A Mother Centered Approach to Treating NAS

Matthew Grossman, M.D.
Associate Professor of Pediatrics
Yale School of Medicine
Quality and Safety Officer
Yale-New Haven Children’s Hospital
The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.
Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs

Veeral N. Tolia, M.D., Stephen W. Patrick, M.D., M.P.H.,
Monica M. Bennett, Ph.D., Karna Murthy, M.D., John Sousa, B.S.,
P. Brian Smith, M.D., M.P.H., M.H.S., Reese H. Clark, M.D.,
and Alan R. Spitzer, M.D.

BACKGROUND
The incidence of the neonatal abstinence syndrome, a drug-withdrawal syndrome that most commonly occurs after in utero exposure to opioids, is known to have
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**Summary**

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**SCORER'S INITIALS**

**STATUS OF THERAPY**

Standard Approach

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
- Staff cares for the baby
Length of Stay: Methadone-Exposed Infants

P < .02
Medication Studies

- **DTO vs. DTO plus clonidine**: 17 days vs. 12 days
- **Morphine vs. Phenobarbitone**: 8 days vs. 12 days
- **Morphine vs. DTO**: 30 days vs. 27 days
- **DTO vs. DTO plus Phenobarbitone**: 79 days vs. 38 days
- **Methadone vs. Morphine**: 17 days vs. 24 days
neonatal withdrawal signs. Clinicians have used discrete or serial scores to assist with therapeutic decisions. The Lipsitz tool, also known as the Neonatal Drug Withdrawal Scoring System,13 was recommended in the 1958 American Academy of Pediatrics statement “Neonatal Drug Withdrawal”14 probably because it is a relatively simple metric with good sensitivity for identifying clinically important withdrawal. The modified Neonatal Abstinence Scoring System (Fig 1,15,16) is the predominant tool used in the United States.17 This more comprehensive instrument assigns a cumulative score based on the interval observation of 21 items relating to signs of neonatal withdrawal.18 In a study administration of this scoring system with infants verified not to have been exposed to prenatal opiates by meconium analysis resulted in a stable median score of 2 during each of the first 3 days of life, with 95th percentile scores of 5.5 and 7 on days 1 and 2, respectively.19 Infants at risk for NAS should be carefully monitored in the hospital for the development of signs consistent with withdrawal. The approximate duration of hospital observation is variable and depends on a careful assessment of the maternal drug history. An infant born to a mother on a low-dose prescription opiate with a short half-life (eg, hydrocodone, average half-life, 4 hours) may be safely discharged if there are no signs of withdrawal by 5 days of age, whereas an infant born to a mother on an opiate with a prolonged half-life (eg, methadone) should be observed for a minimum of 5 to 7 days. Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli (both light and sound) by placing the infant in a dark, quiet environment; avoiding overstimulation by careful swaddling; responding early to an infant’s signs; and adopting appropriate infant positioning and comforting techniques (away, rocking), and providing frequent small volumes of hypocaloric formula or human milk to minimize hunger and allow for adequate growth. Calcium needs may be as high as 150 to 250 mg/kg per day because of increased energy expenditure and loss of calcium from regurgitation, vomiting, and/or loose stools.16,20–22 The infant needs to be carefully observed to recognize fever, dehydration, or weight loss promptly. The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to migrate into a social environment. Maternal screening for comorbidities, such as HIV or hepatitis C virus infections and poly drug abuse, needs to be performed. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and gavage feedings may be necessary to stabilize the infant’s condition in the acute phase and obviate the need for pharmacologic intervention. When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed as long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that presents later and less frequently requires pharmacologic intervention.23,24–26 Methadone is present in very low concentrations in human milk. Cumulative daily intake of methadone in full-term breastfed infants has been estimated to range from 0.01 to 0.15 mg/kg/day in the first 30 days of life 0.17 to 0.19 mg/kg/day between 30 and 180 days of age.25 Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.131

Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff should be trained in the correct use of an abstinence assessment tool in a recent survey of accredited US neonatology fellowship programs, only 55% had implemented a written NAS protocol, and only 86% used a published abstinence scoring system.15,16

RATIONAL AND COMPARATIVE EVIDENCE 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. Since the introduction of the abstinence scales in 1975, published reports have documented that the decision to initiate pharmacologic treatment has been based on single or serial withdrawal scores. However, no studies to date have compared the use of different withdrawal score threshold for initiating pharmacologic intervention on short-term outcomes (eg, severity and duration of withdrawal signs, weight gain, duration of hospitalization, need for pharmacologic treatment, or cumulative drug exposure). Withdrawal from opioids or sedative-hypnotic drugs 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 to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of withdrawal signs. Studies have not addressed whether long-term morbidity related to neonatal drug withdrawal is decreased by pharmacologic management of affected infants, or whether continued postnatal drug exposure augments the risk of neurodevelopmental and other morbidities. It is possible that pharmacologic therapy of the infant may introduce or re-expose a maternal disposition to rely on drugs for the treatment of infant comfort or an anxiety disorder.12,13,16

Clinicians have treated NAS with a variety of drug preparations, including opioids (lactulose of opium, neonatal morphine solution, methadone, and paregoric), barbiturates (phenobarbital, benzo diazepines [diacepam, lorazepam], and phenothiazines [chlorpromazine]), information pertinent to the use of these drug preparations in infants is well summarized in the previous American Academy of Pediatrics statement.10 Recent surveys have documented that, in accord with the recommendations of that statement, 94% of UK and 63% of US clinicians use an opioid (morphine or methadone) as the drug of first choice. The majority of practitioners use phenobarbital as a second drug if the opiate does not adequately control withdrawal signs.10,11,13,15 Daily doses of morphine range from 0.24 mg/kg per day to 1.5 mg/kg per day.12,13 Paregoric is no longer used, because it contains variable concentrations of other opioids, as well as toxic ingredients such as camphor, amasa oil, alopec, and benzoic acid.10 The use of diazepam has also fallen into disfavor because of a documented lack of efficacy compared with other agents and because of its adverse effects on infant sleep and swallow reflexes.14–16 Meta-analyses of published trials regarding the pharmacologic treatment of neonatal withdrawal are available.27,28

In 2004, Dr. N. K. Pednale, in a letter to the editor, recommended the use of "an opioid,"13 while a systematic review of randomized controlled trials of opioid treatment for neonatal withdrawal concluded that there was no difference in the rate of successful withdrawal between opioid and placebo treatments.28,29
Studies have not addressed whether long-term morbidity related to neonatal withdrawal is decreased by pharmacologic management of affected infants, or whether continued pastebial drug exposure augments the risk of neurobehavioral and other morbidities. It is possible that pharmacologic therapy of the infant may introduce or reinforce a maternal disposition to rely on drugs for the treatment of infant discomfort or annoying behavior.12

Clinicians have treated NAS with a variety of drug preparations, including opioids (tincture of opium, neomorphine, morphine, methadone, and parargyric), barbiturates (phenobarbital), benzodiazepines (diazepam, chlordiazepoxide, and lorazepam), and phenothiazines (chlorpromazine). Information pertinent to the use of these drugs in preparations in infants is well summarized in the previously American Academy of Pediatrics.13

Recent surveys have documented that, in accord with the recommendations of that statement, 95% of US clinicians use an opioid (morphine, meperidine, or methadone) as the first choice. The majority of practitioners use neuraxial opioids.14

Opioids are in very low concentrations in human milk. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01 to 0.15 mg/day in the first 30 days of life and 0.15 to 0.30 mg/day between 30 and 180 days of age.15 Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.16

Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff should be trained in the correct use of an abstinence assessment tool. In a recent survey of accredited US neonatology fellowship programs, only 55% had implemented a written NAS protocol, and only 69% used a published abstinence scoring system.17

RATIONAL AND COMPARATIVE EVIDENCE FOR PHARMACOLOGIC TREATMENT

Drug therapy is intended 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. Since the introduction of the abstinence scales in 1975, published reports have documented that the decision to initiate pharmacologic treatment has been based on single or serial withdrawal scores. However, no studies to date have compared the use of different withdrawal scores thresholds for initiating pharmacologic intervention on short-term outcomes (e.g., severity and duration of withdrawal symptoms, weight gain, duration of hospitalization, need for pharmacologic treatment, or cumulative drug exposure). Withdrawal from opioids or sedative-hypnotic drugs 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 to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs...

...was compared with a control treatment that included no pharmacologic intervention, a placebo treatment, or another opioid and/or sedative drug. The authors prospectively designated 4 primary outcomes (failure of treatment to control withdrawal signs, incidence of seizures, survival, and neurodevelopmental outcome) for meta-analysis. Treatment failure was defined very loosely as the inability of the treatment to maintain abstinence scores within a preset “safe” level and/or the need to add another drug therapy. Some studies did not report primary outcomes and instead quantified secondary outcomes (e.g., duration of treatment, duration of hospitalization, rate of weight gain, etc).

Seven studies of opioid treatment that involved a total of 385 infants were identified between 1983 and 2004. Methodologic flaws were common and included random patient allocation, substantial and often unexplained differences in allocation of patients to treatment groups, imbalances in group characteristics after randomization, failure to mask study treatments, and failure to mask outcome measurements. In the single study that assessed oral morphine treatment versus supportive therapy only, 3 consecutive Hinnigan scores >8 prompted hospitalization of the intervention.18

No significant effect of morphine was found on the rate of treatment failure. Oral morphine significantly increased the duration of treatment and the length of hospital stay, but it did not reduce the number of days required to regain birth weight and duration of supportive care. Four studies compared treatment failure rates of opioids (parargyric, oral morphine, or methadone) with phenobarbital.19,20

In 2 Cochrane meta-analyses, either an opioid or a sedative drug treatment compared with no treatment resulted in a significantly lower rate of treatment failure in the phenobarbital group.19,20 One study of phenobarbital versus chlorpromazine20 found no differences in primary or secondary outcomes.

Since 2004, a number of small studies of varying methodologic quality have compared pharmacologic treatments in a prospective randomized double-masked study. Langenfeld et al21 could not identify differences in duration of treatment, duration of hospitalization, or in weight gain (g/day) in infants treated with either DPT or oral morphine. A retrospective study found no difference in length of hospitalization in infants with NAS who were treated with methadone or oral morphine solution, but did correlate higher maternal morphine doses with longer lengths of stay.22 Erker et al23 examined the incidence of NAS in infants born to mothers maintained on methadone, morphine, or buprenorphine and found no correlation in infants affected infants. Sixty-eight percent of infants born to mothers maintained on methadone required pharmacologic treatment at a mean age of 38 hours, compared with 62% of infants with an age of 3 hours in the morphine group and 21% of infants at a mean age of 54 hours in the buprenorphine group. The duration of treatment was significantly shorter for infants who received morphine compared with infants who were treated with phenobarbital. A random comparison trial of sublingual buprenorphine versus nasogastric opioid solution for the treatment of NAS showed a non-significant reduction in length of treatment and duration of hospitalization in the buprenorphine group. Buprenorphine therapy was well tolerated.

Clonidine is an α2-adrenergic receptor agonist that has been used in combination with an opioid or other drug in children and adults to reduce withdrawal symptoms.21,22 A negligible side effect of clonidine is hypotension and bradycardia, and the drug can be used in combination with other medications to reduce withdrawal symptoms.21,22
A recently published case series from France that used a historical cohort for a comparison has suggested that the treatment of NAS with pheno- thiazine, chlorpromazine, as a single drug may be more effective than treat- ment with morphine. Infants treated with oral morphine had significantly longer median durations of treatment and hospitalization in comparison with infants treated with chlorpromazine. No adverse effects were reported.

OUTCOME

Assessment of potential long-term morbidity specifically attributable to neonatal withdrawal and its treatment is difficult to evaluate. Several studies have followed drug-exposed children beyond the first few years of life. Confounding variables, such as environment and dysfunctional caregivers, complicates the interpretation of outcomes. In a small study, developmental scores on the mental index on the Bayley Scales of Infant Development were not affected by the severity of withdrawal or the treatment chosen. Mean scores on the Bayley Scales of Infant Development were similar for all infants treated for withdrawal, including those receiving phenobarbital, paragone, or a combination therapy. Scores of infants whose withdrawal was too mild to qualify for pharmacologic intervention were also similar.

Fourteen drug-exposed infants with withdrawal-associated seizures were reported by Dobrzak et al. The abstinence scores for 5 of these infants were < 7 (the cutoff for treat- ment); hence, they received no pharmacologic therapy before the onset of seizures. Thirteen of the 14 infants were offspring of mothers enrolled in a methadone treatment program; how- ever, the success of maternal treat- ment was not described. Of the 14 infants with seizures, 12 were available for evaluation at 1 year of age, results of neurologic examinations were nor- mal in 9 of the 12 infants evaluated. EEG results were abnormal in 8 mas- nate, however, subsequent EEGs for 7 of the 8 infants normalized during follow-up. Mean scores on the Bayley Scales of Infant Development were also normal by 1 year of age, similar to matched controls that were drug exposed, but in whom withdrawal- associated seizures did not develop. Withdrawal-associated seizures seem to be primarily myoclonic, resulting in eye and eyelid movements or gasping, and carry no increased risk of poor outcome. Withdrawal- associated seizures in neonates are different from those associated with other causes. Based on the depression of nonspecific and specific dis- charges observed in neonates exposed to methadone, withdrawal seizures are speculated to be attributable to lower levels of neurotransmitters. The normalization of the EEG and normal neurologic behavior are believed to reflect recovery of normal neurotransmitter concentrations during early infancy. Barstria et al. have comprehensively reviewed outcomes of infants and toddlers who were exposed prenatally to opioids and cocaine.

MANAGEMENT OF ACQUIRED OPIOID AND BENZODIAZEPINE DEPENDENCY

One of the cornerstones in caring for critically ill children is to provide adequate and safe anesthetics, sedation, amnesia, and analgesia by using both pharmacologic and nonpharmacologic measures. Pharmacologic treatment typically includes medications in the opioid and benzodiazepine drug classes. However, if these drugs cannot be safely discontinued within a few days, physical dependence on 1 or both of these classes of medication can develop and manifest with signs and symptoms of withdrawal on acute cocaine reduction or cessation of therapy. Infants who undergo complex surgical procedures or require prolonged medical intensive care for conditions such as respiratory failure or persistent pulmonary hypertension, or those with severe intracranial pressure, are particularly prone to these problems. In these infants, treatment with neuromuscular paralytic agents or propofol for 24 hours also increases the likelihood of with- drawal. Signs and symptoms of withdrawal from fentanyl commence within 24 hours of cessation of therapy.

The management of pain in children has seen significant advances in the past decades with an expansion of the use of opioids in the intensive care setting. As a result, more children have been treated for acute or potential with- drawal symptoms as a comorbidity of hospitalization. Fentanyl, a pure opioid receptor antagonist, has become the opioid of choice because of its rapid onset of action, short duration of ef- fect (half-life of 0.5–1 hour), excellent potency, and minimal adverse effects. However, fentanyl has not been demonstrated to be safer or more ef- fective than morphine for the provision of long-term analgesia. Indeed, I study has reported that patients who were treated prospectively with a continu- ous morphine infusion during ECMO experienced a significantly lower need for supplemental analgesia, a lower rate of dependency, and a shorter hos- pital stay compared with a previous group of patients treated with fentanyl during ECMO. Prisant have a variety of strategies to treat, or in high-risk patients, to prevent signs and symp- toms of opioid withdrawal in infants and children. Carr and Todres reported success with a gradual taper of the opioid infusion rate. Children who had received continuous opioid infusions for more than a week required 2 to 3 weeks for complete weaning. One disadvantage of this approach was that intravenous access had to be maintained for the entire course of treatment. Tobin et al. were among the first investigators to describe treatment of opioid with- drawal by conversion to enteral morphine. Meade has described the use of the opioid of choice because of its excellent oral bioavailability (70%–100%) and long half-life (19–41 hours), which allowed for long inter- vals between doses.

In this initial report, 3 symptomatic patients who had been exposed to cocaine or tobacco opium for up to 7 weeks were transitioned to a methadone regimen of 0.1 mg/kg orally, every 12 hours. Dose reduction by 10% to 20% of the initial dose over the next few days was successful in weaning in 4 to 6 weeks. In 2000, Robertson and the Pediatric Drug Addiction Study Group reported the outcomes of 16 children 6 months to 18 years of age who had received >7 days of opioids (range 7–55 days). An amount of methadone, equi- potent to the existing daily fentanyl or morphine dose, was deter- mined. This amount was reduced by a factor of 8 because of the larger half-life of methadone to calculate the initial daily methadone dose. Protocols specified different mean- ing schedules, depending on whether the patient had been treated with opioids (fentanyl or morphine) for either 7 to 14 days or for >14 days. Treatment intervals were gradually lengthened from every 6 hours to ev- ery 24 hours when methadone was discontinued. Outcomes of these pa- tients were compared with recent control patients who had also been treated with enteral methadone but not under a standard protocol. Among the protocol patients, there were no treatment failures. Weaning was accom- plished in a median of 8 days (range, 5–10 days), which was signif- icantly less than the median of 20 days (range, 9–31 days) observed in the nonprotocol patients. Concurrent use of benzodiazepines occurred in 6 of the protocol children, compared with 0% of the nonprotocol children.
Length of Stay: Methadone exposed infants
The standard approach: why?

- Medications
Intervention 1

Focus on non-pharmacologic care
Length of Stay: Methadone exposed infants

Standardized non-pharm care

Mean = 22.5

Mean = 13.2
The standard approach: why?

- Medications
- NICU
Intervention 2

Direct transfer to the general inpatient unit
Length of Stay: Methadone exposed infants

- Standardized non-pharm care: Mean = 22.5 days
- Direct transfer to inpatient unit: Mean = 13.2 days
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
<table>
<thead>
<tr>
<th>SYSTEMS</th>
<th>SIGNS AND SYMPTOMS</th>
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“The infant with a score of “7” or less was not treated with drugs for the abstinence syndrome because, in our experience, he would recover rapidly with swaddling and demand feedings. Infants whose score was “8” or above were treated pharmacologically”

Problems with the Finnegan

- Long lengths of stay and lots of meds
- Purpose of treatment is to get the scores below threshold
- Must disturb the infant and exacerbate signs of withdrawal
- Can be slow to respond
- Powerful and potentially harmful meds to give to treat a sneeze or a yawn
Intervention 3

Discontinuation of the Finnegan Scoring tool and adoption of a functional scoring approach
1) Can the baby eat?
2) Can the baby sleep?
3) Can the baby be consoled?
• Analyzed 50 consecutive NAS babies admitted to our general inpatient unit from March 2014 to August 2015

• Assessed every 2-6 hours using the FNASS, but did not guide management

• Management decisions based on ESC
Outcomes

1. Proportion of infants treated with morphine vs. proportion predicted to be treated with morphine using the FNASS approach
2. Days the two approaches disagreed
3. FNASS scores the day after the two approaches disagreed
Results

Proportion of Infants that Received Morphine

- Received Morphine (ESC): 12%
- Would Have Received Morphine (Finneqan): 62%

p<.001
Results

• On 78 days (26.4%) the ESC Led to LESS Morphine than Predicted by The Finnegan
  • The following day, the average Finnegan score decreased by 0.9 points, and decreased in 69% of cases.

• On 2 days (0.7%) the ESC Led to MORE Morphine than Predicted by The Finnegan
  • In both cases the average Finnegan score increased by 1.7 Points the next day
Results

- No readmissions
- No seizures
- No ICU transfers
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
Intervention 4

Decrease in morphine up to 3 times per day
Intervention 5

PRN Dosing
Length of Stay: Methadone exposed infants

- Mean = 22.5
- Mean = 13.2
- Standardized non-pharm care
- Direct transfer to inpatient unit
- Novel assessment tool on inpatient unit
- Spread to NICU team
- Prenatal counseling
- Rapid med weaning
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
- Staff cares for the baby
How do moms feel?

- Addiction is misunderstood
- Guilty
- Judged
- Mistrusting of nurses
“His nurse was like ‘his muscles are locking up because of his junkie mom’. I didn’t want to visit, I would call before and if that nurse was there, I wouldn’t even go.
“...because we’re gonna leave and he’s gonna cry and they’re gonna leave him crying because they’re gonna be like, ‘you know what? His parents are jerks!’”
Intervention 6

Empowering messaging
<table>
<thead>
<tr>
<th>Old Protocol</th>
<th>New Protocol</th>
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<tbody>
<tr>
<td>● Goal: suppress withdrawal signs</td>
<td>● Goal: have infant function as a normal neonate</td>
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<tr>
<td>● NICU: Mom visits</td>
<td>● Mother and child together</td>
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<tr>
<td>● Finnegan Scores: treat the number</td>
<td>● <strong>Eat/Sleep/Console</strong>: treat the infant</td>
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<tr>
<td>● “supportive care”</td>
<td>● SUPPORTIVE CARE</td>
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<td>● “feed on demand”</td>
<td>● No feeding schedule</td>
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<tr>
<td>● Morphine</td>
<td>● Meds on page 3</td>
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<tr>
<td>● Surprise!</td>
<td>● Prenatal preparation</td>
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<tr>
<td>● Staff takes care of infant</td>
<td>● Staff coaches parents</td>
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</table>
Length of Stay: Methadone exposed infants
Total Average Cost of NAS Care

- The graphic shows the total average cost of NAS care from 2003 to 2015.
- The cost fluctuates over the years, peaking in 2008 and 2012.
- A significant decrease is observed from 2012 to 2015.
- The p-value is less than 0.001, indicating statistical significance.

(Yale-New Haven Children's Hospital logo is present on the lower right corner.)
Boston Medical Center

- Had been using FNASS approach
- Finnegan prioritization from June-November 2016
- Developed ESC approach as a scoring tool
- Piloting since December 2016
Boston Medical Center – Results

- Use of morphine decreased from 82% to 40%
- Length of stay decreased from 18 days to 10 days
- No readmissions
Other ESC references


Long-Term Outcomes
Conclusions

- Hugs before drugs
  - Empower families
  - Rooming-in
  - Non-Pharmacologic care as 1st line treatment
  - ESC approach
  - PRN meds

- 3 Keys to treatment
  - Mom is antibiotics
  - Pretend it is a baby
  - Treat the mom like a mom

- Ask why

Source: Grossman Family Album
Acknowledgements

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