Neonatal Abstinence Syndrome (NAS)

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Take home messages

- NAS is common with increasing prevalence
- Treatment pathways being standardized throughout the state
- More work needed on developing maternal screening protocols and counseling families before birth
Case Presentation

- 32 year old G4P1 mother
- Caucasian
- History of heroin use
- Started Methadone first trimester, 110 mg
- Alprazolam (Xanax®), Sertraline (Zoloft®)
- Tobacco use 1 pack/day
- Maternal toxicology screen (+)opiates
- SVD at 39 weeks
NAS

- Signs and neuro-behaviors exhibited by newborn after birth following abrupt discontinuation to substances taken by mother
- Among infants exposed to opioids in-utero, 55-94% develop withdrawal symptoms
Time line of NAS

1804: Morphine isolated
1817: Marketed as analgesic
1827: Commercial production

1853: Hypodermic needle developed

1874: Heroin synthesized
1898: Commercial production

1875: First reported case of neonatal withdrawal

1892: Series of 12 infants, 9 died. Paregoric was tried

1903: Morphine treatment for neonates reported

1937: Methadone developed
1964: Methadone maintenance treatment

1971: Methadone withdrawal in 5 neonates

1967: Buprenorphine developed
1996: Buprenorphine use in France
2002: FDA approval for opioid dependence

Opioid analgesic medications:
- Vicodine (1984)
- Oxycontin (1989)
- Percocet (1999)

2002: First reported case of NAS due to oxycontin
2012: Epidemic of NAS

1997: First reported case of buprenorphine withdrawal

2001: Series of buprenorphine withdrawal in 13 infants
NAS

- Most commonly caused by fetal exposure to opiates
- Increasing prevalence
- Variable clinical expression
- Variability in maternal screening
- Large public health problem
  - High costs
  - Long term development
Fetal Exposure to Opiates

- Heroin
- Methadone
- Prescription drugs
- Buprenorphine
- Common comorbid usage
  - Tobacco
  - Marijuana
  - Benzodiazepines
  - SSRIs
NAS Pathophysiology

- Abrupt withdrawal of opioids
- Exaggerated rebound from acute pharmacologic effects of drug
- Supranormal release of noradrenaline, autonomic and behavioral signs characteristic of withdrawal
A schematic illustration of the mechanism of opioid withdrawal in neonates

- Corticotrophin increase
  - Increased stress
  - Hyperphagia

- Dopamine decrease
  - Hyperirritability
  - Anxiety

- Serotonin decrease
  - Sleep deprivation
  - Sleep fragmentation

- Noradrenaline increase
  - Hyperthermia
  - Hypertension
  - Tremors
  - Tachycardia

- Acetylcholine increase
  - Diarrhea
  - Vomiting
  - Yawning
  - Sneezing
  - Sweating

- Other receptor activity increase
  - Hypermalgesia
  - Allodynia

- Lack of opioids in chronically stimulated receptors
  - Super activation of adenyl cyclase
  - Increased cyclic adenosine monophosphate
  - Increased protein kinase
  - Increased transcription factors
  - Increased release of neurotransmitters

Kocherlakota P Pediatrics 2014;134:e547-e561
Signs

- **Neurologic**
  - Irritability, high pitched cry, tremor, increased tone, seizures

- **GI**
  - Vomiting, diarrhea, poor weight gain, poor feeding, hyperphagia

- **Autonomic**
  - Diaphoresis, nasal stuffiness, temperature instability
Newborn Diagnosis

- Clinical
- History
- Testing
  - Urine
  - Hair
  - Meconium
Incidence and Expenditure 2000-2009

Patrick, JAMA, 2012

- Use of large national inpatient database (KID)
- Between 2000 and 2009 NAS diagnosis increased from 1.2 (1.04-1.37) to 3.39 (3.12-3.67) per 1000 hospital births
- Newborns with NAS more likely to have low birth weight, respiratory distress
- Mean hospital charges increased from $39,400/patient to $53,400/patient
- 77.6% Medicaid
Past-Month Use of Any Illicit Drug* Among Women Aged 18 and Older, by Race/Ethnicity, 2009–2011

*Includes marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, and any prescription-type psychotherapeutic drugs used for non-medical purposes; all estimates are age-adjusted. **Estimate does not meet the standards of reliability or precision.

Delaware Prevalence

- No direct measure of NAS prevalence
- Definition for tracking not standardized
  - Treated babies
  - Exposed mothers
  - Prescription drug use
  - Iatrogenic cases
- Paucity of data on long-term health utilization
  - Rehospitalization
  - Pharmacy
  - Long term services
Number of Deaths and Age-adjusted Death Rate due to Drug Overdoses
Delaware, 1999-2010
NAS Patient Days
Christiana Hospital 2010 - 2014

 Patients (n)  
Patient Days

Number

2010  2011  2012  2013  2014 (projected)

105  123  145  158  170

2622  1935  1445  500

3074  2500  1500  0
Maternal Opiate Use (n=107)

- 54% Methadone
- 31% other opiates (prescription)
- 11% Heroin
- 10% Subutex
CCHS 2014-NAS
Maternal Comorbidities (n=107)

- 79% Tobacco
- 14% Marijuana
- 14% Cocaine
- 8% SSRI
- 8% Benzodiazepines
Length of Stay-NAS
Prithum et al, JOGNN, 2012

- 152 Opioid dependent women
- Factors affecting neonatal LOS
  - Increased maternal methadone dose ↑
  - Maternal Buprenorphine ↓
  - Breast feeding ↓
  - Maternal benzodiazepine use ↑
NAS After Methadone vs Buprenorphine
(Mother Project)
*Jones HE et al, NEJM, 2010*

- 175 mothers randomized to methadone or buprenorphine
- Double blind design
- Decreased neonatal morphine dosing, LOS, duration of treatment with buprenorphine
Maternal Methadone Dose

- Data are mixed on the relationship between maternal dosing and infant symptoms, length of treatment, other outcomes
Tools

- Finnegan scoring system
  - Some variability in scoring
- Scoring initiated shortly after birth for infants at risk
# Modified Finnegan Score

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous high pitched (or other) cry</td>
<td>2</td>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Continuous high pitched (or other) cry</td>
<td>3</td>
<td>Fever 100.4°F–101°F (38°C–38.3°C)</td>
<td>1</td>
</tr>
<tr>
<td>Sleeps &lt;1 h after feeding</td>
<td>3</td>
<td>Fever &gt;101°F (38.3°C)</td>
<td>2</td>
</tr>
<tr>
<td>Sleeps &lt;2 h after feeding</td>
<td>2</td>
<td>Frequent yawning (&gt;3–4 times/interval)</td>
<td>1</td>
</tr>
<tr>
<td>Sleeps &lt;3 h after feeding</td>
<td>1</td>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Hyperactive Moro reflex</td>
<td>2</td>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td>Markedly hyperactive Moro reflex</td>
<td>3</td>
<td>Sneezing (&gt;3–4 times/interval)</td>
<td>1</td>
</tr>
<tr>
<td>Mild tremors disturbed</td>
<td>1</td>
<td>Nasal flaring</td>
<td>2</td>
</tr>
<tr>
<td>Moderate–severe tremors disturbed</td>
<td>2</td>
<td>Respiratory rate &gt;60/min</td>
<td>1</td>
</tr>
<tr>
<td>Mild tremors undisturbed</td>
<td>3</td>
<td>Respiratory rate &gt;60/min with retractions</td>
<td>2</td>
</tr>
<tr>
<td>Moderate–severe tremors undisturbed</td>
<td>4</td>
<td>Excessive sucking</td>
<td>1</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>2</td>
<td>Poor feeding</td>
<td>2</td>
</tr>
<tr>
<td>Excoriation (specific area)</td>
<td>1</td>
<td>Regurgitation</td>
<td>2</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>3</td>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Generalized convulsions</td>
<td>5</td>
<td>Loose stools</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Watery stools</td>
<td>3</td>
</tr>
</tbody>
</table>
Onset of Neonatal Symptoms

- **Heroin**
  - Within 24 hours

- **Methadone**
  - Within 24-72 hours

- **Buprenorphine**
  - Mean 40 hours, peak 70 hours

- Some infants with delay until 5-7 days
Non-pharmacologic Management

- Swaddling
- Holding
- Minimal stimulation
- Breast feeding
- High calorie feeding
- Limited lactose formula
Pharmacologic Management

- **Opioid replacement**
  - Morphine
  - Methadone
  - Buprenorphine

- **Other**
  - Phenobarbital
  - Clonidine
  - Benzodiazepine
Potential Issues

- Alcohol content of formulations
- Neuro toxicity of opioids
- Neuro toxicity of phenobarbital
Family Support

- Parental guilt
- Legal issues involved with substance use
- Need to gain trust of family
- Stigma of drug use
- Infrequent parent visiting
Neurodevelopment

- Most long term studies suggest an environmental effect rather than direct drug in-utero effect
- Concern for long term postnatal exposure to drugs
  - Phenobarbital
- Need for comprehensive services for mother and baby
  - Social support
  - Parenting intervention
  - Maternal treatment
Leading Causes of Infant Mortality USA 2010

1. Congenital malformations, chromosomal abnormalities
   - 21%

2. Disorders related to short gestation and low birth weight
   - 17%

3. Sudden Infant Death Syndrome
   - 8%

4. Maternal complications of pregnancy
   - 6%

Pediatrics, March 2013
Maternal Methadone: Infant Mortality
Kelly et al, J Pop Clin Pharm, 2012

- Ontario, Canada, 2006-2010
- 8 infant deaths, mothers on methadone maintenance
  - 6/8 unsafe sleeping environment
  - Post mortem toxicology negative in all cases
  - All >28 days of age (post-neonatal)
- Odds of death 1.45 (0.47-4.46) for babies born to mother on methadone compared to general population
Universal Maternal Drug Screening
Wexelblatt, J Peds 2014

- Retrospective cohort after implementation of routine maternal screening
- 2956 maternal specimens, 96 positive opiates (3.2%)
- 19/96 (20%) without risk factors
- 7/19 admitted to NICU for NAS
- Sensitivity 77% and specificity of 79% for traditional risk based screening
Delaware-Primary Prevention

- **Prescription Monitoring Program**
  - Collects data on controlled substances
  - Database available to prescribers and dispensers

- **House Bill 154, February, 2014**
  - The law creates a new criminal offense (Felony Offense) and imposes penalties for diverting prescription drugs from a patient in a facility

- **Drug take back program**
20 Ohio Hospitals, 2012-2013
547 medically treated infants
Infants receiving protocol based weans compared to no protocol:
- Decrease opioid exposure, 17 vs 32 days (p<.001)
- Decrease length of stay, 22.7 v 31 days, (p=.004)
NAS Guidelines for Labor & Delivery and Mother-Baby Units

**Identify at risk newborn for NAS (See Table 1).**
- Notify Pediatric Team of at risk newborn in L & D (See Table 1).
- Pediatric Provider evaluates baby in L&D.
- Drug screening recommended for mother and baby.
- Assess for safety to breastfeeding (See Table 3).
- NAS CPG for all at-risk newborns. NAS scoring for all at-risk newborns within 4 hours of birth. Consult Social Work for NAS (and other indications if present).
- Maximize non-pharmacologic therapy.

**Transfer baby to Mother-Baby Unit (or NICU if there are indications for NICU observation or admission.)**
- Consult social work if not yet done.
- Review minimum length of hospital stay with family on admission (See Table 2).
- Continue to assess for safety to breastfeeding (See Table 3).
- Notify physician if NAS score > 8.

**All newborns exposed to long-acting opiates in utero should be observed for NAS for 5-7 days before discharge. (See Table 2).**

**Discharge baby home with mom if otherwise medically and socially cleared for discharge.**

**Two Scores > 8 or one score > 12?**

**Does baby need continued observation after mother is discharged?**

**Transfer to 4a**

**Does baby have physiologic instability OR other significant medical problems?**

**Transfer to NICU**

**Refer to NAS Inpatient Guidelines**

**Babies at risk for NAS that should be seen by Pediatric Team in Labor & Delivery:**
- **Babies exposed in utero to:**
  - Long-acting opiates for pain or opiate addiction (e.g., Methadone, Buprenorphine (Suboxone™), Buprenorphine/Naloxone (Suboxone™))
  - Chronic, short-acting opiates, including pain medications, (e.g., Oxycodone/Acetaminophen (Percocet™), Hydromorphone (Dilaudid™))
  - Benzodiazepines (e.g., Ativan (Xanax™))
  - Illicit / non-prescribed opiates or benzodiazepines (e.g., Heroin)
  - Any other concern for NAS risk

**Minimum observation recommended for at-risk newborns:**
- Long acting opiates (e.g., Methadone): 5-7 days
- Low-dose, short acting opiates: 3-4 days
- Benzodiazepines: 4-7 days

**For all babies at risk of NAS:**
- Breastfeeding is encouraged, unless otherwise medically contraindicated.
  - Illicit drugs ("street drugs") are contraindicated with breastfeeding.*
  - "Adequately nourished narcotic-dependent mothers can be encouraged to breastfeed if they are enrolled in a supervised methadone maintenance program and have negative screening for HIV and illicit drugs."**
- Do not wake a sleeping baby for scoring.
- CPH or Neonatology consultation is available for at risk newborns or newborns having withdrawal.

* AAP, The Committee on Drugs and The Committee on Fetus and Newborn, Neonatal Drug Withdrawal Pediatrics, 1/30/2012

11/18/14
**NAS Inpatient Guidelines**

**Initiation**
- **Are there two scores > 8 or one score > 12?**
  - Yes, **INITIATE Morphine 0.05 mg/kg/dose PO Q 3 hours**.
  - No, **Observe until STABLE (scores ≤ 8 for 48 hours)**.

**Escalation**
- **Are there two consecutive scores > 8 OR one score > 12?**
  - Yes, **ESCALATE morphine by 0.02 mg/kg/dose**.
  - No, **Are there indications for phenobarbital (see Table 1 for dosing)**?
    - Yes, **Add phenobarbital**.
    - No, **Observe until STABLE (scores ≤ 8 for 48 hours)**.

**Stabilization**
- **Observe until STABLE (scores ≤ 8 for 48 hours)**.

**Weaning**
- **WEAN: Decrease morphine dose by 10%. (See Table 1 for phenobarbital weaning)**.
- **Are scores ≤ 8 for the 24 hours following wean?**
  - Yes, **Wean morphine every 24 hours by 10% of the dose when the wean was initiated**.
  - No, **Discontinue morphine when dose is < 0.02 mg/kg/dose and observe 48-72 hours before discharge**.
- **Adjust NAS trigger scores by 2 points if > 43 weeks postmenstrual age**.

**Backslide**
- **WEIGHT ADJUST Or BACKSLIDE: back-up dosing to previous dose in stepwise fashion until scores are ≤ 8**.
- **Are two consecutive scores > 8?**
  - Yes, **Hold wean until scores ≤ 8 for 24 hours**.
  - No, **Adjust NAS trigger scores by 2 points if > 43 weeks postmenstrual age**.

**Table 1: MORPHINE**
- **INITIATE**: Initiate Morphine for two scores > 8 or one score > 12 at 0.05 mg/kg/dose PO Q3 hours or (0.02 mg/kg/dose IV). q3 is best for steady state.
- **ESCALATE**: For two scores > 8 or one score > 12, escalate by 0.02 mg/kg/dose (or 0.01 mg/kg/dose IV). Can consider larger escalation if scores are very high.
- **STABILIZATION**: Scores ≤ 8 for 48 hours.
- **WEAN**: Once stable for 48 hours, begin to wean by subtracting 10% of the stable dose.
  - **CONTINUE WEANING**: q24 hours by 10% of the dose when the wean was initiated if scores ≤ 8 for 24 hours. (i.e., subtract the same number of mg of morphine with every wean.)
  - **DISCONTINUE**: When morphine dose is < 0.02 mg/kg/dose PO.
- **DISCHARGE**: Discharge after observed off morphine 72 hours. (See NAS Discharge Guidelines for discharge home on medication for select population).
- **BACKSLIDE**: During weaning, if two consecutive scores are > 8, backslide to previous stable dose OR weight adjust.

**Phenobarbital**
- **INITIATE**: Consider Phenobarbital for 1) polysubstance exposure AND 2) Morphine exceeds 0.2 mg/kg/dose PO or unable to wean for 2 consecutive days.
- **LOADING DOSE**: 16 mg/kg/dose (same dose IV).
- **MAINTENANCE DOSE**: 5 mg/kg/dose PO daily. Do not weight adjust.
- **WEAN**: By 20% of the dose when the wean initiated every 2 days. **WEAN phenobarbital off before weaning morphine.**
  - **DISCONTINUE**: When phenobarbital ≤ 2 mg/kg/dose.
- **DISCHARGE**: Discontinue phenobarbital prior to weaning morphine AND prior to discharge.

**Table 2: Reminders**
- **Observe opiate exposed babies for 5-7 days for long acting opiates and 3-4 days for short acting opiates**.
- **Babies with physiologic instability or other significant medical problems should be transferred to NICU. Otherwise transfer baby to 4a**.
- **Consider transfer NICU patient to 4a for weaning unless there is other medical indication for continued NICU admission**.
- **Adjust NAS trigger scores by 2 points if > 43 weeks postmenstrual age**.
- **Maximize Nutrition**: Encourage breastfeeding unless contraindicated. Most babies need 22 kcal feeding temporarily. Follow weights closely.
- **Maximize non-pharmacologic management: PT/OT, swaddle, comfort, controlled environment**.
- **Do not wake a sleeping baby to score.**

*Updated 7/7/14*
Variation in NAS Treatment
*Patrick et al, J Perinatology 2014*

- Administrative and pharmacy data from 14 Children’s Hospitals, 2004-2011
- Hospitals differed widely in median:
  - length of stay (8-28 days)
  - length of treatment (5-26 days)
  - Hospital charges ($26,000-$155,000)
  - Primary agent used (6 morphine, 6 methadone, 2 phenobarbital)
- After multivariable modeling use of methadone associated with decrease LOS
Case Follow Up

- Physiologically stable - admit to floor
- Start Finnegan Scoring
- Start non-pharmacologic management
- Two score >8, start oral morphine
- Refer to DFS, + opiate tox screen
- Hold breast feeds, concern for “street drug” use
- Inpatient management initially
Unresolved questions

- Mandatory maternal screening?
- Mandatory reporting?
- Decrease length of inpatient stay?
- Long term follow-up?
Conclusions

- NAS increasing in prevalence
- Need for increased evidence
- Standardized inpatient pathways
- Ongoing public health concerns including risk of home environment and long term outcomes