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Clinical Critically Appraised Topics

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2-2021

## **Low lactose formula in neonatal abstinence syndrome: Summary**

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**Specific Care Question** In term and near-term infants ( $\geq 35$  weeks of gestation) with neonatal abstinence syndrome (NAS) does low-lactose formula (LLF) versus regular standard term formula result in a decrease in NAS duration, length of hospital stay (LOS), or the need for pharmacological therapy, and better growth?

**Recommendations Based on Current Literature (Best Evidence) Only**

*A conditional recommendation is made against LLF as no beneficial effects were found in patients with NAS. This recommendation is based on expert opinion and review of the current literature. The overall certainty in the evidence is very low<sup>a</sup>.*

*The positive benefits of maternal breast milk in infants with NAS has been established (Liu et al., 2015). This review was conducted to determine the benefit of LLF if maternal breast milk is unavailable. Four studies were identified for this review and found that there was no benefit for prescribing LLF to infants with NAS (see Summary by Outcome for substantiation of recommendations). In fact, one study (Kaplan et al., 2020) found that high calorie formula was most beneficial regardless of lactose content. The studies found for this review had serious heterogeneity based on the type of maternal drug use, formula given, calories provided, and whether the patients were given exclusive feedings of one type of formula. Certainty in the evidence is very low.*

**Literature Summary**

**Background.** NAS refers to a group of conditions exhibited in infants who experience withdrawal after intrauterine exposure to opioids (Alsalem et al., 2020). While symptoms may vary, some classic symptoms of NAS include jitteriness, irritability, sleep disturbance, and temperature instability (Alsalem et al., 2020). These infants can also develop poor feeding symptoms as well as gastrointestinal symptoms of diarrhea, and cramping (Maguire & Gröer, 2016). While the positive benefits of maternal breast milk in this population have been established (Liu et al., 2015), the benefit of LLF has not been fully determined. This review will summarize the current literature on the topic.

**Study characteristics.** The search for suitable studies was completed on December 22, 2020. M. Alsalem, MD and G. Akangire, MD, MS reviewed the 41 titles and/or abstracts found in the search and identified<sup>b</sup> four single studies believed to answer the question. After an in-depth review of the single studies<sup>d</sup>, four studies answered the question. The studies included one randomized control trial (RCT) (Pandey et al., 2020), two cohort studies (Alsalem et al., 2020; Lembeck et al., 2020), and one quality improvement study (Kaplan et al., 2020). A meta-analysis could not be completed due to the differences in study type and how outcomes were reported.

**Summary by Outcome**

**Duration of Treatment.** Three studies (Alsalem et al., 2020; Lembeck et al., 2020; Pandey et al., 2020) measured duration of treatment in infants with NAS, ( $N = 428$ ). Alsalem et al. (2020) measured duration of morphine sulfate (MOS4) treatment in infants fed LLF versus standard term formula ( $n = 110$ ). After adjusting for type of drug used by the mother, regular maternal involvement in prenatal care and inborn status, maternal smoking status, and maximum scores prior to MSO4 treatment the  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula),  $p$ -value = .12. Lembeck et al. (2020) measured duration of treatment in infants fed LLF versus standard formula ( $n = 129$ ). The confidence interval (CI) and  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula), -0.5 days,  $p = .89$ , 95% CI [-7.5, 6.5]. Pandey et al. (2020) measured duration of medication treatment in infants fed LLF versus those feed standard formula ( $n = 69$ ). The mean difference (MD) in days indicated the intervention (LLF) was not different to the comparator (standard formula), -3.10 days 95% CI [-11.01, 4.81] (see Figure 2). Treatment length was  $16.5 \pm 13.6$  and  $19.6 \pm 6$  days for LLF and SF, respectively.

**Certainty of the evidence for duration of treatment.** The certainty of the body of evidence was very low based on four factors<sup>a</sup>: *within-study risk of bias, consistency among studies, directness of evidence, and precision of effect estimates*. The body of evidence was assessed to have serious risk of bias, serious inconsistency, and serious imprecision. Risk of bias was assessed as serious as two of the studies (Alsalem et al., 2020; and Lembeck et al., 2020) were retrospective cohorts which can result in selection bias. Inconsistency was serious due the heterogeneity of formulas used, calorie levels, and exclusivity of feeding type. Imprecision was assessed as serious due to the low number of events.

**Length of Stay (LOS).** Three studies (Alsalem et al., 2020; Kaplan et al., 2020; Lembeck et al., 2020) measured LOS in infants with NAS, ( $N = 905$ ). Alsalem et al. (2020) measured LOS in infants fed LLF versus standard term formula ( $n = 110$ ). After adjusting for type of drug used by the mother,

regular maternal involvement in prenatal care and inborn status, maternal smoking status, and maximum scores prior to MSO4 treatment the  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula),  $p$ -value = .16. Lembeck et al. (2020) measured LOS in infants exclusively fed LLF versus standard formula ( $n = 129$ ). The confidence interval (CI) and  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula), -1.1 days, 95% CI [-8.4, 6.3],  $p = .93$ . Kaplan et al. (2020) measured LOS in infants fed low lactose high calorie (LL + HC) versus high lactose high calorie (HL + HC) versus low lactose low calorie (LL + LC) versus high lactose + low calorie (HL + LC) formula. The mean days indicated that the intervention (LL + HC) was less effective to the comparator (HL + HC), though the significance not reported. LOS for LL + HC versus HL + HC was 16.6 days and 14.8 days, respectively.

**Certainty of the evidence for LOS.** The certainty of the body of evidence was very low based on four factors<sup>a</sup>: *within-study risk of bias, consistency among studies, directness of evidence, and precision of effect estimates*. The body of evidence was assessed to have serious risk of bias, serious inconsistency, and serious imprecision. Risk of bias was assessed as serious as two of the studies (Alsalem et al., 2020; and Lembeck et al., 2020) were retrospective cohorts which can result in selection bias. Also, risk of bias was serious as Kaplan et al. (2020) was a quality improvement study that did not report significance. Inconsistency was serious due to the heterogeneity of formulas used, calorie levels, and exclusivity of feeding type. Imprecision was assessed as serious as due to the low number of events.

**Need for Pharmacological Therapy.** Three studies (Alsalem et al., 2020; Lembeck et al., 2020; Pandey et al., 2020) measured the need for pharmacologic treatment in infants with NAS, ( $N = 428$ ). Pandey et al. (2020) measured cumulative morphine dose in infants fed LLF versus standard formula ( $n = 69$ ). The MD indicated the intervention (LLF) was not different to the comparator (standard formula), -2.3 mg/kg, 95% CI [-12.54, 7.94] (see Figure 3). Cumulative morphine for the first 14 days was 20.7 mg  $\pm$  19.8 and 23 mg  $\pm$  23.5 days for LLF and SF, respectively. Alsalem et al. (2020) measured need for pharmacological therapy in infants fed LLF versus standard term formula ( $n = 110$ ). After adjusting for type of drug used by the mother, regular maternal involvement in prenatal care and inborn status, maternal smoking status, and maximum scores prior to MSO4 treatment the  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula),  $p$ -value = .86. Lembeck et al. (2020) measured duration of treatment comparing infants exclusively fed LLF versus standard formula ( $n = 129$ ). The confidence interval (CI) and  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula), -0.5 days, 95% CI [-7.5, 6.5],  $p = .89$ .

**Certainty of the evidence for pharmacological therapy.** The certainty of the body of evidence was very low based on four factors<sup>a</sup>: *within-study risk of bias, consistency among studies, directness of evidence, and precision of effect estimates*. The body of evidence was assessed to have serious risk of bias, serious inconsistency, and serious imprecision. Risk of bias was assessed as serious as two of the studies (Alsalem et al., 2020; and Lembeck et al., 2020) were retrospective cohorts which can result in selection bias. Inconsistency was serious due to the heterogeneity of formulas used, calorie levels, and exclusivity of feeding type. Imprecision was assessed as serious as due to the low number of events.

**Growth.** One study (Lembeck et al., 2020) measured growth in infants exclusively fed LLF versus standard formula ( $n = 129$ ). The confidence interval (CI) and  $p$ -value indicated that the intervention (LLF) was not different to the comparator (standard formula), 6 gm/day, 95% CI [-8, 20],  $p = .39$ .

**Certainty of the evidence for growth.** The certainty of the body of evidence was very low based on four factors<sup>a</sup>: *within-study risk of bias, consistency among studies, directness of evidence, and precision of effect estimates*. The body of evidence was assessed to have serious risk of bias and serious imprecision. Risk of bias was assessed as serious as the study (Lembeck et al., 2020) was a retrospective cohort which can result in selection bias. Imprecision was assessed as serious as due to the low number of events. As only one study (Lembeck et al., 2020) was identified to answer this question consistency could not be assessed.

## Identification of Studies

### Search Strategy and Results (see Figure 1)

((("Neonatal Abstinence Syndrome/diet therapy"[Majr]) OR (("Neonatal Abstinence Syndrome"[Mesh] OR "neonatal abstinence syndrome") AND ("Infant Formula"[Mesh] OR "Enteral Nutrition"[Mesh] OR lactose-reduced formula OR lactose-free formula OR protein partially hydrolyzed formula OR formula[tiab] OR formula[tw] OR Feeds[tiab] OR Feeding[tiab] OR Enteral[tiab]))) NOT "Case Reports"[PT]) Filters: 5 years

Records identified through database searching  $n = 41$   
Additional records identified through other sources  $n = 0$

Studies Included in this Review

Citation	Study Type
Alsaleem et al. (2020)	Cohort
Kaplan et al. (2020)	Quality Improvement
Lembeck et al. (2020)	Cohort
Pandey et al. (2020)	RCT

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Bogen et al. (2018)	Study on calorie level and does not address question

**Methods Used for Appraisal and Synthesis**

<sup>a</sup>The [GRADEpro Guideline Development Tool \(GDT\)](#) is the tool used to create the Summary of Findings table(s) for this analysis.

<sup>b</sup>Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

<sup>c</sup>Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

<sup>d</sup>The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

<sup>a</sup>GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from [gradepro.org](http://gradepro.org).

<sup>b</sup>Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, 5(1), 210. doi:10.1186/s13643-016-0384-4

<sup>c</sup>Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

<sup>d</sup>Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).**

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*Acronyms Used in this Document*

Acronym	Explanation
CAT	Critically Appraised Topic
EBP	Evidence Based Practice
EB	Exclusively breastfeeding
ESF	Exclusively standard formula
ELLF	Exclusively low lactose formula
HC	High calorie
HL	High lactose
LC	Low calorie
LL	Low lactose
LLF	Low lactose formula
LFF	Lactose free formula
MSF	Majority Standard Formula
MLLF	Majority low lactose formula
NAS	Neonatal Abstinence Syndrome (NAS)
PHF	Partially hydrogenated formula
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SF	Standard formula

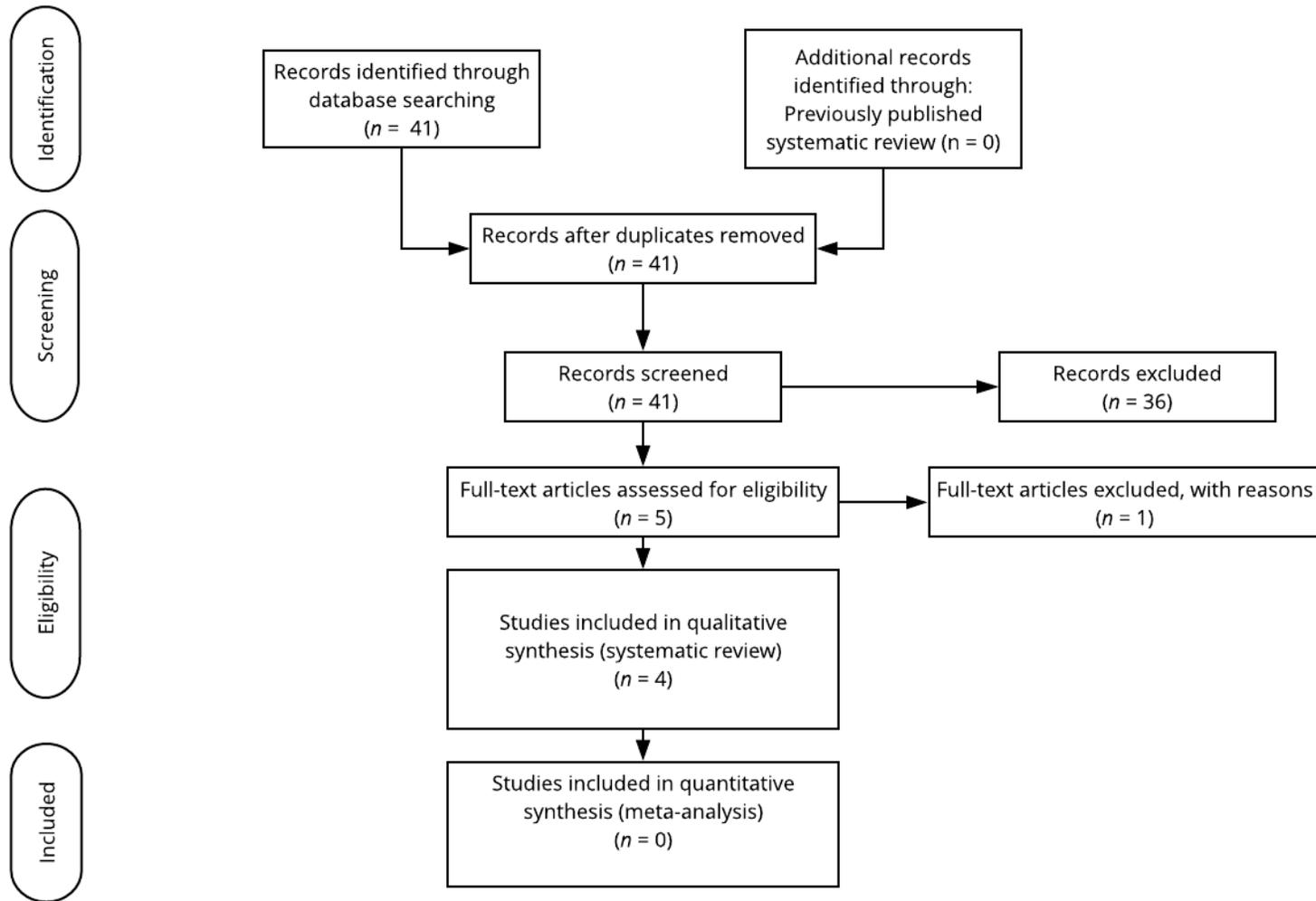


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>d</sup>

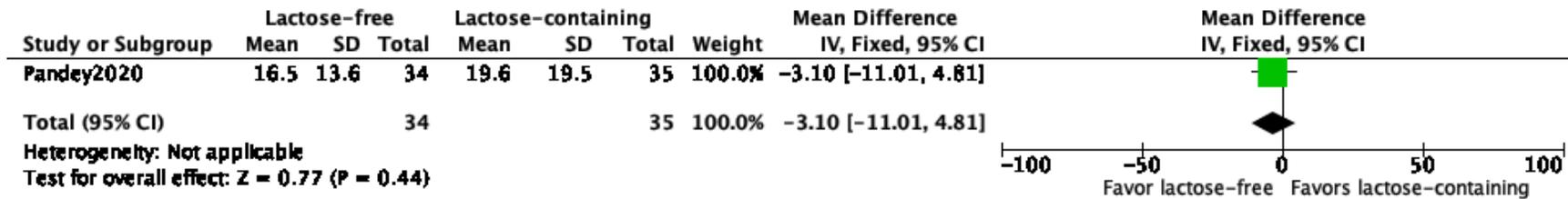


Figure 2. Comparison: Lactose-free formula versus standard formula, Outcome: Length of treatment (days)

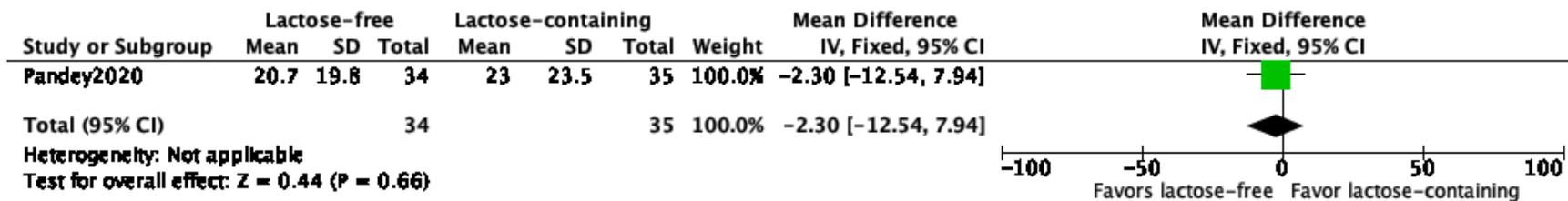


Figure 3. Comparison: Lactose-free formula versus standard formula, Outcome: Cumulative Morphine Dose (mg/kg; first 14 days of life)

Characteristics of Intervention Studies

Alsaleem et al., 2019

Methods	Cohort, Retrospective chart review
<p><b>Participants</b></p>	<p><b>Participants:</b>  <b>Setting:</b> USA, Buffalo, NY. Neonatal Intensive Care Units (NICUs) at Women and Children’s hospital, Suburban Hospital, October 2013 – October 2016.  <b>Number enrolled into study:</b> <math>N = 110</math></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> Partially Hydrolyzed Formula (LFF): <math>n = 34</math></li> <li>• <b>Group 2:</b> Standard Formula (SF): <math>n = 60</math></li> <li>• <b>Group 3:</b> Maternal Breast Milk (MBM): <math>n = 16</math></li> </ul> <p><b>Gender, males (as defined by researchers):</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> <math>n = 47\%</math></li> <li>• <b>Group 2:</b> <math>n = 65\%</math></li> <li>• <b>Group 3:</b> not specified</li> </ul> <p><b>Race / ethnicity or nationality of mother, % Caucasian (as defined by researchers):</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 85%</li> <li>• <b>Group 2:</b> 80%</li> <li>• <b>Group 3:</b> not specified</li> </ul> <p><b>Gestational Age, weeks, mean (+/- SD)</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 38.6 (1.4)</li> <li>• <b>Group 2:</b> 38.4 (1.5)</li> <li>• <b>Group 3:</b> not specified</li> </ul> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Neonates, gestational age <math>\geq 36</math> weeks gestational age</li> <li>• Born to mothers who used an opioid medication(s) with or without additional drugs</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Infants born <math>&lt; 36</math> weeks</li> <li>• Presence of major medical, surgical or social condition that could result in prolonged hospital stay</li> </ul> <p><b>Covariates Identified:</b></p> <ul style="list-style-type: none"> <li>• Birth weight</li> <li>• APGAR score</li> <li>• Maternal smoking</li> <li>• Vaginal vs C-section delivery</li> <li>• Regular prenatal care</li> <li>• Mother is currently enrolled in drug treatment program</li> <li>• Maternal age</li> <li>• Use of various opioid drugs in combination with other legal/illegal prescription medications: <ul style="list-style-type: none"> <li>○ Subutex</li> <li>○ Suboxone</li> <li>○ Methadone</li> <li>○ Multiple drugs, including a combination of above drugs and Selective Serotonin Reuptake Inhibitors, Benzodiazepines, and/or Anxiolytics</li> </ul> </li> </ul>

<p><b>Interventions</b></p>	<p><b>Group 1:</b> PHF feeding (most commonly used at the study hospitals during study time period were Mead Johnson &amp; Co Gentlease and Abbot Similac Sensitive)  <b>Group 2:</b> SF feeding, formula type not specified  <b>Group 3:</b> Infants exclusively fed MBM  <b>All groups:</b></p> <ul style="list-style-type: none"> <li>• NAS assessment by modified Finnegan scale performed every 3 to 4 hours by trained medical staff</li> <li>• Pharmacological therapy (if needed) included Morphine (MSO<sub>4</sub>) and other (unspecified) medications</li> <li>• Growth assessment performed daily by clinicians during morning rounds, caloric concentration of formula increased to maintain adequate weight gain of 15 to 20 g/kg/day after initial expected weight loss.</li> </ul>
<p><b>Outcomes</b></p>	<p><b>Primary Outcomes:</b></p> <ul style="list-style-type: none"> <li>• Required MSO<sub>4</sub></li> <li>• First day of MSO<sub>4</sub></li> <li>• Maximum MSO<sub>4</sub>, dose, mg/kg/dose</li> <li>• Required other medications</li> <li>• *Duration of MSO<sub>4</sub> Treatment</li> <li>• *Length of hospitalization</li> <li>• *Growth</li> </ul> <p>*Outcomes of interest to the CMH CPG /CAT development team</p>
<p><b>Results</b></p>	<p><b>Duration of MSO<sub>4</sub>, treatment, days:</b> Adjusted <i>p</i>-value = .12</p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 24 ± 19</li> <li>• <b>Group 2:</b> 15 ± 14</li> </ul> <p><b>Length of hospital stay, days (SD):</b> Adjusted <i>p</i>-value = .16</p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 29 ± 19</li> <li>• <b>Group 2:</b> 21 ± 12</li> </ul> <p><b>Need for pharmacological therapy, %:</b> Adjusted <i>p</i>-value = .86</p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 85</li> <li>• <b>Group 2:</b> 68</li> </ul> <p><b>Growth:</b></p> <ul style="list-style-type: none"> <li>• Measured as % of neonates requiring 20 kcal/oz, 22 kcal/oz, 24 kcal/oz to maintain an adequate growth rate of at least 15 mg/kg/day.</li> <li>• Growth assessment not feasible.</li> <li>• <b>Group 1:</b> 44% required some increased caloric fortification</li> <li>• <b>Group 2:</b> 27% required some increased caloric fortification</li> <li>• <b>Group 3:</b> Not specified</li> </ul> <p><b>Notes:</b></p> <ul style="list-style-type: none"> <li>• Infants were included in study based on either maternal report of drug use, maternal urine testing and/or infant testing. It is unclear which infants were included in which groups</li> <li>• Mothers took any number of combinations of opioids and/or other medications, it is unclear which of their infants were included in which groups</li> <li>• Major outcome of this study (as reported by authors) was MSO<sub>4</sub> therapy, including requirement of, maximum dose of, and duration of therapy</li> </ul>

Kaplan et al., 2020

Methods	Quality Improvement study
<p><b>Participants</b></p>	<p><b>Participants:</b> Infants that were experiencing neonatal abstinence syndrome (NAS) between October 2015 to June 2016.  <b>Setting:</b> At 47 sites, The Ohio Perinatal Quality Collaborative (OPQC) conducted a quality improvement initiative using orchestrated testing (OT) to improve nonpharmacological care of infants dealing with NAS requiring pharmacological treatment.  <b>Number enrolled into study:</b> <math>N = 546</math></p> <ul style="list-style-type: none"> <li>• <b>Group 1, low lactose formula (LL), high calorie formula (HC):</b> <math>n = 94</math></li> <li>• <b>Group 2, high lactose formula (HL), high calorie formula (HC):</b> <math>n = 74</math></li> <li>• <b>Group 3, low lactose formula (LL), low calorie formula (LC):</b> <math>n = 333</math></li> <li>• <b>Group 4, high lactose formula (HL), low calorie formula (LC):</b> <math>n = 54</math></li> </ul> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• <math>\geq 37</math> weeks gestation</li> <li>• Require pharmacological treatment</li> <li>• Receiving formula (solely or as supplement)</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Breastfed only</li> </ul> <p><b>Covariates Identified:</b></p> <ul style="list-style-type: none"> <li>• None reported</li> </ul>
<p><b>Interventions</b></p>	<ul style="list-style-type: none"> <li>• <b>Group 1, low lactose formula (LL), high calorie formula (HC):</b> Fortify feeds to 22 kcal/oz</li> <li>• <b>Group 2, high lactose formula (HL), high calorie formula (HC):</b> Fortify feeds to 22 kcal/oz</li> <li>• <b>Group 3, low lactose formula (LL), low calorie formula (LC):</b> Missing specifics</li> <li>• <b>Group 4, high lactose formula (HL), low calorie formula (LC):</b> Missing specifics</li> </ul> <ul style="list-style-type: none"> <li>• <i>Groups may discontinue specific formula guidelines once infant has been weaned off opiates for 24 hours.</i></li> </ul>
<p><b>Outcomes</b></p>	<p><b>Primary outcome(s):</b></p> <ul style="list-style-type: none"> <li>• *Length of hospital stay</li> <li>• Treatment failure</li> <li>• Weight loss (<math>&gt;10\%</math> within 7 days of life)</li> <li>• Pharmacological intervention(s) (Morphine was the primary treatment with phenobarbital used as an adjunct)</li> <li>•</li> </ul> <p><b>Secondary outcome(s):</b></p> <ul style="list-style-type: none"> <li>• None reported</li> </ul> <p><b>Safety outcome(s):</b></p> <ul style="list-style-type: none"> <li>• None reported</li> </ul>
<p><b>Results</b></p>	<p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• <b>Length of hospital stay:</b> <ul style="list-style-type: none"> <li>○ <b>Base Analysis:</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 16 days</li> <li>▪ Group 2 (HL+HC): 18.7 days</li> <li>▪ Group 3 (LL+LC): 18.7 days</li> <li>▪ Group 4 (HL+LC): 18 days</li> </ul> </li> <li>○ <b>Adjusted Analysis (accounting for hospital, breastfeeding, weight loss):</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 16.6 days</li> <li>▪ Group 2 (HL+HC): 14.8 days</li> </ul> </li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>▪ Group 3 (LL+LC): 19.7 days</li> <li>▪ Group 4 (HL+LC): 17.6 days</li> <li>• <b>Treatment failure (dose escalation, failed wean, and/or requires secondary pharmacological treatment):</b> <ul style="list-style-type: none"> <li>○ <b>Base Analysis:</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 54%</li> <li>▪ Group 2 (HL+HC): 62%</li> <li>▪ Group 3 (LL+LC): 71%</li> <li>▪ Group 4 (HL+LC): 58%</li> </ul> </li> <li>○ <b>Adjusted Analysis (accounting for hospital, breastfeeding, weight loss):</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 63%</li> <li>▪ Group 2 (HL+HC): 44%</li> <li>▪ Group 3 (LL+LC): 73%</li> <li>▪ Group 4 (HL+LC): 56%</li> </ul> </li> </ul> </li> <li>• <b>Weight loss (&gt;10% within 7 days of life)</b> <ul style="list-style-type: none"> <li>○ <b>Base Analysis:</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 7%</li> <li>▪ Group 2 (HL+HC): 13%</li> <li>▪ Group 3 (LL+LC): 13%</li> <li>▪ Group 4 (HL+LC): 14%</li> </ul> </li> <li>○ <b>Adjusted Analysis (accounting for hospital, breastfeeding, weight loss):</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): 3%</li> <li>▪ Group 2 (HL+HC): 3%</li> <li>▪ Group 3 (LL+LC): 4%</li> <li>▪ Group 4 (HL+LC): 4%</li> </ul> </li> </ul> </li> <li>• <b>Pharmacological intervention(s):</b> <ul style="list-style-type: none"> <li>▪ Group 1 (LL+HC): Balanced use of methadone or morphine</li> <li>▪ Group 2 (HL+HC): Balanced use of methadone or morphine</li> <li>▪ Group 3 (LL+LC): Favored use of morphine (85% of sites)</li> <li>▪ Group 4 (HL+LC): Balanced use of methadone or morphine</li> </ul> </li> </ul> <p><b>Limitations:</b></p> <ul style="list-style-type: none"> <li>• OT cannot fully account for all factors that drive LOS, treatment failure, and/or weight loss</li> <li>• Lack of study randomization</li> <li>• Compliance issues within some of the groups (particularly LL)</li> </ul>
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Lembeck et al., 2020

Methods	Cohort, Retrospective
<p><b>Participants</b></p>	<p><b>Participants:</b> Neonates with Neonatal Abstinence Syndrome (NAS)  <b>Setting:</b> USA, pediatric floor of hospital, July 2014-November 2016  <b>Number enrolled into study:</b> <i>N</i> = 249</p> <ul style="list-style-type: none"> <li>• <b>Group 1a,</b> Majority Breastfeeding (MB): <i>n</i> = 65</li> <li>• <b>Group 1b,</b> Exclusively Breastfeeding (EB): <i>n</i> = 39</li> <li>• <b>Group 2a,</b> Majority Standard Formula (MSF): <i>n</i> = 147</li> <li>• <b>Group 2b,</b> Exclusively Standard Formula (ESF): <i>n</i> = 105</li> <li>• <b>Group 3a,</b> Majority Low-Lactose Formula (MLLF): <i>n</i> = 37</li> <li>• <b>Group 3b,</b> Exclusively Low -Lactose Formula (ELLF): <i>n</i> = 14</li> </ul> <p><b>Gender, males (as defined by researchers):</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> Not specified</li> <li>• <b>Group 2:</b> Not specified</li> <li>• <b>Group 3:</b> Not specified</li> </ul> <p><b>Race / ethnicity or nationality (as defined by researchers):</b></p> <ul style="list-style-type: none"> <li>• Demographic information such as birthweight, gestational age, gender, and ethnicity were extracted from a database maintained on infants with the diagnosis of NAS.</li> <li>• Specific information on demographics of study participants were not mentioned in the paper.</li> </ul> <p><b>Age, mean/median</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> Not specified</li> <li>• <b>Group 2:</b> Not specified</li> <li>• <b>Group 3:</b> Not specified</li> </ul> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Neonates <math>\geq</math> 35 weeks gestation</li> <li>• Diagnosis of Neonatal Abstinence Syndrome (NAS)</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Neonates with NAS who were admitted to the Neonatal Intensive Care Unit</li> </ul> <p><b>Covariates Identified:</b></p> <ul style="list-style-type: none"> <li>• Various maternal drug exposures, based on self-report and urine testing</li> </ul>
<p><b>Interventions</b></p>	<ul style="list-style-type: none"> <li>• <b>Group 1,</b> Majority or exclusively Breastfeeding</li> <li>• <b>Group 2,</b> Majority or exclusively Standard Formula</li> <li>• <b>Group 3,</b> Majority or exclusively Low-Lactose Formula</li> </ul> <p><b>All Groups:</b></p> <ul style="list-style-type: none"> <li>• Few specifics on the brand of formulas or duration of breastfeeding</li> <li>• Few specifics on what infants who were not exclusively feeding were fed</li> </ul>
<p><b>Outcomes</b></p>	<p><b>Primary outcome(s):</b> (Outcomes of interest to the CMH CPG /CAT development team)</p> <ul style="list-style-type: none"> <li>• Duration of NAS</li> <li>• Length of hospital stay</li> <li>• Need for pharmacological intervention</li> <li>• Severity of symptoms</li> <li>• Growth</li> </ul>

<b>Results</b>	<p><b>Duration of NAS:</b> Not specified</p> <p><b>Length of hospital stay, d (adjusted for gestational age) Mean (CI) [p-value] (Majority feeding infants)</b></p> <ul style="list-style-type: none"> <li>• MLLF vs MSF: 3.0, [-1.1, 7.0], .15</li> <li>• MBF vs MLLF: -10.3 [-14.9, -5.8], &lt; .01</li> <li>• MBF vs MSF: -7.4 [-10.7 to -4.1] &lt; .01</li> </ul> <p><b>Length of hospital stay, d (adjusted for gestational age) Mean (CI) [p-value] (Exclusive feeding infants)</b></p> <ul style="list-style-type: none"> <li>• ELLF vs ESF: -1.1 [-8.4, 6.3], .93</li> <li>• EBF vs ELLF: -7.4 [-14.6, -0.3], .04</li> <li>• EBF vs ESF: -8.5 [-12.4, -4.6], &lt; .01</li> </ul> <p><b>Need (length of) pharmacological intervention, d (adjusted for gestational age), Mean (CI) [p-value] (Majority feeding infants)</b></p> <ul style="list-style-type: none"> <li>• MLLF vs MSF: 3.9 [-0.4, 8.1], 0.08</li> <li>• MBF vs MLLF: -10.8 [-15.6, -5.9], &lt; .01</li> <li>• MBF vs MSF: -6.9 [-10.5, -3.4], &lt; .01</li> </ul> <p><b>Need (length of) pharmacological intervention, d (adjusted for gestational age) Mean (CI) [p-value] (Exclusive feeding infants)</b></p> <ul style="list-style-type: none"> <li>• ELLF vs ESF: -0.5 [-7.5, 6.5], .89</li> <li>• EBF vs ELLF: -7.9 [-15.6, -0.3], .04</li> <li>• EBF vs ESF: -8.4 [-13.1, -3.8], &lt; .01</li> </ul> <p><b>Growth, Weight change (g/day) (Adjusted for length of stay): Mean (CI) [p-value] (Majority feeding infants)</b></p> <ul style="list-style-type: none"> <li>• MLLF vs MSF: -2.4 [-11.7, 6.9], .62</li> <li>• MBF vs MLLF: -9.9 [-20.8, 1.0], .07</li> <li>• MBF vs MSF: -12.3 [-20.2, -4.3] &lt; .01</li> </ul> <p><b>Growth, Weight change birth to discharge (gestational/discharge) (Adjusted for length of stay): Mean (CI) [p-value] (Exclusive feeding infants)</b></p> <ul style="list-style-type: none"> <li>• ELLF vs ESF: 6 [-8, 20], .39</li> <li>• EBF vs ELLF: -24 [-39, -9], &lt; .01</li> <li>• EBF vs ESF: -18 [-27, -8] &lt; .01</li> </ul> <p><b>Limitations:</b></p> <ul style="list-style-type: none"> <li>• 158 (63%) of infants were exclusively fed one nutritional source</li> </ul>
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<b>Methods</b>	Randomized Control Trial
<b>Participants</b>	<p><b>Participants:</b> Infants born between 36 and 42 weeks of gestational age with intrauterine exposure to opioids known to cause neonatal abstinence syndrome (NAS)</p> <p><b>Setting:</b> MetroHealth Medical Center, Cleveland, Ohio from December 2014 to June 2018</p> <p><b>Randomized into study:</b> <math>N = 74</math></p> <ul style="list-style-type: none"> <li>• <b>Group 1,</b> Lactose-free (Similac Sensitive®) tolerance formula: <math>n = 37</math></li> <li>• <b>Group 2,</b> Lactose-containing (Similac Advance®) formula: <math>n = 37</math></li> </ul> <p><b>Completed Study:</b> <math>N = 69</math></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> <math>n = 34</math></li> <li>• <b>Group 2:</b> <math>n = 35</math></li> </ul> <p><b>Gender, males (%):</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> <math>n = 20</math> (57%)</li> <li>• <b>Group 2:</b> <math>n = 18</math> (51%)</li> </ul> <p><b>Race, Caucasian (%):</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 33 (97%)</li> <li>• <b>Group 2:</b> 31 (88%)</li> </ul> <p><b>Age, mean gestational age (weeks + SD)</b></p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> 38.6 + 1.1</li> <li>• <b>Group 2:</b> 38.5 + 1.4</li> </ul> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Infants were eligible for the study if they were born between 36 and 42 weeks of gestational age with intrauterine exposure to opioids known to cause NAS. <ul style="list-style-type: none"> <li>○ Infants were considered to have intrauterine exposure to opioids if one or more of the following criteria were met: <ul style="list-style-type: none"> <li>▪ (1) the mother admitted to abusing illicit opioids during the current pregnancy with either active maternal opioid withdrawal at delivery or a positive urine toxicology screen for illicit opioids at delivery, or her infant’s urine toxicology screen was abnormal</li> <li>▪ (2) the mother was enrolled in the Metro Health’s Mother &amp; Child Dependency Program and receiving methadone or buprenorphine for replacement therapy</li> <li>▪ (3) infant developed significant abstinence syndrome that required nonpharmacological and or pharmacological treatment</li> </ul> </li> </ul> </li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Infants with major congenital anomalies or those with surgical and medical conditions that required the use of analgesics were excluded.</li> </ul> <p><b>Power Analysis:</b> Projected sample size of 32 patients per group would allow detection of an effect size of 0.70 (reduction in opiate usage/standard deviation) with a power of 80% and type I error of 0.05 (two-tail).</p>
<b>Interventions</b>	<p><b>Both:</b> Standardized written hospital guidelines were used to monitor and manage NAS. Caloric concentration was adjusted, as requested by the physician, for excessive weight loss or poor weight gain. Mothers with demonstrated sobriety were encouraged to breastfeed as per the Academy of Breastfeeding Medicine guidelines. Mothers were encouraged to stay in the postnatal ward after discharge to participate in the care of their baby. Study formula was supplemented only when breastfeeding was contraindicated, not chosen by the mother, or was inadequate. Study formula</p>

	<p>was used until 14 days of life or until discharge, whichever came first. After 14 days, parents and providers could choose any formula, including the study formula, if the infant remained in the hospital.</p> <ul style="list-style-type: none"> <li>• <b>Group 1:</b> lactose-free formula (Similac Sensitive® reconstituted from concentrated liquid to 20 calorie/ounce)</li> <li>• <b>Group 2:</b> lactose-containing formula (Similac Advance® reconstituted from concentrated liquid to 20calorie/ounce)</li> </ul>
<b>Outcomes</b>	<p><b>Primary outcome(s):</b></p> <ul style="list-style-type: none"> <li>• The primary outcome measure was the cumulative dose of morphine used for the treatment of NAS during the first 14 days of life.</li> </ul> <p><b>Secondary outcome(s)</b></p> <ul style="list-style-type: none"> <li>• Need for second-line medication to treat NAS</li> <li>• Need for NICU admission</li> <li>• Duration of pharmacotherapy</li> </ul> <p><b>Safety outcome(s):</b></p> <ul style="list-style-type: none"> <li>• None reported</li> </ul>
<b>Notes</b>	<ul style="list-style-type: none"> <li>• No significant difference was found in the cumulative morphine dose required to treat NAS (<math>20.7 \pm 19.8</math> vs. <math>23 \pm 23.5</math> mg, <math>p = 0.61</math>) between the two groups. See chart for additional details.</li> <li>• Secondary outcomes and patient characteristics were similar between treatment groups (<math>p &gt; 0.100</math>) except maternal heroin abuse was higher in the lactose-containing group (<math>p = 0.013</math>). <ul style="list-style-type: none"> <li>○ Of note more patients in the lactose-containing formula group required second-line agents for the treatment of NAS, but the difference was not statistically significant for each individual agent.</li> </ul> </li> </ul> <p>Study center changed NAS treatment guidelines mid-way through the study. Criteria for initiating pharmacologic therapy were made less stringent to allow initiation sooner based on NAS scores. This would likely affect both groups equally but remains noteworthy.</p>

<i>Risk of Bias</i>		
<b>Bias</b>	<b>Scholar's Judgment</b>	<b>Support for judgment</b>
Random sequence generation (selection bias)	Low risk	The randomization was done using a computer-generated random sequence (by research statistician DMS) (1:1) coupled with the stratified balanced blocked methodology. Stratification was done based on gender (male/female), gestational age ( $\leq 38$ weeks/ $> 38$ weeks), and intrauterine exposure (polysubstance vs. Methadone or Buprenorphine only).
Allocation concealment (selection bias)	Low risk	Allocation concealment was done using an opaque envelope.
Blinding of participants and personnel (performance bias)	Low risk	One member of the research team, not involved in clinical management, knew the group assignment. All other members of the research and clinical management teams remained blinded to group assignment throughout the study. Study formula preparation and masking were performed in a hospital designated milk laboratory outside the normal nursery or NICU by hospital staff who were not involved in the study recruitment, study management, or data analysis. Study formula was sent to the bedside in identical transparent containers labeled "Study formula A" or "Study formula B". Parents, health care providers, and primary investigators were blinded to the study formula type.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were objective.

Incomplete outcome data (attrition bias)	Unclear risk	Data analyzed per protocol. Two patients withdrew from each group with no explanation from authors. Withdrawal unlikely to be related to study intervention.
Selective reporting (reporting bias)	Low risk	Pre-specified primary and secondary outcomes were reported as expected.
Other bias	Low risk	No additional sources of bias were noted.

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