Purpose: To provide a protocol for feeding of high-risk and premature infants.

Target Client Population: This guideline applies to the NICU population including premature infants and term infants with disorders that prevent establishment of full enteral nutrition at birth.

Background

Premature infants, especially very low birth weight (VLBW) and extremely low birth weight (ELBW) infants are at high risk of post-natal growth failure because of unmet high protein and caloric needs.

Pulmonary and hemodynamic instability in the first few days of life and the immaturity of the gastrointestinal tract may delay the initiation and/or advancement of enteral nutrition after birth. Hence the majority of preterm infants will require total parenteral nutrition (TPN) from the first day of life until enteral nutrition is initiated and advanced to full feeding volume goal.

Optimal nutritional management from birth decreases postnatal catabolism, promotes growth and improves neurodevelopmental outcome.

The World Health Organization (WHO) endorses exclusive breastfeeding for infants until 6 months of age to enhance overall health. (Duijts, 2010)

Preterm infants, especially ELBW and VLBW, require additional caloric, mineral and protein additive to promote optimal growth. (O’Connor, 2008)

Feeding preterm infants maternal milk protects against NEC, ROP, late onset sepsis and BPD and has long-term beneficial neurodevelopmental effects. Donor breast milk can protect against NEC but has been associated with delayed growth. (Meier, 2017)

Treatment Criteria

Clinical evidence supports the use of feedings in the following situations:

- Initiation of TPN within 24 hours to decrease catabolism and prevent hypoglycemia and suboptimal postnatal growth. For ELBW infants, TPN should be initiated as soon as possible after birth to minimize protein catabolism, prevent hyperglycemia and nonoliguric hyperkalemia.

- The use of trophic feeding (≤ 24 mL/kg/day) with human milk or preterm formula to prevent villous atrophy, and to facilitate feeding tolerance and faster attainment of full feeding and better growth in ELBW infants. (Oddie, 2017)

- Use of human milk is preferred for neonates due to its immunologic properties and better tolerance by the immature GI tract. There is a dose-dependent correlation in the first month of life for reduction of feeding intolerance, nosocomial infection, necrotizing enterocolitis (NEC), chronic lung disease (CLD) and retinopathy of prematurity (ROP) compared to formula feeding. (Patel, 2013; Spiegel, 2016)

- An exclusive human milk diet in VLBW infants can reduce the incidence of feeding intolerance and NEC, decrease time to attain full feeds and shorten length of stay (LOS). (Assad, 2015) ELBW infants who remain on an exclusive breast milk diet are at higher risk for metabolic bone disease and may benefit
from periodic electrolyte, calcium and phosphorus monitoring to ensure these remain within acceptable ranges.

- Pasteurized human donor milk is the preferred alternative for premature infants whose mothers are unable to provide an adequate volume of their own milk. (Buckle, 2017) Other forms of donor milk include shelf-stable homogenized milk.

- Feed as early as possible, preferably with mother’s milk or donor milk, within 24 hours. This stimulates gut hormones and primes the gut for tolerating regular feeds.

- Extremely low birth weight infants or growth-restricted infants may warrant a slower advance of 20 ml/kg/day. In larger preterm infants (≤ 1500 gm), increasing enteral feeding volumes by 30-35 ml/kg/day, following GI priming and tolerance of trophic feedings is well tolerated.

- Refer to Discharge Planning guideline for specific glucose values necessary to prevent hypoglycemia.

- Nipple feeding and lactation should be encouraged as tolerated based on demonstrated oral cues and feeding readiness scores and not gestational age or corrected gestational age. (Simpson, 2002)

- Formula supplementation following birth can reduce the number of mothers who ultimately exclusively breastfeed their infant. Maternal perception of inadequate milk production is the most common reason for discontinuation of breastfeeding. Lactation consultants and education can be helpful in improving the success of long term breastfeeding. (Perrine, 2012; Cameron, 2010)

- Formula should be utilized if human milk is unavailable. (O’Connor, 2016)

- To match fetal accretion rates, evaluate human milk (if available) and/or formula energy and protein composition in infants who are not gaining adequate weight at an average of 16-18 gm/kg/day over 48-72 hours and consider making adjustments for those that are VLBW. After reaching 2 kg, daily weight gain should average 20 gm/day. (Brumberg, 2010)

- Separating pumped foremilk from the hindmilk and preferentially feeding the latter can mitigate slow weight gain in the preterm infant that is fed human milk. Excess milk pumped in the morning following a pump-free night will typically have lower caloric content and should be saved for future use.

- The optimal approach to a preterm infant’s oral feeding journey should be based on their maturing behavioral cues rather than just their gestational age or corrected gestational age.

- Coordination of suck-swallow-breathing is a crucial prerequisite for successful oral feeding.

- It is crucial for NICUs to have evidence based guidelines for initiation and cessation of feedings, evaluation and scoring of feeding intolerance, suspected NEC and other feeding setbacks, including re-feeding plans following resolution of NEC. An isolated positive stool test for occult blood in babies with indwelling nasogastric tubes is typically not a sign of NEC unless correlated with clinical and radiological signs associated with NEC. (Pinheiro, 2003) Gastric residuals, including green colored, in asymptomatic infants are
not necessarily associated with NEC. (Mihatsch, 2002)

- Use of semi-demand feeding readiness regimens versus every two-hour feeding, every three hour feeding or every four hour infant feeding regimens is a physiologic approach to attainment of full oral feeds. (Thoyre, 2005)

- Missed oral feeding opportunities can have a detrimental effect on the time to achieve full oral feeding and lead to a prolonged LOS. (Tubbs-Cooley, 2015)

- Consider ad-lib feedings for infants who have demonstrated the ability to orally complete the majority of their feedings. (Kirk, 2007; Thoyre, 2005)

- Early referral to Speech Therapy/Occupations Therapy/Physical Therapy for evaluation of suck and swallow and intervention especially in babies with significant oral aversion.

- The routine use of proton pump inhibitors and antacids for gastroesophageal reflux is not recommended for lack of evidence for efficacy in the neonate. Additionally, antacids have been associated with increased risk for sepsis and NEC.

- The routine use of probiotic supplementation is not recommended. The optimal probiotic formulation, timing and dosage have yet to be established. (Costeloe, 2016) While many probiotic studies have been published in the medical literature, they lack standardization and therefore recommendations for routine use cannot be determined. (Viswanathan, 2016)

- Online tools such as the Newborn Weight Tool (NEWT) are available to assist in identification of weight gain or loss issues: https://www.newbornweight.org/

- Outpatient follow-up is needed to monitor the infant. Earlier follow-up may be considered when there are concerns regarding feeding, weight gain or bilirubin if applicable.

### Clinical Evidence

#### Human Milk and Breastfeeding

- Patel and Kim (2018) provided an overview on the benefits of human milk in reducing NEC. The bioactive ingredients in human milk may not only reduce the incidence of NEC but may also reduce its severity. Although there are nutritional differences between MOM (mother's own milk) and DHM (donor human milk), retrospective cohort studies and randomized trials have demonstrated a beneficial effect with either. In addition to NEC reduction, improvement in feeding intolerance, fewer days to full feeds and shorter hospital stays have been documented with the use of human milk. Lactation support and resources are essential in order to provide adequate milk production for NICU infants.

- A randomized clinical trial by O’Connor et al (2018) compared the use of human milk-based fortifiers (HMBFs) with bovine-milk-based fortifiers (BMBFs) in VLBW infants. Sixty-four infants were randomized to the HMBF group and 63 to the BMBF cohort. No statistically significant differences in feeding interruptions or mortality/morbidity were demonstrated. The authors concluded that in infants receiving an exclusive breast milk diet, HMBFs did not provide any additional benefit to feeding tolerance nor did they reduce the mortality and morbidity as compared to BMBFs.

- A systematic review by Brown et al (2016) sought to determine whether
fortified human breast milk resulted in improved outcomes in preterm infants over unfortified breast milk. Fourteen trials involving 1,071 infants met the authors’ inclusion criteria. The trials were noted as generally small and methodologically weak. Meta-analysis from low-quality evidence and limited available data did not provide confirmation that preterm infant feeds with multi-nutrient fortified breast milk resulted in improved outcomes. However, slightly increased in-hospital growth rates were noted.

- A single center retrospective study by Assad et al (2015) evaluated the cost and benefits of an exclusive human milk diet in VLBW infants. Enrollment included 293 infants with birth weights between 490 and 1700 grams and gestational ages from 23 to 34 weeks. These subjects were divided into four feeding groups: bovine, human, mixed and formula. All groups had similar feeding schedules. Feeding intolerance was found to be significantly worse in the bovine, mixed and formula groups when compared to the exclusive human milk group. Total overall charges were lowest in the human milk group regardless of the associated costs for donor milk and donor milk-derived fortifier.

- Spiegler et al (2016) analyzed whether there was an association between exclusive breast milk feedings and a reduced risk of bronchopulmonary dysplasia (BPD) in VLBW infants born before 32 weeks gestation. The first group of 239 infants received exclusive formula feedings, the exclusive breast milk cohort included 223 infants and the mixed breast milk/formula group included 971 infants. The results of this multicenter cohort study demonstrated the infants who received breast milk exclusively during their hospitalization were less likely to have BPD, NEC or ROP.

- In 2012 the American Academy of Pediatrics (AAP) reaffirmed its position statement that human milk is the normative standard for infant feeding and nutrition and should be provided exclusively for six months followed by continued breastfeeding as complementary foods are introduced. It also stated that breastfeeding is associated with a 64% reduction in the incidence of nonspecific gastrointestinal tract infections and a 77% reduction in NEC.

- In 2013, Underwood reviewed the literature and provided the following points regarding the use of human milk as the optimal nutrition for preterm infants. The use of fortified mother’s own milk is the optimal diet for the premature infant to maximize growth, development and protection against NEC and infection. Fortified pasteurized human donor milk is recommended by the American Academy of Pediatrics Section on Breastfeeding as the preferred alternative for premature infants whose mothers are unable to provide a sufficient volume of their own milk. Pasteurized donor human milk does not provide the same nutrient or biologically active molecules as unpasteurized own mother’s milk. Careful attention to establishing and maintaining milk production in women delivering preterm has significant benefits. The author concluded that fortified human milk has tremendous benefits in improving the growth and short and long-term outcomes for the premature infant.

- In 2009, Meinzen-Derr et al reviewed a multicenter, randomized, double-masked trial performed by the National Institute of Health on glutamine supplementation, to determine whether increasing human milk intake was associated with a decreased risk of NEC or death. The authors concluded that the study findings were consistent with other observational studies that...
reported on varying doses of human milk in relation to a reduced risk of NEC.

- In 2007, Sisk et al performed a prospective cohort study of VLBW infants to analyze the association between human milk and NEC. The authors concluded that enteral feedings containing at least 50% of human milk in the first 14 days of life was associated with a six fold decrease in the odds of NEC.

- In 2013, Ramani et al reviewed the literature and concluded that the evidence was convincing that human milk feeding, compared with formula feeding reduced the incidence of NEC in preterm infants. They also found that in clinically stable VLBW infants, the early introduction of progressive feeds and advancement of feeds at a faster rate (30-35 mL/kg/d) was safe and did not increase the incidence of NEC. In addition they noted that the use of human milk-based fortifier compared with bovine based fortifier may reduce the incidence of NEC although additional studies are still required.

- A study by O'Connor et al (2008) attempted to determine the impact of fortified human milk on the growth of low birth weight infants. Thirty-nine low birth weight infants (750-1800 g) were randomized to receive either unfortified human milk or human milk with a multi-nutrient fortifier. After 12 weeks, the infants receiving the fortified human milk demonstrated increased length, larger head circumference and tended to be heavier compared to those infants receiving unfortified human milk.

- A prospective cohort study by Patel et al (2013) evaluated the effect of early human milk feedings on the incidence of sepsis in 175 VLBW infants. The data demonstrated that an increasing average daily dose of human milk in the first 28 days of life was associated with a decreased risk of sepsis and NICU costs.

- Duijts et al (2010) examined the association of breastfeeding and the incidence of respiratory and gastrointestinal infections in infants. The authors observed that the infants who received breast milk exclusively for up to four months of age demonstrated lower risks for respiratory and gastrointestinal infections. Similar results were identified for infants who were breastfed exclusively for six months or longer. Partial breastfeeding was not associated with a significant risk reduction for these infections.

- Perrine et al (2012) reviewed the results of the Infant Feeding Practices Study II. Included were 1,457 women who prenatally had intended to breastfeed exclusively. Approximately one-third of these women achieved their breastfeeding duration goal. The authors suggested hospital practices that eliminate formula supplementation could lead to an increased number of women who achieve their exclusive breastfeeding intention.

- Cameron et al (2010) investigated whether first-time parent groups could influence a woman’s duration of breastfeeding based on peer influence. A cohort of 501 women provided information on their breastfeeding experience. After data analysis, the authors concluded that peer influence could promote the continuation of breastfeeding (up to six months) and groups such as first-time parents may provide a venue to promote both initiation and continuation of breastfeeding.

**Donor Milk**

- A systematic review by Buckle & Taylor (2017) evaluated the cost of donor human milk to the cost of treating NEC. The cost-effectiveness of formula
versus an exclusive donor milk diet was also evaluated. Seventeen studies providing the costs associated with NEC treatment and seven studies offered the costs associated with donor breast milk. The studies provided incremental LOS estimates to be 50 days for surgical NEC and 18 days for medical NEC. An exclusive human donor milk diet was found to decrease the incidence of NEC in preterm and LBW infants. The authors concluded that because a donor human milk diet demonstrated a reduction in the morbidity and mortality associated with NEC, it is probable that donor milk also provides a short-term cost savings.

- A meta-analysis by Silano et al (2018) reviewed the risk of surgical NEC development when comparing preterm and/or low birth weight infants who were receiving donor human milk versus those who were receiving formula. Four randomized, controlled trials met the authors’ inclusion criteria. Two of these studies evaluated donor milk versus formula feeding as a sole diet and the other two utilized donor milk and formula as supplementation to mother’s milk. The authors concluded mother’s milk was the best feeding choice and that donor milk did not provide any additional risk prevention for surgical NEC over formula although there were several limitations to this analysis. These limitations included a small number of studies, the low quality score of the studies and the heterogeneity of the interventions.

**Oral Feeding Readiness and Progression**

- A systematic review by Watson & McGuire (2016) evaluated scheduled versus cue-based feedings in preterm infants. Nine trials including 593 infants were included for the authors’ meta-analysis. There was some low-quality evidence that supported the positive effects of cue-based feeding in achieving full oral feeding earlier than scheduled feeding regimens. However, the authors note the need for a large randomized controlled trial to confirm these findings.

- Tubbs-Cooley et al (2015) reported on the effects of missed oral feeding opportunities in the NICU. Based on their analysis of clinical data, they stated that for every 1% increase in amount of missed oral feedings the time to achieve full oral feeding is extended by 1.45 days. Time to discharge was also extended by 1.36 days.

- Feeding progression in extremely preterm infants was examined by Park et al (2015). Factors which adversely affected this progression were noted as a younger gestational age at birth, neurological risk, BPD, NEC and patent ductus arteriosus. This study also suggested breast milk-fed infants reached feeding milestones earlier than formula-fed infants.

- A systematic review and meta-analysis on oral feeding readiness was performed by Lima et al (2015). Twenty-nine studies on the transition from enteral to oral feeding in preterm infants met the authors’ inclusion criteria. Due to the heterogeneity of the studies, the authors were unable to generalize the results of the studies. However, they did note the importance of sensory-motor-oral stimulation as a means to decrease the duration of transition to full oral feedings.

- In 2013, Fujinaga et al performed a study of 60 clinically stable preterm infants to determine accuracy, sensitivity and specificity of Preterm Oral Feeding Readiness Assessment Scale cut-offs, compared to milk intake through trans lactation. The global accuracy of Preterm Oral Feeding Readiness Assessment Scale was 74.38%. The highest sensitivity and specificity were
obtained for three cut-offs: 28, 29 and 30. The authors concluded that the Preterm Oral Feeding Readiness Assessment Scale is a valid to assist health professionals to initiate preterm feeding in view of promoting safe and objective breast feeding.

- In a 2012 Cochrane Neonatal Review article by Crowe L et al regarding instruments assessing readiness to feed, they found that there were no randomized or quasi-randomized trials comparing formal instruments to assess a preterm infant's readiness to commence suck feeds with either no instruments (usual practice) or other feeding readiness instruments. However, they did note that there were several feeding readiness scales available including the Preterm Infant Nipple Feeding Readiness Scale and the Early Feeding Skill Assessment Tool. The authors concluded that the benefit of using a formalized instrument over other methods such as clinical judgment or a criterion such as gestational age is that an instrument ensures that a systematic and consistent method of assessing feeding readiness is utilized. However, the absence of randomized or quasi-randomized trials may also be a reflection of the practical difficulties in ensuring that the comparison group is not exposed to the intervention, particularly in the situation where the use of an instrument compared to normal clinical practice with direct caregivers collecting data.

- In 2007, Kirk et al performed a prospective study and compared it against historic cohort controls to determine whether cue based clinical pathway for oral feeding initiation and advancement in premature infants would result in earlier achievement of full oral feeding. The study found that cue based clinical pathway for oral feeding initiation and advancement of premature infants resulted in earlier achievement of full oral feeding.

- In 2008, Puckett et al performed a prospective randomized trial to see if infants fed orally on feeding cues could be discharged home earlier than infants fed by traditional feeding regimens. The authors concluded that cue based feeding was possible for premature infants with similar weight gain as traditional feeding without affecting workload.

- In a 2013 article by White et al, the authors noted that cue-based feeding is an approach that is more developmentally appropriate for a premature infant. They noted that there is a growing body of evidence suggesting that infants may have better neuro-developmental outcomes if they are allowed to demonstrate their emerging feeding competence through their individual behavior, muscle tone, reflexes and movements before, during and after attempts to feed orally. In addition, it has been found that specific gestational age (commonly between 32 and 34 weeks) is not the only criteria for determining when to commence oral feeding and have suggested that observation of infant behavior and physiological maturation are better indicators of feeding readiness.

- In 2013, Swant et al reviewed the literature and concluded that the majority of cue-based feeding studies have demonstrated that best practice entails individualization of care and consideration of the infant experience during feeding interventions to promote the successful development and attainment of full oral feedings. However, as the research currently stands, there is not sufficient evidence to support the implementation of a specific cue-based feeding protocol based on improving weight gain or shortening LOS.
In a 2013 article by Shaker, the author noted that a focus on emptying the bottle or defining an empty bottle as success may negatively affect the preterm infant’s feeding experience and have adverse effects on neuro maturation and on feeding outcomes. Lack of contingent response to infant's communication may lead to maladaptive feeding behaviors, learned feeding refusals and long term feeding aversions.

Simpson et al (2002) sought to determine whether the early introduction of oral feedings in the preterm infant would result in a shortened transition time to complete oral feedings. Thirteen preterm infants (< 30 weeks’ gestation) began oral feeding 48 hours after attainment of full tube feeding. Sixteen additional preterm infants received oral feeding management at the discretion of their physician. The transition time from full tube feeding to exclusive oral feeding was 26.8 (±12.3) days in the early oral feeding group and 38.4 (±14.0) days in the arbitrary feeding management group.

Weight Loss or Gain

Flaherman et al (2015) analyzed weight loss in 108,907 exclusively breastfed infants. The data demonstrated substantially different weight loss based on the type of delivery. This difference continued to be detected for a period of time following birth. The authors also concluded that weight loss in excess of 10% of birth weight commonly occurred in the early postnatal period.

Based on data obtained from 14 Kaiser Permanente Northern California hospitals between 2009 and 2013, Miller et al (2015) developed weight loss nomograms for formula fed newborns. A total of 7,075 infants were included in this analysis, 4,525 who were delivered vaginally and 2,550 who were delivered via cesarean section. The authors identified a median weight loss of 2.9% at 48 hours of age in the vaginally delivered infants and median weight losses of 3.7% and 3.5% at 48 and 72 hours respectively following cesarean delivery. It was uncommon for an infant to demonstrate >7% weight loss following vaginal delivery and >8% weight loss following cesarean delivery.

Brumberg et al (2010) reported on a randomized trial that compared the growth of small infants (birth weight ≤ 1250 g) receiving combined protein and energy supplementation versus energy supplementation alone. These infants were either growing below the average intrauterine rate of 15 g/kg/day or had failed to regain their birthweight in the first two weeks of life. The 11 infants who received both protein and energy supplementation gained more weight per day than the 12 infants who received energy supplementation alone. Protein intake significantly correlated with weight gain.

Parenteral Nutrition

A randomized controlled trial by Vlaardingerbroek et al (2013), was done to assess the efficacy and safety of early parenteral lipid and high dose amino acid administration from birth onwards in VLBW infants. The authors concluded that the administration of parenteral amino acids combined with lipids improved conditions for anabolism and growth as shown by an improved nitrogen balance.

Adamkin (2013) reviewed the literature regarding early parenteral lipid and amino acid administration in VLBW infants. He noted that early nutritional support provided to ELBW infants acted as a mediator between critical illness the first weeks of life and later growth and outcomes which include BPD, late
onset sepsis, hospital stays, neurodevelopmental impairment, cognition and death. He also noted that the administration of intravenous amino acids had decreased the glucose concentrations in ELBW infants, presumably by enhancing endogenous insulin secretion.

- Ben (2008) reviewed the literature regarding nutritional management of newborn infants. He noted that trophic feedings during parenteral nutrition (PN) are a strategy to enhance the feeding tolerance and decrease the side effects of PN and the time to achieve full feeding. Human milk is a key component of any strategy for enteral nutrition of all infants. However, the amounts of calcium, phosphorus, zinc and other nutrients are inadequate to meet the needs of the VLBW infants during growth. Therefore, safe and effective means to fortify human milk are essential to the care of VLBW infants.

- In 2009, Terrin et al performed a randomized retrospective study of 102 infants who presented with feed intolerance. In this study, 51 neonates were given PN only and 51 were given PN plus minimal enteral feedings. The authors found that the neonates who were given the PN plus the minimal enteral feedings achieved full enteral nutrition earlier, had a reduction of sepsis episodes and regained their birth weight and were discharged earlier. The authors concluded that minimal enteral feeding in VLBW infants presenting feed intolerance reduces the time to reach full enteral feeding and the risk of sepsis.

- A multicenter randomized controlled trial by Cristofalo et al (2013) found that there was a significantly greater duration of PN and higher rate of surgical NEC in infants receiving preterm formula than in infants receiving human milk.

### Enteral Feedings

- A retrospective chart review by Khalil et al (2017) evaluated the incidence of feeding tube-related complications that resulted in ER visits, hospitalization or death. Data from 84 infants discharged on NG feedings and 238 infants receiving G-tube feedings were reviewed. The G-tube cohort experienced two tube-related deaths and was found to have a 33.6% complication rate requiring an ER visit. The NG-tube cohort was noted to have a 9.5% complication rate. At six months follow-up, 71.4% of the NG-tube infants had achieved full oral feeding compared to 19.3% who were fed via G-tube.

- A systematic review by Oddie et al (2017) investigated the effect of early enteral feeding advancement in VLBW or very preterm infants on the incidence of NEC, mortality and other morbidities. Ten RCTs (n=3753) met the authors’ inclusion criteria, assessing slow (< 24 mL/kg/day) versus more rapid rates of advancement. The included trials were considered a “moderate” quality of evidence due to the lack of blinding. Meta-analyses did not identify an association between slower enteral feeds (defined as 15-20 mL/kg compared to 30-40 mL/kg in most trials) and the decreased risk of NEC or all-cause mortality. Slow enteral feeding advancement, however, was found to delay attainment of full enteral nutrition by 1-5 days and demonstrated a borderline risk of developing invasive infection. Subgroup analyses that included ELBW, extremely preterm, SGA, growth-compromised or growth-restricted infants also did not provide evidence that slow enteral advancement decreased the risk of NEC or death.

- In 2012, Leaf et al performed a multicenter randomized controlled trial of
growth restricted preterm infants to see if early introduction of enteral feeds increased the risk of developing NEC. The study found that full feeds were achieved at an earlier age in the early group with 18% of those infants having an episode of all stage NEC versus 15% in the late group. The incidence of stages 2 and 3 NEC, which is of greater clinical importance was 8% in both groups. In addition, the early group had less cholestatic jaundice than the latter group, with a shorter duration of PN and high dependency care. There was no difference in overall LOS or duration of intensive care. The authors concluded that there was no evidence of benefit in delaying the introduction of small volumes of enteral feeds in preterm, intrauterine growth restricted infants beyond 24 to 48 hours.

- In 2013, Morgan et al reviewed the literature to determine the effect of slow rates of enteral feed advancement on the incidence of NEC, mortality and other morbidities in very preterm or VLBW infants. They found five randomized controlled trials which defined slow advancement as daily increments of 15 to 20 mL/kg and faster advancement of 30 to 35 mL/kg. Meta-analysis did not detect statistically significant effects on the risk of NEC, or all-cause mortality. The authors concluded that advancing enteral feed volumes at slow rather than faster rates does not reduce the risk of NEC in very preterm or VLBW infants but did result in a several day in regaining birth weight and establishing full enteral feeds.

- In 2013, Karagol et al performed a randomized controlled trial to evaluate the effects of slow vs. rapid rates of advancement of enteral feed volumes on the clinical outcomes in preterm infants with a low birth weight. This study showed that neonates in the rapid feeding advancement group achieved full enteral volume feedings earlier than the slower advancement group. They also received significantly fewer days of PN, exhibited a shorter time to regain birth weight and had shorter duration of hospital stay. The incidence of NEC and the number of episodes of feeding intolerance were not significantly different between the groups. However the incidence of culture-proven late-onset sepsis was significantly less in infants receiving rapid feeding advancement.

- Sturm (2005) described the implementation of a home gavage program for preterm infants. Infants were able to be discharged an average of 10-12 days earlier than those who were required to attain full oral feeds. In 52 infants participating in this program, there were no readmissions related to the gavage feeding. Only one family responded that they would have preferred to wait until their infant was receiving full oral feeds before hospital discharge.

- Mihatsch et al (2002) evaluated 99 ELBW infants who were receiving feedings per a standardized protocol. This study sought to identify whether mean gastric residual volume and green gastric residuals alone were significant predictors of feeding intolerance in the ELBW population. The majority of gastric residuals were of milky color but those of other colors were found to have no impact on feeding volume. When the infants presented with no other signs or symptoms, green gastric residuals at a volume < 2ml/3ml were not identified as a significant sign of feeding intolerance.

**Suck and Swallow Coordination**

- A systematic review and meta-analysis by Foster et al (2016) included 12 randomized and quasi-randomized trials comparing non-nutritive sucking (NNS) versus no provision of NNS in 746 preterm infants. The authors
indicated the trials generally contained small numbers of subjects and various methodological weaknesses. However, based on meta-analysis of the available data, NNS was found to provide a positive effect on the transition from gavage to full oral feeds, transition from start to full oral feeds and length of hospital stay with no trials reporting any adverse effects.

- In 2012, Lau et al performed a randomized study to determine if specific and swallowing exercises versus no intervention accelerated the attainment of independent oral feeding through a faster maturation of infants’ oral feeding skills. The authors concluded that the swallowing exercises were an efficacious intervention in facilitating the attainment of independent oral feeding but not the sucking exercises. The authors speculated that the swallowing benefit resulted from an accelerated maturation of infants’ oral feeding skill level.

- In 2012, a randomized study by Fucile et al investigated the effects of an oral (O), tactile/kinesthetic (T/K) and combined (O + T/K) sensorimotor intervention on preterm infants’ nutritive sucking, swallowing and their coordination with respiration. All three interventions resulted in improved swallow-respiration coordination.

- In 2005, Pinelli conducted a systematic review of 21 studies, 15 of which were randomized controlled trials and concluded that nonnutritive sucking (NNS) decreases significantly the length of hospital stay in preterm infants, facilitates the transition from tube to bottle feeds and better bottle feeding performance. The review did not reveal a consistent benefit of NNS with respect to other major clinical variables (weight gain, energy intake, heart rate, oxygen saturation, intestinal transit time, age at full oral feeds and behavioral state).

- In 2013, a randomized trial by Barlow et al evaluated the effects of a frequency-modulated (FM) orocutaneous pulse train delivered through a pneumatically charged pacifier on enhancing non-nutritive suck (NNS) activity in tube-fed premature infants with or without significant lung disease. The authors of the study concluded that FM PULSED orocutaneous pulse train stimuli are effective in facilitating NNS burst development in tube-fed respiratory distress syndrome (RDS) and CLD preterm infants, with an added benefit of reduced LOS for CLD infants by an average of 2.5 days.

**Gastroesophageal reflux (GER)**

- A 2013 article by Czinn et al noted that GER, defined as the involuntary retrograde passage of gastric contents into the esophagus with or without regurgitation or vomiting, was a physiologic condition, which occurred several times a day. The authors noted that about 70-85% of infants had regurgitation within the first 2 months of life and that it resolved without intervention in 95% of infants by 1 year of age. The authors also noted that GER disease (GERD) occurred when reflux of gastric contents caused symptoms that affected the quality of life or pathological complications such as failure to thrive, feeding or sleeping problems, chronic respiratory disorders, esophagitis, hematemesis, apnea and apparent life-threatening events. For non-complicated reflux, no intervention was required for most infants. Effective parental reassurance and educating parents regarding regurgitation and lifestyle changes, adjusting feeding regimes, positioning and environmental smoke exposure were usually sufficient to manage infant reflux. For infants diagnosed with GERD, non-pharmacologic approaches were first-line therapy. For those infants with

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GERD who did not respond to supportive measures or who relapsed, a limited trial of acid suppression therapy was warranted.

- In 2014, a review of the literature by Rosen, found that GER is a common physiologic process with more than 60% of infants spitting up on a daily basis and as many of 25% of the infants spitting up 4 or more times per day. GER changes to GERD when the reflux of gastric contents causes troublesome symptoms or complications. Treatment therapies fall into 3 categories: non-pharmacologic, pharmacologic and surgical. Non-pharmacologic therapies include positioning, thickening of feedings, changes in formula and modification of meal frequencies. The mainstay of medical therapy for GERD in infants is acid suppression, although acid suppression increases the burden of nonacid reflux, which is already much higher in infants than in older children and may worsen symptoms. The two primary surgical options for the treatment of intractable GER are fundoplication and transpyloric feeding in patients who are fed enterally. The author concluded that acid suppression has not been shown to reduce symptoms typically associated with reflux. Although a role for acid suppression exists in infants with evidence of esophagitis or with gastrointestinal tract bleeding, use of acid suppression in infants with symptoms should be limited to a short trial of acid suppression therapy. In addition, due to conflicting studies, fundoplication cannot be recommended for every infant with ALTE and GER-positive test results. Further, non-pharmacologic measures should be used whenever possible because most infants with GER will resolve without intervention.

- In 2008, a review of the literature by Horvath et al on thickened feeds related to GER found that use of thickened formulas compared with standard formula significantly increased the percentage of infants with no regurgitation, slightly reduced the number of episodes of regurgitation and vomiting per day (assessed jointly or separately), and increased weight gain per day; it had no effect on the reflux index, number of acid gastroesophageal reflux episodes per hour, or number of reflux episodes lasting >5 minutes but significantly reduced the duration of the longest reflux episode of pH<4.

- In 2013, Davidson et al performed a randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of proton pump inhibitors in infants aged < 1 year with GERD. The authors concluded that the signs and symptoms of GERD traditionally attributed to acidic reflux in neonates were not significantly altered by esomeprazole treatment. Esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acidic reflux events in neonates but did not reduce the incidence or severity of nonacidic reflux. Therefore routine use of these agents is not recommended.

**Stool Testing**

- A review by Pinheiro et al (2003) evaluated the evidence on stool testing in newborns. They indicated “there is no evidence that routine stool screening for occult blood or reducing substances predicts NEC or decreases the rate or severity of this disease”. Although stool testing in the NICU may routinely be utilized to identify early NEC in neonates at high-risk, the published evidence did not support the validity of this testing for either diagnostic or screening purposes.

**Probiotics**

- Patel & Underwood (2018) summarized the existing medical literature
available on the effects of probiotics on NEC. Even with the clinical heterogeneity in the randomized trials evaluating probiotics to reduce NEC, death or sepsis, multiple meta-analyses have reported a clinically meaningful effect. The evaluation of long-term efficacy and safety has been hindered by limited follow-up studies of the preterm infants who were enrolled in the probiotic trials. The authors note that additional studies are needed in order to address the most appropriate probiotic product for NEC prevention.

- Viswanathan et al (2016) conducted a study to determine the utilization of probiotics for VLBW infants in U.S. neonatal intensive care units (NICUs). NICUs participating in the Vermont Oxford Network were surveyed and data collected on the specific probiotic brand, timing, dose and duration of probiotic utilized. During the survey period of May-September 2015, 14.0% of the NICUs that responded to the survey (70/500) confirmed using probiotics in VLBW infants with the most common indications noted as feeding intolerance and antibiotic use. Probiotic use in VLBW infants was noted as increasing within the U.S. but utilization is still limited. The authors noted that they found no evidence for safety or efficacy of 90% of the probiotics that are currently being utilized in the U.S. NICUs.

- Dang et al (2015) performed a retrospective chart review of preterm infants (1,250 grams and/or 28 weeks gestation) in order to evaluate their nutritional outcomes resulting from probiotic utilization. Data from 113 subjects prior to the administration of probiotics was compared to data from 108 infants after probiotic administration. The authors identified a significant reduction in TPN days, central line days, episodes of feeding intolerance and time to reach full feedings with no significant difference in the incidence of NEC following probiotic utilization.

- A meta-analysis by Yang et al (2014) evaluated the use of probiotics for prevention of NEC in preterm infants. Twenty-seven randomized controlled trials involving 6,655 preterm neonates met the authors’ inclusion criteria. No differences in weight gain or age at time of full feeds were identified between the infants who received probiotics (n=3,298) and the placebo group (n=3,357). Probiotic supplementation was, however, found to reduce the risk of NEC in preterm infants without additionally increasing the risk of mortality or sepsis.

- Robinson (2014) performed a meta-analysis on the use of prophylactic enteral probiotics for preventing NEC in preterm infants <37 weeks gestation and/or <2,500 grams. Twenty-four randomized or quasi-randomized controlled trials were included for analysis. The author indicated that even though the trials were highly variable in regards to enrollment criteria, feeding regimens, baseline NEC risk and probiotic timing, dosage and formulation, the data identified a significant reduction in severe NEC incidence and mortality when probiotics were administered. No incidence of systemic infection associated with the probiotic organism was reported.

- Costeloe et al (2016) conducted the largest trial to date evaluating the use of probiotics in the preterm population. This double-blind, randomised, placebo-controlled trial included 650 infants who received the probiotic B. breve BBG-001 and 660 infants who received placebo and were part of the final analysis. The authors did not identify any evidence of benefit in reducing late-onset sepsis, NEC or death and thus the findings did not support the routine use of
Bibliography


Revision History
The following are approved changes incorporated into the revision numbers indicated below.

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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<tbody>
<tr>
<td>V1.0</td>
<td>05/16/2013</td>
<td>New guideline (MB)</td>
</tr>
<tr>
<td>V2.0</td>
<td>05/01/2014</td>
<td>Job Aid revised into Medical Necessity Clinical Guideline. (LK)</td>
</tr>
<tr>
<td>V2.0</td>
<td>09/08/2014</td>
<td>Will replace JA2229741 on 01/01/2015. (CE)</td>
</tr>
<tr>
<td>V3.0</td>
<td>05/05/2015</td>
<td>Annual review with update by RS. (CE)</td>
</tr>
<tr>
<td>V3.1</td>
<td>05/05/2016</td>
<td>Annual review with update by RS. Information on the use of an exclusive human milk diet and missed oral feeding opportunities added. (CE)</td>
</tr>
<tr>
<td>V3.1</td>
<td>05/05/2017</td>
<td>Annual review with revisions by AJ but this document is renewed without change at this time pending publication of the revised guideline which will be</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Description</td>
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<tr>
<td>V4.0</td>
<td>11/30/2017</td>
<td>Revised guideline posted. Amount of trophic feeds revised, adequate weight gain revised, additional information on outpatient follow-up, online tools and electrolyte monitoring for ELBW infants on exclusive breast milk diet provided. (CE)</td>
</tr>
<tr>
<td>V5.0</td>
<td>05/05/2018</td>
<td>Annual review by AJ. Shelf-stable homogenized milk as a donor milk option added, volume of tropic feedings in ELBW infants and outpatient follow-up information revised, volume of trophic feedings for priming gut and alternative feeding strategies removed, and weight of a “larger preterm infant” clarified to be ≤ 1500 grams. (CE)</td>
</tr>
<tr>
<td>V6.0</td>
<td>05/05/2019</td>
<td>Annual review by AJ. The timing of trophic feeds was revised to within the first 24 hours. An additional statement regarding the benefits of maternal milk and referral to Discharge Planning guideline for glucose levels related to hypoglycemia were added. (CE)</td>
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