Neonatal Abstinence Syndrome

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Many slides courtesy of Christine Gleason, MD
Disclosure Statement

- I do not have any conflict of interest, nor will I be discussing any off-label product use.

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Objectives

1. Describe the pathobiology of neonatal narcotic exposure
2. Identify babies at risk for neonatal abstinence syndrome
3. Describe essential elements of effective management strategies for neonatal abstinence syndrome
NAS: A Brief History

- 1875—1st Case report Congenital morphinism
- 1903—Survival of neonate after morphine rx.
- 1947—Successful treatment of seizures in an infant with congenital morphinism
- 1950s—Re-named Neonatal abstinence syndrome
- 1964—Methadone for addiction treatment
- 2002—Buprenorphine introduced (USA)
- 2000s—Surge in maternal prescription opioids
#1 How much has the incidence of neonatal abstinence syndrome (NAS) increased in the last decade?

- a. 100%
- b. 200%
- c. 300%
- d. 400%

National inpatient data shows NAS admissions have increased from 1.2 to 5.8 per 1000 hospital births from 2000-2012; an increase of 480%.

2. How much money did the United States spend on infants with NAS in 2012

a. < $ 500 Million
b. $ 750 Million
c. $ 1 Billion
d. > $ 1.25 Billion
Pediatrix Clinical Data Warehouse

- Large, multicenter, de-identified data set
- Includes ~ 20% of infants admitted to US NICUs
- Queries: NAS, Drug Withdrawal or Drug Withdrawal Syndrome
- 2004-2013
- Among 674,845 infants admitted to 299 NICUs, 10,327 with NAS (1.5%)

Sources of drugs for women with NAS infants

Almost half of mothers whose babies were born dependent on drugs in 2013 were legally prescribed the medication that led to the babies’ withdrawal. Here’s a breakdown of where the drugs came from.

- **33.2%**: Only substances prescribed to mother
- **41.7%**: Only illicit or diverted substances
- **21.6%**: Substance exposure unknown
- **3.6%**: Mix of prescribed and nonprescribed substances

Source: Tenn. Dept. of Health

From: The Tennessean: “Born Hurting”, by Tony Gonzalez & Shelley DuBois
Prescription Narcotics

**Indications:**
- Post-procedural/surgical pain
- Chronic pain
- Sleep disorders
- Drug replacement therapy
  - Opioid addiction
  - Opioid dependence

**Commonly Prescribed:**
- Oxycodone (OxyContin)
- Oxycodone + Acetaminophen (Percocet)
- Hydrocodone + Acetaminophen (Vicodin)
- Fentanyl (patch)
- Tramadol (Ultram)
- Methadone
- Buprenorphine (Subutex)
“It is clear that the idea that illegal drugs are more harmful to the unborn fetus than legal drugs is incorrect; this concept, which strongly influences public policy, is not supported by findings from carefully designed and controlled research studies”

Identifying Babies at Risk
Drug Testing:
Newborn urine toxicology

- Poor correlation between maternal and newborn test results
- Earliest newborn urine will contain the highest concentration of substances
- Newborn urine reflects exposure during preceding one to three days
- Cocaine metabolites may be present for 4-5 days; marijuana for weeks
- Alcohol is nearly impossible to detect
Drug Testing:

- **Meconium:**
  - Term meconium reflects substance exposure during the 2nd half of gestation (preterm infants may not be good candidates)
  - High sensitivity for opiates and cocaine
  - Cost is similar to urine toxicology
  - Umbilical cord segments: An evolving technology, but offered clinically and likely equivalent to meconium. More expensive than meconium testing.
- Breast milk: Not a viable alternative
- Hair: High sensitivity for cocaine, amphetamines and opiates but not marijuana; cost of testing is higher than for meconium
Can we predict which exposed infants will be more likely to develop NAS?

- Full-term; normal birth weight; male gender?
- Type(s) of maternal drugs used
  - Maternal tobacco, SSRIs, benzodiazepines
  - Methadone vs. Buprenorphine?
- Higher cumulative opioid exposure to short-acting preparations
- Timing of last drug exposure(s) prior to delivery
NAS in preterm infants
Lower incidence; less severe

- Decreased cumulative exposure?
- Decreased placental transmission during early gestation?
- Decreased drug clearance and excretion (immature kidneys, liver)?
- Decreased fatty tissues?
- Decreased receptor development/sensitivity?
  ✔ Kocherlakota, Pediatr 134: 2014

- Requires each state (as a condition of receiving federal funds) to develop policies and procedures “to address the needs of infants born and identified as being affected by illegal substance abuse or withdrawal symptoms resulting from prenatal drug exposure.”
- Includes a requirement that health care providers notify CPS re: prenatal substance exposure
- Differs from existing legal duty to report suspected child abuse or neglect because these reports
  - “Shall not be construed to be child abuse”
  - “Shall not require prosecution of the mother”
Protecting Our Infants Act of 2015

“To combat the rise of prenatal opioid abuse and neonatal abstinence syndrome”

- Require AHRQ to develop recommendations for preventing/treating prenatal opioid abuse and NAS
- Require review of relevant programming and research in Dept. of Health & Human Services
- Require assistance to states in collection of relevant public health data by the CDC
Neonatal Abstinence Syndrome Pathobiology
Opioids

- Opioid receptors (μ, κ and δ) located in central and peripheral nervous system and GI tract
  - Density and affinity of μ-opioid, but not κ and δ, receptors in neonatal brain similar to adults
- Opioids attach to receptors on neuronal cell membranes to inhibit neurotransmission of excitatory pathways:
  - Acetylcholine; catecholamines; serotonin
Mechanisms of opioid withdrawal in neonates

- Serotonin decrease
- Noradrenaline increase
- Dopamine decrease
- Corticotrophin increase

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

Other receptor activity increase:
- Hyperalgesia
- Allodynia

Increased stress
- Hyperphagia

Hyperirritability:
- Anxiety
- Diarrhea
- Vomiting
- Yawning
- Sneezing
- Sweating

Sleep deprivation
- Sleep fragmentation

Hyperthermia
- Hypertension
- Tremors
- Tachycardia

Acetylcholine increase
Opioid Withdrawal:

**Neurologic Signs**
- Tremors; Jitteriness
- Seizures
- Irritability; Sleeplessness
- High-pitched cry
- Hypertonia; exaggerated Moro
- Yawning; sneezing
- Respiratory pauses/desaturations

**Autonomic Instability**
- Sweating
- Temperature Instability
  - Fever
- Mottling
- Nasal Stuffiness
- Tachypnea

**GI dysfunction**
- Poor feeding
  - Uncoordinated/constant sucking
- “Reflux”/Vomiting
- Diarrhea (leads to diaper rash; pain)
- Dehydration
- Poor weight gain
Timing of Drug Withdrawal

- Alcohol: 3-12 hours after birth
- Tobacco/Nicotine: Few hours
- Opioids
  - Methadone: 3-5 days
  - Heroin: Within 24-48 hours
  - Subutex (Buprenorphine): ~ 72 hours
  - Prescription medications: 24 -72 hours
- Benzodiazepines: 4-7 days
- SSRIs: 24-72 hours
NAS Scoring Tools

- Developed to determine drug treatment thresholds for opioid-exposed neonates
  - But never validated; no biomarkers!
- Designed to be as objective as possible
  - But subject to strong inter-observer variability
- Based upon neurologic, autonomic and GI signs of opioid withdrawal
- Should be performed after feeds, at 3-4 hour intervals, when infant is awake
NAS Scoring Tools

- Finnegan: Complex - score > 8-10 → drug treatment
- Lipsitz: Simple
  - score > 4 → drug treatment
- Neonatal Narcotic Withdrawal Index: Simple; Rapid; MD-based

Modified Finnegan scores in “normal” newborns at < 72 hours of age

Management of NAS
Case definition of “Confirmed NAS”  
[by the CDC—in MMWR 64: 213, March 6, 2015]

Infants meeting all 3 of the following criteria:

1. Clinical signs consistent with NAS (NAS score >8) and not explained by another etiology
2. History of maternal use during pregnancy of prescription or illicit drugs assoc. with NAS or lab confirmation of maternal narcotic use
3. Severity of illness that resulted in a prolonged (>2 days) neonatal hospitalization
NAS Management Goals

- Enable infant to feed and gain weight
  - Frequently need increased caloric density of formula due to high metabolic rate
- Prevent seizures and other morbidities
- Reduce unnecessary hospitalization
- Improve/monitor family interaction/care
- Reduce infant mortality; improve outcomes
- **Limit additional opioid exposure**
AAP Guidelines—Neonatal Drug Withdrawal

- Initiate non-pharmacologic measures first
- The optimal threshold ‘score’ for initiating pharmacologic therapy is unknown
- **Breast-feeding** should be encouraged if no illicit drug use
- Oral morphine, methadone—best evidence (but limited); clonidine—emerging evidence
- Observe exposed infants for 4-7 days
- Treatment of drug withdrawal may not alter long-term outcome
Non-Pharmacologic Treatment

Should *always* be implemented first, and continued as an adjunct to drug treatment

- Decreased environmental stimulation
  - Room in with mother, if feasible
- Tight swaddling; Kangaroo care
- Rocking/swinging
- Non-nutritive/nutritive sucking—**Breast** is best!
- Demand and/or frequent, small feedings
- Butt care – prophylactic to prevent breakdown
Pharmacologic Treatment

[2012 AAP Statement on Neonatal Drug Withdrawal]

- “Withdrawal from opioids…may be life-threatening, but ultimately drug withdrawal is a self-limited process”
- “Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization”
- “The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs”
  - Prompt escalation of treatment to control clinical signs
Medication use in infants with NAS, 2004-2013

Pharmacologic Treatment

Opioids:
- Morphine
- Methadone

Additional Therapies
- Phenobarbital
- Clonidine

Opioid receptor agonist
- Buprenorphine
Morphine

- Natural μ-opioid receptor agonist
- Treats all aspects of opioid withdrawal
- Oral preparation does not contain alcohol

Pitfalls

- Overdose/side effects may be severe
  - Apnea; sedation; constipation
- Treatment may last for several weeks
  - Difficult for caregivers to wean (psychologically)
- Exposes infant to more narcotics
Morphine
Dosing guidelines

- Starting treatment
  - When average daily Finnegan score > 8-10 (minimum of 4 scores needed) \textbf{or}
  - Three consecutive scores are ≥ 11

- Starting dose: 0.05 (0.03 - 0.06) mg/kg/dose q3-4h

- Increase by 0.05 (0.03 - 0.06) mg/kg/dose as needed

- Maximum dose? 1.3 mg/kg/day
  - \text{Kraft WK, van den Anker JN. Ped Clin NA 59, 2012}
Increase dose (by 10%) if:
- Infant has 24 hour average daily score > 8

“Rescue” dose if 2 consecutive scores > 12

Consider adding phenobarbital/clonidine if max dose (1.3 mg/kg/day) is reached

Taper dose (by 10% or 0.05 mg/kg) daily when previous 24 hour average score < 8

Discontinue drug when minimal dose/volume is reached (e.g. 0.1 or 0.15 mL (= 0.04 or 0.06 mg)
Methadone

- Synthetic \( \mu \)-opioid receptor agonist; NMDA antagonist

**Benefits:**
- Long half life (26 hrs)
- Easier to administer (q12h dosing)

**Pitfalls:**
- Longer duration of treatment—hard to wean
- 8% alcohol
- Variable half life (with maturation)
Methadone
Dosing Guidelines

- Initial loading dose 0.1 mg/kg
- Additional 0.025 mg/kg/dose q4h for scores > 8 or until max 0.5 mg/kg reached
- Maintenance dose determined by calculating total dose given over previous 24 hrs—given in two divided doses q12hr
- Weaning? 10% q48hr? No clear guidelines

[Kraft WK & van den Anker JN, Ped Clin NA 59: 2012]
Methadone
Inpatient/Outpatient approach

- Dosing:
  - 0.1 mg/kg/dose q12hr (could be shortened-q6-8h)
  - Increase by 0.05 mg/kg/dose q48hr (max 1 mg/kg/d)
  - Weaned as outpatient: 10% at 1-2 week intervals

- Benefits: Shorter hospital LOS; reduced cost

- Pitfalls: Lengthy weaning; variable outpatient care; methadone availability; “my baby is an addict”; pediatricians wanted babies on apnea monitors

## NAS Score Driven Treatment Algorithm

### Initiating Treatment: GOAL = rare score > 10 & average daily score < 8

<table>
<thead>
<tr>
<th>Score ≤ 8</th>
<th>Score 8-14</th>
<th>Score &gt; 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score every 3 hours</td>
<td>3 consecutive scores 9-14, begin morphine 30-60 mcg/kg/dose q3hrs</td>
<td>Begin morphine 100 mcg/kg/dose q3hrs</td>
</tr>
</tbody>
</table>

### Escalating Treatment: GOAL = score < 10 & average daily score < 8

<table>
<thead>
<tr>
<th>2 Scores 10-14</th>
<th>Score &gt;14</th>
<th>&gt; 3 scores above 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase dose by 10 mcg/kg/dose</td>
<td>One time break-through dose of 30 mcg/kg and increase dose by 20 mcg/kg</td>
<td>Breakthrough dose of 30 mcg/kg</td>
</tr>
</tbody>
</table>

### Breakthrough dosing: for multiple scores > 10 within 24 hours

- Consider adding prn acetaminophen
- One time breakthrough dose of 30 mcg/kg/dose and/or
- Increase maintenance by 10 mcg/kg/dose
- Consider addition of clonidine (or phenobarbital) if morphine is > 170 mcg/kg/dose
**Weaning Treatment:**

- **GOAL:** rare score > 10 & average daily score < 8

<table>
<thead>
<tr>
<th>Average daily score &lt; 8</th>
<th>Average daily score 8-10</th>
<th>2 scores &gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wean dose by 10% each day</td>
<td>Do not wean and reassess</td>
<td>Return to previous dose and reassess</td>
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</tbody>
</table>

**Management of Oversedation:**

- Hold morphine dose and consult physician for:
  - Evidence of respiratory depression: apnea, desaturations
  - Infant is not waking every 3-4 hours to feed for more than 1 feed
  - Consecutive NAS scores of < 3 at least twice

**Stopping drugs & Discharge**

- Once average daily score is < 8 on 40 mcg/dose
  - Monitor for 24-48 hours after discontinuing morphine depending on scores, feeding, and weight gain
  - If infant was on clonidine, wean clonidine to off over 72 hours, either at morphine dose of 40 mcg/dose or after stopping morphine
Clonidine

- Analgesic; antihypertensive; ADHD therapy
- $\alpha$-adrenergic receptor agonist; activates inhibitory neuronal norepinephrine release & blocks neuronal excitation in locus coeruleus
- No oversedation; no lengthy taper; no alcohol
- Pitfalls:
  - Can cause hypotension and bradycardia
  - Potential for 1000-fold error ($\mu$g vs. mg/mL)
  - Abrupt discontinuation can lead to $\uparrow$BP & HR, so must be weaned in the hospital
Clonidine
Adjunctive treatment

- Clonidine 1 μg/kg q4h vs. placebo; all infants received morphine per standard protocol
  - Must be compounded into less concentrated form
- Clonidine treated group had
  - Reduced duration of opioid therapy
  - Less requirement for high dose opioids
  - Fewer “treatment failures”
  - No significant adverse effects

Agthe AG et.al. Pediatr 123: 2009
Clonidine: Adjunctive treatment

- RCT compared efficacy of either clonidine or phenobarbital as adjunct to morphine (n = 68)
- Both adjunctive treatments shortened the duration of morphine, compared to pre-trial: phenobarbital 4.6 days shorter than clonidine
- Shorter hospitalization with phenobarbital
- Overall duration of NAS treatment was shorter for clonidine because babies on phenobarbital were discharged home on it
Clonidine: Primary treatment

- Pilot RCT: Morphine vs. Clonidine (n=30)
- Clonidine dosing:
  - 5 μg/kg per day ÷ into 8 doses (=0.625 μg/kg q3h)
  - Same protocol as morphine for dose increases, decreases, re-escalation (max dose 12 μg/kg/day)
  - Discontinued when dose was < 1 μg/kg/day
- Clonidine: Shorter duration of treatment (28 days vs. 39 for morphine); improved neurobehavioral scores
- Not ready for routine use yet
Phenobarbital

- γ-amino butyric acid (GABA) agonist; often used as an adjunct to morphine or for non-opiate NAS

Dosing guidelines
- Loading dose 5-20 mg/kg
- Maintenance 2-5 mg/kg/day ÷ BID
- Weaning? Taper dose by 20% q other day?

Pitfalls:
- Does not treat narcotic withdrawal signs
- Sedating; impaired infant sucking
- Oral preparation contains 15% alcohol
Buprenorphine

- Long-acting partial μ-opioid receptor agonist
- Used in treatment of adult abstinence therapy
  - Decreased abuse potential, less respiratory depression than other opioid agonists
  - Compares favorably with methadone for use in pregnant women
- Sublingual absorption (within 2 min in adults)
Buprenorphine
Kraft WK et al. Addiction 106: 574, 2010

- Small single-site, open-label clinical trial
- Sublingual burprenorphine vs. oral morphine
- Buprenorphine dosing (prior pilot study)
  - 15.9 μg/kg/day, in 3 divided doses
  - Increased dose 25% until symptoms controlled
  - Phenobarbital added when 60 μg/kg/day reached
  - Weaned 10% per day as tolerated
  - Cessation of therapy when at 10% initial dose
Buprenorphine treatment:
- Decreased LOS (32 vs. 42 days in morphine group)
- Decrease length of treatment (23 vs. 38 days)
- Slightly more phenobarbital use (6 vs. 2)

Unexpected finding:
- Amelioration of NAS signs at plasma drug concentrations below the 0.7 ng/mL threshold for relief of symptoms in adults
  - Different volume of distribution? Pharmacodynamics?
Discharge Criteria
Significant variability

- Timing, duration and type of *in utero* exposure?
- Timing of NAS signs?
- Preterm vs. term?
- NAS treatment medications used?
- Discharging on outpatient medications?
- Other neonatal medical issues?
- Social/child protection issues?
- Plans for long-term follow-up?
Breastfeeding

Benefits:
- Maternal-infant bonding
- Readily available/cheap food source
- Immune factors/Gut protection
  - Particularly important in preterm infants
- May ease drug withdrawal symptoms

Concerns
- Drug toxicity (all cross into breast milk)
- Maternal inattention, sleepiness
- Risk for infection (specifically, HIV)
- Secondary smoke—increased risk for SIDS
Breastfeeding on Methadone

- Growing body of literature supports breastfeeding on methadone maintenance
- Less need for drug treatment of NAS
  - Despite low and unpredictable levels of methadone in breast milk and infant serum
  - And no evidence of significant methadone transfer to infants in breast milk
NAS Management Variations
What percentage of infants born to women using opioids develop NAS?

20-90%

How many infants require drug treatment?

30-90%

What are their average inpatient stay?

2-4 weeks (range 1 week to 3 months)
Pennsylvania (ProgenyHealth): NAS treatment 2007-2013

Lee J et.al. NAS: Influence of a Combined Inpatient/Outpatient Methadone Treatment Regimen on ALOS
Published in *Population Health Management*. Ahead of Print  DOI: 10.1089/pop.2014.0134
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NAS Treatment in Ohio 2012-13

- 20 hospitals; 6 regionally-based strategies
- 417/547 (76%) infants—managed with NAS weaning protocol; 130/547 (24%) without
- “Use of a stringent protocol to treat NAS, regardless of initial opioid chosen, reduces the duration of opioid exposure and LOS...[with] significant potential to reduce health care expenditures”
Outcomes
Multiple Confounders
In-utero opioid exposure

- Lower birth weight
- Increased preterm birth rate
- Reduced fetal growth parameters
- Associated neonatal problems
  - Hypoglycemia
  - Anemia
  - Respiratory distress
  - Delayed transition
Effects of Opioids on the Developing Brain

- Decreased cortical density of neurons
- Decreased DNA synthesis
- Impaired brain growth
- Altered brain reward system
- Altered behavioral pain responses
Environmental/Social Factors

- Poverty
- Maternal depression; chronic pain
- Maternal tobacco & alcohol use
- Poor maternal nutrition
- Child neglect/abuse
- Poor maternal nutrition
Future Directions

- Pharmacokinetic/Pharmacodynamic studies
- Pharmacogenomics
- Standard management approaches (both prenatal and postnatal)
  - Clearly-defined endpoint(s)
  - Simplified assessment scales and/or biomarkers
- Precision/personalized medicine? For babies?
Suggested References
