioid therapy is the preferred treatment based on current literature and AAP recommendations
  - Medications required when:
    - Supportive therapy fails to control the signs and symptom
    - NAS scores remain high
    - Serious signs are observed, such as seizures
    - Withdrawal is associated with severe dehydration because of diarrhea and/or vomiting
  - Initiate pharmacologic therapy using 24 rule for NAS scoring
    - 3 consecutive scores > 8 OR 2 consecutive scores > 12
Pharmacologic Treatment

- Delays in administration of pharmacological therapy are associated with higher morbidity and longer hospital stays
- The AAP clinical report from 2012 recommends that either morphine or methadone are the preferred opioids for treating NAS
- Buprenorphine is a new option for the treatment
  - Given sublingually
  - No large-scale studies are available to support its use
- Paregoric is NOT recommended because it contains multiple opiates and alcohol
- Tincture of opium has 25 times higher concentration of morphine than oral morphine solutions which increases likelihood of overdose
- Sedatives, such as diazepam and chlorpromazine, are not useful due to their prolonged half-lives and associated complications

Morphine
- Most commonly preferred medication
- Decreases incidence of seizures
- Prolongs length of hospital stay
- Short half-life requiring q3-4 hour dosing intervals
- Dose can be escalated rapidly for higher scores
- Weaning must be gradual

Methadone
- Alternative to morphine treatment
- Used more commonly in US than in other countries
- Administered twice per day
- Long half-life
- Difficult to titrate methadone dose
Pharmacologic Treatment

Second medication may be required if the infant’s symptoms are not adequately controlled by a single medication therapy.

- Clonidine and phenobarbital are common adjunctive agents.

Clonidine

- Often is the preferred second line medication.
- Shown to be effective as an adjunctive medication to opioid therapy for the treatment of NAS.
- Theoretical risk of hypotension and bradycardia may always prohibit increasing its dose.

Phenobarbital

- A systematic review compared phenobarbital with supportive care alone and showed that phenobarbital did not reduce treatment failure or the time required to regain birth weight.
- Does not prevent seizures at the dosage administered for withdrawal.
- Used as an adjuvant, especially in infants suffering withdrawal from polydrug abuse.
- Disadvantages: sedating, may be difficult to wean.

Pharmacologic Treatment and Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage/Method</th>
<th>Duration</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>0.05-1 mg/kg</td>
<td>Days</td>
<td>Hourly</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1-2 mg/kg</td>
<td>Days</td>
<td>Hourly</td>
</tr>
</tbody>
</table>

Medication Use in Infants with NAS
Escalating Therapy

- Allow infant to stabilize 12-24 hours after starting initial dose
- Increase dose by 10-20% (of original dose) for combined scores of ≥24 on 2-3 consecutive scores
- Dose may be increased as needed every 12 hours until symptoms are controlled
- Consider adding phenobarbital if:
  - Polysubstance exposure, prominent CNS findings (tremors, increased muscle tone), AND morphine dose exceeding 1 mg/kg/day with NAS scores remaining ≥24 OR unable to wean for 2 consecutive days
- Consider adding clonidine if:
  - NAS score primarily elevated secondary to autonomic over stimulation (sweating, mottling, sneezing, fevers, etc), AND morphine dose exceeding 0.1 mg/kg/dose Q3 hours and still not stabilized
Stabilization and Weaning Therapy

- Once stabilized on morphine dose for 48 hours, use this dose as the starting point for the morphine wean
  - Consider 72 hours of stabilization if morphine dose > 0.4 mg/kg/dose or if adjunctive therapy needed
- Do NOT change the dosing interval during weaning – maintain at Q 2-3 hour interval

**Morphine only:**
- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
  - Discontinue morphine when the morphine dose is 0.02 mg/kg/dose OR 0.05 mg/dose whichever is higher
- When morphine at 0.3 mg/kg/day (or 0.04 mg/kg/dose) then maintain morphine dose and discontinue phenobarbital, observe for tolerance for 48 hrs
- Resume morphine wean of 10% of the stabilizing dose Q 24-48 hours

**Morphine and Phenobarbital:**
- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
- When morphine at 0.3 mg/kg/day (or 0.04 mg/kg/dose) then maintain morphine dose and discontinue phenobarbital, observe for tolerance for 48 hrs
- Resume morphine wean of 10% of the stabilizing dose Q 24-48 hours

**Morphine and Clonidine:**
- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
  - Discontinue morphine when the infant has tolerated a morphine dose of 0.02 mg/kg/dose OR 0.05 mg/dose whichever is higher
  - After patient has been stable off morphine for at least 24 hours, clonidine should be discontinued and the patient monitored for a minimum of 48 hours due to risk of rebound hypertension

Discharge Criteria

Length of hospitalization should be sufficient to detect any subsequent signs of NAS

- Minimum of four to seven days for infants exposed to any opioid
- Small subset of infants may have delayed presentation of NAS

The infant may be discharged when:

- Shows no major signs of withdrawal
- Feeding well
- Sleeping well
- Gaining weight
- Maintaining stable withdrawal scores off of pharmacologic therapy for at least 24 hours

May be discharged with the parents (if the home environment is safe and stable) or to a foster home

Follow-up

- Close follow-up by pediatrician as outpatient is crucial
- Neuropsychological assessments to identify motor deficits and cognitive delays
- Psycho-behavioral assessments to identify hyperactivity, impulsivity, and ADHD in preschool aged children
- Ophthalmologic assessment to look for nystagmus, strabismus, and other visual deficits
- Growth and nutritional assessments to identify failure to thrive/inadequate weight gain and feeding problems
- Family support assessments to exclude ongoing maternal substance abuse and child abuse
Neurodevelopmental Outcomes

- Often difficult to tease out contribution from substance exposure on developmental outcomes given presence of confounding variables
  - Prematurity, IUGR, continued maternal drug use, low socioeconomic and educational levels, etc
- Studies reported developmental and behavioral concerns in children with prenatal opiate exposure
- Methadone-exposed infants have been found to exhibit increased motor rigidity, dysregulated motor patterns and decreased activity by observation and maternal report
  - Deficits persisted into toddler years and were associated with less social responsivity, shorter attention spans, and poorer social engagement

- An Australian study showed children with NAS were more likely to be re-hospitalized for maltreatment, trauma, and mental/behavioral disorders (even after accounting for confounding variables)
- Systematic review of case-control studies showed no clinically significant neurobehavioral difference between children exposed to either methadone or heroin, but there was a trend toward poorer outcomes
- Longitudinal study in Norway showed that prenatal opiate and polysubstance exposure was associated with lower IQ at 8 years of age compared to unexposed (controlled for permanent foster/adoptive home placement and earlier cognitive abilities)

Questions?
### References