ENTERAL NEEDS OF PRETERM INFANTS

A Capstone Seminar Paper for
NTR 690: Seminar in Nutrition
Presented to
Dr. Rayane AbuSabha
Department of Nutrition Sciences
Sage Graduate School

In Partial Fulfillment
Of the Requirements for the Degree of
Master of Science in Applied Nutrition

Susan L. Indilicato

December 2008

ENTERAL NEEDS OF PRETERM INFANTS

As the faculty advisor, I approve the thesis of _____

Date of Signature:

Susan L. Indilicato		
Dr. Rayane AbuSabha Associate Professor of Nutrition Thesis Advisor		

Table of Contents

Abstract

Improved medical treatment in respiratory care and nutritional support for preterm infants has increased neonatal survival rate. A focus on nutrition in the preterm infant is critical to their overall health and development. Early aggressive feeding and the fortification of breast milk with protein and minerals have both been shown to improve weight gain, mineral accretion, and neurological development. There are currently no standard recommendations for nutrient intakes after the preterm infant is discharged from the hospital. Excessive weight gain during the first four months of life has been linked to later risk factors such as hypertension, diabetes, cardiovascular disease, and obesity. Breastfeeding has been shown to reduce these risks when given in amounts that mimic growth patterns of their term peers. It is important to balance the risks of overfeeding with the risks of not promoting optimal growth when providing nutrition support to the neonatal population.

Chapter I

Introduction

Feeding the preterm infant has posed serious challenges to medical staff. Current recommendations of the American Academy of Pediatrics are "designed to provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients" (1). Infants born premature tend to develop complex medical problems and have longer length of stays in the Neonatal Intensive Care Unit (NICU) compared to their term peers. The common medical complications of prematurity can have significant nutritional consequences (2). Common health problems that affect preterm infants include postnatal growth failure (3), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) (4), gastro esophageal reflux (GER) (5), and osteopenia of prematurity (4).

The purpose of this review is to identify the differences between the term and preterm infant physiologically so as to provide the most appropriate medical nutrition therapy to prevent failure to thrive and nutrient deficiencies. Focus will be on appropriate feeding regimens for premature infants both during hospitalization and after hospital discharge.

1. 1. Weight Classification of Newborns

Newborns are classified in a number of ways. A typical classification is according to week of gestation (or gestational age). A term infant is one born between 37 and 42 weeks gestation. A preterm infant refers to an infant who is born less than 37 weeks

gestation (4). Corrected gestational age refers to the age of the infant and subtracts their weeks of prematurity (4). For example, a preterm infant that is four weeks old (born at 30 weeks gestation) is classified as 34 weeks corrected gestational age, not one month old. It would not be appropriate to label this preterm infant as one month old at 34 weeks gestation as this infant developmentally is not equivalent to an infant that is one month old and born at 40 weeks gestation.

A second method of classifying infants is by weight at birth. Infants weighing between 1500g and 2500 g (3 lb 5 oz to 5 lb 8 oz) are classified as Low Birth Weight (LBW). Infants weighing between 1000g and 1500g (2 lb 3oz to 3 lb 5 oz) are considered Very Low Birth Weight (VLBW). Those infants born less than 1000g (less than 2 lb 3oz) are classified as Extremely Low Birth Weight (ELBW). Term infants are expected to weigh more than 2500g (5 lb 8 oz) at birth (4).

Growth charts are used to plot the infant's birth weight and weight over time in order to assess growth pattern and nutritional status. Appropriate for gestational age (AGA) describes a fetus or newborn infant whose size is within the normal range for his or her gestational age (6) and plots between the 10^{th} and 90^{th} percentile on the growth chart. Large for Gestational Age (LGA) refers to infants who are larger than expected for their age and gender or infants with a birth weight above the 90th percentile. Small for Gestational Age (SGA) refers to infants that plot below the 10^{th} percentile on growth charts (7) or whose birth weight is greater than two standard deviations below the average birth weight for gestational age (8). Of preterm infants, about 30 to 40 percent are classified as SGA (9). SGA infants of the same gestational age as their AGA peers have a higher incidence of mortality (10). The reason for the growth restriction may not

always be known; however, maternal causes can include hypertension (chronic or pregnancy induced), smoking, and substance abuse (11). Analyzing head circumference and body length can help determine when growth deprivation occurred (4).

Analyzing the symmetry of growth by focusing on weight, head circumference, and length can help determine when the growth pattern was altered in utero. In asymmetric growth patterns, weight has been stunted, but length and head circumference is normal. This indicates that growth restriction has been of shorter duration. Symmetric growth restriction can be defined as having weight, length, and head circumference all proportionally below the 10^{th} percentile. This type of growth restriction indicates a longer duration of growth retardation and is usually the result of placental insufficiency (4). Intrauterine growth restricted (IUGR) infants fall into the latter category. Infants classified as IUGR can be preterm or term infants and are often SGA due to suboptimal growth in utero, and their growth is generally symmetric in nature. The most growth restricted infants of this group have a more difficult time meeting goals for extra uterine growth (8).

1.2 Growth Expectations of Term and Premature Infants

Weight can be defined as the total mass of body compartments, including lean tissue, fat, extra cellular and intracellular fluid. Changes in weight reflect changes in body composition and growth (4). Initial weight loss after birth is expected in term and preterm infants due to shifts in extra cellular and intracellular water compartments (4). Extra cellular water decreases with gestational age as protein and fat mass increases. Initially, term infants lose up to 10% of their birth weight. Preterm infants can lose up to 15% of their birth weight, as these infants have more extra cellular fluid and less lean

tissue and fat mass. Infants less than 1000 grams with even higher amount of extra cellular fluid present may lose as much as 20% of their birth weight (4). In the absence of adequate nutrition early postnatal, up to 50% of the weight lost can be losses of endogenous glycogen, lipid stores, and lean body mass due to increased metabolic demands after birth (12). These losses can further add to postnatal growth failure common in preterm infants, especially very low and extremely low birth weight infants. Birth weight is expected to be regained by two weeks of age for preterm infants (12-16).

Growth of the premature infant has been shown to be linked to neurodevelopment (17-18). In a recent study by Ehrenkranz et al. (2006) 492 extremely low birth weight, preterm infants were followed after discharge from the NICU at 18 and 22 months corrected age. Researchers compared the rate of weight gain to the incidence of neurodevelopment states such as cerebral palsy and Bayley II Mental Developmental Index (MDI) of <70 (17). Bayley II Mental Developmental Index is considered the gold standard criterion used to assess and diagnose motor and cognitive development. An MDI of 85 to 114 is considered normal, a score of 70 to 84 is considered mildly delayed, while a score of less than 70 is defined as significantly delayed performance (19). Results indicate that during the NICU hospitalization, the growth velocity of infants had a significant effect on neurodevelopment and growth at both 18 and 22 months corrected age. As weight gain increased from 12.0 g/kg/day to 21.2 g/kg/day the incidence of cerebral palsy, Bayley II MDI score of <70, neurodevelopmental impairment, and the need for re-hospitalization decreased significantly. Cerebral palsy incidence decreased from 21% to 6%, Bayley II MDI scores of <70 decreased from 39% to 21%,

neurodevelopmental impairment decreased from 55% to 29%, and the need for re-hospitalization decreased from 63% to 45%. (17).

The long term effect of prematurity on growth patterns has also been examined. Hack et al. (2003) conducted a longitudinal, age-specific cohort study of VLBW infants and collected weight, height, and BMI into adulthood. A total of 103 male and 92 female VLBW infants with an average birth weight of 1,189g and gestational age of 29.8 weeks were included in the study. Infants were followed from birth and compared against a population-based sample of 101 male and 107 female normal birth weight controls at the age of 8 years old. For the VLBW infants, weight and height were determined at birth, 40 weeks gestation, 8 and 20 months, and 8 and 20 years old. Weight and height were determined at 8 and 20 years of age for the control group. VLBW females reached catch-up growth in weight, height and BMI between 8 to 20 years of age, whereas VLBW males remained significantly shorter in stature and BMI than controls. At age 20 years, VLBW males mean weight was 69 kg (controls weighed 80 kg), mean height was 174 cm (compared to 177 cm for controls), and a mean BMI of 23 (controls with a BMI of 26) (20).

Chapter 2

Nutrient Accretion in Preterm Infants

During the third trimester most nutrient accretion, brain development, and somatic growth occur. These processes are interrupted when the infant is born prematurely. The last 3-4 weeks of gestation are important in accumulation of nutrient body stores and overall growth of the fetus. For term infants, more than 80% of total body calcium and iron is accumulated in the last three weeks of pregnancy (21). Preterm infants are born with relatively low stores of many nutrients including vitamins, minerals, and fat (22). Being born with low nutrient stores puts the preterm infant in jeopardy for many potential complications. For example, during a fasting state, adults are able to obtain needed energy in the form of endogenous stores. Glycogen stores are used first followed by fat and protein stores using the gluconeogenesis pathways (23). In a fetus, fat and protein stores increase with gestational age (24). An infant born at 38 weeks weighing 3500 grams will have more fat and protein stores than an infant born at 28 weeks, weighing 1100 grams and therefore would survive longer in the face of starvation (23).

2.1 Mineral Requirements

Fetal accretion of minerals is highest during the last trimester with peak accretion between 36-38 weeks (24). Calcium accretion during 26-36 weeks gestation is estimated at 2.3 to 3.2 mmol (90-120 mg)/kg/d. Phosphorus accretion during this time period is estimated at about 1.9 to 2.5 mmol (60-75 mg)/kg/d and magnesium at 0.1 to 0.14 mmol (2.5-3.4 mg)/kg/d (24). Preterm infants born during or prior to this critical period of growth and development do not achieve adequate mineral stores.

Providing enough calcium and phosphorus to preterm infants in amounts that match the fetal accretion rate is challenging. After birth, preterm infants are often in unstable, critical conditions and have decreased intestinal absorption of minerals. Tsang et al (1993) recommends an intake of 120-230 mg/kg/d of calcium, a phosphorus intake of 60-140 mg/kg/d, and a magnesium intake of 4.3-7.2 mg/kg/d to attempt to match fetal accretion rates (25). It is difficult to provide adequate levels of calcium and phosphorus in parenteral nutrition solutions due to the possibility of precipitation of salts (4). Preterm infant formulas and human milk fortifiers are specifically designed to meet the high mineral needs of preterm infants (4).

Vitamin D accretion is also interrupted when the infant is born prematurely. Vitamin D is important in the maintenance of calcium-phosphorus homeostasis by acting on the kidney and bone. It assists with the absorption of calcium and phosphorus in the gut and may also play a role in normal cell differentiation in the marrow of bone (4). Maintaining an intake of 400 IU's of Vitamin D in most term infants has been shown to normalize serum 25-hydroxyvitamin D levels (26). Measuring serum 25-hydroxyvitamin D levels is the most accurate test for determining levels of Vitamin D in the body (4).

Rickets is a disease of bone formation in children, most commonly the result of Vitamin D deficiency (7). It is marked by inadequate mineralization of developing cartilage and newly formed bone, causing abnormalities in the shape, structure, and strength of the skeleton (7) such as bowed legs or pigeon's breast (protruding chest). Rickets in term babies is not uncommon in developed countries. Adequate sun light exposure and dietary intake of Vitamin D help decrease the prevalence of rickets. Women with limited exposure to sunlight (for example cultures where women wear veils

and/or rarely leave the home) have lower levels of Vitamin D, and if they breastfeed, their babies are at higher risk of deficiency (7).

Preterm infants are at higher risk of developing rickets. According to Dabezies and Warren (1997) the incidence of rickets is about 39% in preterm infants. The bone fracture rate is about 10% in VLBW infants (27) because preterm infants do not have the opportunity to accrete normal intrauterine amounts of vitamins and minerals such as calcium, phosphorus, magnesium, and Vitamin D, leading to compromised bone structure. If supplementation is not provided and maintained after birth, the preterm infant is at an increased risk of developing rickets (28).

Other factors that determine bone mineral accretion in utero include genetic and environmental factors. Environmental factors include diet and lifestyle of the mother. Mothers with low calcium intakes during pregnancy, or those who are especially thin can slow calcium accretion in utero. Lifestyle habits such as smoking can also retard bone mineralization (29). Godfrey et al. (2001) examined the influences parents have on intrauterine skeleton growth. Pregnant females were interviewed by trained research nurses at 14.7 weeks gestation and again at 28 weeks gestation. Menstrual and obstetric histories, anthropometric data, and smoking habits were collected. Fathers' weights and height at birth were also gathered. A total of 145 term infants were included in the study. Once born, infants were weighed and measured (head circumference, mid-arm muscle circumference, and abdominal girth), and dual-energy x-ray absorptiometry was used to measure the bone mineral content (BMC) and bone mineral density (BMD). Infants whose mothers smoked had 11% decrease of whole body BMC compared to infants of non-smoking mothers. Maternal and paternal birth weight and height were positively

correlated with both BMC and BMD. Greater whole body BMC and BMD was seen in infants whose mothers weighed more at birth. There was an even stronger association between the father's birth weight and the infant's whole body BMC and BMD. Both fetal and early post natal skeletal growth is a known determinant of future adult bone mass and risk of hip fractures (30).

2.2 Osteopenia of Prematurity

Osteopenia of Prematurity (decreased bone mass) (4) is common in preterm infants. Osteopenia is a decrease in the amount of calcium and phosphorus in the bone. Low amounts of these minerals in the bone prevent the bone from remodeling, properly mineralizing and growing normally (31). This can cause bones to be weak and brittle, and increases the risk for broken bones. As stated earlier, infants born prematurely do not achieve adequate amounts of calcium and phosphorus, because they are born prior to the highest period of intra uterine accretion of vitamin and minerals. Proper absorption of calcium can not occur in the gut and kidneys in the presence of a Vitamin D deficiency. A lack of sufficient amounts of Vitamin D therefore can also cause osteopenia (4).

Preventative nutrition involves providing enough calcium, phosphorus, and Vitamin D in amounts to match fetal accretion rates. This is not always feasible due to the infant's often unstable status after birth. Partial or total parenteral nutrition is often the first form of nutrition introduced to the neonate. Parenteral nutrition is limited in the amounts of calcium and phosphorus it provides due to solubility issues with calcium and phosphorus salts in solution (32). The goal of parenteral nutrition is to provide enough

calcium and phosphorus to normalize serum levels while preventing precipitation of the salts in solution (4).

Enteral nutrition is the most optimal way for preterm infants to meet vitamin and mineral requirements. Breast milk and term infant formulas do not have adequate amounts of calcium and phosphorus to meet the needs of preterm infants (33-34). Feeding the preterm infant breast milk with fortifiers that include calcium and phosphorus has been shown to improve bone mineral status (35). In addition, breast milk has low levels of Vitamin D (12-60 IU/L) which needs to be provided as a supplement to all breastfed infants. Term infants that are exclusively breastfed should be supplemented with 200 IU/d of vitamin D by two months of age (36) for the duration of breastfeeding. Standard infant formulas provide 400 IU/l of Vitamin D and preterm formulas provide 500 to 1200 IU/l of Vitamin D. Term and preterm infants are recommended to have a daily intake of 400 IU/day Vitamin D (37) if rickets is not present.

The use of low-mineral formulas, soy-based formulas, unfortified human milk, or term infant formulas for preterm infants can increase the risk of osteopenia of prematurity. According to Rigo et al (2007), retention of approximately 60 to 90 mg/kg/d of calcium enterally will provide the preterm infant with adequate levels for appropriate bone mineralization, decrease the signs and symptoms of osteopenia, and decrease fracture risk. An intake of 100-160 mg/kg/d of “highly bioavailable calcium salts”, a phosphorus intake of 60 to 90 mg/kg/d (38), and an intake of vitamin D of 160-400 IU per day are currently recommended (4). According to the American Academy of

Breastfeeding Medicine, fortifying breast milk with calories and nutrients or using preterm infant formulas (39) will meet the needs of preterm infants (39-40).

Alkaline phosphatase is an enzyme that originates mainly in liver, kidney, and bone. It may be elevated in normal growth, liver disease, and/or bone disease. In metabolic bone disease, alkaline phosphatase levels rise due to osteocyte production and calcium deposition in bones (4). This is a common measure used to determine the presence of bone disease in infants. Normal values in preterm infants can be up to five times the adult reference range. Values greater than five times the adult range in infants free of liver disease (500mg/dL or greater) is an indicator of bone disease (4).

2.3 Energy and Protein Requirements of the Term Infant

Energy requirements for the term infant are based on median energy intakes of healthy infants, and take into consideration thermic effect of feeding, activity level of the infant, and need for growth. The current recommended daily allowances (RDA) for term infants is 108 kcal/kg for infants 0-6 months of age, and 98 kcal/kg for infants 6-12 months of age. The current RDA for protein intake is 2.2 g/kg/day for 0-6 months and 1.6 g/kg/day for 6-12 months of age (41).

2.4 Caloric Needs of the Preterm Infant

Caloric needs of the preterm, low birth weight (LBW) infant are higher than their term peers (Table 1). LBW infants expend more energy for tissue synthesis and have a higher basal metabolic rate (BMR). The gold standard of energy needs and growth of the preterm infant is to mimic intrauterine growth rate and nutrient accretion of term infants

(3). General caloric needs are estimated to be 120 kcal/kg/day (enterally), 50 of which are needed for BMR and about 75 kcal/kg/day for calorie expenditure. The infant needs to consume about 5 to 6 kcal per gram of weight gained. LBW infants who consume 120 kcal/kg/day (enterally) gain about 15 g/kg/day which are the current weight gain goals for LBW infants (42). Premature infants that are growth retarded, such as small for gestational age (SGA) or intrauterine growth retarded (IUGR) may require more than 120 kcal/kg/day to achieve and maintain adequate growth (43).

Table 1 Recommended Daily Enteral Nutrient Intake for Preterm, Low-Birth-Weight Infants, Compared to Term Infants

Nutrient	**Recommended Intake**	
	Term Infant	Preterm Infant
Fluid (mL/kg)	150*	150-200**
Energy (kcal/kg)	108***	120†
Protein (g/kg)	2.2***	3.5-4.0‡
Calcium (mg/kg)	67*	120-230‡
Phosphorus (mg/kg)	50*	60-140‡
Zinc (ug/kg)	830*	1000-2000**
Vitamin A	376 (ug/kg) *	1400 (IU/day)*
Vitamin D	300 (IU/day)***	500 (IU/day)*
Iron (ug/kg)	1000*	2000-4000**

***23**
****8**
*****41**
†42
‡ 25

2.5 Protein Needs of Preterm Infants

In an effort to determine the amount of protein required to maintain intrauterine rate of protein accretion, the factorial method is most commonly used. This method estimates the urinary nitrogen losses and estimates the amount deposited in utero (corrected for absorption and deposition). Using this equation for preterm infants, an estimation of 4 g/kg/day is recommended to support uterine growth and protein accretion (44), which is about twice as high as the current RDA of protein for the term infant (41). The American Academy of Pediatrics currently recommends an intake of 3.5-4.0g/kg protein to closely match fetal accretion rates (1). Tsang et al. (2005) revised the recommendations of protein intake for the preterm infant, as guidelines up to this point have been based on stable preterm infants not in acute stress or illness. With the increased knowledge of postnatal growth failure and catch-up growth potential, Tsang recommends an intake of 3.8-4.4 g/kg/day (45).

2.6 Postnatal Growth Failure in Preterm Infants

Postnatal growth failure is common in preterm LBW (46), VLBW and ELBW infants (47). The use of early and aggressive nutrition support can help prevent growth failure among preterm infants. Preterm infants have immature gastrointestinal tracts which can delay the start of enteral nutrition. They also have decreased ability to suck and swallow and decreased gut motility (48). Thus, the use of total parenteral nutrition within the first few days of life is usually the most feasible form of nutrition available (20). Neonatologists are often cautious with starting enteral feeds for fear of development of G.I. intolerances and illnesses (such as necrotizing enterocolitis (NEC)). On the other hand, being too cautious with starting enteral feeds can lead to malnutrition early in life

and postnatal growth failure which may lead to long term nutritional consequences (20, 48).

Preterm infants born LBW, yet appropriate for gestational age (AGA) often become growth restricted by discharge from the hospital. Preterm AGA infants are born between the 10^{th} and 90^{th} percentile on growth charts, but typically fall below the 10^{th} percentile by hospital discharge. Once they fall below the 10^{th} percentile, they are classified as small for gestational age (SGA) (49). In a retrospective chart review of 69 extremely low birth weight infants, of those less than 750 grams, 11% were SGA at birth, and by discharge from the hospital the number rose to 74%. Of those infants that were 751-1000 grams at birth, 7% were SGA at birth and by discharge 40% were considered SGA (46).

Chapter 3

Parenteral Nutrition

The first form of nutrition often given to a preterm infant is total parenteral nutrition (TPN). The goal of parenteral nutrition is to provide enough nutrition to promote weight gain and growth, until adequate enteral feeding can be established (50). According to Heird and Kashyap (1998), providing nutrition early prevents protein catabolism and provides a positive nitrogen balance. Carbohydrates, lipids, and proteins should be advanced as aggressively as tolerated in parenteral solutions. In order to achieve required energy needs by means of TPN, high amounts of glucose would need to be administered which may not be well tolerated in LBW infants (51). The use of insulin can help improve the tolerance of glucose during this critical time period (48). Starting enteral nutrition early and in combination with parenteral nutrition is commonly practiced to better achieve postnatal growth in the preterm infant (52).

Within the first one to two days of life, minimal enteral feeds can be initiated to promote gut function while monitoring tolerance for risk factors such as necrotizing enterocolitis (48). TPN should be gradually decreased as enteral nutrition is tolerated and gradually increased (4). Continuing TPN at the same rate while slowly increasing enteral feeds can cause excessive nutrient intakes and cause azotemia (an excess of urea or other nitrogenous wastes in the blood) (53). TPN should be continued until the infant is tolerating about 75% of nutritional needs enterally (90-100 kcal/kg/day) (4), and then discontinued.

3.1 Effects of Long Term Parenteral Nutrition Use

TPN is formulated to provide adequate serum levels of minerals such as calcium and phosphorus. Although parenteral solutions provide enough calcium and phosphorus to normalize serum concentrations, they do not allow for adequate accretion. For this reason, bone disease can occur with long term usage of TPN. When enteral feeds cannot be established (such as with bowel disease) and TPN must be continued longer than usual, calcium, phosphorus, and Vitamin D intakes are insufficient for proper bone mineralization in the preterm infant. The amount of calcium and phosphorus in TPN solutions is often limited because of poor solubility of calcium and phosphorus salts (32, 54) which results in intakes below fetal accretion rates (4). According to Tsang et al (2005), adding 66 mg/kg/day of calcium and 51 mg/kg/day of phosphorus into TPN solutions will promote normalized circulating levels and create a positive calcium and phosphorus balance. (8). There is an increase risk of hypocalcemia, hypophosphatemia, hypercalciuria and metabolic bone disease the longer the infant is on TPN without supplementation with enteral feeds (27, 55, 56).

Chapter 4

Enteral Nutrition

Enteral nutrition is often not started until the preterm infant is a few weeks old for fears of the development of necrotizing enterocolitis (52) if started too early or advanced too aggressively. When enteral nutrition is started, one of the first forms is usually gavage feeds. Gavage feeds refers to the insertion of a gavage tube either from the nose (nasogastric) or from the mouth (orogastric) to the stomach. Gavage feeds are used for preterm infants who show an inability to effectively suck and swallow, poor gag reflexes, and or have high respiratory rates (4). The use of gavage feeds began in the 1960's and 1970's and with its use preterm infants began reaching full enteral feeds faster than ever before (57).

Nipple feeds are usually feasible when the infant is 32 to 34 weeks gestation, as this is when coordination of suck-swallow-breathe patterns develops. Transition from gavage to nipple feeds is gradual, depending on the infant's condition or schedule (for example, starting with nipple feeds once per day, increasing to once per shift, every other feed, then every feed) (4).

Minimal enteral nutrition (MEN) also referred to as trophic or hypocaloric feeds is usually the first form of enteral nutrition given to the preterm infant. MEN consist of low volume intakes of 10-20 ml/kg/day to stimulate the gut, its hormones, and promote maturity of the GI tract (58). MEN is usually given in the form of gavage feedings. With an increase in full enteral feeds being achieved in this population, an increase in the development of necrotizing enterocolitis has been seen. The combination of both

occurrences has caused many neonatalogists to begin withholding enteral feeds for the first few weeks of life, and use of total parenteral nutrition as the only source of nutrition for low birth weight preterm, often critically ill neonates (57). A growing recognition of the importance of gut stimulation using minimum volume enteral nutrition along with a growing concern over the consequences of prolonged parenteral nutrition, prompted researchers to begin studying the effects of using minimal enteral nutrition in combination with parenteral feeds (57).

Several small research studies have examined the clinical outcomes of minimal enteral nutrition feedings in preterm, low birth weight infants (58-60). In a prospective randomized trial, 20 infants were started on enteral feedings beginning at 48 hours of age and compared them to 19 infant controls not fed enterally until at least 9 days of life. Initially both groups received a majority of their energy from parenteral nutrition. An overall decrease was found in the incidence of cholestasis, osteopenia of prematurity, and the infants in the experimental group who transitioned to full feeds faster (59).

In a similar study, Slagle and Gross (1988) studied the effect of small enteral feeds on gastrointestinal function in 46 infants with a birth weight less than 1500 grams. Group 1 consisted of infants that received enteral feeds of 12 ml/kg/day along with parenteral nutrition beginning at day 8 of life. The second group received only parenteral nutrition until 18 days of life. Following parenteral nutrition, both groups received enteral feeds at a volume of 12ml/kg/day initially and increased 15 ml/kg per day. Outcomes measured included feeding intolerances such as gastric residuals and incidence of necrotizing enterocolitis. Group 1 had improved feeding tolerance as seen by less gastric residuals that totaled more than 10% of feeds (1.3 +/- 0.5 days vs 3.2 +/- 0.6 days) and fewer days

when feeds were discontinued as a result of intolerances (2.7 +/- 0.8 days vs 5.5 +/- 0.9 days). Of the infants in Group 1, 94% (17 out of 18) infants reached enteral intakes of 120 kcal/kg/day by 6 weeks of life, while only 64% (14 of 22) infants in Group 2 reached this intake. The investigators concluded that critically ill, very low birth weight infants had better feeding tolerances when given hypocaloric enteral nutrition along with parenteral nutrition (58).

The advancement rate of enteral feeds remains controversial. Increased gastric residuals and delayed gastric emptying is common in preterm infants; the amount representing clinical significance remains unclear (61). Recent research has shown a connection between increased gastric residuals and incidence of necrotizing enterocolitis (62). Due to fears of developing NEC, feed volume increases tend to be slow in the neonatal population (63). One research study found an increase of 10 to 20 ml/kg/day was safe (64), while another found the rapid increase in volume is associated with increased incidence of NEC (65).

Caple et al (2004) investigated whether an advancement of feeds at 30 ml/kg/day in LBW preterm infants would decrease the amount of days needed to reach full feeds, without increasing incidences of NEC. A total of 72 infants were in the experimental group and 83 infants in the control group. Infants in the experimental group were fed at an advancement rate of 30 ml/kg/day. Infants in the control group were fed at an advancement rate of 20 ml/kg/day. The experiment group reached full feeds faster (7 vs. 10 days), regained birth weight faster (6 vs. 8 days), and overall did not increase the incidence of NEC (3 infants in the experimental group vs. 2 infants in the control group) (63).

Berseth et al (2003) found conflicting results. The main outcome measure for this study was determining the incidence of NEC. In a randomized, controlled trial, 141 preterm infants were divided into two groups: One group fed for 10 days on minimal enteral feeds of 20 ml/kg/day, while the second group was fed at 20 ml/kg/day on day one, followed by an increase in feed volume of 20 ml/kg/day daily up to a goal of 140 ml/kg/day. The study was discontinued early because 7 infants in the increasing feed volume group developed NEC, compared to only one infant developing it in the minimal feed volume group. Berseth et al. (2003) concluded that increasing feeding volumes by 20 ml/kg/day increases the risk of NEC (66). Therefore it appears that further research needs to be conducted to better determine what volume feeds can be increased safely without increasing the risks of developing NEC.

The American Academy of Pediatrics recommends advancement of feeds to be dependent on the infant's birth weight. For infants less than 1,000 grams, an increase in volume should be slow over a 10 to 14 days period, while infants weighing more than 1,500 grams feeds should be advanced over a 6 to 8 day period (40).

4.1 Fortifying Breast milk

The American Academy of Pediatrics recommends breastfeeding as the optimal feeding choice of infants because of its health and wellness benefits (39). The benefits of human milk are well known and include immunological benefits, aid in digestion and promotion of a healthy gut, as well as neurological benefits (67). However, breast milk alone does not provide adequate calories and minerals for the preterm infant (8, 40) and

needs to be supplemented with several nutrients. Table 2 provides nutrient comparisons between various preterm infant feeding methods.

Feeding the preterm infant breast milk fortified with protein, vitamins, and minerals has become a standard practice in most NICU's. The in-hospital practice of adding liquid or powdered human milk fortifiers, premature infant formulas, vitamin/mineral supplements, or modulars to expressed breast milk (4) has become popular due to insufficient amounts of protein, calcium, phosphorus, and other nutrients in breast milk. Infants born at less than 34 weeks gestation or 1500 grams at birth are at increased risk for both macronutrient and micronutrient deficiencies (68) and may need even more supplementation. Research has shown short term growth advantages of fortifying human milk (69, 70).

The American Academy of Breastfeeding Medicine recommends that preterm infants are fed their mother's milk supplemented with calories and nutrients (39) because growth faltering has been observed when preterm infants are fed breast milk without fortification (22, 71).

Table 2 Nutrient Comparison of Term Breast Milk, Preterm Breast Milk, and Breast Milk plus Human Milk Fortifier

Nutrients	**Breast Milk Term Per Liter**	**Breast Milk Preterm Per Liter**	**Breast Milk plus Human Milk Fortifier Per Liter (made to 22 kcal/oz)**
Energy, Cal	680	671	739
Protein, g	10.48	14.09	19.6
Calcium, mg (mEq)	279 (13.9)	248 (12.4)	698 (34.8)
Phosphorus, mg	143	128	378
Magnesium, mg	34.7	30.9	36
Iron, mg	0.27	1.21	8.41
Sodium, mg (mEq)	177 (7.7)	248 (10.8)	328 (14.3)
Potassium, mg (mEq)	531 (13.6)	570 (14.6)	715 (18.3)
Chloride, mg (mEq)	422 (11.9)	550 (15.5)	615 (17.3)
Vitamin A (IU)	2252	3899	8649
Vitamin D (IU)	20	20	770

***72**

Some have speculated that increasing the volume of breast milk given to the infant may solve the calorie, protein, and mineral deficit. Forbes (1989) disproved this hypothesis. Using information previously collected on the retention of nutrients in the preterm infant (for "several dozen" fetuses and newborns within the past 75 years), Forbes plotted the total body content of several elements (including N, Ca, P, Mg, Na, K, Cl, and Zn) against the infant's body weight, using double logarithmic coordinates. Using these pieces of information he was able to determine that very large intakes of preterm human milk would be needed to meet the nutritional needs of the preterm infant. For example, at 30 weeks corrected gestation, the preterm infant (fed preterm human milk) would need to consume 700ml/kg/d and 590ml/kg/d of breast milk to obtain enough calcium and phosphorus respectively. This is significantly above the upper tolerance levels of these infants (73).

Nicholl and Gamsu (1999) studied the effects on growth of adding a human milk fortifier to breast milk by measuring weight gain, changes in lower leg velocity, and other biochemical indicators of nutrition (such as alkaline phosphatase). The study included 53 preterm VLBW infants who weighed less than 1500g at birth, randomized to one of three groups, depending on if the mother intended to breast feed or not. One group received breast milk alone, the second received fortified breast milk, and the third group received standard preterm formula. Infants in the fortified human milk group had significantly lower serum alkaline phosphatase levels (an indicator of rickets) than infants in the other two groups at the end of the study. Infants fed fortified human milk had a median serum alkaline phosphatase of 288 IU/L; whereas infants fed preterm infant formula and human milk had median serum alkaline phosphatase levels of 368 IU/L and 378 IU/L,

respectively. The lower leg velocity was most significant in both the fortified breast milk group and the formula group (33). One can conclude from this study that the use of fortified breast milk appears to be associated with the least incidence of rickets, and the use of either fortified breast milk or preterm infant formulas has a significant impact on bone growth and mineral accretion.

Ronnholm et al. (1986) studied the effects of supplementing breast milk with protein and medium-chain triglyceride on growth of very low birth weight preterm infants. A total of 44 infants weighing less than 1520 grams and average gestational age of 30 weeks, were included in the study. Infants were divided into four groups of either unsupplemented human milk, human milk supplemented with human milk protein, human milk supplemented with medium-chain triglycerides, or both. Infants who were given protein supplemented with human milk grew better (0.99cm/wk) than the other three groups (0.83 cm/wk) and matched intrauterine growth rates (69).

According to Arslanoglu et al. (2006) protein is often the limiting nutrient when breast milk is fortified due to the variability of protein content in breast milk and the variability of protein content of human milk fortifiers, all of which can contribute to inadequate protein intakes. Protein content of human milk has been estimated to provide about 2.1-2.4g/100 kcal (2.2-2.6g/kg protein when intake is 160ml/kg) (70), well short of the estimated 3.5-4.0 g/kg needed by the preterm infant, based on fetal accretion rates (1). Commercial fortifiers generally raise the protein content of milk to about 3.25g/100kcal, which equals 3.8-4.1g/kg protein when given in 160ml/kg volume of either 22 or 24kcal/oz (70).

In a prospective, randomized control trial, Arslanoglu et al. (2006) studied the effects of using an adjustable protein fortification method on weight gain. The researchers hypothesized that adjusting the amount of fortifier added to breast milk based on blood urea nitrogen (BUN) concentrations of the infant would increase protein intakes and improve weight gain in preterm infants. Infants with a weight between 600-1750 grams and gestational age between 26 and 34 weeks were given either their own mother's milk, banked donor milk, or a combination of both. Infants were divided into two groups, to either receive the adjustable fortification regimen, or the standard regimen. The study began when infants reached an enteral intake of 150ml/kg/day and ended once infants weighed 2000 grams. A total of 32 infants completed the study (16 in the experimental group, 16 in the control group). Infants who received the adjustable fortification method consumed more protein, and gained more weight (30.1g/day vs. 24.8g/day in the unfortified group). The adjustable formula group also had larger gains in head circumference (1.4mm/day vs. 1.0mm/day in the unfortified group) (70).

Breast milk remains the optimal feeding of choice for infants (39). However, breast milk does not meet the nutritional needs of preterm infants alone. Preterm infants would have to consume extremely large volumes of breast milk to meet their needs for proper mineral accretion (73). Mothers of infants born less than 1500 grams who wish to breast feed should fortify their breast milk, as research has shown that using fortifiers (liquid, powder, or premature infant formulas) improves growth (69, 70), and decreases the risk of metabolic bone disease (33).

4.2 Infant Formulas

The use of standard formula for preterm infants can result in an increased risk for poor growth and metabolic bone disease (74-76). Mothers who choose not to breast feed their preterm infants should use high mineral content infant formulas during hospitalization, made specifically to meet the needs of preterm infants (40, 42). Premature infant formulas are available in 20 and 24 kcal/oz dilutions. The American Academy of Pediatrics recommends the use of iron fortified formulas for all infants (77).

Protein content of preterm infant formulas is greater than that of standard infant formulas (see Table 3). At an intake of 120 kcal/kg/day preterm infant formulas provide greater than 3 g/kg/day of protein (4). The American Academy of Pediatrics currently recommends an intake of 3.5-4.0 g/kg/day of protein to meet weight gain goals and nitrogen retention (1). Mineral content of preterm infant formulas is also higher than in standard infant formulas. Calcium and phosphorus content of these types of formulas is better able to meet the preterm infant's needs (4) (up to 200 mg/kg/day of calcium and 113 mg/kg/day of phosphorus) (78).

Table 3 Nutrient Comparison of Preterm Formula, Nutrient-Enriched Formula, and Standard Term Formula

Nutrients	Preterm Formula Per 100 kcal 24 kcal/oz	Nutrient-Enriched Discharge Formula Per 100 kcal	Standard Term Infant Formula Per 100 kcal
Energy (kcal)	100	100	100
Protein (g)	2.71-3.0	2.8	2.1
Calcium, mg (mEq)	165-180 (8.2-9.0)	105-120 (5.2-6.0)	78 (3.9)
Phosphorus, mg	83-100	66 (2.1)	53
Magnesium, mg	9-12	8-9.0	8
Iron, mg	1.8	1.8	0.7
Sodium, mg (mEq)	43-58 (1.9-2.5)	33-35 (1.4-1.5)	27 (1.2)
Potassium, mg (mEq)	98-129 (2.5-3.3)	105-142 (2.7-3.6)	108 (2.8)
Chloride, mg (mEq)	81-90 (2.3-2.5)	75-78 (2.1-2.2)	63 (1.8)
Vitamin A, IU	1250	450-460	300
Vitamin D, IU	150-240	70-80	60

***72**

Use of premature infant formulas during hospitalization has become standard care practice across the country. Lapillonne et al. (2004) studied bone mineral content

(BMC) differences between preterm infants fed either a control preterm formula or an isocaloric nutrient-enriched preterm formula during hospitalization, up until 3 months corrected age (expected term). They found that BMC was significantly higher in the isocaloric nutrient-enriched preterm formula group (23 and 35% higher BMC at hospital discharge and expected term, respectively) (34).

Schulze et al. (1987) compared protein and energy intakes of low birth weight preterm infants using three different formula groups. Energy expenditure, weight gain composition, and energy balance were measured. Nineteen infants were placed into three groups: the first group consumed a formula (Formula A) that provided 2.24 g/kg/day protein and 113 kcal/kg/day, the second group consumed a formula (Formula B) that provided 3.6 g/kg/day protein and 115 kcal/kg/day, and the third group consumed a formula (Formula C) that contained 3.5 g/kg/day protein and 149 kcal/kg/day. The rate of energy and protein intake affected the type and amount of tissue deposited. Both Formula B and C groups gained the most amount of weight, due to higher caloric intakes. Group C had increased fat deposition and Group B had highest protein intakes causing increased protein deposition. The authors concluded that both energy and protein intakes had an impact proportionately on the composition of weight gain in the preterm infant. Both should be an important component in the composition of preterm infant formulas for low birth weight infants (79).

Preterm infant formula is the best formula option for the preterm infant during hospitalization. This type of formula provides higher amounts of protein, vitamins, and minerals than standard term infant formulas (4). When preterm infants are fed preterm infant formulas, they have improved growth (79) and higher bone mineral content (34).

4.2.1 Nutrient-Enriched Infant Formula

Nutrient –enriched infant formulas are generally prescribed to preterm infants for use after hospital discharge. They are available in ready to feed bottles for use in the hospital and in powder form for use at home. They come in a concentration 22 kcal/ounce. This type of formula provides a higher amount of calories, protein, vitamins, and minerals compared to a standard infant formula, but lower concentration of these nutrients when compared to preterm infant formulas (4). When preterm infants have caloric needs that are higher than 120 kcal/kg/day (the current recommendation), nutrient-enriched formulas can be concentrated (adding less water to concentrated liquid or powder when mixing the formula) or the use of modular supplements can be used to increase the caloric density of the formula. Modular products, such as oils and glucose polymers, add non-protein calories and will alter the formulas nutrient ratio. Therefore concentrating the nutrient-enriched infant formula is the ideal choice when the preterm infant has increased caloric needs (4).

Bishop et al (1993) studied the effect of using enriched infant formula on bone mineral content of preterm infants and compared the results to the usage of a standard infant formula. He found that using enriched infant formula after hospital discharge improved bone mineral content of preterm infants when compared to infants fed with standard formula at 3 and 9 months corrected age. BMC at 3 months corrected age was 83 vs. 63 mg/cm for enriched and standard formula respectively, while at 9 months corrected age, BMC was 115 vs. 95 mg/cm respectively (74).

Similarly, a double-blind, randomized study by Carver et al. (2001) compared the growth of preterm infants (<1800 grams) fed either 22 kcal/oz nutrient-enriched formula

or standard 20 kcal/oz term formula from hospital discharge to 12 months corrected age. Researchers compared the growth of the infants in both groups from study day 1 to term and at 1, 2, 3, 6, 9, and 12 months corrected age. Infants fed nutrient-enriched formula overall grew better in weight, length, and head circumference. From study day 1 to term, infants fed nutrient-enriched formula gained 34.1g/day, while infants fed standard formula grew 28.9g/kg respectively. Head circumference growth results were the same (1.06mm/d versus 0.88mm/day respectively study day 1 to term) as well as length results (1.24mm/d versus 1.08mm/d study day 1 to term). These results were especially true for infants weighing <1250 grams. Weight gain continued to be greater in the nutrient-enriched formula group up through 12 months corrected age (18.6 g/d in the nutrient-enriched group and 17.4 g/d in the term formula group). Head circumference and length also showed the same type of results (75)

In summary, breast milk is the preferred method of feeding infants born prematurely, because of its confirmed health and wellness benefits. Research studies have shown how variable breast milk can be (80) which is a nutritional concern for adequate preterm infant nutrition. Adding human milk fortifiers has been proven in studies to improve weight gain and mineral accretion in preterm infants (33, 69, 70). When breast milk is not available, premature infant formulas are recommended for use in the hospital due to their high amounts of protein, vitamins, and minerals. It has been shown to improve bone mineral content in preterm infants up to 3 months corrected age (expected term). Nutrient enriched formulas are preferred after hospital discharge. Nutrient enriched preterm formulas have been proven to improve growth (weight, length, and head

circumference) (34, 75). Decreased risk of osteopenia and rickets has been shown when fortified breast milk and nutrient enriched infant formulas are used (33, 34).

Chapter 5

Medical Complications of Preterm Infants and Nutritional Consideration

The organs of infants born premature are immature and do not operate to their full capacity. Premature infants are in need of specialized medical care in the hospital until their bodies are able to function well enough on their own to sustain life. Premature infants are usually not able to maintain adequate body temperature or breathe properly on their own (81). Nursery care is needed to ensure the baby is maintained at the right body temperature, and ventilator assistance is commonly required. Infants are kept in the hospital until they are able to breath on their own, maintain their own body temperature, and tolerate feeds by mouth (81). Medical complications that arise during infants' stay in the intensive care unit can delay discharge.

Infant's born premature face a number of possible medical complications, including respiratory compromise, renal, neurological, gastrointestinal, and hepatic disorders (2).

5.1 Respiratory Distress Syndrome

Pulmonary problems are very common in preterm infants and less frequent in the full-term infant (4). Respiratory Distress Syndrome (RDS) can be defined as severe impairment of respiratory function in a preterm newborn, caused by immaturity of the lungs. Of infants less than 30 weeks gestation, more than 60% develop some degree of RDS. Of term infants, less than 0.05% develop RDS. In 1997, RDS was the fourth leading cause of death among preterm infants (7). Risk factors for term infants include mothers with diabetes, cesarean delivery, brothers or sisters with Respiratory Distress

Syndrome (RDS), acidosis at birth due to delivery complications, multiple pregnancies, and rapid delivery (82). Symptoms can include cyanosis in room air, nasal flaring and tachypnea, expiratory grunting, and sternal and intercostal retractions (4).

Medical treatment of RDS depends on gestational age and severity of RDS. Treatment can include a combination of exogenous surfactant therapy, continuous positive airway pressure (CPAP), supplemental oxygen, and mechanical ventilation (4). In the most severe cases, the neonate may need prolonged mechanical ventilation and exogenous surfactant therapy. Dexamethasone may be used to decrease pulmonary edema, increase the synthesis of surfactant, decrease inflammation, and increase the activity of antioxidants (4).

Infants with RDS are at increased risk of progression to Chronic Lung Disease (CLD) if they require assisted ventilation more than 10 to 14 days after birth (4). Recovery from RDS can range from three to four days or can progress into CLD which can lead to life long decrease in pulmonary function (reactive airway disease and hyperinflation) (83).

5.2 Bronchopulmonary Dysplasia (BPD)

BPD (Bronchopulmonary dysplagia) (also called CLD) is a chronic pulmonary disorder that develops in some premature infants with severe RDS. Most recent diagnostic criteria for BPD have been described as the need for assisted ventilation for at least three days during the first two weeks of life, with clinical signs of respiratory compromise and the need for supplemental oxygen, and radiologic evidence of pulmonary changes characteristic of BPD persisting beyond 28 days of life (4). The incidence of BPD is as high as 38% of infants born less than 1,000 grams (84).

According to LaHood & Bryant (2007), of those infants born at 900g, 50% to 80% will likely develop BPD (2).

The incidence and severity of BPD has decreased over the years with advancements in respiratory management and technology for infants that are greater than 1,000 grams at birth. Technological advances such as improved mechanical ventilation, improved evaluations of blood gases, and improved delivery of supplemental oxygen, have also helped increase survival rates in infants born less than 1,000 grams (4).

The severity of BPD illness can determine the extent of nutritional implications for the preterm infant. Infants with BPD have reduced rates of growth when compared to term peers at the same postmenstrual age (85-90). Increased metabolic needs due to medication use (such as methylxanthines and beta-antagonists) (91), increased energy expenditure to breathe, and fluid restrictions can contribute to poor growth. Ability to effectively suck and swallow in severe BPD cases can delay the progression of feedings. Mechanical ventilation using an endotrachial tube may cause later oral aversions to feeds, gagging, and vomiting (4).

The use of surfactant replacement therapy has contributed to increased survival of the VLBW preterm infants with the prevention of BPD. Infants begin to make surfactant at 24 weeks gestation; however appearance in aveoli fluid may not occur until much later (92). Exogenous surfactant therapy is used to prevent alveoli from collapsing at the end expiration (4). At about 34 week's gestation, adequate amounts of surfactant are produced by the pulmonary cells and there are an adequate amount of pulmonary cells covering the alveolar surface area with the capability of gas diffusion (93).

Providing appropriate nutritional management for preterm infants suffering from BPD is important to their long term health. Failure to thrive can be a complication of BPD as these infants can require up to a 25% higher caloric intake above normal basal metabolic needs due to increased work of breathing and higher basal metabolic rate (BMR). Increasing caloric intake is often provided in the form of increasing the caloric density of formulas or breast milk. There may also be a need for increasing the caloric density of formula when the preterm infant needs a fluid restriction (8).

Infants with BPD are placed on fluid restrictions to prevent pulmonary edema (8). Typically, preterm infants without BPD can take in 160 ml/kg/day of fluid, which when given in the form of enriched 22 kcal/oz formula, will meet preterm infants calorie and protein needs (120 kcal/kg and 3-4 g/kg/ protein) (1, 42). Infants requiring fluid restrictions often due not meet caloric needs, thus contributing to growth failure (94).

Brunton et al (1998) studied whether nutrient malabsorption or lower nutrient intake caused growth delays in infants with BPD. A total of 60 preterm infants (average birth weight 866g and gestational age of 26 weeks) were placed into two groups and fed either a nutrient enriched formula or standard infant formula up to three months corrected age. Infants fed nutrient enriched formula consumed higher amounts of protein, calories, phosphorus, and zinc. By one month corrected age, infants in the enriched formula group achieved greater linear growth (1.0 +/- 0.2 cm/wk vs. 0.8 +/- 0.2 cm/wk), weight gain (28 +/- 9 vs. 21 +/- 6 g/day), and bone mineral accretion (10.0 +/- 5.0 vs. 7.0 +/- 5.0 mg/cm mo^{-1}) (9).

Nutrients play a key role in healing damaged tissue and protecting parenchymal tissue. Vitamin A supplementation used to prevent BPD is a controversial topic. Infants

may develop Vitamin A deficiency due to lower liver stores (96). Vitamin A deficiency can be associated with "acute respiratory infections" (97) as Vitamin A is essential for the differentiation of respiratory epithethial cells and deficiency can cause changes in these cells (96).

Shenai JP et al (1990) studied the effect of vitamin A supplementation on the prevention of BPD. A total of 24 preterm infants were given Vitamin A intramuscularly at a dose of 2,000 IU every other day until enteral feeds were established (75% of energy intake from enteral feeds). Once enteral feeds were established, a multivitamin containing 1,500 IU of vitamin A was added. Twelve of the 24 infants developed BPD (98). Tyson et al (1999) used intramuscular doses of 5,000 IU three times a week for four weeks (99). Low serum retinol levels were seen in 24% of infants studied, despite the high doses given. This has caused researchers to question whether even higher doses of the vitamin are needed. Despite the promising data obtained from current research, the risks for toxicity remain and definite dose/response studies have not been established (100).

Mineral balance is a major concern for preterm infants treated for respiratory illnesses. Infants suffering from BPD are also at high risk of developing osteopenia and nephrocalcinosis. Decreased intake of calcium and phosphorus as a result of fluid restrictions and the use of unsupplemented breast milk can be contributing factors (4).

Another contributing factor includes the use of medications that compromise mineral balance. Use of diuretics such as furosemide can cause electrolyte losses, hypercalciuria, and renal calculi (101, 102). Furosemide is a potent diuretic (water pill) and works by blocking the absorption of salt and fluid in the kidney tubules, causing a profound

increase in urine output (diuresis). The diuretic effect of furosemide can cause body water and electrolyte depletion (103). Furosemide is commonly used and can cause hyponatremia, hypokalemia, hypochloridemia, hypocalcemia, and metabolic alkalosis. Potassium sparing diuretics, such as spironolactone, can help counteract the effects of electrolyte losses (4). Thiazide diuretics can cause electrolyte losses as well, and increase the need for sodium supplements. On the other hand, sodium supplements can enhance calciuria (loss of calcium in the urine), contributing to the incidence of osteopenia and nephrocalcinosis (104). Therefore, careful medical supervision is necessary during treatment.

Steroids are used to help aid in extubation and decrease oxygen exposure and respiratory support. It is recommended however, that steroids only be used in the most severe cases of respiratory failure, which includes maximum ventilation and oxygen support. Serious neonatal complications can occur when using steroids including hyperglycemia, intestinal perforation, hypertension (94, 105), as well as poor growth (both brain and somatic), and neuromotor and developmental growth (including cerebral palsy in early childhood) (94). Steroids can also cause sodium retention, osteoporosis (due to decreased absorption of calcium and phosphorus) and hyperlipidemia (105). The use of steroids (such as dexamethasone) during the first six weeks of life can cause the infant to lose more weight initially after birth, take longer to regain their birth weight, and weight gain and linear growth may be slower than their peers not receiving steroids (106).

BPD is generally thought of as a disease of infancy; however research has shown that the consequences last past childhood and sometimes into adulthood. BPD is

characterized as an “arrest of alveolar development resulting in fewer and larger alveoli”. Alveoli develop mostly during childhood and infants with BPD may end up with life long complications due to fewer alveoli developing (107).

Northway et al. (1990) studied the effects BPD had on lung function during adolescence and into adulthood. The pulmonary function was studied in 26 adolescents and adults who had BPD during infancy (born between 1964 and 1973). Two control groups were included; one group consisted of 26 age matched adolescents and adults who did not require mechanical ventilation during infancy and the other group consisted of 53 age matched normal subjects. Sixty-eight percent of subjects with BPD during infancy had airway obstruction (characterized by a decrease in forced expiratory volume in one second, forced expiratory flow between 25 and 75 percent of vital capacity, and maximal expiratory flow velocity at 50% of vital capacity) compared to controls. Fifty-two percent of subjects with BPD as infants had reactive airway disease and hyperinflation. Six had severe dysfunction or current respiratory symptoms, when compared to controls (83). One can conclude from this study that BPD can be correlated with increased risk of some degree of pulmonary dysfunction later into adulthood.

5.3 GI Complications

Gastrointestinal disease is another complication that affects preterm infants. Three common GI complications include Cholestasis, Gastro esophageal reflux (GER) and Necrotizing enterocolitis (NEC).

5.3.1 Cholestasis

Cholestasis is a condition in which the flow of bile from the liver is blocked. Cholestasis is a complication that occurs mainly in infants, mostly preterm, caused by immaturity of bile ducts. The exact cause of cholestasis is not known (4). Hypoxia, interruption of enteral feeds, drug toxicity, the use of prolonged parenteral nutrition, and sepsis can increase the risk of cholestasis in preterm infants (108). Among preterm infants less than 1000 grams, half develop cholestasis (109). Cholestasis can bring on Vitamin D deficiency due to poor absorption of fat and fat-soluble vitamins such as vitamin D (110). Resolution generally occurs in a few weeks to months with the discontinuation of parenteral nutrition and the introduction of enteral feeds (4). Therefore, the goal treatment for preterm infants suffering from cholestasis is the introduction of enteral feeds and weaning off TPN.

5.3.2 Gastro Esophageal Reflux (GER)

GER is the return of gastric contents into the esophagus (111). Reflux is a common physiological event occurring with varying degrees of frequency in most healthy individuals, but it is particularly common in infancy (4). Preterm infants are more likely to develop GER than their term peers or older children (112, 113) for several reasons: lack of tone of the lower esophageal sphincter (4), increased intra-abdominal pressure, or spontaneous relaxations in the lower esophageal sphincter (114, 115). Delayed gastric emptying and impaired gastric secretions also contribute to GER in premature infants (4).

Infants suffering from asymptomatic GER usually do not develop it until two to four months of age. By the age of one, GER generally diminishes or resolves completely.

GER is experienced more when awake than during sleep. Common signs and symptoms of GER include bradycardia, apnea, vomiting, respiratory problems, and feeding difficulties. Crying has been shown to decrease reflux, as well as offering small frequent meals and prone positioning (lying face down) of the infant (116, 117).

GER can delay or prevent appropriate enteral nutrition. Continuing the feeding regimen of feeds every three hours, adding rice cereal or commercial thickeners to the formula, and concentrating the milk in order to decrease the volume needed (2) are three strategies for the management of GER. The practice of thickening feeds (with dry rice cereal) is controversial. Emesis or vomiting is reduced with the thickening of feeds for some infants (118, 119), while increased regurgitation in long durations occurs in others (118). There are infant formulas currently on the market designed for infants with frequent "spit ups" using easy-to-digest rice starch that thickens in the stomach. The thickening effect of formula in the stomach helps keep the formula from refluxing back up into the esophagus. These products are formulated with an appropriate amount of vitamins and minerals for a term infant, and therefore, are not appropriate for the preterm infant. Adding rice cereal to pumped human milk may not thicken well, presumably due to the amylase content of human milk. Mothers who want to breast feed their infants may not be able to do so when feeds need to be thickened (4). When feeds require thickening, breast milk must be pumped and thickeners added to it.

Non-nutritional treatment for GER includes the use of prone positioning, medications, and surgery. Prone positioning to 30^{o} elevation has been shown to reduce the episodes of GER when compared to 30^{o} supine positioning (120, 121). Prone positioning is not recommended by the AAP unless the infant has symptomatic GER and the infant is on a

monitor (122, 123) as supine positioning has been shown to have the lowest risk for Sudden Infant Death Syndrome (SIDS) (124).

The use of prokinetic medications, such as cisapride, erythromycin, and metoclopramide to treat GER has been researched extensively. Cisapride is a drug that increases muscle contractions of the lower esophagus and the lower esophagus sphincter (125), erythromycin increases gastric antrum contractibility, therefore increasing gastric emptying (5), while metoclopramide increases muscle tone of the lower esophageal sphincter (126). Cisapride has a side effect of causing cardiac arrhythmias, especially when used in combination with certain antibiotics. It has recently been taken off the market (127, 128).

Erythromycin is not the drug of choice to treat GER due to its side effects, including bradyarrhthymias. Honein et al. (1999) found an association between erythromycin usage and hypertrophic pyloric stenosis in the neonatal population. Seven out of 200 infants treated with erythromycin developed hypertrophic pyloric stenosis after vaccination with the pertussis vaccine (129). Also, using antibiotics for noninfectious diseases increases antibiotic resistance (5). The Center for Disease Control has developed an action plan to prevent and reduce antibiotic resistance. They recommend only "prescribing antimicrobial therapy when and only when beneficial to the patient; targeting therapy to the desired pathogens, and using the appropriate drug, dose, and duration (130). There is no pathogen that causes reflux (5).

Metoclopramide is used most frequently for GER in infancy. It is a dopamine antagonist. By blocking the central dopamine receptors in the brain, it helps control emesis (131) and affects the GI tract as well by assisting in gastric emptying (132).

Several studies have shown its effectiveness in increasing gastric emptying, reducing the symptoms of reflux, and decreasing the amount of time the pH of the esophagus is below 4 (133-137). Use of Metoclopramide has some infrequent side effects such as nausea, vomiting, diarrhea, tradive dykinesia, and dystonia (138).

Severe cases of GER require a surgical procedure called Nissan Fundoplication. Surgical intervention is reserved for those who suffer from respiratory compromise, failure to thrive, neurological impairment, anemia due to blood loss from esophagitis, and strictures (139). This procedure involves the wrapping of the gastric fundus around the distal esophagus 360^{o} and then pulling it below the diaphragm (4). Surgical interventions such as a Nissen fundoplication have been shown to be a safe and effective treatment for GER (139).

5.3.3 Necrotizing Enterocolitis (NEC)

NEC is an acquired gastrointestinal disease that in its mildest form appears as feeding intolerance and in its extreme form is characterized by diffuse or patchy areas of necrotic tissue in the small and/or large bowel with or without perforation (4). In Neonatal Intensive Care Unit admissions, the overall incidence is between 1.0-7.7% (140-141). The disease is most common in preterm infants. The percentage of full term infants afflicted with NEC is between 7-10% (140-143). The incidence of NEC in preterm infants among NICU admissions is 1-5%, with 5-10% being very low birth weight infants (144). The overall increased survival of the preterm infant has resulted in an increased incidence of NEC development from 11.5 deaths per 100,000 births (during the pre-surfactant period 1983-1985) to 12.3 deaths per 100,000 births (in the post surfactant period 1990-1992) (4).

The etiology of the development of NEC remains unclear. Both epidemiologic and animal studies have shown that it could be multifactorial, including prematurity, infections leading to inflammation, and aggressively advancing enteral feedings (145, 146). Adamkin (2006) explains that "preoccupation with preventing NEC has contributed to the chronic undernourishment of stable, growing very-low birth weight (VLBW) infants." Undernourishment can later affect neurocognitive development (17, 44) and cause catch-up growth failure (48).

When NEC is diagnosed, feeds are held generally for 10-20 days (4) and antibiotics started (147). Parenteral nutrition becomes the only form of nutrition for the infant during this time period (4). If the infant has to have a portion of the bowel resected, the amount and location of the resection will determine the risk for feeding and nutrient malabsorption. Slow reintroduction of enteral feeds begins after the bowel has been at rest. Breast milk is generally well tolerated. When breast milk is not available and premature infant formula is not tolerated, the use of low-lactose (including premature formula), lactose-free, or protein hydrolysate formulas can be used. The use of protein hydrolysate formulas has not been proven in studies to be more effective than premature infant formulas. Protein hydrolysate formulas are lower in calcium and protein content and do not meet the nutritional needs of the preterm infant (4). When used over long periods of time these formulas increase the risk of osteopenia (148-149).

Chapter 6

Current Practices in Nutrition for the Preterm Infant

6.1 Nutritional Care after Discharge

Much attention and research has been focused on growth and feeding practices of low birth weight infants during hospital stay. The goal for the preterm infant after hospital discharge remains achieving growth and body composition similar to term peers at least for the first year of life (149). Many preterm infants are discharged home between 35 to 40 weeks gestation and weighing between 1800 and 2500 grams. Guidelines for discharge readiness have been developed by the American Academy of Pediatrics. Infant readiness for discharge includes maintaining own body temperature and adequate intake of formula or breast milk to maintain and promote adequate growth (150). Most infants remain below the 10^{th} percentile on growth charts upon discharge from the hospital. Catch up growth often does not occur before discharge from the hospital, and there nutritional requirements are higher than their term peers (21). Special attention should continue to be made the feeding practices of the preterm infant after hospital discharge.

Breast milk remains the optimal feeding for all infants. Preterm infants require breast milk fortified with protein, vitamins, and minerals to meet their nutritional needs for proper growth and development. If human milk is not available, nutrient-enriched infant formulas are the best option for preterm infants (4). Preterm infant formulas are recommended for infants up to 1,850-2,000 grams (151). Volumes should support weight gain greater than 20 g/day (152-153). Additional vitamin supplements are not

required for the premature LBW infant who is receiving fortified human milk, preterm infant formula, or nutrient-enriched formula after discharge if the milk or formula is meeting their energy needs (4).

As stated previously, early aggressive nutrition care during hospital stay has been shown to positively affect growth and prevention of extra-uterine growth restriction. The introduction of parenteral nutrition on day of life 1 or 2 and the introduction of minimal enteral feeds (MEF) early in life have helped improve growth during hospitalization and after discharge. In one study, hospital weight gain and head circumference influenced whether the infants would plot less than the 10^{th} percentile at 18 and 22 months corrected age (17). Ford et al (2000) conducted an inception cohort study comparing the growth and pubertal development of VLBW infants and normal birth weight infants to age 14 years. Eighty six survivors born <1000 grams, 120 survivors born <1000-1499grams, and 60 random children born of normal birth weight were included in the study. Measurements of weight, height, and head circumference were collected at birth and 2, 5, 8, and 14 years of age by pediatricians who were not aware of the child's birth weight. Researchers found that very low birth weight infants at 14 years of age remained smaller in height, weight, and head circumference than those infants born at greater than 2499 grams. At age 14 years, children with a birth weight greater than 2499 grams were heavier (at 59.1 kg) than infants less than 1499 grams (50kg for infants <1000grams and 52 kg for 1000-1499grams). Thus, the very low birth weight infants at 14 years of age remained smaller than their normal birth weight peers (154).

Growth and nutrition of the preterm low birth weight infant has been shown to have a long term impact on health and well-being into adult hood. Disturbances in

growth during these critical periods of human development have been hypothesized to cause alterations in hormones, cardiac output, and metabolism (20).

6.2 Effects of Early Nutrition on Long Term Health

The term "programming," popularized by Alan Lucas (2005) has prompted more research into the long-term effects of promoting optimal growth of the preterm infant. Lucas defines programming as "a stimulus or insult during a critical or sensitive period of development can have long-term or life-time effects on the organism" (155). Investigators have questioned what the long term programming effects early aggressive nutrition may have on later health. Programming has been suggested to contribute to the later development of obesity (156) and cardiovascular risk in adults (157). Many researchers have begun to look at the effects early nutrition in infants has on their later risks for such morbidities as blood pressure, diabetes, and obesity. Several studies have examined the effects of weight gain during the first four months of life (158), during the first full year of life (159), and growth catch-up to two years of age (160) on weight in adulthood. In a longitudinal observation study, body mass index (BMI) was compared with growth and feeding in infancy of 90 full term healthy infants. The researchers showed that rapid growth during the first year of life was associated with an increased BMI by the age of 6. They also revealed a connection between high protein intakes in boys and an increase in childhood obesity (161).

Intrauterine growth restriction (IUGR) has also been researched in epidemiological studies which show a close link with insulin resistance, non-insulin-dependent-diabetes (NIDDM), cardiovascular disease, hypertension, and hyperlipidemia.

Cianfarani et al. (1999) explains the concept of re-programming, which is defined as "intrauterine exposure to insufficient nutrient supply during critical periods of fetal life would permanently affect the development and function of the endocrine system, leading to metabolic changes, including reducing insulin sensitivity" (162).

Breastfeeding has been shown in studies to help reduce the risk of obesity (163), high blood pressure (164), and hyperlipidemia later in life (specifically LDL cholesterol) (165). Gillman et al. (2001) found that infants that were breast fed for longer periods of time (3 months or less versus at least 7 months) were less likely to become overweight during later childhood and adolescence. Use of infant formula, timing of first introduction to solid foods, or intake of cow's milk did not affect the risk of obesity (166). Infants fed preterm formulas grow faster and have greater risk factors for metabolic syndrome (including insulin resistance) (167).

The ultimate goal of nutrition for the preterm infant needs to balance the considerable risks of under-nutrition (which include poor growth and metabolic bone disease) against the risks of over-nutrition (later risk for obesity, increased lipid profiles, and increased blood pressure). Beginning enteral feeds early, supplementing breast milk with fortifiers, or using nutrient-enriched preterm formulas have been shown to improve growth and BMC, and therefore preventing extra-uterine growth failure and metabolic bone disease. The use of human milk fortifiers and/or nutrient enriched formulas, post discharge, have been shown to prevent growth failure and bone disease in many clinical research studies (21, 71, 74, 168).

Chapter 7

Conclusion

The purpose of this literature review was to identify the differences between term and preterm infants physiologically so as to provide the most appropriate medical nutrition therapy to prevent failure to thrive and nutrient deficiencies in the preterm infant population. Improved medical treatments and technology have lead to increases in survival rates of preterm infants, especially the youngest and smallest. Health care professionals are dealing with increasing medical complications not seen 50 years ago when mortality rates were higher. Common medical complications of prematurity involve most body systems, including pulmonary, renal, neurological, gastrointestinal, and hepatic disorders. Understanding how each medical condition affects the infant helps to most appropriately feed the preterm infant.

Energy, protein, and mineral requirements are higher in the preterm infant compared to the term infant. The American Academy of Pediatrics recommends an intake enterally of at least 120kcal/kg/day and 3.5-4.0g/kg protein per day (compared to 108kcal/kg/day and 2.2g/kg/day of protein in the term infant) (42). Infants with growth retardation, such as SGA or IUGR, have even higher energy and protein needs to provide catch-up growth and maintenance. Tsang et al (2005) have revised the protein requirements to 3.8-4.4 g/kg/day to help prevent neonatal extra-uterine growth failure (8). Similarly, infants with chronic lung disease such as BPD have been shown to need more calories and protein (95). This latter group of preterm infants often requires fluid restrictions (8), limiting the amount of formula they are able to consume. To complicate

matters, these infants expend more energy to breath, and their ability to effectively suck and swallow may be compromised due to prolonged mechanical ventilation using endotrachial tubes (4).

When enteral feedings are started, the American Academy of Pediatrics recommends breast milk as the best feeding option in most infants (39). Human milk is known to have immunological benefits, aiding in digestion and promotion of a healthy gut, as well as neurological benefits (67). Research has shown that adding protein and minerals, in the form of infant formula or human milk fortifiers, to breast milk improves weight gain (69, 70), lower leg velocity, serum alkaline phosphatase levels (indicator of rickets) (33), and neurological development (improved MDI scores) (70).

If breast milk is not available or parents choose not to breast feed, nutrient enriched formula is the next best option for the preterm infant. Preterm infant formulas are widely used in NICU's across the country. Preterm formulas contain high amounts of protein, vitamins, and minerals. The American Academy of Pediatrics recommends the use of high mineral content formula during hospitalization to improve BMC (34), growth (75), and decrease the incidence of rickets (33, 34). Such formulas are available in 20kcal/oz and 24kcal/oz concentrations. When these formulas are given at an intake of 120kcal/kg/day (100% of preterm infant's nutritional needs) they provide more than 3g/kg/day of protein (169), 200mg/kg/day of calcium and 113mg/kg/day of phosphorus. These concentrations meet calcium and phosphorus needs for most preterm infants (77). The use of standard term formulas in the preterm infant population is not recommended (4).

The ultimate goal of nutrition care of the preterm infant involves providing nutrients in sufficient amounts to match intrauterine growth rates. Risks of under nutrition include extra uterine growth failure and metabolic bone disease (33). Risks of over nutrition include rapid weight gain (exceeding intra uterine growth rates) causing an increased risk of obesity (166) and cardiovascular disease later in life (165). The AAP recommends the use of supplemented breast milk for all preterm infants during and after hospital discharge. If breast milk is not an option or not available, AAP recommends the use of preterm formulas in the hospital, followed by nutrient enriched discharge formulas after discharge (40). Modern technology has allowed for the survival of the youngest and sickest preterm infants. Although there are no standardized recommendations for the nutrition of the preterm infant after hospital discharge, the limited research available has suggested that these infants require continued special attention to nutrition well beyond discharge from the hospital.

APPENDIX

DEFINITIONS

Alkaline phosphatase (Alk Phos): an enzyme that originates mainly in liver and bone. It may be elevated in normal growth, liver disease, and/or bone disease. In metabolic bone disease, alkaline phosphatase levels rise due to osteocyte production and calcium deposition in bones (4).

Apnea: Temporary cessation of breathing and, therefore, of the body's intake of oxygen and release of carbon dioxide. Apnea of prematurity is a condition of the premature newborn, marked by repeated episodes of apnea lasting longer than 20 seconds (7).

Basal Metabolic Rate (BMR): The metabolic rate as measured 12 hours after eating, after a restful sleep, no exercise or activity preceding the test, elimination of emotional excitement, and in a comfortable temperature. It is usually expressed in terms of kilocalories per square meter or body surface per hour (7).

Blood Urea Nitrogen (BUN): Nitrogen in the blood in the form of urea, the metabolic product of the breakdown of amino acids used for energy production. The level of urea in the blood provides a rough estimate of kidney function (7).

Bradycardia: a slow heartbeat marked by a pulse rate below 60 beats per minute in an adult (7).

Chronic Lung Disease (CLD): a need for increased oxygen. Infants <32 weeks gestational age (GA): oxygen requirements at 36 weeks GA or at discharge (whichever comes first). Infants > or = to 32 weeks GA: oxygen requirements at > 28 days old or at discharge (whichever comes first) (170).

Extremely Low Birth Weight (ELBW): birth weight less than 1000 grams (4).

Gastro Esophageal Reflux (GER): the return of gastric contents into the esophagus (Orenstein SR. Gastro esophageal reflux. Pediatr Rev 13:174, 1992). Reflux can either be occult (asymptomatic) or regurgitant (symptomatic). Reflux is a common physiological event occurring with varying degrees of frequency in most healthy individuals, but it is particularly common in infancy (4).

Intrauterine Growth Retardation (IUGR): A decreased rate of fetal growth; most commonly related to inadequate placental perfusion resulting from pre-existing or coexisting maternal or placental factors. The infant's birth weight is below the 10^{th} percentile on the intrauterine growth curve for the calculated gestation period (7).

Low Birth Weight (LBW): birth weight less than 2500 grams (4).

Minimal Enteral Feeds (MEF): also called hypocaloric or priming feedings, consists of very low volume feedings (10-20ml/kg/day) initiated to acclimate the G.I. tract to feedings, stimulate gut hormones, and promote G.I. maturation (58).

Rickets: A disease of bone formation in children, most commonly the result of vitamin D deficiency, marked by inadequate mineralization of developing cartilage and newly formed bone, causing abnormalities in the shape, structure, and strength of the skeleton (7).

Small for Gestational Age (SGA): An infant whose birth weight falls less than the 10^{th} percentile for weight, length and/or head circumference on a growth curve (4).

Term Infant: an infant born between 37-42 weeks gestation (4).

Total Parenteral Nutrition (TPN): The intravenous provision of dextrose, amino acids, emulsified fats, trace elements, vitamins, and minerals to patients who are unable to assimilate adequate nutrition by mouth (7).

Very Low Birth Weight (VLBW): birth weight less than 1500 grams (4).

REFERENCES

1. American Academy of Pediatrics. Nutritional needs of the preterm infant. In: American Academy of Pediatrics Committee on Nutrition. *Pediatric Nutrition Handbook*. 5th ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 2004.
2. LaHood A, Bryant CA. Outpatient care of the premature infant. *Am Fam Physician.* 2007;76(8):1159-1164.
3. McLeod G, Sherriff J. Preventing postnatal growth failure: The significance of feeding when the preterm infant is clinically stable. *Early Hum Dev*. 2007;83:659-665.
4. Groh-Wargo ST, Thompson M, Cox JH. *Nutritional Care for High Risk Newborns. 3rd edition* Chicago, Illinois: Precept Press, Inc; 2000. Hartline JV, ed.
5. Hammer, D. Gastroesophageal Reflux and Prokinetic Agents. *Neonatal Network*. 2005;24(2):51-8.
6. O'Reilly D. Appropriate for gestational age (AGA). Medline Plus. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/002225.htm. Accessed June 15, 2008.
7. Davis FA. *Taber's Cyclopedic Medical Dictionary.*19th ed. Philadelphia, PA: F.A. Davis Company; 2001:143,218,259,272,1076,1813,2118.
8. Tsang RC, Uauy R, Koletzko B, Zlotkin S. *Nutrition of the preterm infant. Scientific Basis and Practical Guidelines*. 2nd ed. Cincinnati, OH: Digital Educational Publishing; 2005:67,201,357.
9. Hack MB, Breslan N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med*. 1991;325:231.
10. Bertino E, DiBattista E, Bossi A, Pagliano M, Fabris C, Aicardi G, Milani S. Fetal growth velocity: kinetic, clinical and biological aspects. *Arch Dis Child Fetal Neonatal Ed.* 1996;74:F10.
11. Ross, MG. Fetal Growth Restriction. Emedicine. Available at: http://www.emedicine.com/med/topic3247.htm. Accessed April 14, 2008.
12. Heird WC, Wu C. Are we discharging preterm infants in a suboptimal nutritional state? In: Post hospital nutrition in the preterm infant, report of the 106th Ross Conference on pediatric research. Columbus, Ohio: Ross Products Division, Abbott Laboratories, 1966:81-89.
13. Dancis J, O'Connell JR, Holt LE Jr. A grid for recording the weight of premature infants. *J Pediatr*. 1948;33:570-572.
14. Shaffer SG, Quimiro CL, Anderson JV, Hall RT. Postnatal weight changes in low birth weight infants. *Pediatrics*. 1987;79:702.
15. Brosius KK, Ritter DA, Kenny JD. Postnatal growth curve of the infant with extremely low birth weight who was fed enterally. *Pediatrics*. 1984;74:778.
16. Wright K, Dawson JP, Fallis D, Vogt E, Lorch V. New postnatal grids for very low birth weight infants. *Pediatrics*. 1993;91:922.
17. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and

growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006;117(4):1253-61.
18. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ*. 1998;317(7171):1481-7.
19. Bayley N. *Manual for the Bayley Scale of Infant Development*. New York, NY: The Psychological Corporation. 1969:15.
20. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. *Pediatrics*. 2003;112(1 Pt 1):e30-8.
21. Greer FR. Feeding the preterm infant after hospital discharge. *Pediatr Ann*. 2001;30(11):658-665.
22. Lucas A, Bishop NJ, King FJ, Cole TJ. Randomised trial of nutrition for preterm infants after discharge. *Arch Dis Child*.1992;67:324-7.
23. Shils ME, Olson JA, Shike M, Ross AC. *Modern Nutrition in Health and Disease*. 9th edition. Baltimore, MD. Williams and Wilkins, 1999.
24. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. *Growth*. 1976;40:329-41.
25. Tsang RC, Uauy R, Lucas A, Zlotkin S, eds. *Nutritional needs of the preterm infant: Scientific basis and practical guidelines*. Baltimore, MD: Williams and Wilkins, 1993.
26. Greene HL, Moore MEC, Phillips B, Franck L, Shulman RJ, Ament ME, Murrell JE, Chan MM, Said HM. Evaluation of a pediatric multiple vitamin preparation for total parenteral nutrition. II. Blood levels of vitamins A, D, E. *Pediatrics*. 1986;77:539-547.
27. Dabezies EJ, Warren PD. Fractures in very low birth weight infants with rickets. *Clin Orthop Relat Res*. 1997;(335):233-9.
28. Callenbach JC, Sheehan MB, Abramson SJ, Hall RT. Etiologic factors of very low-birth-weight infants. *J Pediatr*. 1981;98:800.
29. Butler NR, Goldstein H, Ross EM. Cigarette smoking in pregnancy: its influences on birthweight and perinatal mortality. *Br Med J*. 1972;2(5806):127-30.
30. Godfrey K, Walker-Bone K, Robinson S, Taylor P, Shore S, Wheeler T, Cooper C. Neonatal Bone Mass: Influence on parenteral birthweight, maternal smoking, body composition, and activity during pregnancy. *J Bone Miner Res*. 2001;16(9):1694-703.
31. Koo WWK, Steichen JJ. Osteopenia and rickets of prematurity. In: Polin SA, Fox WW, eds. *Fetal and Neonatal Physiology*. Philadelphia: Saunders, 1998;2335.
32. Eggert LD, Rusho WJ, MacKay MW, Chan GM.Calcium and phosphorus compatibility in parental nutrition solutions for neonates. *Am J Hosp Pharm*. 1982;39(1):49-53.
33. Nicholl RM, Gamsu HR. Changes in growth and metabolism in very low birthweight infants fed with fortified breast milk. *Acta Paediatr*. 1999;88(10):1056-61.
34. Lapillonne A, Salle BL, Glorieux FH, Claris O. Bone mineralization and growth are enhanced in preterm infants fed an isocaloric, nutrient-enriched preterm formula through term. *Am J Clin Nutr*. 2004;80(6):1595-603.

35. Greer FR, Steichen JJ, Tsang RC. Effect of increased calcium, phosphorus and Vitamin D intake on bone mineralization in very low birth weight infants fed formula with polycose and medium-chain triglycerides. *J Pediatr*. 1982;100:951.
36. Tomashek KM, Nesby S, Scanlon KS, et al. Commentary: nutritional riskets in Georgia. *Pediatrics*. 2001;107:e45.
37. Demarini S. Calcium and phosphorus nutrition in preterm infants. *Acta Paediatr Suppl*. 2005;94(449):87-92.
38. Rigo J, Pieltain C, Salle B, Senterre J. Enteral calcium, phosphate and vitamin D requirements and bone mineralization in preterm infants. *Acta Paediatrica*. 2007;96:969-974.
39. American Academy of Pediatrics, Work Group on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 1997;1006:1035-1039.
40. American Academy of Pediatrics, Committee on Nutrition. Nutritional Needs of preterm infants. In: Kleinman RE, ed. *Pediatric Nutrition handbook*. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1998:55-87.
41. Tsang RC, Zlotkin SH, Nichols BL, Hansen JW. *Nutrition during infancy: Principles and practice*. 2nd ed. Digital Educational Publishing, Inc; Cinncinnati, OH, 1997.
42. American Academy of Pediatrics, Committee on Nutrition. Nutritional Needs of Low-Birth-Weight Infants. *Pediatrics.* 1985;75:976-986
43. Brooke OG, Alvear J, Arnold M. Energy retention, energy expenditure, and growth in healthy immature infants. *Pediatr Res*. 1979;13(4 Pt 1):215-20.
44. Adamkin, DH. Nutrition Management of the very low birthweight infant: Optimizing enteral nutrition and post discharge nutrition. *Neo Reviews*. 2006;7:e608-e614.
45. Tsang R, Uauy R, Koletzko B, Zlotkin S. Consensus recommendations; summary of reasonable nutrient intakes for preterm infants. IN: *Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines*. Cincinnati, Ohio: Digital Publishing Inc; 2005:415-6.
46. Ernst KD, Radmacher PG, Rafail ST, Adamkin DH. Postnatal malnutrition of extremely low birth-weight infants with catch-up growth postdischarge. *J Perinatol.* 2003;23(6):477-82.
47. Ehrenkranz RA, Younes N, Lemons JA. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics.* 1999;104(2 Pt 1):280-9.
48. De Curtis M, Rigo J. Extrauterine growth restriction in very-low-birth-weight infants. *Acta Paediatr*. 2004;93:1562-1568.
49. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics.* 2003;111(5 Pt 1):986-90.
50. Zlotkin SH, Bryan MH, Anderson GH. Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants. *J Pediatr*.1981;99(1):115-20.
51. Heird WC, Kashyap S. Protein and amino acid requirements. In: Polin RA, Fox WW, editors. *Fetal and Neonatal Physiology*. Vol. 1. Philadelphia, PA: WB Saunders; 1998:654-65.

52. Flidel-Rimon O, Branski D, Shinwell ES. The fear of necrotizing enterocolitis versus achieving optimal growth in preterm infants- An opinion. *Acta Pediatrica*. 2006;95:1341-1344.
53. Azotemia. Merriam-Webster Online Dictionary. 2008. Available at http://www.merriam-webster.com/dictionary/azotemia. Accessed on October 16, 2008.
54. Dunham B, Marcuard S, Khazanie PG, Meade G, Craft T, Nichols K. The solubility of calcium and phosphorus in neonatal total parenteral nutrition solutions. *J Parenter Enteral Nutr*. 1991;15(6):608-11.
55. Klein GL, Coburn JW. Parenteral nutrition: Effect on bone and mineral homeostasis. *Annu Rev Nutr*. 1991;11:93-119.
56. Smith SL, Kirchhoff KT. Metabolic bone disease in very low birth weight infants: Assessment, prevention, and treatment by neonatal nurse practitioners. *J Obstet Gynecol Neonatal Nurs* 1997;26(3):297-302.
57. Thureen PJ. Early Aggressive Nutrition in the Neonate. *NeoReviews*. 1999;20(9):e45-e55.
58. Slagle TA, Gross SJ. Effect of early low volume enteral substrate on subsequent feeding tolerance in very low birthweight infants. *J Pediatr*. 1988;113:526.
59. Dunn L, Hulman S, Weiner J, Kliegman R. Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: preliminary report of a randomized trial. *J Pediatr*. 1988;112(4):622-9.
60. Berseth CL. Effect of early feeding on maturation of the preterm infant's small intestine. *J Pediatr*. 1992;120:947-953.
61. Mihatsch WA, von Schoenaich P, Fahnenstich H, Dehne N, Ebbecke H, Plath C, von Stockhausen HB, Muche R, Franz A, Pohlandt F . The significance of gastric residuals in the early enteral feeding advancement of extremely low birth weight infants. *Pediatrics*. 2002;109:457-459.
62. Cobb BA, Carlo WA, Ambalavanan N. Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2004;113:50-53.
63. Caple J, Armentrout D, Huseby V, Halbardier B, Garcia J, Sparks JW, Moya FR . Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. *Pediatrics*. 2004;114(6):1597-1600.
64. Book LS, Herbst JJ, Jung AL. Comparison of fast and slow feeding rate schedules to the development of necrotizing enterocolitis. *J Pediatr*. 1976;89:463-466.
65. Anderson DM, Kliegman RM. The relationship of neonatal alimentation practices to the occurrence of endemic necrotizing enterocolitis. *Am J Perinatol*. 1991;8:62-67.
66. Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2003;111(3):529-34.
67. Lonnerdal B. Nutritional and physiologic significance of human milk proteins. *Am J Clin Nutr* 2003;77(6):1537S-1543S.
68. Hawthorne KM, Abrams SA. Safety and efficacy of human milk fortification for very-low-birth-weight infants. *Nutr Rev*. 2004;62(12):482-5.

69. Ronnholm KAR, Perheentupa J, Siimes MA. Supplementation with human milk protein improves growth of small premature infants fed human milk. *Pediatrics*. 1986;77(5):649-653
70. Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: Does it make a difference? *J Perinatol*. 2006;26(10): 614-21.
71. Schanler RJ, Burns PA, Abrams SA, Garza C. Bone mineralization outcomes in human milk-fed preterm infants. *Pediatr Res*.1992;31(6):583-6.
72. Forbes, G.B. Nutritional adequacy of human breast milk for prematurely born infants. In: Lebenthal E., editor. *Textbook of Gastroenterology and nutrition in infancy*. New York: Raven Press;1989:27-34.
73. Young TE, Mangum B. *Neofax*. 19th ed. Acorn Publishing, Inc. Raleigh, NC; 2006:255, 257.
74. Bishop NJ, King FJ, Lucas A. Increased bone mineral content of preterm infants fed with a nutrient enriched formula after discharge from hospital. *Arch Dis Child*. 1993;68(5 Spec No):573-578.
75. Carver JD, Wu PY, Hall RT, Ziegler EE, Sosa R, Jacobs J, Baggs G, Auestad N, Lloyd B. Growth of preterm infants fed nutrient-enriched or term formula after hospital discharge. *Pediatrics*. 2001;107(4):683-689.
76. Lucas A, Fewtrell MS, Morley R, Singhal A, Abbott RA, Isaacs E, Stephenson T, MacFadyen UM, Clements H. Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. *Pediatrics*. 2001;108(3):703-711.
77. American Academy of Pediatrics Committee on Nutrition. Iron fortification of infant formulas. *Pediatrics*. 1999;104(1):119.
78. Tsang RC. Vitamin and mineral requirements in preterm infants. New York: Marcel Dekker;1985:vii.
79. Schulze KF, Stefanski M, Masterson J, Spinnazola R, Ramakrishnan R, Dell RB, Heird WC. Energy expenditure, energy balance, and composition of weight gain in low birth weight infants fed diets of different protein and energy content. *J Pediatr*. 1987;110(5):753-759.
80. Weber A, Loui A, Jochum F, Obladen M. Breast milk from mothers of very low birthweight infants: variability in fat and protein content. *Acta Paediatr*. 2001;90(7):772-775.
81. O'Reilly, D. Premature Infant. Medline Plus. Available at http://www.nlm.nih.gov/medlineplus/ency/article/001562.htm. Accessed on March 8, 2008.
82. Greene, A. Neonatal Respiratory Distress Syndrome. Medline Plus. http://www.nlm.nih.gov/medlineplus/ency/article/001563.htm. Accessed on April 5, 2008.
83. Northway WH, Pitlick PT, Eichler I, Lamm RL, Brown BW. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med*. 1990;323(26):1793-1799.
84. Escobedo MB. Gonzalez A. Bronchopulmonary dysplasia in the tiny infant. *Clin Perinatol*. 1986;13:315.

85. Bozynski ME, Albert JM, Vasan U, Nelson MN, Zak LK, Naughton PM. Bronchopulmonary dysplasia and postnatal growth in extremely premature black infants. *Early Hum Dev*. 1990;21(2):83-92.
86. Davidson S, Schrayer A, Wielunsky E, Krikler R, Lilos P, Reisner SH.. Energy intake, growth, and development in ventilated very-low-birth-weight infants with and without bronchopulmonary dysplasia. *Am J Dis Child*. 1990;144:553.
87. Meisels SJ, Plunkett JW, Roloff DW, Pasick PL, Stiefel GS. Growth and development of preterm infants with respiratory distress syndrome and bronchopulmonary dysplasia. *Pediatrics*. 1986;77:345.
88. Yu VYH, Orgill AA, Lim SB, Bajuk B, Astbury J. Growth and development of very low birthweight infants recovering from bronchopulmonary dysplasia. *Arch Dis Child*. 1983;58:791.
89. Vohr BR, Bell EF, Oh W. Infants with bronchopulmonary dysplasia: Growth pattern and neurologic and developmental outcome. *Am J Dis Child*. 1982;136:443.
90. Markestad T, Fitzhardinge PM. Growth and development in children recovering from bronchopulmonary dysplasia. *J Pediatr*. 1981;98:597.
91. Gibson AT, Pearse RG, Wales JKH. Growth retardation after dexamethasone administration: assessment by knemometry. *Arch Dis Child*. 1993;69:505.
92. Hansen T, Corbet A. Lung Development and Function. IN: Taeush HW, Ballard RA. *Avery's Diseases of the Newborn*. 7th ed. Philadelphia, PA. Saunders, 1998;546.
93. Stahlman MT. Acute respiratory disorders in the newborn. In: Avery Gb, ed. Neonatology: Pathophysiology and management of the newborn, 3d ed. Philadelphia: Lippincott, 1987;418.
94. Vaucher YE. Bronchopulmonary dysplasia: an enduring challenge. *Pediatr Rev*. 2002;23(10):349-357.
95. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. *J Pediatr*. 1998;133(3):340-345.
96. Coutsoudis A, Adhikari M, Pillay K, Kuhn L, Coovadia HM. *S Afr Med J*. 2000;90(7):730-736.
97. Sempertegui F, Estrella B, Camaniero V, Betancourt V, Izurieta R, Ortiz W, Fiallo E, Troya S, Rodríguez A, Griffiths JK. The beneficial effects of weekly low-dose vitamin A supplementation on acute lower respiratory infections and diarrhea in Ecuadorian children. *Pediatrics*. 1999;104(1):e1.
98. Shenai JP, Rush MG, Stahlman MT, Chytil, F. Plasma retinol-binding protein response to vitamin A administration in infants susceptible to bronchopulmonary dysplasia. *J Pediatr*. 1990;116:607.
99. Tyson JE, Ehrenkranz RA, Stoll BJ. Vitamin A supplementation to increase survival without chronic lung disease in extremely low birth weight (ELBW) infants: a 14-center randomized trial. *Pediatr Res*. 1999;45:199A
100. Lawson EE, Stiles AD. Vitamin A therapy for prevention of chronic lung disease in infants. *J Pediatr*. 1987;111:247.

101. Southall DP, Samuels MP. Bronchopulmonary dysplasia: A new look at management. *Arch Dis Child*. 1990;65:1089-1095.
102. Robinson CM, Cox MA. The incidence of renal calcification in low birthweight infants on lasix for bronchopulmonary dysplasia. *Pediatr Res*. 1986;20:359A.
103. Furosemide. Medicine Net. Available at http://www.medicinenet.com/furosemide/article.htm. Accessed on March 14, 2008.
104. Campfield T, Braden G, Flynn-Valone P, Powell S. Effect of diuretics on urinary oxalate, calcium, and sodium excretion in very low birth weight infants. *Pediatrics*. 1997;99:814.
105. Yoder MC, Chua R, Tepper R. Effect of dexamethasone on pulmonary inflammation and pulmonary function of ventilator dependent infants with bronchopulmonary dysplasia. *Am Rev Respir Dis*. 1991;143(5 Pt 1):1044-1048.
106. Mammel MC, Johnson DE, Green TP, et al. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet*. 1983;1:1356.
107. Hudak, B. Bronchopulmonary dysplasia: Beyond the Neonatal Period. Available at http://www.dcmsonline.org/jaxmedicine/2001journals/dec2001/bronchopulmonary.htm. Accessed on April 2, 2008.
108. McKiernan PJ. Neonatal cholestasis. *Semin Neonatol*. 2002;7(2):153-165.
109. Haber BA, Lake AM. Cholestatic jaundice in the newborn. *Clin Perinatol*. 1990;17:483.
110. Zieve D, Juhn G, Eltz DR, Stacy KA. Gastro Esophageal Reflux Disease. Medline Plus. Available at http://medlineplus.gov/. Accessed on March 8, 2008.
111. Orenstein SR. Gastro esophageal reflux. *Pediatr Rev*.1992;13:174.
112. Newell SJ, Morgan ME, Durbin GM, Booth IW, McNeish AS. Does mechanical ventilation precipitate gastro-oesophageal reflux during enteral feeding? *Arch Dis Child*. 1989;64(10 Spec No):1352-1355.
113. Marino AJ, Assing E, Carbone MT, Hiatt IM, Hegyi T, Graff M. The incidence of gastroesophageal reflux in preterm infants. *J Perinatol.*1995;15(5):369-371.
114. Omari TI, Barnett C, Snel A, Goldsworthy W, Haslam R, Davidson G, Kirubakaran C, Bakewell M, Fraser R, Dent J . Mechanisms of gastroesophageal reflux in healthy premature infants. *J Pediatr.* 1998;133(5):650-654.
115. Omari TI, Barnett C, Snel A, Davidson G, Haslam R, Bakewell M, Dent J. Mechanisms of gastroesophageal reflux in preterm infants with chronic lung disease. *J Pediatr Surg.*1999;34:1795.
116. Orenstein SR. Crying does not exacerbate gastroesophageal reflux in infants. *J Pediatr Gastroenterol Nutr.*1992;14:34.
117. Sutphen JL, Dillard VL. Effect of feeding volume on early postcibal gastroesophageal reflux in infants. *J Pediatr Gastroenterol Nutr.* 1988;7:185.
118. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. *J Pediatr*. 1987;110:181.
119. Vandenplas Y, Sacre L. Milk-thickening agents as a treatment for gastroesophageal reflux. *Clin Pediatr.* 1987;26:66.
120. Orenstein SR. Prone positioning in infant gastroesophageal reflux: Is elevation of the head worth the trouble? *J Pediatr.* 1990;117:184.

121. Tobin JM, McCloud P, Cameron DJS. Posture and gastro-oesophageal reflux: A case for left lateral positioning. *Arch Dis Child*. 1997;76:254.
122. American Academy of Pediatrics Task Force on Infant Positioning and SIDS. Infant sleep position and sudden infant death syndrome (SIDS) in the United States: Joint commentary from the American Academy of Pediatrics and selected agencies of the federal government. *Pediatrics*.1994;93:820.
123. American Academy of Pediatrics Task Force on Infant Positioning and SIDS. Positioning and Sudden Infant Death Syndrome (SIDS): Update. *Pediatrics*. 1996; 98:1216.
124. American Academy of Pediatrics Task Force on Infant Positioning and SIDS. Positioning and Sudden Infant Death Syndrome. *Pediatrics*. 1992;89:1120.
125. Medicine Net. Available at http://www.medicinenet.com/cisapride/article.htm. Accessed on May 15, 2008.
126. Medicine Net. Available at http://www.medicinenet.com/metoclopramide/article.htm. Accessed on May 15, 2008.
127. Scott RB, Ferreria C, Smith L, Jones AB, Machida H, Lohoues MJ, Roy CC. Cisapride in pediatrics gastroesophageal reflux. *J Pediatr Gastroenterol Nutr*. 1997; 25:499.
128. Hill SL, Evangelista JK, Pizzi AM, Mobassaleh M, Fulton DR, Berul CI. Proarrhythmia associated with cisapride in children. *Pediatrics*. 1998; 101:1053.
129. Honein MA, Paulozzi LJ, Himelright IM, Lee B, Cragan JD, Patterson L, Correa A, Hall S, Erickson JD. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet*. 1999; 354(9196):2101-2105
130. Centers for Disease Control and Prevention. 2004. Public health action plan to combat antimicrobial resistance. http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf. Accessed on October 11, 2008.
131. Lehne RA. Other gastrointestinal drugs. In: *Pharmacology for Nursing Care*, 5th ed., Lehne, RA, ed. St. Louis: WB Saunders; 2004:839-850.
132. Hay AM. Pharmacological analysis of effects of metoclopramide on guinea pig isolated stomach. *Gastroenterology*. 1977;75(5 part 1):864-869.
133. Hyman PE, Abrams CE, and Dubois A. Gastric emptying in infants: Response to metoclopramide depends on underlying condition. *J Pediatr Gastroenterol Nutr.* 1988;7(2):181-184.
134. Rode H, Stunden RJ, Millar AJ, Cywes S. Esophageal pH assessment of gastroesophageal reflux in 18 patients and the effect of two prokinetic agents: Cisapride and metoclopramide. *J Pediatr Surg*. 1987;22(10):931-934.
135. Tolia V, Calhoun J, Kuhns L, Kauffman RE. Randomized, prospective double-blind trial of metoclopramide and placebo for gastroesphageal reflux in infants. *J Pediatr*. 1989;115(1):141-145.
136. Sankaran, K, Yeboah E, Bingham WT, Ninan A. Use of metoclopramide in preterm infants. *Dev Pharmacol Ther.* 1982;5(3-4):114-119.

137. Meadow WL, Bui KC, Strates E, Dean R. Metoclopramide promotes enteral feeding in preterm infants with feeding intolerance. *Dev Pharmacol Ther.* 1989;13(1):38-45.
138. Wilson CM, Bird SG, Bocash W, Yang LL, Merritt RJ. Methemoglobinemia following metoclopramide therapy in an infant. *J Pediatr Gastroenterol Nutr.* 1987;6(4):640-642.
139. Rothenberg S. The first decades experience with laparoscopic Nissen Fundoplication in infants and children. *J Pediatr* Surg. 2005;40:142-147.
140. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: Pathogenesis, classification, and spectrum of illness. *Curr Probl Pediatr.* 1987;17(4):213.
141. Kosloske AM. Epidemiology of necrotizing enterocolitis. *Acta Pediatr Suppl*. 1994;396:2.
142. Kliegman RM, Fanaroff AA. Neonatal necrotizing enterocolitis: A nine year experience. *Am J Dis Child*. 1981;135:603.
143. Walsh MC, Kliegman RM. Necrotizing enterocolitis: Treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33(1):179.
144. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs*. 2008; 68(9):1227-1238.
145. Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. *Pediatr Clin North Am*. 1996;43(2):409-432.
146. Hsueh W, Caplan MS, Qu XW, Tan XD, De Plaen IG, Gonzalez-Crussi F. Neonatal necrotizing enterocolitis; clinical considerations and pathogenic concepts. *Pediatr Dev Pathol*. 2003;6:6-23
147. Neu, J. Neonatal necrotizing enterocolitis: An update. *Acta Paediatrica*. 2005;94(suppl 449):100-105.
148. Giles MM, Fenton MH, Shaw B, Elton RA, Clarke M, Lang M, Hume R. Sequential calcium and phosphorus balance studies in preterm infants. *J Pediatr.* 1987;110:59.
149. Greer FR, Tsang RC. Calcium, phosphorus, magnesium, and vitamin D requirements for the preterm infant. In:Tsang RC, ed. *Vitamin and mineral requirements in preterm infants*. New York: Marcel Dekker;1985:99.
150. American Academy of Pediatrics. Hospital Discharge of the High Risk Infant-Proposed Guidelines. *Pediatrics*. 1998;102(2):411-417.
151. American Academy of Pediatrics and American College of Obstetrics and Gynecology. *Guidelines for perinatal care*. 3rd edition. Elk Grove Village, Ill: American Academy of Pediatrics; and Washington, D.C.: American College of Obstetricians and Gynecologists; 1992.
152. Manser JJ. Growth in the high-risk infant. *Clin Perinatol*. 1984;11:19.
153. Altigani M, Murphy JF, Newcombe RG, Gray OP. Catch-up growth in preterm infants. *Acta Pediatr Scand (suppl)*. 1989;357:3.
154. Ford GW, Doyle LW, Davis NM, Callanan C. Very Low Birth Weight and Growth into Adolescence. *Arch Pediatr Adolesc Med*. 2000;154:778-784.
155. Lucas A. The developmental origins of adult health and well-being. *Adv Exp Med Biol*. 2005;569:13-15.

156. Singhal A, Farooqi IS, O'Rahilly S, Cole TJ, Fewtrell M, Lucas A. Early nutrition and leptin concentrations in later life. *Am J Clin Nutr*. 2002;75(6):993-999.
157. Owen CG, Whincup PH, Gilg JA, Cook DG. Effect of breast feeding in infancy on blood pressure in later life: systematic review and meta-analysis. *BMJ*. 2003;327(7425):1189-1195.
158. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter cohort study. *Pediatrics*. 2002;109(2):194-199.
159. Stettler N, Bovet P, Shamlaye H, Zemel BS, Stallings VA, Paccaud F. Prevalence and risk factors for overweight and obesity in children from Seychelles, a country in rapid transition: the importance of early growth. *Int J Obes Relat Metab Disord*. 2002;26(2):214-219.
160. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*. 2000;320(7240):967-971.
161. Gunnarsdottir I, Thorsdottir I. Relationship between growth and feeding in infancy and body mass index at the age of 6 years. *Int J Obes Relat Metab Disord*. 2003;27(2):1523-1527.
162. Cianfarani S, Germani D, Branca F. Low Birthweight and adult insulin resistance: the "catch-up growth" hypothesis. *Arch Dis Child Fetal Neonatal Ed*. 1999;81(1):F71-F73
163. Von Kries R, Koletzko B, Sauerwald T, von Mutius, Barnert D, Grunert V, von Voss H. Breast feeding and obesity: cross sectional study. *BMJ*. 1999;319(7203):147-150.
164. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet*. 2001;357(9254):413-419.
165. Singhal A, Cole TJ, Fewtrell M, Lucas A. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomized study. *Lancet*. 2004;363(9421):1571-1578.
166. Gillman MW, Rifas-Shiman SL, Camargo CA Jr., Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA. Risk of Overweight Among Adolescents Who Were Breastfed as Infants. *JAMA*. 2001;285(19):2461-2467.
167. Fewtrell MS, Cole TJ, Bishop NJ, Lucas A. Neonatal factors predicting childhood height in preterm infants: evidence for a persisting effect of early metabolic bone disease? *J Pediatr*. 2000;137(5):668-673.
168. Chan GM. Growth and bone status of discharged very low birth weight infants fed different formulas or human milk. *J Pediatr*. 1993;123(3):439-443
169. Fairey AK, Butte NF, Mehta N, Thotathuchery M, Schanler RJ, Heird WC. Nutrient accretion in preterm infants fed formula with different protein: energy ratios. *J Pediatr Gastroenterol Nutr*.1997;25(1):37-45.
170. UCSF Children's Hospital, Intensive Care Nursery House Staff Manual. Retrieved from http://www.ucsfhealth.org/childrens/health_professionals/manuals/31_ChronicLungDis.pdf on February 16 2008