Donor human milk for infants with Neonatal Abstinence Syndrome (NAS)

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Background

Neonatal Abstinence Syndrome (NAS) is a drug withdrawal syndrome that occurs primarily after antenatal exposure to opiates. Symptoms may be present at birth, but often peak at 48-72 after delivery. The onset of symptoms is affected by the half-life of the opiate used during pregnancy in combination with maternal and infant metabolism. The incidence of NAS has increased substantially since 2000 both nationally and in the Commonwealth of Kentucky, leading to a significant increase in healthcare resource utilization and (Figure 1).

The 2012 National Survey on Drug Use and Health found that illicit drug abuse affected ~130,000 pregnancies in the United States from 2011-2012 and that approximately 20% of those pregnancies (26,000) involved opiates. (SAMSA Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2009-2012). Patrick et al. utilized the Kids' Inpatient Database (KID) from the Agency for Health Care Research and Quality to evaluate the incidence of maternal opiate use during pregnancy[1]. He and his team noted a substantial increase in the number of mothers using opiates - 1.19 per 1000 hospital births in 2000 to 5.63 per 1000 hospital births in 2009. As a result, there was an increased diagnosis of NAS from 1.20 per 1000 hospital births in 2000 to 3.39 per 1000 hospital births in 2009. This is a 2.8-fold increase which means that every hour of every day, 1 neonate in the United States undergoes drug withdrawal.

The Kentucky Injury Prevention and Research Center reported that 824 infants in the state of Kentucky were hospitalized for neonatal withdrawal after exposure to opiates in 2012. This represents an 18% increase from 2011 and a 4.5 fold increase from 2005. (Kentucky Injury Prevention and Research Center. Data for 2010-2012). Neonatal Abstinence Syndrome is an issue of epidemic proportions both for Kentucky and the nation. It results in prolonged hospitalizations and increased healthcare costs. In 2009, the total charges for NAS treatment were noted to be approximately $720 million nationally, up from approximately $190 million in 2000[1]. Kentucky data from 2012 report a $40 million dollar cost for neonatal drug withdrawal treatment, which has increased from $200,000 in 2000. (Kentucky Injury Prevention and Research Center. Data for 2010-2012). The majority of these costs (75-80%) are paid by the state Medicaid program (Figure 2).

Precipitous removal of exogenous opiates at the time of delivery results in unopposed stimulation by cAMP and which increases norepinephrine levels and results in clinical symptoms of drug withdrawal in the neonate[2]. Symptoms include central nervous system (CNS) signs (seizures, irritability, tremors), autonomic disturbances (sweating, yawning, nasal stuffiness, low grade fever, mottling) and gastrointestinal (GI) dysfunction (diarrhea, vomiting, poor feeding, and regurgitation). The cohort of withdrawal symptoms is dictated by the location of μ opioid receptors, which are concentrated in the brain but are also found in sensory nerves, mast cells and in the GI tract[3].

Treatment of withdrawal symptoms includes symptomatic care for mild symptoms and pharmacological intervention in addition to symptomatic care for moderate to severe symptoms. The American Academic of Pediatrics and experts in the field recommend opioid replacement therapy as the

first line pharmacologic intervention in opioid-induced withdrawal. The most commonly used medication is oral morphine. Phenobarbital and clonidine have been used as adjuvant therapies with some success in infants with more severe symptoms. Initiation, escalation and weaning of pharmacologic therapy are based on observer rated scales, the most common of which is the Finnegan Scale[4]. Although observer-rated scales are an essential component in the assessment and treatment of neonatal drug withdrawal, they lack rigorous psychometric testing to establish reliability and validity, are subjective and have been difficult to standardize across nurseries[5].

Infants undergoing opiate withdrawal, as noted above, have feeding difficulty, including spitting, regurgitation and diarrhea. The Finnegan scoring tool includes a series of feeding assessments within the total scoring algorithm (Table 1). Human milk has been shown to be the best tolerated nutritional support for most infants and is cited by the AAP as the preferred method for feeding all infants[6]. However, the AAP considers the use of marijuana, cocaine, methamphetamines and unsupervised opiate use during pregnancy to be a contraindication to breastfeeding[7]. For most street drugs, the risks to the infant of ongoing active use by the mother outweigh the benefits of breastfeeding because the doses of the drug(s) being used and contaminants within the drug are unknown[8-11]. The AAP does recognize that if a mother is in a supervised methadone treatment center and is free from using other drugs of abuse then breastfeeding is an essential component of the infant's care. However, most infants with NAS are fed formula for a variety of reasons, including concerns about continued maternal use.

Human milk is a complete nutritional food for the first 6 months of life in the term infant. Aside from its nutritional composition (specific for the support of the human infant), it contains hormones, immunoglobulins and growth factors that stimulate gastrointestinal growth and motility which, in turn, promote the maturation and protection of the GI tract. Mediators such as neurotensin and motilin promote GI motility while free amino acids feed intestinal growth [12, 13]. Human milk feeding has been shown to increase gastric empyting[14, 15] and lactase activity[16] in the gut which improves feeding tolerance. A human milk diet is also associated with post-natal intestinal colonization by beneficial bacteria (Lactobacillus and Bifidobacteria). In summary, when compared to formula feeding, human milk appears to be a more suitable diet for the neonate at risk for GI dysfunction.

Two retrospective studies of the effect of breastfeeding on clinical symptoms of NAS have been reported. McQueen et al reviewed 28 mother-infant pairs with maternal methadone exposure and infant symptoms of NAS[17]. Maternal and infant demographics were recorded along with feeding type, Finnegan scores and infant medication utilization during withdrawal. Feeding cohorts were created by quantifying the duration of breastfeeding during hospitalization. Formula fed infants received >75% of all feedings as formula (n=9), breastfed infants received >75% of feedings at the breast (n=8). The rest were considered combination feeders (n=11). Combination feeders were slightly less mature (35.6 weeks) and of lower birth weight (2608 g) than breastfed (38.8 weeks and 3025 g) or formula fed (39.1 weeks and 3302 grams). Breastfed infants received fewer scores, had significantly lower overall Finnegan scores and fewer scores >8 when compared to formula and combination fed infants ($p \leq 0.001$).

Dryden et al. performed a retrospective cohort study of 437 infants born to women prescribed methadone in varying doses for their addiction[18]. Median gestational age at birth was 38 weeks and birth weight was 2730 grams. Twenty-two percent of infants were breastfed for at least 72 hours. Multivariate logistic regression showed that the prescribed dose of methadone in these women

independently influenced the likelihood of pharmacologic treatment for NAS ($p<0.001$). However, for infants that were breastfed for at least 72 hours, the odds of needing pharmacologic treatment for NAS was significantly reduced (OR 0.55, 95% CI 0.34 – 0.88, p=0.013).

Maternal opiates are transmitted through the breast milk to the infant. The amount of methadone and buprenorphine transfered in the breast milk has been found to be small, but may be significant enough to lead to some improvement in scores.

While these studies have reported improvements (decreases) in NAS scoring or reduced duration of treatment with breastfeeding, there are no reports that have looked at donor human milk, which is tested to be free of illicit drugs, and its effect on the GI sub-scores of the Finnegan algorithm. Given the general benefits of human milk for the human infant and these limited reports of improved neonatal well-being in breastfed infants with NAS, this study is designed to develop pilot data on the acceptability and benefit of donor human milk for infants undergoing pharmacologic treatment for NAS. Specifically, GI sub-scores, as well as total scores, will be compared between infants historically fed formula and those enrolled in a 2-week donor human milk study period.

Purpose of study: to test the following null hypothesis:

Infants with a diagnosis of neonatal abstinence syndrome (NAS) due to in-utero exposure to opiates, fed donor human milk, will have similar GI/feeding sub-scores of the Finnegan scoring tool when compared to (historic) infants fed formula.

A rejection of the null hypothesis will be used to design a randomized trial of donor human milk in infants with NAS.

Eligibility for study enrollment:

Inclusion criteria:

- Term infants ($\geq$37 completed weeks) with a diagnosis of NAS, due to maternal use of opiates (only)
- Infants will have had moderate to severe NAS symptoms (Finnegan scores >8) that required pharmacologic therapy but have been stabilized (captured) on oral morphine (Finnegan scores less than 8 for 24 hours)
- Breastfeeding is contraindicated or the mother has chosen formula feeding for her baby

Exclusion criteria:

- Preterm infants (<37 completed weeks at birth)
- Infants with intrauterine growth restriction (BW <10th percentile for gestational age) Mother is providing her own milk

Methods:

Once the infant's withdrawal symptoms have been stabilized with oral morphine and the mother has agreed to participation (signed ICF/RA), infants will be assigned to receive only donor human milk (Co-op donor milk, Medolac Laboratories, Lake Oswego, OR) for a period of 2 weeks. Vitamin supplementation or other nutritional adjustments will be at the discretion of the attending physician.

Infant Finnegan scores will be assessed according to the current NAS protocol. Oral morphine dosing (increases or weaning doses) will be consistent with the current NAS protocol.

Primary outcome:

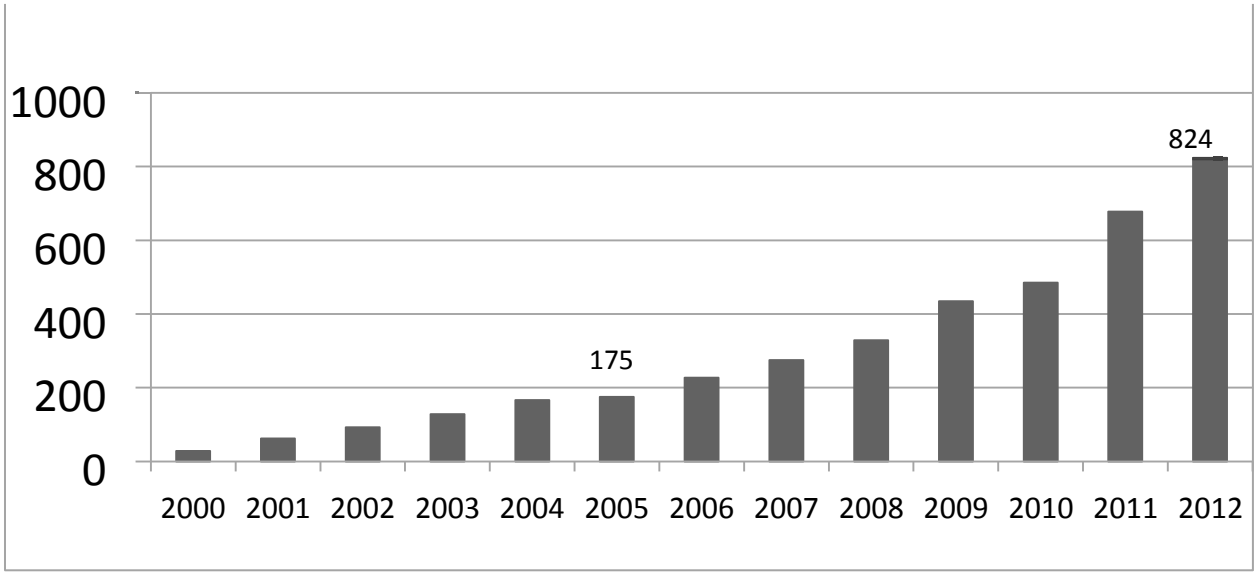
Acceptability (no increase in GI sub-scores compared to historic formula-fed controls) Appropriate growth

See data collection sheet for detailed list of variables.

Statistical analysis:

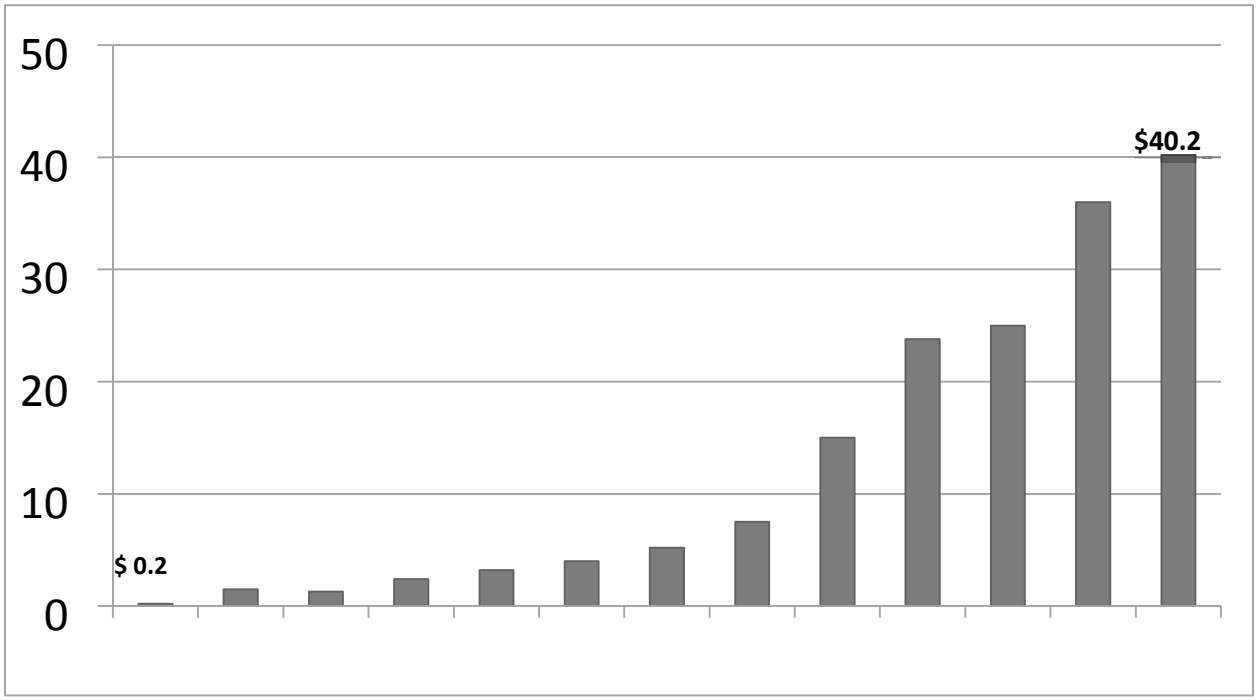
Descriptive statistics will be provided. As this is a pilot study, no inferential statistics will be applied.

Figure 1. Cases of neonatal abstinence syndrome (NAS) in Kentucky (20002012)*



***Data from Kentucky Injury Prevention Research Center, January 2014**

Figure 2. Healthcare expenditures (in $ millions) for treatment of neonatal abstinence syndrome (NAS) in Kentucky (2000-2012)*



***Data from Kentucky Injury Prevention Research Center, January 2014**

Table 1. Modified Finnegan Scoring Tool[4]

System symptoms	Total (frequency)
CNS	
High-pitched cry Continuous high-pitched cry	2 3
Sleeps <1 h after feeding Sleeps <2 h after feeding Sleeps <3 h after feeding	3 2 1
Hyperactive Moro reflex Markedly hyperactive Moro reflex	2 3
Tremors disturbed Mild tremors undisturbed Moderate severe tremors undisturbed	2 3 4
Increased muscle tone	2
Excoriation (specify area)	1
Myoclonic jerks	3
Generalized convulsions	5

Metabolic	
Sweating	1
Fever 37.2°C – 38.3°C Fever >38.4°C	1 2
Frequent yawning >4 x per interval	1
Mottling	1
Vasomotor	
Nasal stuffiness	1
Frequent sneezing >4 x per interval	1
Respiratory	
Nasal flaring	2
Respiratory rate >60/min Respiratory rate >60/min + retractions	1 2
Gastrointestinal	
Excessive sucking	1
Poor feeding	1
Regurgitation	2
Projective vomiting	3
Loose stools Watery stools	2 3
GI sub-score range: 0 to 10	
Total score range	**0 to 44**

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