Nutritional Support of the Very Low Birth Weight Infant

Quality Improvement Toolkit

California Perinatal Quality Care Collaborative

(rev 2008)

NUTRITIONAL SUPPORT OF THE VLBW INFANT

Revised December 2008

SUMMARY OF CHANGES from Nutrition Toolkit 1 (2004) and Nutrition Toolkit 2 (2005)

Acknowledgements: Toolkits 1 & 2:

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Toolkits 1 and 2 Combined & Reorganized.

As human milk was felt to be a major factor in improving nutrition and long-term outcome for VLBW infants, Toolkit 1 provided a detailed list (divided into small steps) of best practices for establishing a source and continued access to a mother's milk for her NICU infant. Toolkit 2 covered the other essential best practices, including parenteral nutrition, early enteral feeding, transition to oral feedings, discharge nutrition and continued breastfeeding. Understandably, there was some duplication.

The 2008 revised Nutrition Toolkit combines all of the best practices from the original 2 Toolkits, reorganized for easier access to specific issues, into 7 sections: 1. General principles/CQI, 2. Parenteral nutrition, 3. Establishing enteral nutrition, 4. Human Milk/Breastfeeding, 5. Transition to oral feedings, 6. Discharge planning/post-discharge nutrition, 7. Special/Controversial issues. **New research has reinforced the prior best practices - they have not changed.** The appendices have also been reorganized by section, with additional examples and tools added.

References.

Over 100 additional references have been added, including new 2005-2008 papers, books and other sources.

General Principles/CQI.

This section has been greatly expanded with several new suggested measurement tools and grids complete with justification, forms and additional references. Everyone should be able to find something to measure in their nutritional quality improvement efforts.

Section 7: Special/Controversial Issues.

A new section on probiotics and prebiotics has been added, and all best practices updated with new information and references. The CMV section has been completely revised with newer references.

NUTRITIONAL SUPPORT OF THE VLBW INFANT – REVISED 2008 - OUTLINE

Section 1: General Principles
Best Practice # 1.1: Establish consistent, comprehensive, nutritional monitoring
Best Practice # 1.2: Establish standards of nutritional care
Best Practice # 1.3: Track nutritional continuous quality improvement data

Section 2: Parenteral Nutrition
Best Practice # 2.1: Parenteral amino acids within the first 24 hrs
Best Practice # 2.2: Parenteral lipid within the first 24 hrs
Best Practice # 2.3: Discontinue TPN and central lines appropriately

Section 3: Establishing Enteral Nutrition
Best Practice # 3.1: Human milk as the feeding of choice
Best Practice # 3.2: Start with minimal enteral nutrition
Best Practice # 3.3: Standardized feeding management
- **BP # 3.3.1:** Standardized definition of feeding intolerance
- **BP # 3.3.2:** Minimize fat loss by syringe position
- **BP # 3.3.4:** Feeding advancement for optimal growth

Best Practice # 3.4: Use fortification appropriately

Section 4: Human Milk/Breastfeeding
Best Practice # 4.1: Educate and advocate for human milk for NICU infants
- **BP # 4.1.1:** Appropriate knowledge, skills and attitudes for all perinatal professionals
- **BP # 4.1.2:** Appropriate education for mothers and families
- **BP # 4.1.3:** Hospital policies and procedures should support breastfeeding

Best Practice # 4.2: Establish and maintain maternal milk supply
Best Practice # 4.3: Handle human milk safely and appropriately
Best Practice # 4.4: Know when human milk is contraindicated

Section 5: Transitioning to oral feedings
Best Practice # 5.1: Transition to oral feedings based on physiologic maturity, not gestational age or weight.
Best Practice # 5.2: Use methods to support transition to breastfeeding

Section 6: Discharge Planning & Post-Discharge Nutrition
Best Practice # 6.1: Establish post-discharge nutritional needs and plan
Best Practice # 6.2: Facilitate post-discharge transition to direct breastfeeding

Section 7: Special/Controversial Issues
Best Practice # 7.1: Probiotics and Prebiotics
Best Practice # 7.2: Pacifiers
Best Practice # 7.3: CMV and Human Milk feeding

Best Practice # 7.4: Use of Insulin for Hyperglycemia
Best Practice # 7.5: Total Nutrient Admixture (TNA or “3-in-1”)

Nutritional Support of the Very Low Birth Weight (VLBW) Infant (Revised November 2008)

INTRODUCTION:

As survival rates for preterm infants and all NICU patients improve, more attention is being focused on improving the quality of survival through optimal nutritional management.(McLeod and Sherriff, 2007, Morales and Schanler, 2007, Thoyre, 2007, Vasu and Modi, 2007, Wight et al., 2008, Ziegler et al., 2007, Embleton, 2007, Kuzma-O'Reilly et al., 2003) Increasingly, both researchers and clinicians are recognizing that nutrition during critical periods in early life may permanently affect the structure and/or function of organs and tissues. (Lucas, 1990, Lucas, 2005a, Lucas, 2005b, Lucas et al., 1999, Singhal, 2006, Singhal and Lucas, 2004, Wells, 2007, Gluckman et al., 2008, Thureen, 2007b) There are good animal data and some evidence now in humans that early diet can influence long-term health (e.g. brain development, obesity, bone mineralization, blood pressure) and the risk of certain diseases (e.g. diabetes, chronic digestive diseases, some cancers).

Timing is crucial. Suboptimal nutrition, starting early in the neonatal period, contributes to the accumulation of growth deficits early in postnatal life.(Olsen et al., 2002) Infants provided only glucose solutions as nutrition in the first few days rapidly develop large protein and essential fatty acid deficits, with the smallest, most immature infants suffering the worst postnatal malnutrition.(Thureen, 1999, Thureen, 2007a) Likewise, postnatal gut luminal starvation, after active GI activity in utero, results in nutritional deficits, morphological and developmental changes in the gut, and reduced host resistance to infections.(La Gamma and Browne, 1994, Tyson and Kennedy, 2000, Tyson and Kennedy, 2005) On the other hand, excessive growth acceleration may lead to adverse health effects including obesity, elevated blood pressure, diabetes, and cardiovascular disease via reported long-term effects on insulin and leptin metabolism.(Vasu and Modi, 2007, Singhal, 2006, Singhal et al., 2004, Singhal et al., 2002, Singhal et al., 2003, Thureen, 2007b)

The more immediate goals of nutrition in the very low birth weight infant are the provision of adequate energy stores and nutrients for optimal growth. Growth of premature babies in the NICU setting usually falls far short of that compared to comparable gestation fetuses,(Carlson and Ziegler, 1998, Ehrenkranz, 2000, Ehrenkranz et al., 1999, Embleton et al., 2001, Radmacher et al., 2003, Clark et al., 2003b, Clark et al., 2003a) with approximately 90% of VLBW infants falling below the 10th percentile of expected intrauterine growth by 36 weeks gestational age.(Dusick et al., 2003, Lemons et al., 2001) Thirty to forty percent of these infants are still considered growth-retarded by 18-22 months of age. The term “extrauterine growth restriction” has been used to describe the phenomenon of turning appropriate for gestational age infants at birth into small for gestational age infants at discharge.(Clark et al., 2003b, Sakurai et al., 2008) Despite efforts to improve growth,(Bloom et al., 2003, Clark et al., 2003b) the incidence of

growth failure remains high. By the time the preterm infant reaches term corrected age, clear differences in brain and somatic development are apparent in comparison to healthy infants born at term.(Vasu and Modi, 2007) Although other factors may contribute, inadequate nutrition appears to be the predominant cause of growth failure.(Ziegler et al., 2007) Nutrient intakes have been documented to fall short of calculated required intakes, especially during the early days and weeks of life.(Carlson and Ziegler, 1998, Embleton et al., 2001, Radmacher et al., 2003) Early nutrient deficits tend to continue throughout the hospital course.(Radmacher et al., 2003, Embleton et al., 2001) The inadequate nutrition that causes growth failure is also responsible for much of the poor neuro-cognitive outcome seen among VLBW infants.(Morley, 1999, Ziegler et al., 2007, Neubauer et al., 2008, Bolduc and Shevell, 2005, Cooke and Foulder-Hughes, 2003, Cooke, 2006, Gale et al., 2006) There are several reasons why nutrient intakes of VLBW infants may be inadequate. Early in the hospital course parenteral and enteral nutrition may be delayed because of fears of toxicity (parenteral) and of necrotizing enterocolitis (enteral). Later in the hospital course and after discharge, misperceptions about nutrient requirements and maximal fluid intakes, and practical difficulties in providing adequate nutritional intake predominate.(Ziegler et al., 2007)

During the VLBW infant's neonatal period, nutrition will have profound effects on:

0. Organ development – especially the lungs and brain, which are undergoing the most pronounced developmental differentiation. Retinol has been shown to accelerate healing of injured fetal lamb cells.(Stahlman et al., 1988) More recently, prospective trials have associated Vitamin A administration with reduced oxygen requirements in the immediate postnatal period.(Darlow and Graham, 2007, Tyson et al., 1999) Similarly, fatty acid supplementation improves neurodevolopmental outcomes in the VLBW infant.(O'Connor et al., 2001)
0. Immune status – with antibody production dependent on adequacy of protein production and susceptibility to infection significantly related to nutritional status.(Brumberg and La Gamma, 2003)
0. Gastrointestinal integrity and the incidence of necrotizing enterocolitis - feeding practices have long been implicated as risk factors that affect NEC rates; conversely, the presence of NEC markedly compromises the provision of nutrition and affects metabolic demands.

Infections other than NEC will likely affect the nutritional status of premature newborns, either by compromising the ability to give enteral or parenteral feeds, or by altering other organ functions and overall metabolism. Environmental support mechanisms in the NICU, including the type of bed (warmer vs. incubator) and ventilator support will also impact metabolism and nutritional needs of the VLBW infant.

The goals of nutrition are straightforward: achieving a standard of short-term growth; meeting the unique nutritional needs of prematurity; preventing feeding-

related morbidities; and optimizing long-term outcome. Achieving those goals may not be so simple in the NICU population. The first step is to understand the short-term and life-long importance of nutrition for premature newborns. Only then, with assessment of current practices, outcomes and beliefs, can opportunities for practice improvements be developed and implemented locally. The CPQCC Nutrition Toolkit 2008, most recently revised in November 2008, has been developed to promote rapid assessment of current practices, outline evidence-based best practices, and enable rapid multidisciplinary improvement cycles to improve nutritional outcomes for premature newborns. This toolkit combines, reorganizes and updates 2 prior CPQCC Toolkits. The first of theseToolkits ("Nutritional Support of the VLBW Infant: Part I; 2004) was designed to provide background information regarding the importance of nutrition and human milk in the VLBW population, and to optimize human milk production and utilization. The second of these Toolkits ("Nutritional Support of the VLBW Infant: Part II; 2005) which focused on practices to optimize parenteral nutrition and the numerous transitions of enteral feedings, from their introduction through discharge and beyond. We hope you find it useful.

SECTION I. GENERAL PRINCIPLES

Best Practice #1.1: Establish consistent, comprehensive, multidisciplinary nutritional monitoring as an integral component of improving nutrition outcomes in the neonatal population.

Rationale: Poor growth, whether it occurs during antenatal or early postnatal life, is associated with increased risk to long-term health. However, the acceleration that follows a period of poor growth in utero or infancy also increases risk. The optimal growth velocity during the recovery phase is not known (Vasu and Modi, 2007). "Satisfactory" weight gain is associated with shortened lengths of hospital stay,(Schanler et al., 1999b) reduced health care costs,(Wight, 2001a) and later better growth and cognitive development (Ehrenkranz et al., 2006, Lucas et al., 1998, Hayakawa et al., 2003, Peterson et al., 2006). Excessive catch-up growth may result in increased risk for adult-onset diseases, such as obesity, hypertension and diabetes (Vasu and Modi, 2007).

Growth is considered an important health outcome measure in the NICU, but what is optimal growth for preterm infants? Optimal nutritional outcomes of VLBW infants are difficult to define for lack of ideal targets and benchmark data. The most commonly applied and accepted standard for postnatal growth is that of intrauterine growth,(American Academy of Pediatrics Committee on Nutrition, 2008, McLeod and Sherriff, 2007) (**see Appendix 1-A**) however this standard has inherent limitations (McLeod and Sherriff, 2007). Preterm birth is already the end result of a compromised pregnancy (Vasu and Modi, 2007). The optimal reference standard may ultimately be different given the significant differences in the in utero and extrauterine environments, the extreme differences in condition at birth, and the degrees of illness manifest by the wide range of VLBW infants (Wight et al., 2008). Normative growth data, adjusted by birth weight was published in 1999 by Ehrenkrantz et al (Ehrenkranz et al., 1999) (**see Appendix 1-B**). Pauls published growth curves for infants born at less than 1000 g who were started on combined enteral and parenteral nutrition on day one, and rapidly advanced to 92 kcal/kg/d within the first week of life, and suggested that these are more appropriate growth curves to use for VLBW infants than other older published growth curves (Pauls et al., 1998) **(see Appendix 1-C).** A recent preterm growth chart, the Fenton Chart,(Fenton, 2003) combines several large birth data sets from multiple countries. After term corrected age, Centers for Disease Control (CDC) data (2003) or WHO data (2008) is used. (**see Appendix 1-D1 and 1-D2**).

Simply following mean growth velocity of the VLBW population in an NICU could be misleading as this measure may confound those patients with excessive growth with those babies that are growth-restricted. It may be more helpful to track the variability of gestational age corrected weights close to discharge, as well as the percentage of infants who remain below the 10th percentile for predicted growth. Head circumference growth may also be an important marker

of nutrition given its association with later neurodevelopmental outcomes,(Cooke and Foulder-Hughes, 2003, Cooke, 2006, Bolduc and Shevell, 2005, Neubauer et al., 2008) however database analyses should exclude outliers with post-hemorrhagic hydrocephalus and ventriculomegaly on one end, and extreme cortical atrophy due to perinatal events, on the other end.
Nutritional assessment of all VLBW infants should include daily calculations of energy and nutrient intake. It is controversial as to whether to use the birthweight or actual weight for all calculations during the first week or until the infant regains birthweight. Similarly, there is no clear standard about whether to use actual weight or "estimated dry weight" for infants who are significantly edematous. In addition, weight should be followed frequently enough to monitor growth. Multiple studies have shown that, in most centers, VLBW infants receive significantly less protein and fewer calories than ideal. Monitoring of intake should be structured so that day-by-day evaluation of nutritional adequacy is possible. Given the high risk of post-natal growth failure among VLBW infants, maintaining adequate growth should take precedence over merely reaching some theoretical target of protein or energy intake.

In addition to growth parameters, several biochemical parameters have proven useful in monitoring nutritional states. The exact biochemical measures and frequencies will vary based on postnatal age of the infant, relative contributions of parenteral and enteral nutrition, specific disease entities and expert opinion, given that no monitoring schedule is research-based. A recent monitoring schedule has been suggested for both initial and stable phases of parenteral and enteral nutrition (Moyer-Mileur, 2007). **(See Appendix 2-C)** Infants on parenteral nutrition are usually premature and/or moderately ill, and are at risk of abnormalities in electrolyte and mineral balance. Prolonged parenteral nutrition predisposes infants to both cholestasis and osteopenia. While there are little data to support choices of the most cost efficient way to monitor the VLBW infant receiving parenteral nutrition, it seems prudent to follow electrolytes, hepatic function, renal function, triglyceride levels, bone metabolism, and a marker of protein synthesis on a regular basis (Kerner Jr, 2003, Schanler, 2003, Valentine et al., 2003). This includes sodium, potassium, chloride, calcium, phosphorus, magnesium, direct bilirubin, BUN, creatinine, alkaline phosphatase, and triglycerides, at least weekly but more frequently with parenteral nutrition changes. Measurement of albumin and/or pre-albumin may also be useful. Serum albumin has a half-life of 18-20 days and can reflect the severity of malnutrition. Prealbumin (transthyretin) has a shorter half-life (2 days) and is often used to monitor acute nutritional changes (Benjamin, 1989, Cardoso and Falcao, 2007).
An initial step towards assessing and improving the nutrition of VLBW infants is determining who is going to be held responsible for evaluating and tracking nutritional outcomes. There are data documenting the benefit of including a nutritionist and having a team approach to this clinical challenge (Valentine and Schanler, 1993, Kuzma-O'Reilly et al., 2003, Rubin et al., 1997). Potential participants include nutritionists, physicians/nurse practitioners/ physician

assistants, nursing staff, discharge planners, pharmacy staff, developmental specialists and occupational therapists (who may have expertise and interest in oral feeding practices). An individual database should facilitate the nutritional care of a particular patient, but more collective analyses of nutritional processes and outcomes are needed for global NICU quality improvement interventions. (**see BP 1.3 below**)

Implementation Strategies:

- Readily accessible growth curves, including both weight, length and head circumference
- Standing orders for monitoring of patients on parenteral nutrition
- Readily accessible flow charts which display fluid intake, glucose intake (g/kg/d), protein intake (g/kg/d), fat intake (g/kg/d), and caloric intake (kcal/kg/d)
- Non-protein IV caloric intake is calculated as the sum of the calories from glucose and the calories from lipid, i.e.: [(g/kg/d glucose) x (3.4 kcal/g glucose)] + [(mL/kg/d 20% Intralipid®) x (2 kcal/mL Intralipd®)]
- In most nurseries, the protein component of parenteral nutrition is not included in the calculation of calories, since amino acids are used for both calories and protein building.
- Readily accessible flow charts which display “total energy deficit” and “total protein deficit”
- Total energy deficit is calculated by subtracting the total number of calories the infant has received to date from the total ideal number of calories the infant would have received to date.
- Total protein deficit is calculated by subtracting the total amount of protein the infant has received to date from the total ideal amount of protein the infant would have received to date in utero.
- Infant weight should be monitored at least daily while on parenteral nutrition or advancing enteral feedings. After full enteral feedings have been established and the infant is otherwise stable, weight can be monitored less frequently, but plotted at least weekly, and plotted against standard preterm growth curves (Anderson, 2002, Kuzma-O'Reilly et al., 2003, Schanler, 2003, Fenton, 2003)
- Ehrenkranz, and the website version of it (http://neonatal.rti.org/) (Ehrenkranz et al., 1999)
- Wright et al. (Wright et al., 1993)
- Pauls 1998 (Pauls et al., 1998)
- Fenton (http://members.shaw.ca/growthchart/).(Fenton, 2003)
- Infant length and head circumference should be measured weekly. (Anderson, 2002, Ehrenkranz et al., 1999, Kuzma-O'Reilly et al., 2003, Schanler, 2003, Fenton, 2003)
- Infant biochemical parameters should be monitored frequently in infants on parenteral nutrition (**see Section II**). Expert opinion suggests that once full enteral feeding is achieved, biochemical monitoring should be done weekly for 2 weeks, then every other week (**see Appendices 2-A,B,C:**

Recommendations for Enteral and Parenteral Nutritional Monitoring).

- Mothers' milk production should be monitored.(Wight et al., 2008) Mothers should be assisted in maintaining a full milk supply, even though the infant may be consuming only a small amount of the milk produced. Adequacy of milk supply is a key factor in transitioning to breastfeeding. RN and LC to check with mom periodically and assist her to keep a breastmilk log (Furman et al., 2002, Meier, 2003, Meier et al., 2004, Wooldridge and Hall, 2003) (**see Section 4, Best Practice # 4.2).**
- Every NICU that cares for VLBW infants should have a Neonatal Nutritionist as part of the team to monitor infant growth and outcomes, calculate and relate parenteral nutrition and enteral intakes to current growth and medical conditions, suggest improvements in nutritional management, manage the formulary of premature infant feedings and supplements, and make nutritional plans with goals and resource referral information at discharge.(Anderson, 2002, Kuzma-O'Reilly et al., 2003, Olsen et al., 2005, Rubin et al., 1997, Valentine and Schanler, 1993)
- Develop a nutritional database (**see BP 1.3 below**)

Barriers:

- Lack of appreciation of the importance of nutrition on short- and long-term outcomes of VLBW infants.
- Cost associated with registered dietician and lactation consultation
- Perception that nutritional status can be adequately managed on a day-by-day basis without looking at trending data
- Perception that "ad hoc" monitoring is adequate
- Lack of standardized flow-sheets or charting tools
- Lack of personnel for doing accurate daily calculations
- Lack of systems to support daily calculation and trending

Measurement:

- Growth charts on every VLBW infant chart
- Documented assessments by registered dieticians
- Use of established monitoring protocols with nutritional goals
- % of infants with "unacceptable" values
- Consistent appraisal of mother's milk supply (pumping log, discussion on rounds)
- Rate of conversion of AGA infants at birth to SGA infants at discharge (i.e. B Wt/EGA vs Discharge Wt/CGA)

Best Practice #1.2: Establish standards of nutritional practice based on best evidence or expert opinion if evidence is lacking.

Rationale: Nutritional management of the VLBW is marked by a lack of practice uniformity. This heterogeneity of practice applies to every aspect of nutritional management and persists from the first few hours of life all the way to the time of

hospital discharge and beyond. Multicenter studies have found that mean growth varies significantly among NICUs (Clark et al., 2003a, Clark et al., 2003b, Bloom et al., 2003, Rubin et al., 1997). In one such study, variations in nutritional intake had the largest impact on explaining growth differences among sites (Olsen et al., 2002). Use of breastmilk and breastfeeding is also extremely variable across sites (Powers et al., 2003). Although the diversity of practice is greatest between nurseries, for instance see reports from Boston, (Olsen et al., 2002) and North Carolina,(Porcelli et al., 2004) it often exists between individual neonatologists within the same institution (Ziegler et al., 2002). "Diversity of practice thrives where there is uncertainty" (Ziegler et al., 2002). Although there is some agreement regarding the concept that nutrition should support "the rate of growth and composition of weight gain for a normal fetus of the same postconceptional age and to maintain normal concentrations of nutrients in blood and tissue." (American Academy of Pediatrics - Committee on Nutrition, 1985, American Academy of Pediatrics Committee on Nutrition, 2008) and estimates of amounts of nutrients needed to achieve that model of growth, there is far less agreement, and much more uncertainty, about the details of how to provide those nutrients. As few evidence-based standards of care are available for complex nutritional practices, such differences are understandable, but not desirable.

Notwithstanding the current state of uncertainty surrounding so many current practices, we urge a decrease in practice diversity for three reasons. First, consistent practice makes for perfectible practice. This notion is at the heart of the randomized control trial (RCT) technique, an exercise in which trialists attempt to control as many practice process variables as possible. In these rigorous studies, control groups often do better than those not enrolled in RCTs (Braunholtz et al., 2001, Schmidt et al., 1999). Second, more intense process control, such as experienced by patients being treated with "algorithms" or "guidelines," is consistently associated with significant improvements in adherence to care guidelines and often with better disease control (Ofman and Lubeck, 2004). Third, the quality improvement (QI) literature demonstrates the effectiveness of continuing cycles of planning a process, implementing it consistently, studying its use and effectiveness and then acting on ones' conclusions (Horbar et al., 2003). **(See Best Practice #1.3)**

Implementation Strategies:

- **Define nutritional team composition.** Consider including nutritionists, physicians/nurse practitioners/physician assistants, nursing staff, discharge planners, pharmacy staff, developmental specialists and occupational therapists.
- **Determine the mission of the nutritional assessment team.** It is essential for the interdisciplinary team to develop a set of common goals and purpose. The Nutrition Toolkit is designed to facilitate this discussion. There should be a regular assessment of the nutritional team's structure and function as a quality improvement body. A center's outcomes may be compared to normative data on VLBW infant growth

adjusted for birthweight. As reported benchmarks become available regarding breastfeeding practices, it will be increasingly important to track use of breastmilk as the preferred nutritional source of VLBW infants.(Henderson et al., 2008)

- **Review current practice.** Begin by re-evaluating as a team what current practices are thought to be and actually are, as often there may be a significant disconnect between the two. Determine how nutritional recommendations for an individual patient are chosen. Develop a process to track deviations from these consensus practices.
- **Develop or renew nutritional protocols.** Develop consensus about nutritional practices including parental and enteral nutrition based on best evidence or expert consensus. Areas of discussion may include the following:
    - Initial parenteral nutrition
    - Feeding intolerance
    - Enteral feeding initiation and advancement
    - Lactation support
    - Oral feeding progression
    - Breastfeeding initiation
    - Nutrient fortification in hospital
    - Addressing growth restriction
    - Postdischarge nutrition
- **Decide what nutrition information needs to be collected. (See Best Practice # 1.3 below)**

Barriers:

- Large current variation in practice
- Shortage of time and staff to address nutritional issues
- Lack of data collection and analysis capability
- Territorial or control issues surrounding nutritional decisions and feeding practices
- Lack of appreciation about the importance of standardization of care practices

Measurement:

- Health care provider variation
- Regular assessment of the nutritional team's structure and function
- Comparison of center outcomes with VON, published data, available benchmarks, and internally established metrics
- Track the use of breastmilk as the preferred nutritional source

Best Practice # 1.3: Track nutritional continuous quality improvement (CQI) data and use it to modify current practice.

Rationale: The efficacy of the QI approach is illustrated by reports on improving

neonatal nutritional practices in particular (Bloom et al., 2003, Kuzma-O'Reilly et al., 2003, Ziegler et al., 2007) and medical practices in general (Galvin and McGlynn, 2003). By evaluating and sharing nutritional practices of several best performing NICUs, Bloom (Bloom et al., 2003) demonstrated improvement in nutritional outcomes of over 75% of NICUs where process improvements were implemented along with evaluation of site-specific weight-gain performance. These interventions led to a 20% increase in average daily growth of VLBW infants with no change in the incidence of NEC, IVH or ROP (Bloom et al., 2003). A more recent evidence-based quality improvement collaborative effort reported significant improvements in all 5 of their "Potentially Better Practices" (Ziegler et al., 2007, Seger et al., 2007). The "measure to improve" paradigm is buttressed by both data and theory and leads to pragmatic steps that improve performance (Galvin and McGlynn, 2003).

Implementation Strategies:

- **Decide what nutrition information needs to be collected.** Relevant stakeholders, presumably based in the Nutritional Team that has developed within a NICU, should compare data forms in use to other models. Some forms may need to be completed daily; others may contain data elements that are stable or trended over time. Decisions should be made about what nutritional data (individual and population-based, e.g. <1500 gm birth weight) will be tracked and how (format and frequency) individual patient data will be available to the bedside caregivers. Data elements to be considered for inclusion in data forms should include:
- prenatal education and parental decision-making, especially regarding breastfeeding
- growth trends (compared to norms, see Appendix A), incl. weight, length and head circumference
- date/time of initiation of TPN, enteral feeding, discontinuation of TPN, ultimate volume and caloric density of enteral feedings
- initial, interval and ultimate composition of enteral feeds (all, some or no breastmilk)
- timing of skin-to-skin contact, non-nutritive breastfeeding
- relative contribution of gavage vs. nipple vs. breastfeeding intake
- maternal milk production
- nutritional discharge planning
- Daily information can include
- daily caloric intake, incl. protein, dextrose, fat calories and ratios
- when appropriate, electrolyte, vitamin and trace element intake
- weight change and overall fluid balance
- Prepare, adapt or adopt Nutrition Dashboard Summary Chart and Justification **(See Appendix 1-E1 and 1-E2)**
- See VON Potentially Better Nutritional Practices (PBNP) **(Appendix 1-F)**
- For additional examples of data collection tool, measurement grid, dashboard and survey, see **Appendices 1-G, H, I, J**.

Barriers:
- Lack of data collection and analysis capability and resources
- Lack of appreciation of the importance of nutrition on short- and long-term outcomes of VLBW infants.
- Perception that nutritional status can be adequately managed on a day-by-day basis without looking at trending data

Measurement:
- Development/adaptation/use of measurement tools
- # PDCA cycles
- Data updated and shared with all staff regularly and visible on unit.

SECTION II. PARENTERAL NUTRITION FOR VLBW INFANTS

The development of sophisticated techniques for providing short- and long-term parenteral nutrition to critically ill infants has been one of the major advances in neonatology of the last several decades. While there is still a wide variation in practice in how parenteral nutrition is used to support VLBW infants, there is a growing body of literature to support evidence-based recommendations for best practices. There are a number of excellent reviews of neonatal nutrition, including information on early parenteral nutrition (Thureen and Hay, 2000, Thureen and Hay, 2001, Pinchasik, 2001, Ziegler et al., 2002, ASPEN Board of directors and the clinical guidelines task force, 2002, Yeung and Smyth, 2003, Hay, 2005, Adamkin, 2007, Denne and Poindexter, 2007, Ehrenkranz, 2007).

At birth, a VLBW infant is abruptly disconnected from the placenta, the ideal source of parenteral nutrition. If the goal of post-natal nutrition in the VLBW infant is to mimic *in utero* nutrition, then the VLBW infant should be immediately placed on balanced parenteral nutrition, including sugar, protein, lipids, trace elements, and vitamins. It is clear that current parenteral nutrition does not entirely mimic *in utero* nutrition and is not without some undesired side effects. It is also clear that the preterm infant is in many ways a fundamentally different organism than an infant of the same gestation who is still *in utero*. Thus, decisions about how and when to implement parenteral nutrition in the VLBW infant are really best estimates, based on incomplete information and utilizing a still-evolving technology. Despite these limitations, there is no reason to believe there are advantages to under-nourishing the VLBW infant.

There is considerable evidence that nutritional status early in gestation and in post-natal life effect health status throughout life. The fact that infants who are small at birth appear to be more at risk for subsequent diabetes and cardiovascular disease suggests that the fetal adaptation to limited nutrition has long term consequences (Barker et al., 1993). Presumably, post-natal under-nutrition (or over-nutrition) could cause similar significant long-lasting effects.

Best Practice #2.1: Parenteral nutrition, including protein and lipids, should be started within the first 24 hours of life. Parenteral nutrition should be increased rapidly so infants receive adequate amino acids (3.0-4.0 g/kg/d) and non-protein calories (80-100 kcal/kg/d) as quickly as possible.

Rationale: By the late 1980s it was clear that earlier institution of parenteral nutrition was associated with improved growth and outcome (Georgieff et al., 1989). Since the late 1980s, there has been a gradual shift in most US nurseries toward beginning total parenteral nutrition within the first day or two. Despite what most clinicians consider “aggressive” nutritional support, post-natal growth of VLBW infants is usually significantly less than in-utero growth rates. While 60-80 kcal/kg/d is probably adequate to support the basal metabolic needs of the VLBW infant, a minimum of 90 non-protein kcal/kg/d is a more realistic estimate

of what is required to achieve growth (Dusick et al., 2003). Similarly, approximately 3.0-4.0 g/kg/d of protein is required to achieve adequate growth in the VLBW infant. Other reviewers have concluded that even higher caloric intake (125-130 kcal/kg/d and 3.5-4 g/kg/d of protein) is required to achieve normal growth (Denne, 2001).

A review of the growth pattern of all surviving infants with birth weight less than 1300 g showed that, despite an average of 75 kcal/kg/d and 1.9 g/kg/d protein in the first two weeks of life and subsequent increases in both total calories and protein, growth was less than the in utero rate (Carlson and Ziegler, 1998). In a similar study from the UK, 105 infants less than 1750 g at birth developed a significant calorie and protein deficit, despite aggressive attempts to meet recommended nutritional intake (Embleton et al., 2001). Unfortunately, for many VLBW infants the initial calorie and protein deficit is never entirely corrected, and infants remain below their ideal growth curves long after hospital discharge (Ernst et al., 2003). Data from the NICHD Neonatal Research Network suggests that by 36 weeks corrected age, nearly 90% of VLBW infants have growth failure, and that this growth failure persists into early childhood in a significant proportion of these infants (Dusick et al., 2003).

Berry analyzed the course of 109 AGA infants who weighed less than 1000 g at birth to determine the factors that influenced their growth. Not surprisingly, better caloric and protein intake early in their course were associated with better growth (Berry et al., 1997). Pauls recently published growth curves for infants born at less than 1000 g who were started on combined enteral and parenteral nutrition on day one, and rapidly advanced to 92 kcal/kg/d within the first week of life, and suggested that these are more appropriate growth curves to use for VLBW infants than the older published growth curves (Pauls et al., 1998). Increasing the early nutritional status of infants can improve their growth curves without any adverse effects on their clinical course (Wilson et al., 1997).

Data that supports immediately beginning VLBW infants on parenteral nutrition with amino acid content adequate to match *in utero* protein accretion rates has been steadily accumulating over the last two decades. Saini showed that sick infants who were started on parenteral amino acids in the first day of life had better protein intake, energy intake, and nitrogen retention than infants who were not started on amino acids until 72 hours of age (Saini et al., 1989). In a more recent study, Thureen randomized 28 infants with a mean birth weight 946 g to either 1 or 3 g/kg/d of amino acids, starting at approximately 48 hrs of age (Thureen et al., 2003). She was able to show a difference in protein balance after only 12 hours of amino acid administration, with more protein synthesis occurring in the 3 g/kg/d group. There was no evidence of toxicity in the high amino acid group. Ibrahim recently published a randomized trial in which ventilator-dependent preterm infants were randomized to begin early total parenteral nutrition, including 3.5 g/kg/d of amino acids and 3 g/kg/d of 20% Intralipid® within one hour of birth, vs later parenteral nutrition. Infants in the

early parenteral nutrition group had better energy and nitrogen balance with no adverse clinical or laboratory effects (Ibrahim et al., 2004). Looking at even higher amino acid doses, Porcelli randomized VLBW infants to receive a maximum of 3 vs 4 g/kg/d amino acids. The high amino acid group reached a mean of 3.3 g/kg/d by the end of week one, and a mean of 3.8 g/kg/d by the end of week two (Porcelli Jr and Sisk, 2002). They tolerated the high dose amino acids well, with no evidence of acidosis and only a minimal increase in BUN. The high dose amino acid group had better growth from week one. Amino acids at 2.4 g/kg/d when started on day 1 are well tolerated and result in an anabolic state as soon as the amino acids are introduced, compared to infants who are not started on amino acids until the second day (te Braake et al., 2007). Beginning amino acids on day 1 improves albumin synthesis rate (van den Akker et al., 2007). In a study comparing beginning amino acids immediately or delaying them until 12-30 hrs, infants started on amino acids immediately had a reduced incidence of sepsis and slightly reduced time to regain birth weight (Kotsopoulos et al., 2006).

A recent multi-center study randomized 122 VLBW infants to start amino acids at either 0.5 g/kg/d and advance by 0.5 g/kg/d to a maximum of 2.5 g/kg/d, or to start at 1.5 g/kg/d and advance by 1 g/kg/d to a maximum of 3.5 g/kg/d. There was no difference in growth between the groups, but the group that received more amino acids had significantly different serum amino acid profiles (Clark et al., 2007). This raises the theoretical possibility that overly aggressive administration of parenteral amino acid solutions could result in toxicity from elevated amino acid levels.

Ideally, the total non-protein calories and the amount of amino acid infused will be matched, so that the amino acids can be used for protein deposition, rather than as an energy source. The ideal ratio has been estimated as 24-32 non-protein calories per g of protein infused (Kerner Jr, 2003). However, there is evidence that the fetus can effectively utilize amino acids as an energy source, so there is probably little downside in administering maximum amino acid amounts, even to the infant who is receiving slightly sub-optimal calories (Ziegler et al., 2002).

One of the old rationales for slowly introducing amino acids was the concern that a high amino acid load would lead to azotemia. While amino acid intake may be correlated with BUN level in the first days of life, it does not appear to be a clinically significant effect (Ridout et al., 2005, te Braake et al., 2005, Clark et al., 2007).

Implementation Strategies:

- Standardized policies and admission order sets which include balanced parenteral nutrition as the “maintenance” fluid
- Availability of “pre-mixed” amino acid (Beecroft et al., 1999) containing parenteral nutrition solutions in hospital pharmacy

Barriers:
- Perception that early amino acid administration is of no benefit
- Perception that early amino acid administration is potentially toxic
- Perception that early amino acid administration is more expensive
- Pharmacy policies regarding limited timeframe of ordering parenteral nutrition

Measurement:
- % of VLBW infants started on amino acids at admission
- % of VLBW infants on amino acids by 24 hours of age
- % of VLBW infants receiving 3-4 g/kg/d parenteral protein by 72 hours of age
- % of VLBW infants receiving 80-100 non-protein kcal/kg/d by 5 days of age

Best Practice #2.2: Start parenteral lipids within the first 24 hours of life. Lipids can be started at doses as high as 2 g/kg/d. Lipids can be increased to doses as high as 3.0-3.5 g/kg/day over the first few days of life.

Rationale: There is convincing evidence that early lipids are well tolerated by VLBW infants, and that delaying the introduction of lipids has adverse consequences. In patients on exclusively parenteral nutrition, administering 0.5 g/kg/day Intralipid® is necessary to prevent essential fatty acid deficiency (ASPEN Board of directors and the clinical guidelines task force, 2002). Lipid administration should advance to 3.0-3.5 g/kg/day in patients who remain NPO (ASPEN Board of directors and the clinical guidelines task force, 2002, Kerner Jr, 2003, Putet, 2000, Simmer and Rao, 2005, Kerner and Poole, 2006).

In most centers, VLBW infants are started on lipids at a relatively low dose (0.5 g/kg/d), then gradually increased. However, several studies have suggested that lipids can be (and perhaps should be) started at higher doses. In Thureen's study of early aggressive amino acid administration, infants were started on Intralipid® at 1 g/kg/d within 48 hrs of life and appeared to tolerate this dose well (Thureen et al., 2003). In a study of very early parenteral nutrition (3.5 g/kg/d amino acids and 3 g/kg/d of Intralipid® starting in the first hour of life), there was no evidence of hyperlipidemia or other adverse effect of the early aggressive lipid administration (Ibrahim et al., 2004). One recent study suggests that lipids are well tolerated by VLBW infants when started at 2 g/kg/d on the first day of HA, then increased by 0.5 g/kg/d to a max of 3 g/kg/d (Drenckpohl et al., 2008). In this study, triglyceride levels were followed closely, and lipid doses were adjusted to maintain serum triglyceride levels $\leq$ 200 mg/dl. Interestingly, the infants who were started on 2 g/kg/d of lipid also tolerated higher glucose infusion rates during the first week of life than did control infants who were started on 0.5 g/kg/d of lipid. With the higher glucose and lipid infusion rates, infants in the 2 g/kg/d group received significantly more calories than the control group infants, reaching 80 kcal/kg/d by day 4.

Hyperlipidemia is a concern in VLBW infants who are receiving high doses of

parenteal lipids. Monitoring to maintain triglyceride levels ≤ 200 mg/dl should be a part of routine care. The Drenckpohl article presents a simple algorithm for adjusting lipid administration based on triglyceride levels (Drenckpohl et al., 2008). A retrospective study showed that patients who receive lipids delivered in plastic bags are more likely to have hypertriglyceridemia than those who receive lipids from glass bottles, possibly because of a higher proportion of large-diameter fat globules in plastic bags (Martin et al., 2008).

Because of the potential complex relationships between lipids and multiple disease processes, a number of questions about the safety of lipid administration to VLBW infants have been raised. Some of these are addressed below.

Lipids and glucose: The relationship between lipid administration and hyperglycemia is unclear. At least one study suggested that infants receiving lipids in addition to parenteral glucose, with or without amino acids, have higher serum glucose levels than infants who are not receiving lipids (Savich et al., 1988). There are also data that suggest parenteral lipids play an important role in supporting neonatal gluconeogenisis (Sunehag, 2003). In contrast, the Drenckpohl study mentioned above suggested that infants receiving higher doses of lipids tolerated higher glucose infusion rates than did infants on lower dose lipids (Drenckpohl et al., 2008).

Lipids and bilirubin: A recent Cochrane database review failed to find any relationship between early parenteral nutrition and jaundice (Faber and Mills, 2003). There is some intriguing evidence that alternative lipids based on fish-oil, with omega-3 fatty acids, improves cholestasis (Gura et al., 2006, Gura et al., 2008).

Lipids and brain development*:* Both arachadonic acid and docosahexaenoic acid are essential components of brain structure, and animal studies have shown that early essential fatty acid deficiency has long term adverse effects on brain development (Crawford, 1993). The ability to synthesize arachadonic acid and docosahexaenoic acid from linoleic acid is decreased in preterm infants (Decsi and Koletzko, 1994). Given the high rate of long-term CNS abnormalities in the smallest of preterm infants, one wonders about the advisability of delaying the introduction of lipids in these infants.

Lipids and free-radicals: The lipids which make up Intralipid® can easily undergo peroxidation to form hydroperoxides, potentially damaging substances which might alter arachidonic acid metabolism and/or form free radicals (Helbock et al., 1993). However, whether these hypdroperoxides are of any clinical consequence is unknown. In contrast, Tomsits' data suggests that VLBW infants who are not given lipids during the first week of life develop essential fatty acid deficiency, a condition which when combined with Vitamin E deficiency, leads to increased free radical formation (Tomsits et al., 2000). Multivitamins given together with Intralipid® (3-in-1) prevent lipid peroxidation and vitamin loss in the

infusate (Silvers et al., 2001). Light exposure has been associated with the formation of malondialdehyde (MDA) in light exposed lipids (Picaud et al., 2004).

Lipids and nosocomial infection: Of particular concern for protracted use of parenteral nutrition are the data which link Intralipid® administration to a significantly increased risk of coagulase negative *Staphylococcus* sepsis (Freeman et al., 1990, Avila-Figueroa et al., 1998). For this reason, parenteral lipid administration should probably be discontinued in infants who are receiving a significant amount of enteral nutrition (e.g. 80 kcal/kg/d).

Lipids and bronchopulmonary dysplasia (BPD): Although there is some concern that early administration of lipids might increase the risk of BPD, clinical trials have not supported this. In a trial, which randomized 129 infants who weighed less than 1750 g to early vs late parenteral nutrition with lipids, there was no difference in the incidence of BPD (Brownlee et al., 1993). Another small trial randomized VLBW infants to initiation of Intralipid® at 5 vs 14 days of age and failed to show any difference in the risk of BPD (Alwaidh et al., 1996).

The most concerning data about the potential adverse effect of early lipids on BPD comes from a study designed to determine whether early administration of Intralipid® decreased the incidence of BPD (Sosenko et al., 1993). In this study, 133 infants weighing between 600 and 1000 g at birth were randomized to receive lipids starting within the first 12 hours of life vs no lipids for the first 7 days. Overall, there was no difference in the mortality rate or incidence of BPD between the two groups. However, sub-group analysis showed that for infants with birth weight 600-800 g, infants receiving early lipids were more likely to have pulmonary hemorrhage and had a higher mortality rate than the control infants. Whether this was related to lipid administration, or was a statistical anomaly in this group is unclear. Somewhat reassuring is the fact that there were no differences in the 800-1000 g sub-group.

In contrast to the theoretical concerns about the possibility of lipids contributing to BPD, there is good evidence that under-nutrition can worsen the condition of the infant with BPD (Frank and Sosenko, 1988). There is also intriguing animal evidence that maternal under-nutrition decreases lung surfactant lipid content in the early neonatal period (Chen et al., 2004). Whether this indicates that early post-natal lipid deprivation could interfere with surfactant lipid formation is unknown.

***Lipids and pulmonary hypertension*:** When intravenous lipids were first introduced into adult critical care units, there were a number of publications showing an association between lipid administration and hypoxia. Similar results were also reported in neonates (Periera et al., 1980). Based primarily on animal data, it appears that the rapid administration of a large dose of lipid led to a significant increase in pulmonary vascular resistance. Presumably, the prostinoid precursors in the Intralipid® led to a thromboxane-mediated

constriction of the pulmonary vascular bed. However, this effect has been seen only with rapid administration of large doses of lipid (Hammerman and Aramburo, 1988). It is probably not a clinically significant problem in neonates who are given the usual dose of Intralipid® over 24 hours. In a clinical trial in which critically ill VLBW infants were randomized to receive 1 g/kg/d of Intralipid® on day one and increasing to 3 g/kg/d by day four, or to receive no lipid until day eight, there were no differences in oxygenation or in any other marker of lipid toxicity (Gilbertson et al., 1991).

Lipids and stability of parenteral nutrition mixtures: One approach to lipid administration is to combine lipids with the other components of parenteral nutrition in a single solution. This combination, variously called Total Nutrient Admixtures (TNA) or 3-in-1 solutions make use of the fact that under certain conditions the glucose/amino-acid solution may be mixed with intravenous fat emulsion and administered to the patient in one bag. These admixtures, commonly used in adults and pediatrics, have been successfully used by some NICUs under carefully controlled conditions using manufacturer and published data on emulsion stability specific for pediatric/neonatal amino acid formulations (Bullock et al., 1992). A recent study of all-in-one preparations including glucose, protein, fat, and vitamins showed no impact of fat emulsion and fat-soluble vitamins on physical stability of the solution.(Skouroliakou et al., 2008)

Implementation Strategies:

- Standardized policies and admission order sets which include Intralipid® administration starting within the first 24 hours of life. Lipids can be started as at doses as high as 2 g/kg/d on day 1, and advanced by 0.5 g/kg/d to a maximum of 3 g/kg/d, so long as serum triglycerides are less than 200 mg/dl.

Barriers:

- Perception that early lipid administration is of no benefit
- Perception that early lipid administration is potentially toxic

Measurement:

- Measure provider consistency in implementation
- % of VLBW infants receiving lipids by 24 hours of age

Best Practice #2.3. Discontinue parenteral nutrition, with removal of central catheters, as soon as adequate enteral nutrition is established.

Rationale: At some point in the progression from parenteral to enteral nutrition, every infant reaches a point where the advantages of more parenteral nutrition are outweighed by the risks of continued central vascular access and infection. Central lines are a clear risk factor for infection, and there is some data to suggest that 21 days is a “break point” at which the risk of line-associated sepsis increases significantly (Chathas et al., 1990). Of particular concern for protracted

use of parenteral nutrition are the data which link Intralipid® administration to a significantly increased risk of coagulase negative *Staphylococcus* sepsis (Avila-Figueroa et al., 1998, Freeman et al., 1990). Although we are unaware of any good data from controlled trials on when to discontinue parenteral nutrition, an "expert opinion" strategy would suggest that when an infant is tolerating 80 -100 kcal/kg/d of enteral nutrition, and there are no other risk factors, it should be possible to discontinue all parenteral nutrition and continue advancing enteral nutrition (Kilbride et al., 2003, Kuzma-O'Reilly et al., 2003). The current California Children's Hospital Association and California Children's Services (CCHA-CCS) collaborative on reducing catheter associated blood stream infections suggests removing central lines when an infant reaches $\geq$ 120 mL/kg/d of enteral nutrition.

Implementation Strategies:

- Standardized policies and order sets which include discontinuation of parenteral lipids when adequate enteral calories established
- Standardized policies and order sets which include discontinuation of central catheters when adequate enteral nutrition established

Barriers:

- Perception that the benefit of several more days of lipid administration outweighs the risk of catheter-associated infection
- Perception that leaving a central line in place "just in case" caries no risk of catheter-associated infection

Measurement:

- Number of central line days in patients receiving $\geq$ 120 mL/kg/day of enteral nutrition

See Appendices 2-A, B, C, D1 & D2: Recommendations for Laboratory Monitoring and Examples of TPN order sheets.

SECTION 3: ESTABLISHING ENTERAL NUTRITION

Best Practice #3.1: Human milk should be used whenever possible as the enteral feeding of choice for VLBW infants.

Rationale: The benefits of human milk for term infants are well recognized.(American Academy of Pediatrics Section on Breastfeeding, 2005, Cunningham, 1995, Office on Women's Health, October 2000, Agency for Healthcare Research and Quality, April 2007, Horta et al., 2007) Human milk provides not only optimal nutrition for term infants,(American Academy of Pediatrics Committee on Nutrition, 2004b, American Academy of Pediatrics Section on Breastfeeding, 2005) but also key digestive enzymes, direct immunologic protective factors, immunomodulators, anti-inflammatory factors, anti-oxidants, growth factors, hormones and other bioactive factors, and multiple cellular elements, with new components and interactions being discovered regularly.(Lawrence and Lawrence, 2005, Lawrence and Pane, 2007, Hanson, 2004) Breastfed infants do not share the same illness or mortality rates of artificially fed children, even in developed countries.(Eglash et al., 2008) Artificially fed infants have significantly higher rates of acute otitis media, non-specific gastroenteritis, lower respiratory tract illnesses including respiratory syncytial virus infection, urinary tract infections, infant botulism (with increased severity and mortality seen in formula fed babies), atopic dermatitis, necrotizing enterocolitis and sudden infant death syndrome (SIDS).(American Academy of Pediatrics Section on Breastfeeding, 2005) The special properties of human milk also provide long-term protection from many diseases seen at higher rates in artificially fed infants, including an increased risk of obesity, type 1 and 2 diabetes, lymphoma, leukemia, asthma and hypercholesterolemia.(American Academy of Pediatrics Section on Breastfeeding, 2005, Horta et al., 2007)

Breastfeeding also promotes strong families by improving the health of the mother,(Horta et al., 2007, Labbok, 2001) establishing a close bond between mother and infant and fostering communication and emotional development.(Office on Women's Health, October 2000) Breastfeeding provides significant economic benefits to the family (and the community) by reducing unnecessary expenditures for infant formula, reducing health care costs, reducing employee absenteeism to care for a sick child, and decreasing scarce resource use and waste.(Office on Women's Health, October 2000, Ball and Bennett, 2001) Breastfeeding cost effectiveness studies reveal that as little as three months of exclusive breastfeeding can save $200 - $400 per child in health care costs during the first year of life.(Ball and Wright, 1999) The American Academy of Pediatrics,(American Academy of Pediatrics Section on Breastfeeding, 2005) the American College of Obstetricians and Gynecologists,(American College of Obstetrician-Gynecologists, 2000) the American Academy of Family Physicians, (American Academy of Family Physicians, 2002) the American Dietetic Association,(American Dietetic Association, 2005) the US Surgeon General,(Office on Women's Health,

October 2000) the WHO/UNICEF(World Health Organization and UNICEF, 2003, World Health Organization and United Nations Childrens Fund, 1989) and many other organizations recognize that the promotion and support of breastfeeding is a key public health issue. Breastfeeding has been rediscovered by modern science as a means to save lives, reduce illness, foster optimal development. Policy makers are increasingly recognizing that breastfeeding promotion efforts can reduce healthcare costs and enhance maternal and infant well-being. (Ball and Bennett, 2001, Ball and Wright, 1999, Weimer, 2001)

Current research confirms that human milk (with appropriate fortification for the very low birth weight infant) is the standard of care for preterm, as well as term infants.(Schanler et al., 1999a, Wight et al., 2008, Ziegler et al., 2007, Patel et al., 2007, American Academy of Pediatrics Section on Breastfeeding, 2005, Schanler, 2001) Benefits of human milk for VLBW infants include:

- Breastmilk empties from the stomach faster,(Cavell, 1981, Ewer and Yu, 1996) and reduces intestinal permeability faster.(Catassi et al., 1995)
- The use of breastmilk results in less residuals and faster realization of full enteral feedings.(Schanler et al., 1999b, Lucas and Cole, 1990, Uraizee and Gross, 1989)
- Many factors in human milk may stimulate gastrointestinal growth, motility and maturation.(Sheard and Walker, 1988, Groer and Walker, 1996, Barlow et al., 1974, Walker, 2004, Donovan, 2006)
- Enzymes in breastmilk help immature infants absorb and utilize nutrients more efficiently(Hamosh, 1994) and may also improve absorption of nutrients when breastmilk and artificial milks are combined.(Alemi et al., 1981)
- Reaching full feedings faster with the use of human milk means fewer days of IV's, less side effects from TPN, less infections and infiltrations from IV's, and less costly and fewer hospital days.(Schanler et al., 2005, Schanler et al., 1999b)
- Breastmilk-fed infants have a reduced incidence of necrotizing enterocolitis. (Boo and Goh, 1999, Buescher, 1994, Gross, 1983, Guthrie et al., 2003, Kliegman et al., 1979, Santulli et al., 1975, Lucas and Cole, 1990, Narayanan et al., 1980, Narayanan et al., 1984a, Pitt et al., 1977, Schanler et al., 1985, Schanler et al., 2005, Schanler et al., 1999b, Yu et al., 1981, Eibl et al., 1988, Henderson et al., 2007b, McGuire and Anthony, 2003, Narayanan et al., 1981, Sisk et al., 2007, Stout et al., 2008, Chauhan et al., 2008)
- Breastmilk use leads to reduced episodes of bacteremia and sepsis. (Schanler et al., 1999b, Narayanan et al., 1980, Narayanan et al., 1981, Narayanan et al., 1984a, el-Mohandes et al., 1997, Furman et al., 2003, Hylander et al., 1998, Narayanan et al., 1982, Ronnestad et al., 2005, Uraizee and Gross, 1989, Schanler et al., 2005)
- Breastmilk use is associated with fewer urinary tract infections.(Goldblum et al., 1989, Pisacane et al., 1992, Marild et al., 1990)
- VLBW infants fed human milk tend to have higher IQ scores.(Lucas et al., 1992c, Anderson et al., 1999, Hagan et al., 1996, Vohr et al., 2007, Vohr et al., 2006, Morley, 2002, Morley et al., 1988, Morley and Lucas 2000, Feldman

and Eidelman, 2003, Amin et al., 2000, Bier et al., 2002, Elwood et al., 2005, Smith et al., 2003a, Lucas et al., 1994, Gale and Martyn, 1996, Pollock, 1989, Jacobson and Jacobson, 1992, Hart et al., 2003, Horne et al., 2004, Sacker et al., 2006)

- VLBW infants receiving breastmilk have improved visual development and less retinopathy of prematurity.(Schanler et al., 2005, Furman et al., 2003, DiBiasie, 2006, Hylander et al., 2001, Hallman et al., 1992, Uauy et al., 1990, Faldella et al., 1996, Carlson et al., 1993)
- Human milk has anti-oxidant properties that assist the preterm infant in coping with increased oxidative stress.(Friel et al., 2002, Shoji et al., 2004, Tsopmo and Friel, 2007)

While there are occasional medical contraindications to the use of a mother's breast milk, the most likely reason given for not providing human milk to VLBW infants is lack of availability. It stands to reason that mothers of VLBW infants should be directed and supported to ensure that their milk is available for their baby. A mother's successful commitment to supplying her milk is likely to have significant medical benefit for her VLBW infant in both the short and long-term. Human milk is more than nutrition. It is medicine for both the infant and his mother: the milk for the infant, and the provision of it for his mother. (Wight et al., 2008)

The preferred feeding is human milk, preferably started on day 1.(Ziegler et al., 2002, Schanler, 2003, American Academy of Pediatrics Section on Breastfeeding, 2005) The objective of feeding during the early days of life is to stimulate gut hormone maturation, stimulate gut hormone release, and to induce gut motility. (Wight et al., 2008) A frequently encountered practical limitation is that lactogenesis II (milk "coming in") does not occur for 2-5 days after birth. During that time, only small quantities of colostrum are available but are especially useful for the infant ("liquid gold") and should be fed. Colostrum (the first milk) contains high concentrations of antimicrobial, anti-inflammatory and immunomodulating factors, and prepares the gut for the mature milk.(Goldman et al., 1994, Goldman, 2000, Goldman, 2007, Caicedo et al., 2005) In general, as milk protein decreases over time, human milk should be used in the order pumped for the first 2-3 weeks, then fresh milk as available.(Ziegler et al., 2007, Ziegler et al., 2002) Feedings should be started with full strength milks.(Berseth et al., 1992, Koenig et al., 1995) Routine culturing or heat treatment of mothers' own milk has not been demonstrated to be necessary or cost-effective.(American Academy of Pediatrics Committee on Infectious Diseases, 2006)

If mother's own milk is not immediately available, the clinician should consider the use of pasteurized donor human milk (PDHM), which has most of the properties of fresh human milk (immunoglobulins, growth and developmental hormones, enzymes, anti-inflammatory factors, etc.), is sterile, and reduces NEC while improving feeding tolerance.(Lucas and Cole, 1990, Ziegler et al., 2007, Ziegler et al., 2002, Arnold, 2005, Wight et al., 2008)

When infant formulas must be used, premature formulas should be used instead of elemental formulas designed for full term infants, unless there is a compelling contraindication. A hydrolyzed protein preterm formula might be preferred, but this is only currently available in Europe.(Mihatsch et al., 2002) A partially hydrolyzed premature formula made with 100% whey protein has just been introduced to the US market, but there is currently no published information and to its safety or efficacy.

Implementation Strategies:

- Create a supportive environment to maximize milk production in the early postpartum period.
- Teach every mother hand expression and collection techniques to maximize colostrum availability. (See Jane Morton MD DVDs: "Combining Hand techniques with Electric Pumping to Increase Milk Production" and "Making Enough Milk, The Key to Successful Breastfeeding…Planning for Day One", available from www.breastmilksolutions.com)
- Establish a relationship with the nearest milk bank and procedures for obtaining heat-treated donor milk quickly or maintain a reserve supply. (www.hmbana.org) **(See Appendix 4-A)**

Barriers:

- Maternal disappointment over small expressed volumes
- Because other issues are perceived as higher priority, there may be a lack of appreciation of the importance of small volumes of colostrum,
- The desire to initiate trophic feeds regardless of breastmilk availability
- Difficulty with collection and labeling of small expressed volumes
- Mother's own milk not always available
- Lack of knowledge regarding use of pasteurized donor human milk (PDHM):
- No policy available. (**SEE APPENDIX 4-D**)
- Not aware of resources to obtain PDHM
- Lack of knowledge regarding use of premature formulas.
- Resistance to changing current practices.
- Lack of recognition of the role of pumping in the mothers' recovery process

Measurement:

- Documentation of utilization of colostrum or breastmilk for the initial feeding
- Maternal education on manual expression, breast massage and colostrum collection **(SEE APPENDIX 4-E**)
- Documentation of post-partum provider's competency in helping mothers collect colostrum (**SEE APPENDIX 4-F**)
- If colostrum or breastmilk is not available in the NICU, are there documented efforts to contact the mother before providing alternatives?
- Survey of NICU staff attitudes and knowledge regarding human milk and breastfeeding (**SEE APPENDIX 4-G**)

Best Practice #3.2: Enteral feeds, in the form of trophic or minimal enteral feeds (also called GI priming), should be initiated within 1-2 days after birth, except when there are clear contraindications such as a congenital anomaly precluding feeding (e.g. omphalocele or gastroschisis), or evidence of GI dysfunction associated with hypoxic-ischemic compromise.

Rationale: In utero, the fetal gastrointestinal tract is constantly active: swallowing amniotic fluid, absorbing fluid and some nutrition, performing rudimentary peristalsis, and forming meconium.(Wight et al., 2008) The objective of feeding during the early days of life is to stimulate gut maturation, hormone release, and motility.(Wight et al., 2008) Although it was never shown that prolonged withholding of feedings actually prevented necrotizing enterocolitis (NEC,) some form or other of this strategy was widely adopted in the 1970s and 1980s.(LaGamma et al., 1985) Starvation leads to atrophy of the gut,(La Gamma and Browne, 1994) so withholding feedings may actually render subsequently introduced feedings less safe.(Ziegler et al., 2002) Withholding of feedings was eventually re-evaluated with a number of trials of early introduction of feedings.(Heicher and Philip, 1976, LaGamma et al., 1985, Lucas et al., 1986, Ostertag et al., 1986, Dunn et al., 1988, Slagle and Gross, 1988, Berseth, 1992, Meetze et al., 1992, Thureen, 1999, Schanler, 2003) A systematic review of these trials(Tyson and Kennedy, 2005) concluded that early introduction of feedings shortens the time to full feeds and to discharge and does not increase the incidence of NEC. A controlled study involving 100 LBW infants(McClure and Newell, 2000) confirmed these findings and found, in addition, a significant reduction in serious infections with “early” introduction of feedings. A pilot study of a sterile, isotonic, noncaloric enteral solution patterned after human amniotic fluid found improved tolerance of human milk feedings in infants with a history of feeding intolerance.(Barney et al., 2006)

Another practice, implemented with the idea of detecting NEC earlier, is to focus particular attention on gastric residuals as a presumed early manifestation of NEC. However, in the first few days following birth, gastric residuals are extremely common and are rarely associated with NEC.(Ziegler, 1999, Ziegler et al., 2007, Moody et al., 2000, Mihatsch et al., 2002, Cormack and Bloomfield, 2006) The paradoxical motility, which is responsible for most of the residuals, transitions more rapidly to a normal progressive pattern if feedings are started early and are persistently offered, than when feedings are withheld.(Berseth, 1992) A retrospective case-control study of 51 VLBW infants and 102 matched controls found that the maximum residual in the previous 6 days, maximum residual as a percentage of a feed, and the total residuals as a percentage of feeds were all higher in the NEC group. Although these differences were statistically significant, there was much overlap of these variables with those of control infants, limiting the clinical utility of these observations.(Cobb et al., 2004)

Yet another strategy aimed at preventing NEC has been to slow the rate of

feeding advancement. A retrospective analysis of 19 cases of NEC(Anderson and Kliegman, 1991) found that infants who went on to develop NEC had feedings advanced more rapidly than in control infants; they advocated feedings not be advanced by more than 20 mL/kg/day. Rayyis, in a randomized controlled trial that compared increments of 15 mL/kg/d with 35 mL/kg/d, found that the infants who advanced faster achieved full feedings and weight gain sooner, and there was no difference in the incidence of NEC.(Rayyis et al., 1999) On the other hand, a study of prolonging minimal enteral feedings (20 mL/kg/d for 10 days) before advancement was closed early because of significantly increased NEC in the group who were started on 20 mL/kg/day and advanced to 140 mL/kg/d over the same 10 days.(Berseth et al., 2003) The prolonged use of small enteral feeds resulted, as expected, in greater need for central venous line placement and prolonged use of parenteral nutrition. The incidence of death was the same in both groups. Although the prolonged use of small enteral feeds reduced the risk for NEC, it did so by delaying the establishment of full feedings by 10 days and prolonged the hospital stay.(Berseth et al., 2003)

The most recent randomized, controlled single center trial of intermediate rates of feeding advancement (20 mL/kg/d vs. 30 mL/kg/day) done in 1000-2000 gm, 35-week infants (Caple 2004) found no difference in NEC.(Caple et al., 2004) The infants in the faster advancement group achieved full volume feedings sooner, regained birth weight faster and had fewer days of intravenous fluids. Approximately 30% of infants in both the intervention and control groups in this study received breastmilk. The day of life at which feedings were initiated was determined by the attending physician and was not specified in the paper, although < 1000 gm infants were excluded “because their feedings are often started many days after birth”.(Caple et al., 2004) The most recent Cochrane Database Review of slow advancement of enteral feeding concluded that currently available data do not provide evidence that slow advancement of feedings in VLBW infants reduces the risk of NEC, but time to establish full feedings was longer.(McGuire and Bombell, 2008) There was no statistically significant difference in length of hospital stay. Whether protective against NEC or not, limiting feeding increments to 20 mL/kg/d still permits achievement of full feedings in a reasonable period of about 8 days.(Ziegler et al., 2002)

Additional controversial areas are feeding infants who have umbilical artery catheters in place and/or who exhibit cardiovascular instability. Data from randomized controlled trials are insufficient to exclude an effect of “high” (descending aorta above the diaphragm) vs. “low” (above the aortic bifurcation but below the renal arteries) UAC tip position on the risk of NEC. High UAC tip placement results in a lower incidence of aortic thrombosis, fewer ischemic complications and a longer duration of catheter use.(Barrington, 1998) Evidence exists that enteral feeding with a UAC in place does not affect superior mesenteric blood flow, the risk of feed intolerance or the incidence of NEC.(Havranek et al., 2007, Davey et al., 1994) Most infants in the GI priming studies were fed with umbilical artery catheters (UAC) in place and the studies

still noted a decreased incidence of NEC.(Davey et al., 1994, Dunn et al., 1988, Schanler et al., 1999a)

The presence of a PDA has been inconsistently reported as an independent risk factor for the development of NEC.(Chauhan et al., 2008) Currently, no evidence exists that withholding enteral feeds in infants with a PDA affects outcomes.(Bellander et al., 2003, Patole and de Klerk, 2005) Similarly, meta-analyses of trials of non-steroidal anti-inflammatory agents for PDA closure have not demonstrated any significant effects on the incidence of NEC.(Fowlie and Davis, 2003, Shah and Ohlisson, 2006) Further research is needed to ascertain just how "unstable" an infant needs to be before feedings are withheld.

Use of diluted feeds has been suggested for premature infants. However, intestinal motility responses to feeds were elicited earlier and persisted longer following the use of full-strength formula in comparison to 1/3 and 2/3 dilutions. (Koenig et al., 1995) Enteral water, although possibly useful in hypernatremic/hyperglycemic infants, does not affect intestinal motility when compared to milk.(Berseth et al., 1992) In light of the current variations in feeding practice, paying close attention to feeding parameters with a standardized feeding regimen appears to significantly decrease NEC and improve nutrition.(Kamitsuka et al., 2000, Patole et al., 2003, Patole and de Klerk, 2005, Chauhan et al., 2008, Patole, 2007, Pietz et al., 2007)

Implementation Strategies:

- Enteral feeding policies should be available in each NICU specifying:
- Early (day 1-2) initiation of feedings for most infants
- Initiation of feedings with full strength human milk (preferred), heat-treated donor human milk or formula
- Consider extending minimal enteral feedings in the presence of cardio-respiratory instability
- Progressive advancement of feeding is dependent on clinical status and should be standardized as much as possible within each NICU **(See Appendix 3-A)**
- Definition of feeding intolerance (**See Best Practice #3.3.1**)
- Reasons for withholding feedings should be documented in the hospital chart/progress notes and discussed on rounds.

Barriers:

- Lack of staff information about the hazards of delayed feedings in VLBW infants
- Current practices/beliefs regarding contraindications of umbilical artery catheters and PDA
- Lack of consensus about physiology and definition of feeding intolerance (**See Best Practice #3.3.1**)
- Lack of consistency across studies about content and advancement of feeds and relationship to outcomes

Measurement:
- Hour or day of life when trophic feeds initiated
- Day of life when feeding advancement begun
- Day of life when full enteral feeds achieved
- Day of life when birthweight regained
- Days of parenteral nutrition

Best Practice #3.3: NICU's should standardize feeding management based on best available evidence.

Best Practice # 3.3.1: NICUs should standardize their definition of feeding intolerance, with specific reference to acceptable residual volumes, changes in abdominal girth and the presence of heme-positive stools.

Rationale: Enteral feedings of VLBW infants are frequently stopped, or feeding advances held, based on "feeding intolerance." The definition of intolerance may include the presence and quality (normal, yellow, green, blood-tinged) of gastric residuals , emesis, an increase in abdominal girth or abdominal tenderness, the presence of heme-positive or abnormal-appearing stools, the presence, absence or quality of bowel sounds, or any combination thereof.(Jadcherla and Kliegman, 2002, Mihatsch et al., 2002) As all of these phenomena may occur in a healthy premature infant tolerating feedings(Moody et al., 2000) it is important to put these findings into a clinical context that is understood by nursing and physician staff. Failure to do so may lead to unnecessary limitation of enteral feeds and reliance on parental nutrition. In one study, when feeding intolerance was more clearly defined, nutritional outcomes were dramatically improved.(Patole et al., 2003)

Cobb demonstrated that maximum residuals in prematures (expressed as a percentage of the feeding volume) who developed NEC were 40% (interquartile range: 24-61) vs. 14% (interquartile range: 4-33) in those who did not, and residuals were noted to increase most dramatically in the 3 days preceding the onset of NEC.(Cobb et al., 2004) Given the variability of residuals upon initiation of feedings, it may be more appropriate to use significant increases in residual only as one part of the decision to limit feeding advancement. One should be cautious about using residuals as the sole reason to completely stop enteral feedings.

Implementation Strategies:
- Key NICU team members should discuss and come to a conclusion on the definition of feeding intolerance **(See Appendix 3-B)**
- Education for staff regarding the new definition, clinical context and potential practice changes

Barriers:

- Difficulty in coming to a consensus on definition
- Difficulty in understanding clinical context of phenomena in healthy vs sick infants

Measurement:
- Chart review of VLBW infants at risk for feeding intolerance:
- Feeding stops and starts
- Documentation of protein and caloric deficits associated with feeding interruption

Best Practice # 3.3.2: Enteral feeds should usually be given by intermittent bolus, rather than continuously, and by gastric, rather than transpyloric administration.

Rationale: VLBW infants are usually started on feedings before they are able to suck and swallow. Tube feeding is an essential tool in enteral nutrition. There are various methods of tube feeding including continuous, semi-continuous or intermittent bolus, and a number of approaches such as orogastric, nasogastric, transpyloric or gastrostomy.

Milk feedings given by intermittent bolus gavage method are thought to be more physiologic because they promote the cyclical surges of gut hormones seen in normal term infants and adults.(Aynsley-Green et al., 1982) Premature infants had more feeding intolerance(Schanler et al., 1999b) (Dollberg et al., 2000) and a slower rate of weight gain with continuous infusion when compared to the bolus technique.(Schanler et al., 1999b) The Cochrane analysis concluded that infants fed by the continuous tube method took longer to reach full feeds, but there was no significant difference in somatic growth, days to discharge, or the incidence of NEC.(Premji and Chessell, 2005)

Occasionally, intolerance is seen in the bolus-fed preterm infant, with duodenal motility decreasing following the bolus feeding.(de Ville et al., 1998) A bolus feeding given over a longer time interval, such as 30-120 minutes, results in a return of motility and improved tolerance.(Schanler, 2003, Schanler et al., 1999b) In infants with gastrointestinal disease fed formula, continuous infusion has been associated with better nutrient absorption.(Parker et al., 1981) A more recent report of a 20 year experience with a strict feeding protocol which included, as one parameter, continuous feeds, reported lower rates of NEC than VON averages.(Pietz et al., 2007) Unfortunately, few infants were fed human milk, and there is no way to determine which feeding strategies, or which combination of strategies had the most impact. Based on theses 2 studies(Parker et al., 1981, Pietz et al., 2007) Ziegler recommended continuous feeds.(Ziegler et al., 2007) We disagree, and recommend bolus, or modified bolus feedings for most VLBW infants.

Delivery of tube feedings into the stomach elicits the associated physiologic

stimulation and digestive processes. Transpyloric feedings have the potential benefit of delivering feeds past the pylorus and gastroesophageal junction. Transpyloric (e.g. NJ) feeds must be continuous, which may account for decreased gastroesophageal reflux symptomatology. Transpyloric feedings are not recommended for routine use in preterm infants, as no benefit was found in a meta-analysis, and they are associated with a greater incidence of gastrointestinal disturbance and possibly death.(McGuire and McEwan, 2004, McGuire and McEwan, 2007)

Implementation Strategies:
- NICU feeding policy specifying bolus, intra-gastric feeds
- Documentation of reason for variance in medical record and discussed on rounds

Barriers:
- Staff resistance to change current practice

Measurement:
- Chart audit of enteral feeding practices on 10 VLBW infants

Best Practice # 3.3.3: Pumps delivering breastmilk should be oriented so that the syringe is vertically upright, and the tubing (smallest caliber and shortest possible) should be positioned and cleared to prevent sequestration of fat.

Rationale: Fats in breastmilk are of lower density than other components, and will therefore rise and separate. If a syringe is horizontal, fat may float to the top and therefore will be the last fluid emptied into the tubing, resulting in variable fat administration rates and causing some of the highest caloric feed to never reach the baby.(Spencer and Hull, 1981, Greer et al., 1984, Mehta et al., 1988, Narayanan et al., 1984b, Stocks et al., 1985) As fortifiers may fall to the bottom of the feeding, the feeding syringe may need to be gently manipulated several times during a continuous or prolonged “bolus” feed to ensure all nutrients are received **(SEE APPENDIX 3-C for photographic example).**

Implementation strategies:
- Education for MDs and RNs regarding the rationale and importance of the pump’s position during breastmilk administration
- Policy and procedure regarding pump positioning

Barriers:
- Lack of equipment for pumps and syringes to be positioned on
- Resistance to change in practice

Measurement:

- Survey pump positioning after education/implementation

Best Practice # 3.3.4: Enteral feeds should be advanced until they are providing adequate nutrition to sustain optimal growth (2% of body weight/day). For infants fed human milk this could mean as much as 170 - 200+ mL/kg/day.

Rationale: The goal of enteral feedings is to provide optimal nutrition and growth and eliminate the need for parenteral nutrition. The historic target for premature infants of 150 mL/kg/day of enteral feedings may be inadequate to overcome prior nitrogen deficits and establish optimal growth. A randomized trial of enteral feeding volumes (150 and 200 mL/kg/d) of infants born less than 30 weeks gestation, once they reached full enteral feeds, found that individual milk volume requirements for adequate weight gain without significant adverse effects varied between 150-200 mL/kg/d.(Kuschel et al., 2000) Increased milk intakes were associated with increased daily weight gains and a greater weight at 35 weeks, but no difference in any growth parameter at 1 year or difference in morbidity.(Kuschel et al., 2000) Ziegler suggests that feeding volume should be increased until the infant shows signs that GI capacity has been reached, then kept at that volume through daily adjustment of the feeding volume.(Ziegler et al., 2007, Ziegler et al., 2002) Restricting feeding volume until a weight plateau has been identified is the most common cause of growth delay.(Hay et al., 1999) It has been suggested that fortified human milk must be fed at approximately 180 mL/kg/d if ELBW infants are to achieve adequate growth, nutrient retention, and biochemical indices of nutritional status.(Hay et al., 1999) Multifactor supplementation may be required to meet nutritional goals, especially if feeding volume must be restricted for some reason (e.g. pulmonary disease).

Implementation Strategies:
- Daily monitoring of feeding volumes
- Automate calculations of feeding volumes and calories

Barriers:
- Reluctance to go above previous recommendations of 150 mL/kg/d
- Effort to calculate feeding volumes
- Reliance on feedings by the clock rather than relying on early infant clues (i.e., fussiness or excessive pacifier use)

Measurement:
- Chart review for serial recording of feeding volume

Best Practice # 3.4: VLBW infants fed human milk should be supplemented with protein, calcium, phosphorus and micronutrients. Multinutrient fortifiers may be the most efficient way to do this when feeding human milk. Formula fed infants may also require specific caloric and micronutrient supplementation.

> Multicomponent fortification of human milk is associated with short-term improvements in weight gain, linear and head growth. Despite the absence of evidence of long-term benefit and insufficient evidence to be reassured that there are no deleterious effects, it is unlikely that further studies evaluating fortification of human milk versus no supplementation will be performed. Further research should be directed toward comparisons between different proprietary preparations and evaluating both short-term and long-term outcomes in search of the "optimal" composition of fortifiers.(Kuschel and Harding, 2004)
>
> Kuschel & Harding, 2004

Rationale: Studies have repeatedly demonstrated that protein and multinutrient fortification of human milk is associated with short-term growth advantages (weight, length and head circumference) for infants < 34 weeks gestation or birthweight <1800g when fortified human milk is given both during and after the infant's initial hospitalization.(Kuschel and Harding, 2004, Schanler, 1998, Schanler, 2003, Schanler, 2005b) In addition, VLBW infants grow faster and have higher bone mineral content up to 1 year of age if provided with additional nutrients, especially protein, calcium and phosphorus.(Friel et al., 1993, Lucas et al., 1992a, Wheeler and Hall, 1996b, Worrell et al., 2002)

However, exclusively breastfed former preterm infants tend to "catch-up" if given sufficient time (2-8 yrs).(Backstrom et al., 1999, Morley and Lucas 2000, Schanler et al., 1992) Although a weight gain of greater than 15 g per day is currently recommended, the optimal growth rate (reference target) has not yet been established for post-discharge preterm infants. It is unclear whether the rapid catch-up growth seen with aggressive supplementation is of benefit or harm for long term overall health, growth and neurodevelopment.(Griffin, 2002, Hall, 2001)

Fortification of breastmilk should be initiated well before a full feeding volume is reached (Ziegler 2002, Lee 2003).(Lee et al., 2002, Ziegler et al., 2002) Studies of feeding types and their advancement have usually started fortifiers at enteral feeds of 100 mL/kg/d, but there is no research to suggest that starting earlier (50-75 mL/kg/day) is harmful. Also, many studies do not specify whether "full" fortification (1 packet powder per 25 mL EBM) or "half" fortification is used to start. There is no research as to how fast to "advance" fortification, but multiple studies demonstrate no increase in feeding intolerance or NEC with multinutrient fortifiers.(Kuschel and Harding, 2004, Lucas et al., 1996, Moody et al., 2000, Schanler et al., 1999b) Care must be taken that large doses of multiple additives do not raise the osmolality of breastmilk (or formula) to unacceptable levels.(Srinivasan et al., 2004) Although increasing the osmolality of breastmilk

with fortifiers can delay gastric emptying and intestinal peristalsis, trials of nutrient fortification of breastmilk have not found any evidence of an increased incidence of feeding intolerance or NEC.(Fenton, 2006, Kuschel and Harding, 2004) As no formula powders made today are “commercially sterile”, the CDC has recommended that powdered infant formulas be used in the NICU only if no other method of fortification is appropriate for that infant. (Centers for Disease Control and prevention, 2002a, American Dietetic Association (ADA) and Pediatrics Nutrition Practice Group, 2004)

VLBW infants fed human milk can benefit from vitamin supplementation, most specifically vitamins A, C and D. Most NICU’s provide such supplementation in the form of a multivitamin solution, 1 mL/day, which may be divided into twice daily dosing for extremely premature infants and for those who do not tolerate full doses. Patients with, or recovering from, cholestasis may also required additional fat-soluble vitamins (A, D, E, K).

Vitamin E supplementation may increase hemoglobin production and decrease the incidence of IVH, but aggressive intravenous administration has been associated with increased sepsis.(Brion et al., 2003) True Vitamin E deficiency has been associated with hemolytic anemia in prematures, however such a severe deficiency is exceedingly rare. Vitamin E supplementation (50 IU/day) did not reduce anemia or transfusion requirements for VLBW receiving erythropoietin.(Pathak et al., 2003) The AAP currently recommends that preterm infants (<1000 gm birthweight) receive 6 –12 IU/kg/day enterally, which may be supplied either by preterm formula or by supplementation of human milk.(American Academy of Pediatrics Committee on Nutrition, 2004a) It is also possible to measure vitamin A and E levels to use as a guide for supplementation of these vitamins. However, as clinical presentations do not consistently correlate with such levels, and the laboratory tests themselves vary in clinical relevance, we can find no evidence-supported basis for following such levels.

Iron supplementation should be given to VLBW infants fed human milk at a dose of 2 mg/kg/d starting at 1 month until 12 months of age.(American Academy of Pediatrics Committee on Nutrition, 2004a) Multivitamins with iron contain 10 mg/mL, which is adequate for supplementation. VLBW infants receiving most or all of their feedings from infant formulas should not require additional iron supplementation when intake is 180 mL/kg/day. Preterm and term infants receiving recombinant erythropoietin require supplemental iron, up to an additional 4-6 mg/kg/day. Folate supplementation, usually dosed at 50 mcg p.o. daily, may increase serum folate levels in prematures, however the clinical relevance of this remains unproven.

VLBW infants are at significant risk for chemical and clinical osteopenia due to inadequate calcium and phosphorous intake, dysfunctional vitamin D metabolism and/or excessive renal losses of these minerals (which may be exacerbated by

diuretics, especially furosemide). In one series, over half of infants with a birthweight < 1000 g and nearly 25% of those with a birthweight < 1500 gm. had radiographic evidence of rickets.(Backstrom et al., 1996) Nutritional screening usually includes testing for these minerals.

VLBW infants receiving breastmilk that is fortified with commercially available products receive additional calcium and phosphorus, in a quantity associated with improved growth.(Kuschel and Harding, 2004, Wauben et al., 1998) Babies considered to be osteopenic may need to be supplemented with calcium and phosphorus, although the effect of such supplementation on bone density remains unproven.(Faerk et al., 2000) Similarly, supplementation of a premature infant's diet with vitamin D beyond 200-400 IU/day has not been found to increase later bone density.(Backstrom et al., 1999)

Protein nutritional status indicators are lower in infants fed unfortified human milk than with preterm formula or fortified human milk. (Atkinson et al., 1981, Kashyap et al., 1990, Polberger et al., 1990) While the milk of mothers who deliver preterm has increased protein, IgA and sodium, the milk changes over the first few weeks to a composition similar to term human milk.(Schanler and Atkinson, 1999) Beyond that time, protein content continues to fall over the first six months of milk production which further compromises the adequacy of nutrients for the rapidly growing preterm graduate.(Saarela et al., 2005) Unfortunately the nutrient needs of the preterm infant, especially those less than 1500 grams, do not change nearly as fast. A recent study demonstrated that premature infants (EGA 26-34 weeks, birth weight 600-1750g) on adjustable fortification (protein added to keep BUN 9 to 14) had significantly higher weight and head circumference gains than infants managed with standard multinutrient fortification.(Arslanoglu et al., 2006)

Consensus Recommendations for Enteral Intake for Stable Growing Preterm Infants. (American Academy of Pediatrics Committee on Nutrition, 2008, Tsang et al., 2005)

Element	**< 1000g**	**1000-1500g**
Water/fluids (mL/kg/d)	160-220	135-190
Energy (kcal/kg/d)	130-150	110-130
Protein (g/kg/d)	3.8-4.4	3.4-4.2
Vitamin A (IU/kg/d)	700-1500	700-1500
Vitamin D (IU/kg/d)*	150-400	150-400
Vitamin E (IU/kg/d)	6-12	6-12
Vitamin K (µg/kg/d)	8-10	8-10
Ascorbate (mg/kg/d)	18-24	18-24
Iron (mg/kg/d)	2-4	2-4
Zinc (µg/kg/d)	1000-3000	1000-3000
Folate (µg/kg/d)	25-50	25-50

Calcium (mg/kg/d)	100-220	100-220
Phosphorus (mg/kg/d)	60-140	60-140

Goal and max 400 IU/day

Implementation Strategies:

- Fortification should be used for all VLBW infants on breastmilk and may be started when enteral feeds reach 50-100 mL/kg/day.
- Every NICU should have a set of guidelines for supplementation of human milk. (**SEE APPENDICES 3-D1,2,3**)
- Supplemental iron should be provided to premature infants receiving breastmilk as well as all VLBW infants on erythropoietin
- Regular assessment of mineralization should be done for VLBW infants, with provision of appropriate supplementation when indicated
- Consider addition of protein to keep the BUN 9-14 (eg. Beneprotein powder)

Barriers:

- Lack of research specific to various types of fortification and timing of their start and advancement
- Fear of NEC due to alteration of human milk with fortifiers or other supplements
- Lack of inpatient neonatal/pediatrics nutritional services and expertise
- Lack of consistent unit-based nutritional practices

Measurement Strategies:

- Documentation of guidelines in use for fortification
- Documentation of compliance with guidelines
- Documentation of a nutritional monitoring schema for stable preterm growing infants
- Documentation that nutritional assessments are completed prior to discharge on infants with nutritional risk factors

SECTION 4: HUMAN MILK/BREASTFEEDING

Best Practice # 4.1: Educate & advocate for human milk for NICU infants.

Best Practice # 4.1.1: Obstetric, Perinatal, neonatal and pediatric professionals should have the knowledge, skills and attitudes necessary to effectively support the provision of breastmilk to the VLBW infant.

Rationale: With the Office of Women's Health, DHHS, CDC, AAP, AAFP, ACOG, NMA, ADA, NANN, ICEA, AWHONN, NAPNAP, NPA and many other organizations actively promoting and supporting breastfeeding, our families are becoming more knowledgeable about breastfeeding issues. They depend on us, the members of the healthcare team, for accurate, consistent information. Inconsistent, inaccurate information and lack of support by health care professionals have been cited as reasons for breastfeeding failure among many groups of mothers.(Ellis and Hewat, 1983, Winikoff et al., 1986, Winikoff et al., 1987, Raisler, 1993, Humenick et al., 1998) Unfortunately, some healthcare providers may not have not had the opportunity during training to gain the knowledge and skills needed to assess, support, and assist women reach their breastfeeding goals.(Ellis and Hewat, 1983, Freed et al., 1995a, Freed et al., 1995b, Freed et al., 1996, Freed et al., 1995c, Freed et al., 1995d, Freed et al., 1992, Humenick et al., 1998, Raisler, 1993, Winikoff et al., 1986, Winikoff et al., 1987, US Department of Health & Human Services, 1984, US Department of Health & Human Services, 1985, Office on Women's Health, October 2000) All perinatal care providers should be knowledgeable about the basics of lactation and their role in encouraging and managing breastfeeding. (American Academy of Family Physicians, 2002, American Academy of Pediatrics Section on Breastfeeding, 2005, American College of Obstetrician-Gynecologists, 2000)

Existing studies also suggest that nursing knowledge or attitudes can influence mothers' breastfeeding decisions in the NICU.(Jaeger et al., 1997, Bernaix, 2000, Wheeler et al., 1999, Kavanaugh et al., 1997, Kavanaugh et al., 1995) Significant increases in knowledge are possible with nursing education, but attitudes are more difficult to change.(Siddell et al., 2003) A recent study using a 4 hr nursing educational program demonstrated improved nursing lactation knowledge and attitudes, as well as maternally perceived breastfeeding-supportive atmosphere in the NICU, lasting at least 3 months.(Bernaix et al., 2008)

Despite adjustment for other significant variables, the site of care significantly influences breastmilk use at the time of discharge.(Powers et al., 2003) High breastmilk use sites tended to have physicians who openly expressed support for breastmilk use, nurses who facilitated breastmilk use and helped maximize breastmilk supply, and maternity nurses who conveyed the need for and expectation of breastmilk production while guiding mothers through the process. Low breastmilk use sites had physicians who had no position or were silent on

breastmilk use, had nurses who did not facilitate breastmilk use or help maintain maternal milk supply, and maternity nurses who avoided breastmilk issues and provided no guidance regarding breastmilk production.(Powers et al., 2002)

Obstetric and perinatal professionals should screen for risk factors for insufficient lactation or breastfeeding problems. Both general medical, social, psychological, environmental and breast-specific factors play a role in successful lactation. As with any physiologic process, historical or physical findings may signal potential or actual barriers to breastfeeding success.(Berens, 2001, Neifert, 2001)

Implementation Strategies.

Healthcare Provider Education:

- Hold regular CME, CEU and other inservices, both multidisciplinary and physician-only, re lactation issues.
- Make key resources (e.g. drugs & breastfeeding information, basic text or handbook) available in all care areas (hard copy and/or digital).
- Develop/test for competencies regarding breastfeeding knowledge and skills.
- Subsidize utilization of on-line breastfeeding management courses (www.umdnj.edu/lactweb, www.breastfeedingbasics.org, http://breastfeeding1.com, www.breastfeedingtraining.org , http://www.health-e-learning.com/).
- Utilize existing self instructional materials (e.g. Wellstart Lactation Management Self Study Modules- www.wellstart.org)
- Develop “scripts” for common or difficult situations.
- Designate a Director of Lactation as a resource person. The advantage to having a physician in this position is the added medical knowledge base, prescriptive ability and credibility of physician-to-physician communication.

Lactation Risk Screening

- Women should be screened for risk factors at the first prenatal visit by history and physical exam using a standardized format. **(See Appendix 4-H)**
- Continued risk screening (history and physical exam) should occur as appropriate during prenatal visits, especially if the pregnancy becomes complicated and early delivery is anticipated.
- Risk factors for insufficient lactation or other breastfeeding problems should be communicated to the perinatal and postpartum staff as well as the infant’s physician.

Barriers.

- Education alone will not change professional behavior. Attitudes of perinatal and neonatal staff should be addressed.
- The development, training and implementation of policies and procedures take time to become implemented and to become part of NICU culture.
- Adding another risk screen takes time. Standardized prenatal records may need to be amended to record feeding choice and risk factors.
- Physicians, nurses and other staff may not be aware of resources available when risk factors are encountered.

Measurement. Knowledge, clinical skills and attitudes must all be addressed.

- Use nursing /physicians surveys of lactation knowledge, skills and attitudes to guide incremental program planning.
- Is there a Director of Lactation?
- Are key resources immediately available to physicians and nursing staff?
- Process measures may help assure appropriate attention is being devoted to breastfeeding anticipatory guidance.
- Is there a risk-screening tool in the prenatal record?
- Patient survey regarding questions about breast surgery, breast enlargement during pregnancy and previous breastfeeding history taken.

Best Practice # 4.1.2: Mothers and families should be given accurate information about human milk for VLBW infants, and their decisions respected.

"Teaching the pregnant woman and her partner about childbirth and breastfeeding is an integral part of good prenatal care. ….The advice and encouragement of the obstetrician-gynecologist are critical in making the decision to breastfeed. …. The health benefits of breastfeeding warrant efforts in professional cooperation and coordination among all health care workers to educate and encourage women and their families to choose breastfeeding." (American College of Obstetrician-Gynecologists, 2000)

ACOG, 2000

The decision to breastfeed is usually made early in the pregnancy if not before.(Ekwo et al., 1983, Hill, 1988, Noble et al., 2003) Provider encouragement significantly increases breastfeeding initiation among women of all social and ethnic backgrounds.(Kuan et al., 1999, Lu et al., 2001, Miracle et al., 2004, Meier et al., 2000a, Sikorski et al., 2003a, Sikorski et al., 2003b, Taveras et al., 2003) Obstetric and family practice physicians, nurses and other staff are especially well placed to begin education, risk screening and anticipatory guidance regarding lactation.(American Academy of Family Physicians, 2002, American College of Obstetrician-Gynecologists, 2000) Counseling allows patients to become familiar with the fact that breastfeeding is best from a medical perspective.(Berens, 2001) Prenatal intention to breastfeed is one of the strongest predictors of initiation and duration of breastfeeding.(Coreil and Murphy, 1988, Donath and Amir, 2003, Dennis, 2002, de Oliveira et al., 2001) As breastfeeding is even more important for preterm/NICU patients than for term infants, physicians and other healthcare providers have a responsibility to provide accurate information of the consequences of a mother's decision, just as we do with recommendations regarding immunizations, car seats, bicycle helmets, fencing around pools, etc.

Antepartum hospital stays are opportunities for dispelling myths (e.g. "I can't

breastfeed because I have a premature infant.") and for providing anticipatory guidance regarding procedures to ensure a full milk supply and safe storage and use of pumped milk. After controlling for mothers' prenatal breastfeeding intentions, fathers' feeding preference, and demographic and psychosocial variables, a study by the CDC concluded that the mother's perceptions of her prenatal physician's and hospital staff's attitudes on infant feeding was a strong predictor of later breastfeeding. Adjusted analyses indicated that "no preference" regarding infant feeding by hospital staff was a significant risk factor for failure to breastfeed after 6 weeks.(DiGirolamo et al., 2003)

A meta-analysis of the impact of education on breastfeeding success identified trials and review articles by conducting a search of MEDLINE (1996-2001), HealthSTAR, the Cochrane Database of Systematic Reviews, the National Health Service Centre for Reviews and Dissemination Databases, and bibliographies.(Guise et al., 2003) They identified 30 randomized and nonrandomized controlled trials and 5 systematic reviews of breastfeeding counseling. Based on the review of evidence and meta-analysis, the task force found that:

- Overall, programs with key educational components (i.e., sessions that review the benefits of breastfeeding, principles of lactation, myths, common problems, solutions, and skills training) increased breastfeeding initiation and short-term duration up to 3 months. Education did not have a significant impact on long-term duration up to 6 months.
- Overall, support alone significantly increased short- and long-term breastfeeding duration but did not have a significant effect on initiation.
- The impact of education and support combined was not substantially different from that of education alone.
- There was insufficient data to determine the effectiveness of peer counselor programs.
- Written materials were not effective in increasing breastfeeding initiation or duration.
- Commercial discharge packs, often containing samples and coupons for formula, were associated with reducing the rates of exclusive breastfeeding.(Guise et al., 2003)

Obstetricians, pediatricians, family practitioners and hospital staffs often unintentionally undermine breastfeeding by providing formula company access to patients via commercial literature and formula marketing strategies such as baby clubs, gift bags and free formula. (Howard et al., 1994a, Howard et al., 1994b, Howard et al., 1997, Howard et al., 1993, Donnelly et al., 2003) Despite evidence to the contrary, breastfeeding is still perceived by some as a lifestyle choice, not a healthcare issue. Health care providers are afraid to "push" breastfeeding for fear of making mothers feel "guilty" if they do not breastfeed.(Wight, 2001b) Patient education materials and "gifts" are attractive and perceived as "free". In reality, formula prices include the costs of those materials and gifts in their pricing. Because marketing clearly influences

physician choice,(Wazana, 2000) the AMA, ACOG, AAP and other professional societies have developed ethical guidelines that recognize and advise how to mitigate the influence of pharmaceutical company marketing messages and gifts (nofreelunch.org).(American College of Physicians-American Society of Internal Medicine, 2002a, American College of Physicians-American Society of Internal Medicine, 2002b, Wazana, 2000, Lexchin, 1993) The AAP's policy statement "Breastfeeding and the Use of Human Milk encourages "…physicians to work actively toward eliminating hospital practices that discourage breast feeding (e.g. infant formula discharge packs…".(American Academy of Pediatrics Section on Breastfeeding, 2005)

Listening to the mothers themselves often generates effective support for breastfeeding in the NICU. A recent study interviewed 13 mothers of Swedish infants 2 to 6 months after their infants' discharge from the hospital.(Nyqvist and Kylberg, 2008) The interviews generated 13 steps (a modification of the Baby-Friendly Hospital Initiative "10 Steps"(World Health Organization and United Nations Childrens Fund, 1989)) which included: respect for mothers' individual decisions about breastfeeding, education of staff in specific knowledge and skills, antenatal information about lactation in the vent of a preterm birth, skin-to-skin care, breastmilk expression, early introduction of breastfeeding, facilitation of mothers' 24-hr presence in the hospital, preference for mothers' own milk, semi-demand feeding before transition to demand breastfeeding, special benefits of pacifier sucking, alternative strategies for reduction of supplementation, use of bottle-feeding when indicated, a family-centered and supportive physical environment, support of the father's presence, and early transfer of infants' care to parents.(Nyqvist and Kylberg, 2008)

Implementation Strategies.

- Patient education should begin during routine pre-pregnancy obstetric/gynecologic visits and continue through the pregnancy.
    - If a mother indicates a choice not to breastfeed, the reasons for that decision should be explored, as they are often based on misunderstanding of the value and challenges of breastfeeding.
    - Continued education should occur during prenatal visits, especially if the pregnancy is complicated and early delivery anticipated.
    - Specific anticipatory guidance should be provided if problems are discovered.
    - Mothers hospitalized with preterm labor or other complications should receive additional encouragement and education about breastfeeding.
    - Patients should be referred to appropriate, culturally competent, breastfeeding resources: breastfeeding classes; lactation consultants; mother-to-mother support groups.
    - Toward the latter part of pregnancy, patients should be instructed regarding potential barriers to breastfeeding that routine hospital care may place in their path, and suggested ways to resolve these barriers.
- Remove formula company influence **(See Appendix 4-I)**

  - No donation or sale of patient lists/contact information to formula or marketing companies (HIPPA).
  - Use non-formula company materials.
  - Remove formula "baby-club" materials in office.
- No discharge formula company marketing bags should be distributed. See http://banthebags.org/
  - Provide visual cues (artwork, posters, calendars) that actively support breastfeeding, e.g. AAP Breastfeeding Welcome Here posters (www.aap.org/advocacy/hcca/hccaposters.htm)
- Support breastfeeding patients and staff by providing space and supplies for pumping and breastfeeding.
- Nurses, physicians and other staff caring for either hospitalized or outpatient high-risk antepartum mothers should communicate the importance of breastfeeding to the mother and infant.
  - Hospitals should have videotapes, DVDs or closed circuit television programs delineating the "why" and "how" of providing breastmilk for preterm or ill NICU infants. **(See Appendix 4-A)**
  - Inventory all current educational materials (written, audio, video, DVD, etc.) for content and bias. Establish a mechanism for periodic review.
  - Neonatal prenatal consults should include discussion of the importance of a mother's own milk and the steps to be taken to assure a good milk supply.
  - Prenatal lactation consults should be available for both inpatient and outpatient high-risk patients.
  - The physician(s) in charge of the mother's care should reinforce the importance of breastmilk by inquiring about the mother's pumping or breastfeeding progress during routine post-partum care.
  - The first visit in the NICU with the neonatologist or pediatrician should include discussion of the value and benefits of human milk for the VLBW infant (with documentation in the medical record). Care should be taken to separate the decision to provide a few weeks of pumped breastmilk from the commitment to long-term, exclusive breastfeeding.
  - Physicians should find opportunities to praise mother's efforts to provide this "liquid gold" for their VLBW infant.
  - Preprinted or standing admission orders should include "Lactation Consultation for all VLBW infants."

Barriers.

- Despite evidence to the contrary, breastfeeding is still perceived by some as a lifestyle choice, not a healthcare issue.
- Health care providers are afraid to "push" breastfeeding for fear of making mothers feel "guilty" if they do not breastfeed.
- Communication about neonatal nutrition is not perceived as important or urgent as other acute care concerns, such as lung maturity or fetal malformation.
- There may be a lack of understanding of the importance of breastmilk for short and long-term outcomes of the VLBW infant.

- Providing access to relevant videotapes and DVDs maybe a challenge.
- Physicians are not in the habit of discussing infant nutrition in the immediate post-partum period.
- Assumption that someone else is responsible.
- Lack of awareness of potential impact.

Measurement. Measurement should focus on the timing, frequency, quality and extent of education given patients regarding breastfeeding.

- Does the prenatal record have a specific check box or blank regarding intention to breastfeed and education given?
- Patient survey re when breastfeeding 1st mentioned and how many times during pregnancy was it mentioned by physician and support staff.
- Survey of staff re attitudes towards breastfeeding as a health care issue. **(See Appendix 4-G)**
- Measurement methods should also call attention to the presence or absence of appropriate and inappropriate, direct and indirect, messages about breastfeeding.
- Have a plan to regularly inventory your educational materials, artwork calendars in the environment and office/hospital surroundings
    - Office and hospital scavenger hunt **(See Appendix 4-I)**.
- Review of policies and procedures regarding vendors and vendor materials in the environment.
    - Survey staff awareness of corporate compliance issues regarding vendor gifts.
- Periodic scheduled evaluation of these process variables will assist in identifying opportunities to educate and support the breastfeeding family.
- Presence or absence of appropriate audio-visual materials and written materials on breastmilk and breastfeeding for antepartum patients.
- Chart audit of 10 antepartum consults by neonatal service to determine if breastmilk use was discussed
- Is a Lactation Consult routinely ordered on antepartum high-risk patients?
- Chart audit of breastfeeding education for mothers during the antepartum period.
- Advocacy and facilitation are difficult to measure directly, but attention must be placed on increasing opportunities to discuss human milk for VLBW infants and documenting these interventions.
- Documentation of such discussions in the medical record by chart review.
- Presence of LC order on standing postpartum or NICU admission orders.

Best Practice # 4.1.3: Hospital policies and practice should support breastfeeding in a coordinated, consistent manner.

Rationale. Mothers of VLBW infants are less likely to breastfeed than mothers of healthy, term infants.(Ehrenkranz et al., 1985, Lefebvre and Ducharme, 1989, Meier et al., 1993, Yip et al., 1996, Bell and McGrath, 1996, Hill et al., 1997, Furman et al., 1998, Merewood et al., 2006a) Family members and health care

professionals sometimes discourage these mothers from initiating lactation as they think that providing milk will be an added stress.(Meier, 2001) Mothers may be advised, in error, that their medications preclude the use of their milk. Similarly, mothers may be inappropriately advised that their high-risk conditions may interfere with adequate volumes or composition of milk.

Mothers of VLBW infants often feel a loss of control of their lives and a loss of role as a mother. The infant is in the hands of strangers and she is the outsider. Several studies indicate that providing milk for their infants helps mothers cope with the emotional stresses surrounding the NICU experience and gives them a tangible claim on their infants. Providing breastmilk is something only the mother can do.(Kavanaugh et al., 1997, Spanier-MIngolelli et al., 1998) One of the most consistent complaints of mothers is the often confusing, contradictory advice they receive regarding lactation.

Implementation Strategies:

- All post-partum and NICU nurses should have a basic level of knowledge re lactation physiology and breastfeeding support, as evidenced by "competencies". **(See Appendix 4-F)**
- Breastfeeding supportive postpartum and nursery breastmilk policies and procedures should be in place for:
- Collection, storage and handling of mothers' own milk for hospitalized infants **(See Appendix 4-B)**
- Accidental feeding of the wrong mother's milk to an infant **(See Appendix 4-J)**
- Use of fresh and pasteurized donor human milk, as appropriate **(See Appendix 4-C and4-D)**
- Skin-to-skin (kangaroo care) **(See Appendices 5-A1 and 5-A2)**
- An NICU breastfeeding support committee or task force should be multidisciplinary, including physicians, nurses, dieticians, occupational therapists, pharmacists, lactation consultants, and, if appropriate, breastfeeding mothers.

Barriers:

- Misinformation on the part of families and staff regarding the efforts and rewards of breastfeeding an NICU infant
- Lack of nursing time
- Overspecialization of breastfeeding responsibilities

Measurement: Regular review of policies, procedures and competencies will assist in focusing attention toward areas for possible improvement.

- Do appropriate policies exist?
- Are all caregivers competent to provide needed education and support?
- Regular review of policies mentioned above in strategies.
- Education of staff on competencies
- Assessment and measurement of competencies

Best Practice #4.2: Mothers' milk supply should be established and maintained.

Rationale:

The Decision to Provide Milk. For a mother, the decision to provide milk for a VLBW infant is quite different from the decision to breastfeed a healthy, term infant. First, the decision is usually made based on health-related issues (i.e. The vulnerability of the infant puts him at greater risk of diseases from which breastmilk may protect him). Second, mothers who did not intend to breastfeed, often decide to pump, while not planning to feed at the breast.(Meier, 2003, Meier et al., 2000a, Meier and Engstrom, 2007) Third, mothers are highly influenced by the advice of professionals who care for the infant, feeling thankful for (not coerced by) their guidance and even resentful if misinformed about formula being equally acceptable.(Miracle et al., 2004)

Contact with Infant. Visual and tactile contact with her infant allows the mother to recognize the "reality" of the birth and the need for provision of breastmilk. Early maternal-infant contact (<1 hour) is associated with increased initiation and duration of breastfeeding.(Righard and Alade, 1990, De Chateau and Wiberg, 1977a, De Chateau and Wiberg, 1977b, Salariya et al., 1978, Mikiel-Kostyra et al., 2002) Skin-to-skin care is associated with increased amounts of milk, longer duration of breastfeeding, and breastfeeding "success" .(Furman et al., 2002, Kirsten et al., 2001, Hurst et al., 1997, Bier et al., 1996, Anderson, 1991) Contact with her infant stimulates the maternal entero-mammary system. Antigens (e.g. viruses, bacteria, fungi) stimulate lymphocytes in a mother's intestine and respiratory tract, which then "home" to her breasts and there stimulate the production of specific antibodies, targeted against those antigens in the baby's environment. (Goldman et al., 1994, Goldman, 2007, Goldman et al., 1998, Groer and Walker, 1996, Hanson, 2004, Hanson et al., 1985, Kleinman and Walker, 1979) Skin to skin care has been shown to be safe and effective in promoting physiologic stability and breastfeeding in premature infants.(Kirsten et al., 2001, DiMenna, 2006) Contact may also facilitate bonding and attachment.(Kirsten et al., 2001)

Non-Pharmacologic Milk Stimulation. Non-pharmacological means to stimulate milk production include expressing milk while relaxed at the bedside (or in proximity to the infant),(Feher et al., 1989, Meier, 2001) skin-to-skin care (see above) and non-nutritive tasting at the breast.(Narayanan, 1990, Pinelli and Symington, 2005) In many nurseries skin to skin care in VLBW infant maybe practiced when the infant is stable on or off the ventilator.(Kirsten et al., 2001) Non-nutritive tasting may be accomplished while the baby is on nasal-CPAP.(Pinelli et al., 2001) These interventions may stimulate both prolactin and oxytocin as mothers become conditioned to readily let down with psychological and tactile stimulants. Psychological inhibitors of the neuroendocrine let-down reflex include fear, pain and embarrassment, while positive stimuli include the sight, sound or feel of the infant.(Newton and Newton, 1967) The average

pumped milk yield without letdown is less than 4% of available milk.(Mitoulas et al., 2002, Kent et al., 2003) The key to milk production is milk removal, which is partially dependent on the let-down reflex.

Early Use of Expressed Milk. Aside from the health advantages for the infant of initiating early feedings with colostrum, there are benefits for the mother and staff as well**.** The use of human milk for trophic feeds in VLBW infants is associated with improved milk production. The authors of this study suggest that this may be related to a subtle psychological benefit mothers experience in knowing their own milk is being utilized.(Schanler et al., 1999b) In addition, the use of human milk for the first feedings sends the important message to staff that preterm formula is not equivalent to human milk for this vulnerable population.

Expressing Milk. Early, frequent, and effective breastfeeding or pumping appears to be the most important factor in establishing normal lactation.(Furman et al., 2002, Smith et al., 2003b, Wooldridge and Hall, 2003) Prolactin bursts associated with the infant suckling or the mother breast pumping support the continued growth of secretory tissue in the maternal breast for several weeks or months after birth.(Cox et al., 1999) Initiating early pumping (within the first day) is associated with higher levels of milk production.(Bier et al., 1996, Flacking et al., 2003, Furman et al., 2002, Hill et al., 1999b, Smith et al., 2003b, Wooldridge and Hall, 2003) Recommendations for the ideal frequency of pumping (8-10 times every 24 hours) are based on the frequency of breastfeeding a term infant, but research has demonstrated most mothers pump 5-6 times per 24 hrs.(Furman et al., 2002, Morton et al., 2008) An individual mother may need to pump more or less frequently depending on her breast storage capacity and rate of milk synthesis.(Daly et al., 1996, Jones and King, 2005) **The object is to maximize each mother's milk supply while minimizing the the number of minutes per day she needs to spend on milk expression.**(Jones and King, 2005, Jones and Spencer, 2007)

Mothers who deliver prematurely are often unprepared and perhaps too medically compromised themselves to assume primary responsibility for acquiring the information and equipment to manage timely initiation of pumping.(Hill et al., 2005c, Hill et al., 2006) Pumping and providing milk also contributes to the physical and emotional recovery of the mother.(Kavanaugh et al., 1997) Therefore, the hospital staff is integral to the initiation of pumping and establishment of a regular pumping schedule. An organized care system needs to automatically provide assistance with, and remove obstacles to, establishing a consistent pumping routine.(Wight et al., 2008)

The most important determinant of the exclusivity and duration of breastfeeding for the mother-infant dyad is the volume of milk produced which typically plateaus by 1-2 weeks postpartum.(Neville et al., 2001) The average baseline milk production on days 6-7 postpartum is highly predictive of adequacy of milk volume (defined as 500 mL/d) at 6 weeks post-partum.(Hill et al., 2005a)

Mothers of preterm infants were 2.8 times more at risk of not producing adequate milk than term mothers who were fully breastfeeding, although a better comparison group would have been mothers of full-term infants who were exclusively pumping and not breastfeeding.(Hill et al., 2005a)

It is not clear to what extent, if any, preterm birth contributes to limitation of milk supply in mothers of VLBW infants. Lactogenesis I (the hormonal preparation and growth of breast tissue) starts during pregnancy.(Neville et al., 2001) Some experts suggest that the mother of an extremely preterm infant may be at a disadvantage regarding milk production as she has not had the full time for breast growth and development. Based on the usual changes in lactogenesis II markers (milk citrate, lactose, sodium, and total protein), Cregan et al. (Cregan et al., 2002) concluded that 82% of preterm women had compromised initiation of lactation. Also, Lactogenesis II may be delayed in mothers of very preterm infants and affected by maternal steroid administration.(Cregan et al., 2002, Henderson et al., 2008) In one study(Chatterton et al., 2000) milk production in the first week of breast pumping was not related to gestational age. In other studies(Henderson et al., 2008, Hill et al., 2005a, Hill et al., 2005b) infant gestational age was inversely related to onset of lactogenesis II and milk volume.

Mothers of VLBW infants typically must express milk for several weeks before the infant can be put to breast, and for several weeks after discharge, before full exclusive breastfeeding is achieved, if ever.(Furman et al., 2002, Wooldridge and Hall, 2003) The initiation and maintenance of lactation for mothers of VLBW infants is best accomplished with a hospital grade, automatic-cycling electric "double" pump.(Hill et al., 1996, Slusher et al., 2004, Wight et al., 2008) "Double" electric pumps, enabling a mother to pump both breasts simultaneously, should be consistently available to the mother during her hospital stay and at discharge. In addition, staff should be available and committed to helping the mother establish a regular pumping schedule with this equipment. In contrast to sequential pumping, the double pump results in higher milk yield, reduced time, and a higher prolactin level.(Hill et al., 1996, Jones et al., 2001, Jones and Spencer, 2007)

Frequent pumping (8 times every 24 hours) with a hospital grade pump should begin within the first day, as soon after delivery as the mother is stable (not "recovered"). Early initiation of pumping (within the first 8 postnatal hours) results in higher prolactin levels and is more likely to yield the targeted goal of 20 ounces/day by 7-10 days.(Furman et al., 2002) The aim is to mimic the optimal breastfeeding stimulation provided by a healthy full term infant.(Neville et al., 2001) Because of lactation physiology a full milk supply must be established for the tiny preterm infant, just as it is for a full term healthy infant.(Hartmann et al., 2003) Just "keeping up" with the VLBW infant's needs is not sufficient, as the mother will be unable to call upon a larger milk supply when the infant's needs increase.

Massage & Manual Expression. Breast massage has been shown to improve milk production both in mothers who double pump (both breasts simultaneously) as well as those who pump sequentially.(Jones et al., 2001, Morton et al., 2007) Presumably, massage detects poorly emptied glandular tissue and facilitates milk removal. Effective emptying is critical to maximizing milk production and preventing engorgement and mastitis. Massage of the areolar-nipple area, immediately prior to pumping, may help stimulate a let-down reflex, a prerequisite to effective emptying. In one study, the continuous co-action of vacuum and compression stimuli in a novel breast pump seemed to enhance milk secretion.(Alekseev et al., 1998) Manual expression, used in conjunction with electric pumping, may facilitate the collection of small volumes of colostrum and help initiate milk flow when the breasts are engorged. Later, manual expression, when practiced synchronously with breastfeeding, may improve milk transfer from the breast to the baby.

A recent study of preterm mothers with infants less than 30 weeks, demonstrated a beneficial influence on milk volume in mothers who used two practices: hand expression of colostrum and "hands-on pumping" after lactogenesis II.(Morton et al., 2008) Despite pumping with the same frequency as other study mothers, those who used hand expression of colostrum more than 5 times per day in the first 3 postpartum days demonstrated sustained high output over the 8-week study. After lactogenesis II, mothers were taught "hands-on pumping". Instead of passively relying only on pump suction during the expression session, mothers were taught to use breast compression, massage, and, if needed hand expression. The overall increase in milk volume for 42 mothers was 63%. To achieve this, the mean duration of pumping sessions increased by 2 minutes. However, the longest unpumped interval (sleeping time) significantly increased, and the frequency of daily pumping decreased. By week 8, mothers who used frequent, early hand expression as well as hands-on pumping had a mean daily milk volume of over 950mL/day. The duration for expression ranged from 15 to 45 minutes, averaging 25 minutes, suggesting the risks in advising time limits.

Increasing Milk Supply. It is very common for a mother of a VLBW infant to have her milk supply decrease after 4-6 weeks of pumping, as she resumes her normal daily routine or returns to work.(Ehrenkranz and Ackerman, 1986, Hill et al., 1999a) Even if a full milk supply was never established, every effort should be made to help mothers of VLBW infants to maintain the supply they have. Returning to an increased pumping schedule (including night-time expression) s may be useful after evaluation of the mother's situation.(Wight and Montgomery, 2004) If impaired let-down is a problem, relieving pain with analgesics and topical treatment of sore nipples may help. Forcing fluids has been shown to have no benefit in increasing a milk supply.(Daly and Hartmann, 1995b, Daly and Hartmann, 1995a, Dusdieker et al., 1990, Stumbo et al., 1985) Mothers also need to be educated that they do not need to drink milk to make milk.

Many medications and herbal therapies have been recommended as

galactogogues (a material that stimulates the production of milk).(Dusdieker et al., 1985, Wight and Montgomery, 2004, Wight, 2001b, Anderson and Valdes, 2007) Growth hormone, chlorpromazine thyrotropin-releasing hormone,and sulpiride have all been shown to induce lactation.(Wight and Montgomery, 2004, Wight, 2001b) Metoclopramide (Reglan®) is the most frequently used in the United States due to its safety, efficacy, availability, and relative lack of side effects when compared to the other known galactogogues. A more recent randomized controlled trial of metoclopramide did not show any difference in milk supply from placebo.(Hansen et al., 2005) Domperidone (Motilium™) is widely used in Canada and Mexico and has fewer side effects because it does not cross the blood-brain barrier, but is not available in the United States.(da Silva et al., 2001, Hofmeyr et al., 1985, Petraglia et al., 1985) The most recent placebo-controlled RCT of domperidone use in mothers with insufficient milk volumes(Campbell-Yeo et al.) found an increase in breastmilk volume of 238% in the domperidone group vs. 14% in the placebo group. An incidental finding was a significant increase (62%) in breastmilk calcium in the domperidone group vs. a 4.4% decrease in the placebo group.

More than thirty herbs are considered to be powerful galactogogues.(Low Dog and Micozzi, 2005) Fenugreek (Trigonella Foenum-graecum) is one of the oldest medicinal plants, dating back to Hippocrates and ancient Egyptian times. As Fenugreek is a food additive, it is felt to be safe, although mothers' perspiration and milk often smells like maple syrup. Galactogogues are generally prescribed along with recommendations regarding the frequency and thoroughness of expression.

Monitoring Milk Supply. Ongoing monitoring of a mother's milk supply via a pumping log and lactation vital signs can provide opportunity for intervention before the milk supply is irretrievably low. Keeping a pumping diary of milk production is the equivalent to charting lactation vital signs in the mother of the VLBW infant. In centers with successful implementation of lactation support, a NICU-designed diary-log for mothers to record their pumping history cues mothers to visit, pump and hold their infants frequently.(Meier, 2001) Such charting, if regularly recognized by the NICU staff, may encourage pumping and skin-to-skin care. **(See Appendix 4-K1,2,3)**

Lactation Experts. Although all healthcare professionals who care for mothers and infants should have a general knowledge of lactation physiology and breastfeeding management, supporting the mother of a NICU infant often requires special knowledge, skill and experience. International Board Certified Lactation Consultants (IBCLC) are one method to assist in increasing breastfeeding rates in the NICU through staff and mother education, clinical consultation and support.(Baker and Rasmussen, 1997, Gonzalez et al., 2003, Kuzma-O'Reilly et al., 2003, Merewood et al., 2003) Lactation counseling by health care professionals for mothers of VLBW infants has been shown to increase the incidence of lactation initiation and breastmilk feeding without

increasing maternal stress and anxiety.(Sisk et al., 2006) In this study the most common reasons for stopping milk expression were low milk supply, returning to work or school, and inability to pump as needed. A recent study comparing NICU breastfeeding rates found breastfeeding rates at hospital discharge of 50% in hospitals with lactation consultants and 37% in those hospitals without lactation consultants.(Castrucci et al., 2006) In some units, well-trained NICU RNs and peer counselors may have the knowledge and experience to counsel and manage complicated NICU breastfeeding issues.(Meier, 2003, Meier, 2001) NICU peer counselors have been shown to significantly increase the odds of breastfeeding at 2, 4, 8 and 12 weeks after birth.(Merewood et al., 2006b) Postnatal peer counseling was also found to increase both exclusive and any breastfeeding of term LBW infants at 6 months.(Agrasda et al., 2005)

Implementation Strategies:

- Peripartum caretakers should begin a discussion, as appropriate, of provision of breastmilk as something only the mother can do.
- Develop practices and policies to encourage skin-to-skin contact. Such contact should be an expectation for the development of the parental-VLBW baby relationship.
- Those infants without immediate problems (e.g. borderline preemie, Infant of a Diabetic Mother, asymptomatic congenital anomalies) should be allowed skin-to-skin care and immediate post-partum breastfeeding, before being removed to the NICU for diagnostic or therapeutic procedures.
- All awake mothers should be given the opportunity to see, and if possible, touch, their ill infants prior to transfer to the NICU.
- Identify knowledgeable personnel who can assist positioning and supporting mother and baby
- Provide chairs (semi-reclining), space, and screens for privacy as requested
- Educate staff re the physiological and psychological benefits of skin-to-skin care
- Provision should be made for every mother separated from her infant to have access to an appropriate breast pump both at home and in the NICU post maternal discharge.
- Secure sufficient number of pumps to ensure access
- Hospital staff should be trained in acquiring pumps for women. (For a draft letter to justify insurance coverage **see Appendix 4-L1)**
- Develop a breast pump loan program for the first few weeks for those mothers with no other resources.(Philipp et al., 2000)
- Adjust the postpartum nurse/patient ratio to support breastfeeding care and to physically assist with pumping whenever needed.
- Nursing staff should determine who will be responsible for assisting the mother to initiate pumping (post-partum RN? NICU RN?) and who will be consistently be available to assist a newly delivered mother with pumping (NICU RN, postpartum RN?)
- Teach mother the adjunctive skills of manual expression and breast massage
- Identify skilled staff to demonstrate hand expression and breast massage to

mothers
- Utilize available handouts or videos which demonstrate this technique (e.g. A Premie Needs His Mother, J. Morton: **see Appendix 4-A)**
- Have equipment to collect small volumes
- Identify tools and methods of assuring complete collection and transport of small volumes of colostrum
- Improve staff and MD awareness of the importance of the numerous gastrointestinal and immunological effects of the use of colostrum.
- Establish policies and ordering practices that limit early feeds to colostrum/human milk. (Avoid orders such as: "maternal breastmilk **or** preterm formula…")
- Each mother's milk supply should be monitored continuously
    - Use a pumping log **(See Appendix 4-K1,2,3)**
    - Identify responsible care providers to assist mother with initiation and maintenance of pumping record
    - Milk supply as a "vital sign" to be monitored by the RN
- NICU staff members should be familiar with galactogogues which may be used or requested by NICU mothers **(SEE APPENDIX 4-M1,2 and 4-N)**
    - Establishment of communication and education with the mother's Obstetrician or primary care provider around issues of lactation.
- Provide appropriately educated and experienced experts to assist mothers and train staff
    - Hire or contract with an appropriately experienced IBCLC.
    - Train an existing NICU RN or RD to be an IBCLC or lactation resource person.
    - Train all NICU personnel to manage complicated lactation problems and issues.
- Develop guidelines for IBCLC/lactation resource person interaction as part of the multidisciplinary care team
    - Participation in multidisciplinary rounds and teaching rounds
    - Consultations and systematic follow-up
    - Creation and evaluation of patient literature
    - Education for other NICU staff
    - NICU breastfeeding support committee or program
    - Research as appropriate
    - Key lactation facts as part of RN "Kardex" or separate lactation "Kardex"
- If lactation consultants (LC) are used, LC's should "bill" (i.e. keep records of services performed) even if their services are not directly reimbursed at present.
- Maternal discharge educational and skills checklist.

Barriers:
- Misconceptions:
    - that pumping can be delayed without adverse consequences
    - that the mother is too sick
    - that mothers of VLBW infants can't produce as much milk as a mother of

full term infants
    - Unfounded concerns about perinatal maternal complications and medications related to the safety of breastmilk for the infant and pumping for the mother.
    - Misconception that lactation management is the responsibility of a small number of specialized providers (e.g. lactation consultants) or even the mother herself.
    - Failure to view pumping as integral to the mother's recovery and infant's outcome
- Lack of knowledge about lactation physiology
    - Inappropriate delay in focusing on nutrition until VLBW infant is stabilized
    - Staff lack of appreciation for the importance of small volumes
    - The desire to initiate trophic feeds regardless of breastmilk availability
    - Difficulty with collection and labeling of small expressed volumes
    - Lack of appreciation for the difficulty in achieving consistent, effective emptying with a pump, and the relationship between incomplete emptying and compromised production and/or mastitis
    - Lack of appreciation that mothers' milk supply is a priority in the normal care of a VLBW infant
        - No mention of milk supply on rounds
        - Not encouraging the use of a pumping log
        - Lack of a care plan
- Language barriers
- Financial
    - Buying or renting an effective breast pump may be beyond the means of some families and many insurance companies still will not cover breast pumps for mothers. Breast pumps readily available in discount stores may be low cost and are typically ineffective. A loner/transitional pump may not be available.
    - Lack of adequate equipment
- Distance (mother in ICU or referral hospital)
- NICU-experienced lactation consultants (LC) are difficult to find in some areas. Given current NICU reimbursement methods, LC time may not be compensated.
    - Tendency to abdicate <u>all</u> lactation support to LCs, rather than appropriate training for all NICU staff.
    - Lack of time and skilled staff
- Under-appreciation of the physiological benefits of skin-to-skin care
    - Issues related to modesty
    - Privacy issues
    - Lack of space and chairs
    - Lack of uninterrupted time for maternal contact
    - Unwarranted anxiety of the physiologic stability of the infant during transfer to skin-to-skin care, diminishing the frequency and duration of sessions

Measurement:

Outcome Measures:

- What percent of informed mothers initiated pumping?
- What percentage of mothers is providing breastmilk at any given time?
- What percentage of infants is getting any/exclusive human milk at discharge?
- What percentage of VLBW infants receive colostrum as their first feed?
- What percentage of charts have mother's milk supply documented?
- Survey of maternal satisfaction with lactation education and support.
- Incidence and extent of skin-to-skin care.
- Periodic assessment of number (%) of mothers with inadequate milk supply after day 14 (< 350 mL/24 hrs)
- All mothers who need them have appropriate pumps?
- Time of mother's first pumping.

Process Measures:

- Is maternal-infant contact documented in nursing or medical record?
- Regular review of availability of appropriate pumps and supplies (including loaner pumps)
- Is there a facility in or near the NICU for mothers to use for pumping when they are visiting or is provision made for mothers to pump at their infant's bedside?
- Review all policies regarding human milk in the NICU – what is missing?
- One person designated to monitor discussion of milk supply on rounds
- Hours of availability of lactation support in the NICU and for mothers of NICU infants on the post-partum unit.
- Reimbursement for LC services
- Presence and utilization of a lactation documentation tool
- Availability of a personalized diary-log for mother
- Review infant's chart for notation of milk production
- Maternal education on manual expression, breast massage and colostrum collection documented?
- Are post-partum providers competent in helping mothers collect colostrum?
- Are NICU staff encouraging and willing to use even small volumes?
- If colostrum is not available in the NICU, is there an effort to contact the mother before providing alternatives?
- Review policies for visitation, skin-to-skin care, etc.
- Assess adequacy of bedside pumping equipment and appropriate chairs

Best Practice # 4.3: Human milk should be handled to ensure safety and maximal nutritional benefit to the infant.

Rationale: Although human milk has remarkable antibacterial properties, it is not sterile and should be handled and stored properly to maintain its nutritional, developmental and immunological potential, and prevent transmission of infection. (American Academy of Pediatrics Committee on Infectious Diseases,

2006, Human Milk Banking Association of North America, 2005, Tully, 2000) Storage in a monitored, appropriately controlled hospital freezer is preferred over storage at home whenever possible. The California Tissue Bank Licensing Act does not apply to the storage of a mother's milk for use for her own infant in the hospital (Ca Health & Safety Code §1648). Appropriate steps should be taken to ensure an individual mother's milk is given only to her own child, unless the milk has been heat-treated under standardized conditions.(American Academy of Pediatrics Committee on Infectious Diseases, 2006, Warner and Sapsford, 2004) Although the risk of transmission of infectious agents with a few feedings of another mother's milk is incredibly small, many families are quite concerned and need careful explanations and to see action being taken.

Mastitis is a complication for pump-dependent mammals and has been associated with irreversible compromise of milk production.(World Health Organization, 2000, Thomsen et al., 1984) In addition to increasing the frequency of emptying, prompt antibiotic treatment may protect milk production.(Thomsen et al., 1984, World Health Organization, 2000) Mothers need to exercise vigilance in examining themselves for areas in the breast which have not been well drained. Although usually not a problem for a healthy term infant or relatively healthy growing preterm infant,(Thomsen et al., 1984, World Health Organization, 2000) some extremely preterm or ill infants have been shown to acquire pathogens from human milk, usually streptococcus or staphylococcal species. (Arias-Camison, 2003, Bertini and Dani, 2008, Byrne et al., 2006, Dinger et al., 2002, Gastelum et al., 2005)

Implementation Strategies:

- Every NICU should have a policy regarding safe storage, handling and administration of human milk. (**SEE APPENDIX 4-B**)
- Every NICU should have a policy regarding misadministration of human milk i.e. a mother's milk given to the wrong infant **(SEE APPENDIX 4-J)**
- Mothers should be appropriately treated for mastitis should it occur. Discarding the milk from the affected breast is not recommended, except in unusual circumstances (**SEE APPENDIX 4-O: Handout "Mastitis in the Pump-Dependent Mother of a NICU or ICN Infant")**
- Although it is neither clinically necessary nor cost-effective to routinely culture all mothers' milk in the NICU, (American Academy of Pediatrics Committee on Infectious Diseases, 2006) appropriate evaluation of recurrent feeding intolerance, recurrent infection, or unusual infections should include a review of mothers' handling, storage and transport of milk, and possibly microbiologic assessment of the milk.

Barriers:

- Lack of policies regarding:
    - Misadministration of human milk
    - Safe storage, handling and administration of human milk
    - Evaluation of a mother when infectious transmission via breastmilk is

suspected
- Lack of knowledge regarding treatment of mothers mastitis
    - Reluctance of NICU staff to get involved in maternal medical issues
    - Lack of ready referral sources for maternal treatment

Measurement:
- Monitor misadministration cases for number and appropriate handling of the case
- Monitor cases of maternal mastitis and staff's awareness of treatment of mastitis

Best Practice # 4.4: Obstetric, perinatal, and neonatal professionals should counsel mothers when breastfeeding may be of concern or contraindicated.

Rationale. As important as breastmilk is to the VLBW infant, prenatal, perinatal, and neonatal care providers should be aware there are cautions and contraindications regarding use of an individual mother's breastmilk for her infant.(American Academy of Pediatrics Committee on Infectious Diseases, 2006, American Academy of Pediatrics Section on Breastfeeding, 2005, Hale, 2003, Lawrence and Pane, 2007, Lawrence and Lawrence, 2001) The physician will need to weigh the risks of using breastmilk from a mother with potentially transmittable diseases or medications against both the short-term and long-term risks of withholding breastmilk from the VLBW infant. Pharmaceutical manufacturers' inserts typically discourage breastmilk use, often due to lack of safety data and legal concerns. Similarly, discontinuing breastfeeding for a self-limited or treatable maternal illness deprives the infant of the maternal antibodies after having been exposed to that illness.(American Academy of Pediatrics Committee on Infectious Diseases, 2006) A drug that is not compatible with breastfeeding can often be changed to another drug that is compatible.(Anderson et al., 2003)

Current **contraindications** to receiving breastmilk in the USA:
- Certain maternal Illnesses(American Academy of Pediatrics Committee on Infectious Diseases, 2006, Lawrence and Lawrence, 2001)
- HIV/AIDS
- Human T-Lymphotropic Virus Type I & II
- Active tuberculosis in mother prior to treatment. Pumped milk may be used.
- Certain maternal medications(Hale, 2003, Hale, 2008, Lawrence and Lawrence, 2001)
- Anti-metabolite or cytotoxic medications (e.g. anti-cancer)
- I^{131}
- Drugs of abuse: heroin, cocaine, amphetamine, marijuana, and phencyclidine.(American Academy of Pediatrics Committee on Drugs,

2001, Hale, 2008) (See below for discussion of methadone, smoking, alcohol)
- Infants with galactosemia should not receive breastmilk.(Lawrence and Lawrence, 2001) Infants with the Duarte variant may receive *some* of their nutrition via human milk with careful metabolic monitoring.

Current medication concerns include diagnostic and therapeutic agents and non-prescribed substances. Most medications are safe for breastfeeding mothers and their infants.(Wight, 2007) As *not* receiving breastmilk carries significant risks for both mother and infant, recommending that a mother of an NICU infant stop providing her milk to take a medication is almost never required and should only be done as a last resort.(Wight, 2007) Most common maternal post-partum medications are not contraindications to breastfeeding or the use of expressed breastmilk for VLBW infants ((e.g. magnesium sulfate, tocoloytics, antihypertensives, pain medications, antibiotics). However, some medications may be preferred over others due to decreased excretion into milk, or experience with preterm infants (Hale, 2003, Hale, 2008, American Academy of Pediatrics Committee on Drugs, 2001, Wight, 2007)

Methadone is listed by the AAP as "usually compatible with breastfeeding", (American Academy of Pediatrics Committee on Drugs, 2001) regardless of maternal dosage. Milk yield was significantly decreased in **smoking** mothers of premature infants who initiated lactation by pump.(Hopkinson et al., 1992) Nicotine is present in human milk of women who smoke, but there is no evidence whether the nicotine presents a health risk to the nursing infant.(American Academy of Pediatrics Committee on Drugs, 2001) Mothers of VLBW infants should be advised (as with all mothers) to minimize or eliminate smoking. Although the AAP lists **alcohol** as "usually compatible with breastfeeding",(American Academy of Pediatrics Committee on Drugs, 2001) the consumption of alcohol during lactation deserves careful consideration because of potential effects on the VLBW infant and a wide range of intakes. More than occasional consumption should be discouraged.

Psychotropic Drugs are *not* contraindicated for breastfeeding mothers. They are listed by the AAP as "drugs for which the effect on nursing infants is unknown but may be of concern", but most have "none" listed as a reported or possible side effect.(American Academy of Pediatrics Committee on Drugs, 2001) Because concentrations in breastmilk differ, some medications are preferred over others. For a current, evidence-based discussion of various types of psychotropic drugs, see Hale, Hale and Berlin.(Berlin and Briggs, 2005, Committee on Drugs American Academy of Pediatrics, 2001, Hale, 2004b, Hale, 2004a)

Radioactive medications should be approached with caution. Most, but not all, radioactive substances can be used in breastfeeding mothers after withholding the milk for an appropriate period.(Hale, 2005) A useful website for

recommendations regarding specific radiopharmaceuticals is: http://neonatal.ama.ttuhsc.edu/lact/. Iodine is the only radioisotope that requires complete cessation of breastfeeding. **Radiocontrast agents** are composed of gadolinium for magnetic resonance imaging (MRI) and iodinated compounds for computed tomography (CT). Virtually no gadolinium passes into milk or is orally available to the infant. The few iodinated contrast agents that have been studied also appear safe due to minimal milk transfer and poor oral bioavailability. There is no need to pump and discard any milk after these procedures.(Hale, 2005, Wight, 2007, Chen et al., 2008)

Lactating women may be **immunized** as recommended for other adults to protect against measles, mumps, rubella, tetanus, diphtheria, influenza, Streptococcus pneumonia infection, Hepatitis A, Hepatitis B, and Varicella.(American Academy of Pediatrics Committee on Infectious Diseases, 2006) If previously unimmunized or if traveling to a highly endemic area, a lactating mother may be given inactivated poliovirus vaccine. Rubella seronegative mothers should be immunized during the postpartum period.(American Academy of Pediatrics Committee on Infectious Diseases, 2006)

Certain maternal infectious diseases may pose challenges to breastfeeding or the utilization of expressed milk in the NICU. Infants of women with **Hepatitis B Virus** (HBV) should receive HBIG and HB Vaccine within the recommended time period. The medications do not need to be given before breastfeeding is initiated.(American Academy of Pediatrics Committee on Infectious Diseases, 2006) Mothers infected with **Hepatitis C Virus** (HCV) should be counseled that transmission of HCV by breastfeeding theoretically is possible but has not been documented. According to current guidelines of the US Public Health Service, maternal HCV infection is not a contraindication to breastfeeding. The decision to breastfeed should be based on informed discussion between a mother and her health care professional.(American Academy of Pediatrics Committee on Infectious Diseases, 2006) Infants of mothers with active **Varicella-Zoster Virus** (VZV) may breastfeed after mothers are no longer infectious. The infant may require VZIG. Expressed breastmilk may be given to the infant if no skin lesions involve the breasts and the infant has received VZIG.(American Academy of Pediatrics Committee on Infectious Diseases, 2006, Lawrence and Lawrence, 2005) Milk supply should be established and maintained while mother and infant are isolated.

Infants of mothers with **measles** should be given IG and may breastfeed when the mother is no longer infectious (72 hrs after onset of the rash). The breastmilk may be pumped and given to the infant.(Lawrence and Lawrence, 2005, American Academy of Pediatrics Committee on Infectious Diseases, 2006) Women with **Herpes Simplex Type 1** lesions on their breasts should refrain from breastfeeding or feeding expressed breastmilk from the affected breast until the lesions have healed. Active lesions elsewhere should be covered during

breastfeeding, and careful hand hygiene should be used. Women should be encouraged to pump until lesions are clear, so milk supply is not interrupted.

Cytomegalovirus (CMV). "Infants born to CMV-seronegative women who seroconvert during lactation and premature infants with low concentrations of transplacentally acquired maternal antibodies to CMV can develop symptomatic disease with sequelae from acquiring CMV through breastfeeding. Decisions about breastfeeding of premature infants by mothers known to be CMV seropositive should include consideration of the potential benefits of human milk and the risk of CMV transmission. Pasteurization of milk seems to inactivate CMV; freezing milk at -20C (-4F) will decrease viral titers but does not reliably eliminate CMV".(American Academy of Pediatrics Committee on Infectious Diseases, 2006) **(For more complete discussion see Section 7.3)**

Implementation Strategies

- A current, reliable reference for drugs and breastfeeding should be immediately available in all antepartum, perinatal and post-partum areas, especially the NICU. The PDR is NOT a reliable reference. Recommended references are:
  - Thomas W. Hale R.Ph, PhD, Medications and Mother's Milk (updated every 1-2 years), available at www.ibreastfeeding.com
  - Lawrence and Lawrence, Breastfeeding: A Guide for the Medical Profession 6th Ed, 2005
  - Briggs, G.G., Freeman, R.K., Yaffe, S.J.Drugs in Pregnancy and Lactation, 6th Ed, 2005, Baltimore, MD, Williams-Wilkins
  - US Drugs and Lactation Database: LactMed, available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
  - The current edition of the Report of the AAP Committee on Infectious Diseases should also be available in the NICU or on-line.
  - Nursing competencies should include information on maternal illnesses and medications and human milk.
  - Infection control policies and procedures should include information and recommendations regarding breastfeeding and expressed human milk.

Barriers:

- It is often easier to proscribe breastmilk than to research current recommendations.
- Physician knowledge in this area is often outdated.
- There is a lack of familiarity of where to turn for resources.
- There is inadequate documentation of safety for newer drugs.

Measurement: Measurement should focus on efforts to use mothers' milk safely for the VLBW infant.

- Inventory of availability of resources: Are appropriate references available in key antepartum, perinatal, post-partum and NICU areas?
- Survey staff to assess their awareness of resources.

- Are infectious disease/isolation policies consistent with current breastfeeding policies, and up to date with current references?
- Is there a consistent policy as to when breastmilk is allowed to be discarded and those reasons are documented?

SECTION 5: TRANSITION TO ORAL FEEDINGS

Best Practice #5.1: Infants should be transitioned from gavage to oral feedings when physiologically capable, not based on arbitrary weight or gestational age criteria.

Rationale: Nyqvist and colleagues(Nyqvist et al., 1999) and Lau(Lau, 2006) have described the development of preterm infants' breastfeeding behavior in detail. Irrespective of gestational age, infants demonstrated rooting and sucking behaviors with the first contact at the breast.(Nyqvist et al., 1999) Infants should be transitioned to oral feedings when physiologically capable, not based on arbitrary weight or gestational age criteria.(Nyqvist et al., 1999, Lau, 2006, Lau and Hurst, 1999, Medoff-Cooper, 2000) Infants have been shown capable of breast or bottle-feeding much sooner than previously believed, with some breastfeeding as early as 28 weeks, and achievement of full nutritive breastfeeding at 36 weeks.(Nyqvist et al., 1999, McCain et al., 2001, Nyqvist et al., 2001, Simpson et al., 2002, Nyqvist, 2001, Nyqvist, 2008) A recent study of 15 infants from Upsala, Sweden born at gestational ages of 26-31 weeks had breastfeeding initiated as early as 29 weeks corrected age, semi-demand feeding, and use of the PIBBS (Preterm Infant Breastfeeding Behavior Scale).(Nyqvist, 2008) Mothers roomed-in with their infants, performed the PIBBS scores, and did the tube and cup feeding in addition to breastfeeding. These infants achieved full, direct breastfeeding at a mean corrected age of 35 weeks (range 32-38 weeks).(Nyqvist, 2008)

Infants can be introduced to the breast (or bottle) as soon as the infant is deemed stable. An infant is deemed stable for the introduction of the breast or bottle when the infant does not have a persistent physiologic decompensation such as bradycardia or desaturation when handled, the infant is handling his/her own secretions, and shows sucking behavior on a finger, pacifier or the emptied breast. Introducing the infant to breastfeeding before introducing a bottle may facilitate breastfeeding. (Auer et al., 2004) There is current evidence that early attempts at oral feeding may facilitate more rapid maturation of sucking characteristics.(Pickler et al., 2006)

There is no reason to "test" a preterm infant on a bottle before offering the breast. Controlled studies confirm that breastfeeding infants have more stable oxygen saturations and body temperature as compared to bottle-feeding infants,(Blaymore Bier et al., 1997, Meier, 1988, Meier and Anderson, 1987) although less milk is transferred with breastfeeding.(Blaymore Bier et al., 1997, Martell et al., 1993, Meier and Brown, 1996, Furman and Minich, 2004, Meier, 1996) The mechanism for this improved stability with breastfeeding seems to be less interruption in breathing with breastfeeding. Bottle-fed preterm infants frequently do not breathe during sucking bursts – instead they breath rapidly during pauses in sucking. (Meier and Brown, 1996, Meier, 1996) In contrast, the same preterm infants integrated breathing within sucking bursts, approximating a

suck-breathe pattern of 1:1 as they reached 34-35 weeks gestation. It appears a self-paced(Lau and Schanler, 2000) or restricted flow(Lau et al., 1997) system improves duration and efficiency of oral feedings for infants with immature suck-swallow-breathe patterns.

Best Practice # 5.2: A definitive protocol for transition to oral feedings of human milk or formula does not currently exist. NICU healthcare providers should make use of safe techniques for which some evidence exists (skin-to-skin care, non-nutritive breastfeeding, test-weighing, alternate feeding methods) to effectively facilitate transition to full oral feeding.

Rationale: Skin-to-skin care has been shown safe and effective in promoting physiologic stability and breastfeeding in preterm infants.(DiMenna, 2006) It is the first step towards a mother being comfortable holding her preterm infant for feeding.(Wight et al., 2008) Kangaroo care (skin-to-skin care), non-nutritive breastfeeding (practicing breastfeeding on an "emptied" breast) and early introduction of the breast have been associated with increased breastmilk production and longer breastfeeding post discharge.(Furman et al., 2002, Kirsten et al., 2001, Hurst et al., 1997, Bier et al., 1996, Wight et al., 2008)

Test weighing, done by standard protocol, is a valid measure of intake at the breast and can be used to determine need for supplementation.(Scanlon et al., 2002, Meier et al., 1994) Mothers can test weigh accurately(Meier et al., 1994, Meier et al., 1990) and without stress, (Hurst et al., 2004) although there were no significant differences in infant weight gain over the first 4 weeks post-discharge between the infants who were test-weighed, and those who were not.(Hurst et al., 2004)

Transitioning directly from gavage to breastfeeding is possible, and seems to prolong both exclusive and any breastfeeding,(Kliethermes et al., 1999) but requires the mother to be continuously present, which may not be possible because of physical limitations of many NICUs and the mothers' own outside commitments. Mothers of preterm infants in the USA, in contrast to other countries (e.g. Sweden) are not expected or facilitated to remain with their infants to encourage earlier development of breastfeeding competence, or enable use of at-the-breast supplementation methods such as a supplemental nursing system. Transported infants' mothers may not be available for frequent feeding practice. The increasing use of individual room NICU care, enabling parents to remain with their ill infants, may facilitate earlier and increased direct breastfeeding.

Although research as to efficacy is limited, cup-feeding appears safe for preterm infants(Marinelli et al., 2001, Howard, 2003, Malhotra et al., 1999, Kramer et al., 2001, Schubiger et al., 1997, Lang et al., 1994) and may facilitate longer breastfeeding post-discharge(Collins et al., 2004) although may necessitate a somewhat longer hospital stay.(Collins et al., 2004) Clinical experience suggests other methods of feeding may be appropriate for specific infants, e.g. finger-

feeding for neurologically impaired, or supplemental nursing systems at the breast for mothers with insufficient milk supply.(Oddy and Glenn, 2003, Wolf and Glass, 1992) Nipple shields can be used, when appropriate, to maximize milk transfer at the breast.(Meier et al., 2000b) In the absence of good research, every effort should be made to accommodate mothers' preferences as long as appropriate weight gain is maintained.

Implementation Strategies BP # 5.1 and 5.2:

- Kangaroo care and non-nutritive breastfeeding policies and procedures should be available **(SEE APPENDIX 5-A1,2 and 5-B)**
- Policies containing corrected age or weight criteria for initiation of breast- (or bottle-) feedings should be revised based on the information above
- Have at least 1 electronic scale (accurate to 1-2 g) and a protocol available for pre-post breastfeeding test weighing **(SEE APPENDIX 5-C1,2**)
- Nipple shields in various sizes should be available for use in the NICU as appropriate
- Policies and procedures, education, and competency verification, should be available for all feeding methods **(SEE APPENDIX 5-D1,2)**
- Routine assessment by skilled providers of oral readiness

Barriers:

- Outdated policies that infants must prove they can feed by bottle, before being allowed to go to breast
- Over-reliance on a single feeding method for all infants
- Lack of maternal availability
- The pressure and desire to get preterm infants discharged home at the earliest possible date
- Varying expertise and comfort level of NICU nursing staff with alternate feeding methods
- Lack of substantive research on optimal feeding methods for preterm infants

Measurement Strategies:

- Survey of postnatal and corrected age at first kangaroo care, first non-nutritive breastfeeding, first nutritive breastfeeding
- Protocol availability for test weighing, non-nutritive breastfeeding and kangaroo care

SECTION 6: DISCHARGE PLANNING & POST-DISCHARGE NUTRITION

Best Practice #6.1: Nutritional discharge planning should be comprehensive, coordinated and initiated early in the hospital course. Planning should include appropriate nutrient fortification and nutritional follow-up.

Rationale: Discharge planning should be initiated upon admission to the NICU with an assessment of mother's breastfeeding goals and preferences.(Morton, 2003, Wight, 2003, Wight et al., 2008) Prenatal intention to breastfeed is one of the strongest predictors of initiation and duration of breastfeeding.(Coreil and Murphy, 1988, Donath and Amir, 2003, Dennis, 2002, de Oliveira et al., 2001) Due to the physiology of breastfeeding, milk expression should begin soon after the infant's birth. A full milk supply at discharge is one of the best predictors of successful breastfeeding post-discharge.(Furman et al., 2002, Wooldridge and Hall, 2003)

Many parents of VLBW infants perceive incorrectly that feeding problems are resolved pre-discharge, and that the infant will be able to breastfeed exclusively at discharge and thrive. If a rooming-in suite is available and parents are amenable, a 1 to 2 night stay before discharge can point out problems and maximize learning.(Wight, 2004, Wight et al., 2008, Morton, 2003) At present, however, there are no randomized controlled trials that address whether rooming-in prior to discharge is associated with higher exclusive or any breastfeeding rates, or better long term outcomes for VLBW infants.

Adequate nutrition during early infancy is essential for the overall well-being of the child and can have a major impact on long-term development. At the time of discharge, many VLBW infants have cumulative deficits in the accretion of energy, protein, minerals and other nutrients, resulting in higher nutrient requirements per kg of body weight than healthy AGA term infants. Preterm and small for gestational age (SGA) term infants carry a high risk for continued growth deficits, neurodevelopmental abnormalities, and behavioral problems.(Aggett et al., 2006) In a recent study of VLBW infants, postnatal growth pattern, rather than SGA status was significantly associated with neurodevelopmental outcome at 2 years of age.(Latal-Hajnal et al., 2003) However, increasing evidence also suggests that either low birth weight or rapid post-natal weight gain, or the combination of both, may predispose to adverse long-term effects, such as increased risk for hypertension, cardiovascular diseases, type 2 diabetes and osteoporosis in adulthood.(Aggett et al., 2006) On the other hand, the window for catch-up growth in human infants appears to be narrow: approximately the first year for head circumference and first 3 years in regard to final height. (Aggett et al., 2006, Eriksson, 2001, Gale et al., 2004, Victora et al., 2001) Bone mineralization improves somewhat more rapidly, with adjusted values reaching those of comparable healthy term infants between 6

and 12 months of age.(Fewtrell et al., 1999)

In theory, human milk is inadequate to support the nutritional requirements for the post-discharge VLBW infant. However, studies that evaluated the feeding of human milk after discharge found that despite slower early growth, human milk-fed LBW infants had development at least comparable to that of infants fed enriched formula from birth to 12 months corrected age, with a positive correlation between the duration of human milk feeding and the later Bayley mental Index.(Lucas et al., 2001, O'Connor et al., 2003, Wheeler and Hall, 1996a) Human milk feeding was also associated with a reduction in the number of readmission hospital days after discharge.(O'Connor et al., 2003)

At the time of discharge, when infants are allowed ad libitum intake, the intake varies widely, and varies inversely with caloric density.(Aggett et al., 2006, Wight et al., 2008, Lucas et al., 1992b) In various studies, the use of preterm formula does not seem to have an advantage over the use of post-discharge formulas.(Aggett et al., 2006) A recently updated Cochrane review on the effect of energy- and protein-enriched formula for improving growth and development in preterm or LBW infants after discharge concluded there was little evidence of improved growth and development up to 18 months post-term.(Henderson et al., 2007c) There are no data from randomized controlled trials to determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development.(Henderson et al., 2007a) However, fortification of human milk has been demonstrated to have short-term growth advantages for preterm infants born less than 34 weeks or 1800 grams birthweight, when given both during and after initial hospitalization. (Griffin, 2002, Carver, 2005, O'Connor et al., 2003, Schanler, 2005c)

A recent randomized controlled pilot study of powdered formula added to half of an infant's intake of breastmilk over 12 weeks post-discharge found increased length in all intervention infants and increased head circumference in intervention infants born ≤ 1250 g.(O'Connor et al., 2008) There was also a trend toward higher weight in the infants fed fortified human milk. At 12 weeks after discharge, 71 ± 38% and 88 ± 15.4% of daily feedings in the control and intervention groups, respectively, were provided as human milk. The high percentage of infants still being fed human milk at 12 weeks post-discharge is credited to the high level of lactation support provided in the home.(O'Connor et al., 2008)

As hindmilk (the fat-rich milk at the end of a breastfeed) may have a two- to three-fold greater fat content than foremilk, hindmilk can be used to increase caloric intake if the mother's milk production is in excess of the infant's needs. Although one study demonstrated increased weight gain with short-term hindmilk fortification,(Valentine et al., 1994) a subsequent study showed no difference in weight, length, head circumference, mid-arm circumference or skin fold thickness after 28 days of hindmilk feeding.(Payanikli and et al, 2004) There were no

adverse effects on serum chemistries. Hindmilk may supply extra calories, but in most studies provides no clinically significant extra protein or minerals.(Valentine et al., 1994, Bishara et al., 2008)

In the week prior to discharge an individualized nutritional plan should be prepared in coordination with the neonatologist, lactation consultant, dietitian, and family. If possible, the plan should be reviewed with the post-discharge primary physician at the time of discharge. Post-discharge nutrition is a newly understood concern and many physicians may not be aware of the need for special diets and frequent visits to monitor growth and biochemical status.(Academy of Breastfeeding Medicine, 2004) The plan should be based on the skills of the infant, the mother's milk production, and the infant's nutritional needs, parenting skills and support, and should include provisions for making the transition to full breastfeeding.(Morton, 2003, Morton, 2002) Included in this plan should be the "type" of feeding, (unfortified human milk, fortified human milk, formula, combination, etc.), frequency of feeding, "amount" of feeding (measurement, test weights if necessary), "method" of feeding (breast, bottle, cup, feeding device at breast, gastrostomy tube, etc.), "adequacy of growth" based on in hospital growth and expected growth and plotted on growth chart (see table below), "adequacy of nutrition" based on in-hospital biochemical nutritional status, when feasible.(Academy of Breastfeeding Medicine, 2004)

All infants < 34 wks or < 1800 g at birth, and other larger infants with nutritional risk factors (CLD, short gut, neurologic impairment, etc.), should have a complete nutritional assessment prior to discharge. Experts have suggested this assessment should include both growth parameters (weight, length, head circumference) and biochemical measurements (phosphorus, alkaline phosphatase, urea nitrogen, transthyretin (prealbumin), retinol binding protein).(Academy of Breastfeeding Medicine, 2004, Griffin, 2002, Hall, 2001) Additional specific laboratory studies may be necessary for the larger, high-risk infant. If the infant is taking 160-180 cc/kg/day and growth parameters have been normal or improving on human milk alone for a week or more prior to discharge, human milk alone should provide adequate nutrition post-discharge.

If supplementation is necessary, the mother can directly breastfeed, but substitute post-discharge transitional formula for 1 to 4 feedings per 24 hours as needed, to reach growth and biochemical goals. Alternately, powdered transitional formula (e.g. NeoSure or EnfaCare) can be added as a fortifier to expressed breastmilk given in substitute for feedings at the breast. This should be tailored to the specific preparation and calculations must be done carefully by the nutritionist. Human milk fortifier and powdered preterm formula are not usually recommended post-discharge because the nutrient content is far too great for the infant at the time of discharge, is expensive, and is difficult to prepare correctly.(Academy of Breastfeeding Medicine, 2004) Multivitamins, dosed to deliver at least 1500 IU/day of Vitamin A, 20-70 mg/day of Vitamin C, and 400 IU/day of Vitamin D should be added at discharge. B

vitamins are also necessary for the former premie receiving unfortified human milk. A multivitamin preparation dosed at 1 mL/day will usually supply all of the above. If formula constitutes >50% of an infant's daily intake, the dose should be 0.5 mL per day. Multivitamin administration should be continued for at least 3 to 6 months, although the optimum length of use has yet to be determined. (Hall, 2001, Griffin, 2002, Wight, 2004, Wight et al., 2008)

At discharge, elemental iron should be continued/added at 2 mg/kg/day. If formula constitutes 50% of the diet, the dose should be reduced to 1 mg/kg/day.(Hall, 2001) When the multivitamin with iron preparation is stopped, the infant should be started on oral vitamin D drops or ACD vitamins to provide at least 200 IU per day until such time as the child is drinking sufficient milk to provide that amount of vitamin D.(American Academy of Pediatrics Section on Breastfeeding and Committee on Nutrition, 2003)

A repeat biochemical assessment has been recommended at 1 month post-discharge.(Academy of Breastfeeding Medicine, 2004, Hall, 2001) Some authors also suggest repeat biochemical assessments approximately every 2 months until at least 1 year corrected age. Follow-up should also be arranged with the dietitian as needed to adjust caloric, protein, and other nutrient intake.

Biochemical & Growth Monitoring for Premature Infants in the Post-Discharge Period (ABM Clin Protocol #12, 2004, www.bfmed.org) Level of Evidence: Expert Opinion	
PARAMETER	**ACTION VALUES**
Growth	
Weight gain	< 20 g/day
Length increase	< 0.5 cm/wk
Head circumference increase	< 0.5 cm/wk
Biochemical Markers	
Phosphorus	< 4.5 mg.dL
Alkaline phosphatase	> 450 IU/L
Blood Urea Nitrogen	< 5 mg/dL

Implementation Strategies:
- Standing order for lactation consultation and discharge planner to consult with mother upon admission to NICU
- Provide for rooming-in for a few nights prior to discharge if appropriate
- Develop a discharge plan with the parents and follow-up physician and provide a copy to both (**SEE APPENDIX 6-A and 6-B1,2**)
- A repeat biochemical assessment done at 1 month post-discharge may be helpful
- Follow-up may be arranged with the dietician 2-4 weeks post discharge, then as needed to adjust caloric, protein, and other nutrient intake

Barriers:
- Early discharge of the VLBW infant, before breastfeeding is completely established
- Assumption that breastfeeding needs to be addressed only immediately before discharge
- Lack of communication with the follow-up physician
- Lack of research to establish optimal growth patterns and feeding regimens for the post-discharge VLBW infant
- Inadequate diffusion of the emerging recommendations for nutritional surveillance post discharge
- Fear of non-payment for outpatient nutritional services

Measurement:
- Presence of a discharge nutritional plan as developed in concert with the parents and private physician (**SEE APPENDIX 6-Aand 6-B1,2**)
- As part of the dictated or computerized discharge summary
- As part of nursing discharge papers
- As a separate document prepared by the nutritionist
- Are nutritional assessments completed prior to discharge on infants with nutritional risk factor?

Best Practice #6.2: Mothers should be encouraged to eventually achieve exclusive breastfeeding after discharge while ensuring appropriate growth for the infant.

Rationale: In the US the average corrected age of preterm infants at discharge is 35-36 weeks and weight is 1800-2000 gm, but infants vary enormously in age, weight, medical condition and nutritional needs. In many parts of the world, preterm infants are discharged much heavier and older than in the USA and have therefore had much more opportunity to mature and learn to breastfeed. The multiple benefits of breastmilk and breastfeeding should not terminate at hospital discharge. Adequate support should be arranged to allow each mother to reach her breastfeeding goal while ensuring appropriate growth and nutrition for the infant. Exclusive breastfeeding without supplementation at hospital discharge is

not the primary goal for most ex-VLBW infants.

While the decision to provide milk for the preterm infant is frequently based on health concerns specific to the premature, the decision to continue breastmilk expression or direct breastfeeding may be more complicated. While mothers may be well informed about the health and developmental advantages, which are dependent on the duration and exclusivity of breastmilk feedings, they may be unable to transition to direct breastfeeding, and thus are more likely to abandon milk expression.(Smith et al., 2003b) Influential factors include foremost, milk production. Mothers are most likely to eventually succeed in transitioning their infants when they are exclusively breastmilk fed by discharge(Wooldridge and Hall, 2003) and the duration of human milk feedings is significantly longer for those who transition to breastfeeding vs. those who receive expressed milk. In one study(Smith et al., 2003b) the breastfeeding rates at 4 months of age for these two groups was 72% vs. <10%. Healthier infants with shorter hospital stays and singletons vs. multiples were more likely to be breastmilk fed for an extended duration.(Smith et al., 2003b, Flacking et al., 2003, Geraghty et al., 2004) The availability of post discharge assistance has inconsistently been demonstrated to be beneficial.(Lasby et al., 2004, Pinelli et al., 2001)

What is known (and not known) about strategies and tools to promote this transition? Prior to discharge, the majority of infants receive supplementary feeds (a feeding in place of a breastfeeding session and/or a feeding given in conjunction with a breastfeeding session). It remains unclear how the type of delivery system of these feeds, i.e. tube, cup or bottle, affects the long term likelihood of breastfeeding. Studies, which report an advantage with one method over another, have not controlled for milk production, and therefore may self-select mothers with copious production, already more likely to succeed.(Collins et al., 2004, Kliethermes et al., 1999) More specifically, in mothers with milk production less than approximately 500cc/day, the infant will have more difficulty accessing his entire feed at the breast, in contrast to the efficient, high flow rate of other systems, such as the bottle.(Blaymore Bier et al., 1997, Furman and Minich, 2004) Strategies to protect milk production must be integral to the discharge plan. Keeping milk production ahead of infant requirement allows the infant a faster rate of flow and therefore an advantage in effective milk transfer.

Continue pumping:

Mothers should continue to pump to maintain milk supply for at least 1 to 2 months post-discharge. A common mistake is to advise the pump-dependent mother to stop pumping and just breastfeed. As the hospital-grade electric pump is typically more effective in milk removal than the infant, and the infant more successful in milk transfer when the flow rate is high,(Schrank et al., 1998) “triple feeding” (breastfeeding for a limited time, complementing by expressed milk or formula, then pumping) may be an acceptable initial and temporary option. When the volume of supplementation decreases, the mother can alternate between limited breastfeeds followed by supplementation and limited breastfeeds

followed by pumping. Initially, as small infants fall asleep at the breast due to fatigue rather than satiety, time limits of 20-30 minutes are advised. Once unlimited demand breastfeeding is undertaken, the frequency of feeding typically increases, while the pumping frequency can be tapered, dropping a session every 2 to 3 days.(Morton, 2003, Morton, 2002, Wight, 2004, Wight et al., 2008, Wooldridge and Hall, 2003)

Maximize skin-to-skin care:
Kangaroo care should be continued after discharge home. The multiple benefits of so-called "kangaroo care", even in limited sessions, include improved milk production and faster transitioning to direct breastfeeding.(Blaymore Bier et al., 1997, Hurst et al., 1997) Although medical centers in advanced countries encourage this skin-to-skin contact for restricted periods, in its country of origin, Columbian mothers are taught to literally "wear" their infants, in an upright position between the breasts, with a blanket swaddling the mother's chest and infant together. In a center where 93% of infants are breastmilk-fed at discharge and 80% have established full breastfeeding at a mean post menstrual age of 36.0 weeks (33.4-40.0 weeks), the time spent holding and feeding the infant was highly correlated with developing competency at the breast.(Nyqvist et al., 1999, Flacking et al., 2003) It would seem that, in some respects, this intimacy addresses the developmental needs of infants who do not receive the "holding" of the 3rd trimester. In a recent randomized controlled trial of kangaroo care vs. standard nursery care in preterm infants of 32-36 weeks and 1300 to 3000 grams, kangaroo care dyads breastfed significantly longer (5.08 vs. 2.05 months, p=0.003) and more exclusively at each measurement (p=0.047).(Hake-Brooks and Anderson, 2008)

Provide mothers with tools to assess milk intake:
Test weighing pre- and post-breastfeeding enables mothers of preterm infants to quantify milk intake without increasing their stress level or jeopardizing the success of breastfeeding.(Hurst et al., 1999, Hurst et al., 2004, Scanlon et al., 2002, Meier et al., 1994) Daily weight gains, averaging 15-30 gm/day may relax the need for frequent clinic visits. As the risk for under consumption is significantly greater in the preterm infant, who may not have the same reserves or behavioral cues as the term infant, close monitoring is critical. Other strategies involve giving mothers a 24-hour minimum intake goal.

Provide realistic time guidelines and frequent follow-up:
A recent study provides anticipatory guidance. During the first week home for a group of preterm infants (corrected age of 35-36 weeks), the mean milk intake at breast was approximately 1/3 of the total daily milk intake, with the remaining 2/3rd coming from expressed milk by bottle. By the end of week 4 at home, 2/3 of the total daily milk intake was at breast and 1/3rd from the bottle.(Hurst et al., 2000)

Routine primary care follow-up should be arranged as needed, usually 2-5 days

post discharge. The method of supplementation initiated in the hospital and agreed upon by mother, physician, nurse, and lactation consultant should be continued at home. Lactation follow-up should be scheduled for 2 to 3 days post-discharge and thereafter as needed until full direct breastfeeding is achieved, or the mother ceases breastfeeding.(Morton, 2003, Morton, 2002, Wight, 2004, Wight et al., 2008) Dietician follow-up is recommended for approximately 2 - 4 weeks post-discharge for both infant assessment and maternal nutrition counseling.

Breastfeeding educational and promotional efforts, as well as support groups, have been shown to improve breastfeeding rates in the hospital and at discharge.(Meier et al., 2004, Meier et al., 2007, Merewood et al., 2006b, Merewood and Philipp, 2003) "Graduate" mothers should be encouraged to continue to attend these support groups as they can both give and receive support and information. The mother should also be referred to other community nutritional and breastfeeding support resources such as Women Infant and Children (WIC), La Leche League International and other services locally available.(Morton, 2003, Morton, 2002, Wight, 2004, Wight et al., 2008)

Implementation Strategies:

- Establish a breastfeeding support group for mothers of inpatient and discharged premies
- Create a local resource list for mothers of preterm infants to include breastfeeding support resources
- Include referrals to breastfeeding resources on discharge instructions
- Ensure continued pump availability for every discharged mother/ infant dyad for at least 1-2 months post-discharge
- Provide families with written guide for breastfeeding ex-premature infants at home (**SEE APPENDIX 6-C – A guide for breastfeeding your premature baby at home**)
- Infants who are not breastfeeding at discharge will also need additional nutritional support

Barriers:

- Language barriers
- Equipment barriers
- Transportation barriers to follow-up
- Financial constraints to lactation and nutritional follow-up
- Insufficient milk volumes (< 500-600mL/d) to permit the premature easy access to maternal milk
- Maternal exhaustion, illness or multiple gestation
- Lack of appreciation about the usefulness of test weighing
- Staff may inappropriately recommend abrupt discontinuation of pumping
- Mothers may feel overwhelmed with care of a vulnerable preterm infant, especially if one twin remains hospitalized, or if another young child is having adjustment issues

- Inability to ensure the mother's access to medical support, e.g. for galactogogues or for mastitis treatment, to protect and augment her milk supply
- Family may have unrealistic expectations on how quickly infants transfer from supplemental feedings to exclusive breastfeeding
- Pediatricians may not be aware that the behavior of preterm infants may not match their expectations for term infants

Measurement:
- Attendance at breastfeeding support group
- Survey of VLBW discharged infants receiving any breastmilk at various times post discharge
- Percentage of VLBW discharged infants breastfeeding at various times post discharge
- Assess growth history, exclusivity of breastmilk feeds, and mode of feeds

SECTION 7: CONTROVERSIES/UNRESOLVED ISSUES

7.1: Prebiotics and Probiotics.

Probiotics are live microbial feed supplements that beneficially affect the host by improving the microbial balance of the host (Fuller, 1989). The establishment of the intestinal microflora takes place quickly after birth and is an essential part of lifelong health of the individual (Hallstrom et al., 2004, Benno et al., 1984). Premature infants have been shown to have disturbances in the establishment of their intestinal microflora (Fanaro et al., 2003). These include a delay in bacterial colonization, reduction in total number of bacteria and reduced diversity of their microbiotic community. These effects may be attributed to the lack of contact with normal maternal flora, early antibiotic exposure, and limited use of human milk, especially for the initiation of feedings (Parish and Bhatia, 2008). Systemic antibiotics can heavily affect the anaerobic population of microbes in the large intestine.

Probiotics have been extensively studied in several medical conditions, most notably diarrheal disease. Lactobacillus rhamnosus strain GG, which was originally isolated from human intestinal flora, is the most widely studied probiotic agent for adults and children (Gorbach, 2000). In pediatrics, probiotics have been demonstrated to be of benefit in a variety of disorders including diarrheal and immune mediated disorders (Vanderhoof and Young, 2005). Probiotics are efficacious in reducing the incidence of or preventing diarrheal illness in hospitalized infants (Saavedra et al., 1994), in formula fed infants in Peru (Oberhelman et al., 1999), in day care centers (Rosenfeldt et al., 2004) and in association with C. difficile (Pochapin, 2000). Probiotics are also effective in preventing antibiotic associated diarrhea (Vanderhoof et al., 1999) (Arvola et al., 1999) and as well lactobacillus has been demonstrated in randomized trials to reduce the severity and duration of rotavirus diarrhea (Isolauri et al., 1991, Guandalini et al., 2000). Oral probiotics have also been demonstrated to reduce the incidence of non-gastrointestinal infections (Hatakka et al., 2001, Weizman et al., 2005), as well as to decrease the frequency of antibiotic use in children with cystic fibrosis (Bruzzese et al., 2007).

Recent reviews in necrotizing enterocolitis (NEC) expound on the therapeutic potential of probiotic use in the reduction of NEC (Caplan and Jilling, 2000, Cucchiara et al., 2002, Reber and Nankervis, 2004). Probiotics have been studied in regard to the prevention of NEC in animals (Akisu et al., 2003, Caplan et al., 1999). Recent randomized trials have found that supplementing the diet of preterm infants with non-pathogenic “probiotic” bacteria, principally lactobacilli and bifidobacteria, reduces the incidence of NEC, nosocomial infection and mortality from all causes (Deshpande et al., 2007, Schanler, 2006, Lin et al., 2008, Samanta et al., 2008). Despite encouraging results of trials to date, questions of safety, including the risk of invasive infection with probiotics bacteria remain (Chauhan et al., 2008). The choice of probiotics is especially challenging, however, since some probiotic data using single agent therapy showed no effect

(Millar et al., 1993). Since the colonic flora is a balanced competition of over 400 different bacterial strains, greater emphasis in clinical research trials has been on poly-probiotic strategies (Collins and Gibson, 1999, Vanderhoof and Young, 2005). As yet, optimal strains and dose regimens have yet to be defined.

Prebiotics are non-living substances that beneficially affect the host by selectively stimulating the growth and activity of a limited number of bacteria in the colon thereby improving the health of the host. Human milk contains over 150 different prebiotics primarily in the form of oligosaccharides that are small sugar chains, typically 3 to 7 monosaccharides in length (Bode, 2006). Adding "prebiotic" oligosaccharides to formula milk can also help establish balanced GI microbial flora. These substances are naturally present in breastmilk, are not degraded by gastric acid, and support the growth of probiotics species in the GI tract (Chauhan et al., 2008). Supplementing formula milk with a mixture of galacto- and fructo-oligosaccharides stimulates intestinal growth of bifidobacteria similar to those found in preterm infants fed human milk (Boehm et al., 2002). Prebiotic related health benefits in preterm infants have not yet been demonstrated. While term formulas contain probiotics or prebiotics, current preterm formulas do not contain either. Continuing research needs to be done on the effects of prebiotics on intestinal flora, feeding tolerance and the risk of NEC in preterm infants.

In summary:

- Human milk is the preferred choice for preterm infants to promote the growth of a healthy microflora since it contains a multitude of different oligosaccharides that promote the growth of favorable bacteria such as bifidobacteria and lactobacilli.

- Therapeutic colonization of the preterm gut with the use of probiotics has the potential for reducing neonatal morbidity including necrotizing enterocolitis and its severity, but larger multicenter studies are required before instituting this practice.

- The addition of artificially synthesized probiotics to infant formula has shown some benefits for term infants but data for preterm infants is lacking.

- Clinical trials with prebiotics are required before establishing any recommendations.

7.2: Pacifiers.

In term infants, early (2-5 days) vs late (> 4 weeks) pacifier use has been shown to be detrimental to exclusivity and duration of breastfeeding in term infants. (Howard, 2003, Dewey et al., 2003) In preterm infants, non-nutritive sucking (NNS) has been associated with decreased hospital stay and faster transition from gavage to bottle feeding. (Pinelli and Symington, 2005) There is controversy about whether the use of pacifiers while gavage feeding is associated with more rapid gastric emptying and more rapid weight gain.(Premji and Paes, 2000)

Recent studies have not demonstrated any detrimental effect on short or long term breastfeeding rates in preterm infants.(Collins et al., 2004) Indeed, a preliminary study of a motorized "pulsating" pacifier seemed to accelerate the development of NNS and facilitate improved oral intake.(Barlow et al., 2008) When the mother is absent, a pacifier may be beneficial for soothing, when other techniques are not available or are ineffective. Pacifiers should not be used to delay feedings, even in anticipation of the mother's arrival. Crying in a term infant is a late sign of hunger .(American Academy of Pediatrics Section on Breastfeeding, 2005) A fretful infant expends calories better reserved for growth, and an exhausted infant is less capable of feeding at the breast.

7.3: Cytomegalovirus Transmission to Preterm Infants during Lactation

In our prior nutrition toolkits we have offered a formal review of the literature and recommendations for minimizing cytomegalovirus (CMV) exposure in breastmilk-fed very low birthweight (VLBW) preterm infants. Since 2005 there have been several excellent new papers and full reviews of the literature.(Hamprecht et al., 2005, Hamprecht et al., 2008, Lambeth, 2006, Lanari et al., 2008, Meier et al., 2005, Miron et al., 2005, Neuberger et al., 2006, Schanler, 2005a, Schleiss, 2006b, Schleiss, 2006a, Stranska et al., 2006, Stronati et al., 2007, Doctor et al., 2005, Kerrey et al., 2006, Knorr et al., 2007, Maschmann et al., 2006, Radi et al., 2007, Takahashi et al., 2007) Our prior references are contained within these newer references. Instead of repeating a literature review, we will present what is known and our current recommendations for minimizing CMV transmission to VLBW infants using the most current literature.

What is Known:

- Unseparated human milk has high intrinsic toxicity for CMV cell cultures.(Dworsky et al., 1982) (Earlier studies noted a lower rate of CMV transmission than current ones which use culture and DNA and RNA PCR techniques.)
- In contrast to results of earlier studies, milk cells do not play a predominant role in CMV transmission via breastmilk.(Hamprecht et al., 2003, Hamprecht et al., 2000)
- Infectious virus, viral DNA and RNA can be isolated easily from whole breastmilk and cell and fat-free milk whey. (Hamprecht et al., 2008)
- The incidence of postnatal CMV reactivation during lactation equals the maternal seroprevalence (virtually all CMV Seropositive mothers reactivate post-partum).(Hamprecht et al., 2008)
- The dynamics of CMV reactivation can be described by unimodal kinetics with interindividual variation.(Hamprecht et al., 2008)
- Most breastmilk becomes positive for CMV DNA 2 weeks after delivery.(Yasuda et al., 2003)
- DNA copy numbers increased to a peak at 3-6 weeks.(Yasuda et al., 2003, Vochem et al., 1998)
- CMV excretion into breastmilk declines to undetectable by 8-12 weeks

postpartum.(Yasuda et al., 2003, Hamprecht et al., 2008)
- Viral reactivation during lactation is a self-limiting, local (breast tissue) process.(Hamprecht et al., 2008)
- The transmission event takes place close to the maximum of viral DNA-lactia or virolactia, which normally coincide.(Hamprecht et al., 2008)
- The average “incubation period” from birth to the onset of symptomatic CMV infection is 47 days.(Hamprecht et al., 2001)
- The maximum viral load as well as viral genome copy numbers are significantly higher for a maternal transmitter (to the infant) vs. a non-transmitter.(Hamprecht et al., 2008)
- The most immature preterm infants (< 30 weeks and <1000g) are at the greatest risk of acquiring an early and symptomatic CMV infection.(Hamprecht et al., 2008)
- Sepsis-like-syndrome has been temporally-related to CMV detection in infants.(Kerrey et al., 2006, Knorr et al., 2007, Maschmann et al., 2006, Radi et al., 2007, Takahashi et al., 2007)
- In preterm infants positive for CMV, granulocytopenia, thrombocytopenia, elevated CRP and hepatic involvement were more frequent than in infants without evidence of CMV, but there was no difference in CLD, IVH, PVL, NEC, ROP > Grade 2, length of hospital stay, duration of mechanical ventilation, oxygen administration and head circumference and weight at discharge.(Neuberger et al., 2006)
- Limited data are available on the clinical long-term outcome of postnatally CMV-infected preterm infants, but suggest no increased risk for delay in neuromotor development or sensorineural hearing loss (over risks of prematurity). (Jim et al., 2004, Miron et al., 2005, Vollmer et al., 2004)
- Freeze-thawed breastmilk significantly decreases, but does not prevent CMV transmission or symptomatic disease.(Hamprecht et al., 2008, Maschmann et al., 2006, Takahashi et al., 2007, Buxmann et al., 2008) The viral titer at the time of freezing, not the length of time frozen, correlates with the risk of transmission.
- Pasteurization (62.5°C x 30 min) or high temperature short time (HTST: 72°C x 5 to 15 sec) destroy viral infectivity, but also alter the milk.(Hamprecht et al., 2004)
- An ideal, cost-effective method to remove CMV infectivity while preserving the important anti-infective, developmental and nutritional qualities of maternal milk is not currently available for clinical use.

Literature-Supported Recommendations:
General:
- The use of human milk for NICU infants should be continued.
- Established practice and guidelines for the prevention of CMV via blood products should continue.
- Breastfeeding or providing mother’s breastmilk for full-term infants and preterm infants with CMV seronegative mothers should continue without further laboratory investigation.

- The possible low risk of symptomatic CMV infection in the premature infant of a CMV-positive mother should be discussed with the mother and balanced against the known risks associated with lack of breastmilk use.
- The current frequency and nature of CMV infections in each neonatal unit should be tracked.
- CMV policies should be updated as new data become available.

Clinical:

- The mother's blood (CMV IgG) of all VLBW infants (< 1500 g or < 32 wks) admitted to the NICU should be screened for CMV serostatus. Maternal screening can be done on the high risk perinatal unit prior to delivery.
- All infants of CMV seropositive mothers should be screened for congenital CMV by culture or DNA PCR in urine, if the infant is to receive his own mother's breastmilk.(Lawrence, 2006)
- Appropriately pasteurized or HTST heat-treated human milk products may be used at any time without risk of CMV transmission.
- Fresh, refrigerated or frozen donor milk should not be used for VLBW infants unless the donor is CMV negative.
- Given the peak time of virolactia (and therefore transmission) of 3-4 weeks postpartum, colostrum (the first week of milk) may be used fresh or frozen.
- If the mother is CMV seropositive, freeze all maternal breastmilk for at least 24 hrs prior to feeding until the infant is > 32 weeks corrected age or feeding directly at the breast.
- Infants greater than 3 weeks of age with signs and symptoms consistent with CMV (respiratory deterioration, hepatitis, leucopenia, thrombocytopenia) or a sepsis-like syndrome should be evaluated for CMV:
- Quantitative plasma PCR for CMV
- Urine culture for CMV
- Review admission maternal CMV status and initial infant status if mother was CMV positive.
- An example of a suspected CMV infection control protocol is available in **Appendix 7-A**.

7.4: Use of insulin for hyperglycemia.

VLBW infants frequently do not tolerate "adequate" glucose infusion rates in the first week of life, leaving clinicians with three choices: (1) accept hyperglycemia, (2) restrict calories to avoid hyperglycemia, (3) use insulin to treat hyperglycemia. A clear best practice in this controversy has not been identified.

While most neonatologists would agree that glucose levels associated with significant glycosuria, and a concomitant osmotic diuresis, should be avoided, there is no consensus about milder levels of hyperglycemia. Most experts agree that glucose levels above 220 mg/dL should be avoided. Whether glucose

should be “tightly” controlled to avoid levels of 140-220 mg/dL remains entirely untested. There are data from both adult and pediatric intensive care units, which suggest a relationship between hyperglycemia and increased morbidity and mortality, although whether there is a causal relationship is still unknown.(Faustino and Apkon, 2005, Izquierdo, 2005, Ulate et al., 2008) At least some adult child ICU trials suggests that the use of insulin to maintain blood glucose tightly controlled in the 80-110 mg/dl range leads to reduced mortality and/or morbidity.(Ulate et al., 2008, Van den Berghe et al., 2006, van den Berghe et al., 2001)

A retrospective study suggested that while hyperglycemia with persistent glucose levels above 150 mg/dl occurs in more than 50% of ELBW infants, both morbidity and length of hospital stay were adversely effected by persistent hyperglycemia.(Hays et al., 2006) There is also reason to be concerned that protracted exposure of the VLBW infant to high glucose levels may “program” the infant’s glucose/insulin homeostasis system abnormally. (Farrag and Cowett, 2000, Schwitzgebel and Gitelman, 1998) Similarly, the possible link between *in utero* growth retardation and later diabetes raises serious concerns about the importance of maintaining normal glucose homeostasis.(Farrag and Cowett, 2000) Given the profound effects of a hyperglycemic environment of the developing fetus of a diabetic mother, there is reason to be concerned about protracted exposure of the VLBW infant to hyperglycemia.

Hyperglycemia is a significant problem in extremely low birth weight infants, with the degree of hyperglycemia apparently inversely related to birth weight.(Farrag and Cowett, 2000) The mechanism of this hyperglycemia is complex, and includes abnormalities in both glucose production and in insulin metabolism. In VLBW infants, gluconeogenisis is actually increased, and is relatively independent of serum glucose levels. The rate of glucose production appears to be inversely related to weight, with the smallest infants making the most glucose.(Keshen et al., 1997) At least part of the hyperglycemia seen in extremely low birth weight infants is due to decreased insulin production in the presence of high glucose levels. In addition, the very preterm infant has a decreased response to insulin.(Farrag and Cowett, 2000) The end result of this, and of possibly other mechanisms, is persistent hepatic glucose production despite high levels of circulating glucose.(Farrag and Cowett, 2000, Ziegler et al., 2002)

It is clear that insulin administration is an effective tool for decreasing serum glucose levels in VLBW infants.(Collins et al., 1991, Thabet et al., 2003, Vaucher et al., 1982) A study of term infants on ECMO suggests that insulin administration also improves protein balance.(Agus et al., 2004) A recent large randomized trial of VLBW infants comparing routine insulin administration to standard care during the first week of life showed no benefit of routine insulin.(Beardsall et al., 2008) In this study, there was a highly significant increase in the number of hypoglycemic episodes, and a borderline significant

increase in the 28 day mortality, in the routine insulin group. It is important to note that in this trial, infants in the control group could receive insulin, suggesting that insulin therapy is best used to target infants with persistent hyperglycemia despite "reasonable" glucose infusion rates, rather than as routine therapy in VLBW infants. It also suggests that extra caution must be taken to protect infants on insulin from hypoglycemia. Unfortunately, there are no data on the long-term effects of prolonged exogenous insulin administration to the VLBW infant on health later in life.

Ziegler recommends starting insulin if an infant is hyperglycemic while receiving > 6 mg/kg/hr of glucose, and discontinuing insulin if an infant is able to tolerate 50-60 kcal/kg/d of glucose without hyperglycemia.(Ziegler et al., 2002) However, this recommendation does not address the management of the infant who does not tolerate more than 60 kcal/kg/d of IV glucose, but who is not growing appropriately. We suggest that, with careful consideration and monitoring, insulin might be used with even higher glucose infusion rates if that is needed to provide good growth. In any infant for whom insulin is administered, care should be taken to avoid hypoglycemia.

7.5: Total Nutrient Admixture (TNA or "3 in 1" TPN)

Introduction

Total Nutrient Admixtures (TNAs), also called 3-in-1 or All-in-One solutions make use of the fact that under certain conditions the glucose/amino-acid solution may be mixed with intravenous fat emulsion and administered to the patient in one bag. These admixtures, commonly used in adults and pediatrics, have been successfully used by some NICUs under carefully controlled conditions using manufacturer and published data on emulsion stability specific for pediatric/neonatal amino acid formulations.(Bullock et al., 1992)

Potential benefits:

- Decreased risk of infection: Intravenous lipid emulsions promote bacterial growth and are a major determinant of coagulase negative bacteremia in very low birth weight infants.(Avila-Figueroa et al., 1998) In contrast, TNAs are a poor growth medium for most nosocomial pathogens and no better then D5/W.(Didier et al., 1998) The use of TNA is associated with decreased touch contamination—fewer breaks into the line with less manipulation of IV fluids. These factors decrease the risk of infection from lipid emulsions infused by TNA allowing the lipid to be infused over 24 hours, instead of 12 hours when lipid is infused separately.(Centers for Disease Control and Prevention, 2002b)

- Minimized volume of infusion: The lipid emulsion replaces all or most of the sterile water used to dilute the ingredients of parenteral nutrition solution, minimizing fluid administration while providing the desired fat, dextrose and amino acids.

- Improved delivery of fat soluble vitamins: TNA mitigates the adherence of fat soluble vitamins to the tubing and bag improving the delivery of retinol, vitamin D and tocopherol to the patient.(Baeckert et al., 1988, Dahl et al., 1994)
- Decreased cost: The primary source of cost saving is the improved use of fat emulsion (as single bottle may be used to produce several TNA). Additionally, the single-component delivery system reduces the I.V. equipment cost in half and decreases the nursing time required in administration.(Eskew, 1987)
- Convenience: A single I.V. site is required instead of the two needed for separate infusion of lipid. Small volumes of lipid are more easily administered over a 24 hour period.

Potential disadvantages:

- Opaque emulsion: The opaque emulsion inhibits visual inspection for particulate matter. However, the trained human eye is only capable of distinguishing particulate matter 50 µm in diameter or larger. The neonatal capillary diameter varies between 2-10 µm with the majority 3-5 µm. Particles greater than 3-5 µm may obstruct pulmonary capillaries and lead to pulmonary embolism. The greatest risk of particulate formation in admixtures occurs with calcium and phosphate salts.(Lumpkin, 1994) Although the TNA formulation may obscure the presence of precipitation, the opaque mixture is not the culprit. In fact, it is likely that the fat emulsion protects against calcium phosphate precipitation. If the proper concentrations of calcium and phosphate are added in the correct sequence and an inline filter is used, it is unlikely that pulmonary embolization will occur.(Driscoll, 1995)

- Disruption of lipid emulsion: In the United States, commercially available lipid emulsions contain anionic surfactant derived from a mixture of egg-yolk phosphatides. Negative forces at the surface confer stability to the fat emulsion by forming an energy barrier to coalescence. This stability can be disrupted by high concentrations of electrolytes, especially multivalent cations, and low pH allowing for coalescence of droplets. Although in vitro studies indicate that some of the droplets increase in size immediately after mixing a TNA, the practice of “Y’ing” 2-in-1 with lipid into 1 catheter has also been shown to lead to emulsion instability and droplet coalescence.(Murphy et al., 1996) Stable lipid emulsions have been defined physicochemically as emulsions in which < 0.4% of the fat particles are > 5 µm diameter. The physiologic significance of this definition is unknown.(Driscoll et al., 1995) Visual identification of emulsion destabilization is limited to two stages: creaming and coalescence. Creaming is a layer electrically destabilized lipid particles but their droplet identities are preserved. Creamed TNA emulsions are common and are generally safe for patient administration. Coalescence,

the terminal stage of emulsion destabilization, is associated with droplets 5 to 50+ μm and poses potential clinical danger. Visually, at this stage, yellow-brown droplets may be seen at or near the TNA surface. The presence of free oil in any form is considered unsafe for patient administration.(Driscoll, 1995, Driscoll et al., 1995) The dose of unstable fat globules capable of producing embolic syndromes is not known. The risk of inadvertent administration of unsafe fat globules can be significantly reduced by the use 1.2-μm air eliminating filter which has been shown to be able to trap enlarged and potentially dangerous lipid droplets without inducing instability in otherwise stable lipid droplets.(Driscoll et al., 1996)

Clinical Guidelines:

- Nutrient prescription: Ingredients should be carefully reviewed assure complete balanced nutrient formulation and components assessed for compatibility and stability based on the best available data from the literature and/or manufacturer.

- Compounding: The additive sequence in compounding should be optimized and validated as safe and efficacious. The combinations of ingredients used should be based on data showing the stability, compatibility and safety of the final formulation. When adding calcium and phosphate to the admixture, phosphate is added first. The TNA should be inspected closely for phase separation prior to and during administration.

- Quality assurance: Gravimetric and chemical analysis during the compounding process is recommended to assure a quality product. The sterility of the final product should be assured.

- Administration: If stored at room temperature, the TNA infusion should start with 24 hours of mixing or if refrigerated within 24 hours of rewarming.

- In line filtration: An inline air eliminating 1.2-μm filter is used with all neonatal TNAs (central or peripheral) and TNA is never infused without the filter. The filter may be replaced if plugged, however plugging of the filter should raise concern regarding the stability of the TNA (calcium phosphate precipitate or emulsion instability).

For a more thorough review of TNA implementation and use, the reader is referred to the bibliography, especially the ASPEN guide to safe practices. The practitioner must evaluate the benefit/risk to their patient of a specific form of parenteral nutrition.

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