CLINICAL GUIDELINE:

NUTRITION OF THE PREMATURE AND LOW BIRTH WEIGHT INFANT

Metropole Pediatric Interest Group: Western Cape

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Tygerberg Hospital

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Paediatric Working Group Guidelines: Developers Summary

Scope and Purpose

The Guidelines for Nutrition of the Premature and Low Birth Weight Infant have been developed by the Western Cape Paediatric Nutrition Working Group. The aim of this Guideline is to provide an evidence based nutrition management resource tool, which may be used by health professionals involved in the prescription and supply of nutrition support to premature and low birth weight infants.

This Guideline uses an "A, B, C, D" approach e.g. Anthropometry, Biochemistry, Clinical and Dietary, to provide a step by step reference as to how to approach nutrition support.

These guidelines outline nutrition support in premature and low birth weight infants. They are not meant to be prescriptive and there may be individual case variations.

Stakeholder Involvement

Members of the Paediatric Working Group are outlined in table 1:

Table 1: Paediatric Working Group Members and Reviewers

Principal Author	Affiliation
Elisna van Wyk	Department of Human Nutrition, Tygerberg Academic Hospital
Pediatric Working Group Members	
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Rigour of Development

A Pubmed search was completed using key words such as "premature/preterm infant/baby nutrition/feeding". Table 2 was used to define the type of articles desired. The recommendations are primarily drawn from expert consensus documents produced by the Committee for Premature Infant Nutrition of the American Academy of Pediatrics (Tsang et al, 2005). (See reference nr 17.)

Table 2: Grading of levels of evidence (LOE) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000

Grading	Level of evidence
1+++	High quality meta analyses, systematic reviews of RCT's or RCT's with very low risk of bias
1+	Well conducted meta analyses, systematic review of RCT's or RCT's with low risk of bias
1-	Meta analyses, systematic reviews of RCT's or RCT's with a high risk of bias
2++	High quality systematic reviews of case controlled or cohort studies
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies e.g. case reports, case series. Evidence from non analytical studies e.g. case reports, case series
4	Evidence from expert opinion

The principle author was responsible for compiling the "Nutrition of the Premature and Low Birth Weight Baby" guideline, which was circulated amongst members of the working group in addition to some of the ad hoc members and specialists. All guidelines went through a process of first to third drafts. The recommendations within the guidelines were drafted following a review of the literature and discussions within the group.

All benefits and potential harm of the nutrition recommendations within the guidelines have been discussed and reviewed by the panel at length. The recommendations provided within the text and summary tables are referenced and evidence based.

The Neonatology Team at Tygerberg Children's Hospital, who are considered to be experts in their field have reviewed this guideline. Comments received have been incorporated into the clinical guideline.

The contents of this guideline should be reviewed in two years from the date of publishing, with a view to incorporating the latest developments and research findings and field experiences.

Clarity and Presentation

The format of this clinical guideline aims to direct the health professional through a logical Nutrition Care Plan using an A, B, C, D e.g. Anthropometry, Biochemistry, Clinical and Dietary approach. A flow diagram for quick reference summarizes the feeding approach for this patient group. In addition to this flow diagram the full text may be consulted as required.

A variety of management options have been present targeting clients within the Public and Private Health Care sector. The guideline provides a stratified management approach and identifies current nutrition support systems through which they could be implemented.

Applicability

The working group did not perceive any potential barriers as all nutrition support strategies are currently available within Public and Private Health Care centers and are available on national tenders. All cost implications have been considered and the most cost effective nutrition management strategies have been recommended.

Editorial Independence

The principal author, working group and or reviewers did not receive any funding to complete these guidelines and the team records no conflicts of interest.

FLOW DIAGRAM FOR THE ENTERAL FEEDING OF THE ELBW AND VLBW PREMATURE INFANT:

START HERE AND READ CLOCKWISE:

DAY 0:

Doctor initiates IV fluid administration at:
110ml/kg/d: ELBW
75ml/kg/d: VLBW
Plus:
NPO/Minimal enteral feeding: 0.5 – 1ml/6hr via orogastric route

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Day 1 to full feed volume (±10 – 14 days):

Daily fluid increase of 10 – 20ml/kg IF no signs of complications present

Feeding route:
<33-34 weeks: Orogastric
>33-34 weeks: Breastfeeding/ Cupfeeding

Frequency:
Bolus: 2 hourly or Intermittent Constant Infusion

±Day 10 -14 and onwards:
Full feed reached (150ml/kg/day)
Refer to Dietitian for initiation of fortification of all breast milk feeds.
Commence with half the recommended dosage on day 1 of fortification. Full fortification the next day (if no signs of intolerance present).

Doctor prescribes multivitamin drops (e.g. 0.3ml Vidaylin).
When indicated:
1-2mg/kg elemental Iron is added.
Supplementation must be continued until hospital discharge.

Choices for feeding in order of preference:
1. Expressed Breast Milk (pasteurized if RVD exposed)
2. Pasteurised Donor Breast Milk
3. Preterm Infant milk Formula (only if no EBM is available)

Preparation for Hospital Discharge:
Prior to discharge the following aspects must be assessed:
1. Infant gaining weight when breastfed ad lib (or on full volume infant milk formula)
2. All vital signs remain stable.
3. Parental competence confirmed.
4. Weight of ideally 1.8 kg reached.
5. Gestational age ≥34 weeks reached.
5. Doctor prescribes supplementation:
   0.6 ml multivitamin drops,
   1-2 mg/kg elemental Iron,
   Supplementation must continue for the first year of life.
6. Doctor books first follow-up appointment for infant at preterm follow-up clinic for growth and neuro-developmental assessment (Individual adjustments of the broad guideline for follow-up may be needed, i.e: <1kg: 6 weeks corrected age, 1.0 – 1.5kg: 3 months corrected age.)

Follow-up by Dietitian in hospital:
Growth Monitoring:
Daily weight
Weekly length and head circumference.

Feed evaluation:
Re-evaluation of nutrition prescription.
Daily volume and/or fortifier dosage adjustment.

GLOSSARY

(Abbreviations followed by Definitions)

Abbreviations:

AA: Arachidonic Acid
AGA: Appropriate for gestational age
BMF: Breast Milk Fortifier
BPD: Broncho Pulmonary Displasia
DBM: Donor Breast Milk
DHA: Docosahexaenoic Acid
EBM: Expressed Breast Milk
ELBW: Extremely Low Birth weight
GR: Growth Retardation
HIV: Human Immuno-deficiency Syndrome
HMF: Human Milk Fortifier
IUGR: Intra-uterine Growth Retardation
KMC: Kangaroo Mother Care
LBW: Low Birth Weight
LGA: Large for gestational age
MUAC /MAC: Mid-upper Arm Circumference
NEC: Necrotising Enterocolitis
NNL: Neonatelyte
NPO: Null per os
PCA: Post-conceptional age
PER: Protein: Energy Ratio
PMTCT: Prevention of Mother to Child Transfer
PN: Parenteral nutrition
PDA: Patient Ductus Arteriosus
ROP: Retinopathy of Prematurity
SBS: Short Bowel Syndrome
SGA: Small for gestational age
TPN: Total Parenteral Nutrition
VLBW: Very Low Birth weight

Definitions:

AD LIBITUM FEEDING: The enteral feed starts in response to the infant's hunger cues and ends when the infant demonstrates satiation. The infant therefore determines the duration and volume of intake.[42]

ATELECTASIS: The incomplete expansion or collapse of pulmonary alveoli, or of a segment, lobe or lobes of a lung.[6]

DEMAND FEEDING: The feed starts in response to the infant's hunger cues but ends when a prescribed volume of intake is reached. This strategy is more suited to infants who are receiving gastric tube feed, or who are fed orally from a bottle or cup. It is much more difficult to determine when a target volume of intake has been reached in breast fed infants.[42]

GASTROSCHISIS: Developmental anomaly resulting from faulty closure of the body wall along the mid-ventral line.[37]

HYDROPS FETALIS: Abnormal accumulation of fluid in the entire body of the neonate, in hemolytic disease due to antibodies present in the blood of the Rh-negative mother.[37]

OMPHALOCELE: Protrusion, at birth, of part of the intestine through a defect in the abdominal wall at the umbilicus.[37]

PRSL: *Potential Renal Solute Load:* Refers to solutes of dietary origin that would need to be excreted in the urine if none were diverted into synthesis of new tissue or lost through non-renal routes.[12] (Includes available phosphorus in the formula together with protein, sodium, potassium and chloride)

RSL: *Renal Solute Load:* Refers to all solutes, of endogenous or dietary origin, that require excretion by the kidneys. Most of the RSL is of dietary origin and is closely related to the nitrogen and electrolyte content of the diet.[12] (Available Phosphorus not included in the calculation.)

SEMI-DEMAND FEEDING: The infant's hunger cues are assessed at scheduled intervals. If hunger cues are noted the infant is offered a feed. If the infant is sleeping the assessment is delayed for about 30 – 60 minutes. If hunger cues are then noted the infant is offered a feed. If the infant remains asleep, the infant is given a gavage feed. The volume of intake is recorded.[42]

TACHYPNOEA: Respiratory rate > 60/ minute

3. MAIN DOCUMENT

3.1 INTRODUCTION

MOTIVATION FOR THE GUIDELINE:
The aim of this guideline is to provide health care professionals and health care workers with standardized evidence-based guidance on the nutrition of the premature and low birth weight infant.

PATIENTS TO WHOM THE GUIDELINE APPLIES:
All premature and low birth weight infants as defined in section 3.1.1.

3.1.1 DEFINITIONS:
Premature Infant: Any baby born before 37 weeks gestation [4, 92]

Low Birth Weight (LBW) Infant: Any infant born with a birth weight less than 2,5 kg[4,26]. (Sub-classification of LBW discussed in section 3.2.)

3.1.2 PATHOGENESIS OF THE PREMATURE AND LOW BIRTH WEIGHT INFANT:

Premature infant:

Risk factors associated with premature birth [10]

FACTOR	DESCRIPTION
Behavioral	• Low pre-pregnancy weight for height • Smoking, especially > 11 cigarettes/day • Substance abuse
Demographic	• Age < 18 years • Age of first pregnancy > 35 years • Less than high school education • Poverty • Non-Caucasian race • Unmarried • Under- (BMI<18.5) or overweight (BMI>25) prior to pregnancy
Reproductive System	• Cervical abnormality, surgery, biopsy • Dilated or effaced cervix • History of infertility • Hypertension during pregnancy • Multi-parity > 5 • Multiple gestation • No prenatal care • Oligohydramnios (diminished amniotic fluid) • Placental abnormalities • Previous preterm birth • Previous still birth or neonatal loss • Previous first or second trimester abortions • Polyhydramnios (excessive amniotic fluid) • Uterus abnormalities • Short inter-pregnancy interval

Risk factors associated with premature birth (continued)[10]

FACTOR	DESCRIPTION
Psychosocial	• Domestic abuse • Exposure to job related teratogens • High stress • Inadequate housing • Strenuous job activity

Risk factors associated with fetal intrauterine growth restriction [11]

FACTOR	DESCRIPTION
Fetal	• Chromosomal abnormalities • Multifactorial congenital malformations • Multiple gestations • Infection
Placental	• Small placenta • Circumvallate placenta • Chorioangiomata (a cyst-like mass that forms in the uterus)
Maternal	• Extremes of under- and/or malnutrition • Vascular/ renal disease • Congenital or acquired thrombophylic disorder • Drugs/ lifestyle • High altitude or significant hypoxic disorder

Problems associated with prematurity [3],[4]

SYSTEM	PROBLEM
Respiratory	• Respiratory distress syndrome (RDS) or Hyaline membrane disease (HMD)* • Chronic lung disease, i.e. Broncho Pulmonary Displasia (BPD)*
Cardiovascular	• Patent Ductus Arteriosus (PDA)*
Renal	• Fluid and electrolyte disturbances (e.g. hyponatremia)
Neurologic	• Apnoea • Intraventricular bleeding
Gastro-intestinal	• Hyperbilirubinaemia • Feeding intolerance • Necrotizing enterocolitis (NEC)*
Haematologic	• Anaemia
Immunologic	• Sepsis • Pneumonia • Meningitis
Ophthalmologic	• Retinopathy of prematurity (ROP)
Other	• Bradycardia • Cyanosis • Osteopenia

*See section 3.8 for the treatment of some of these complications of prematurity.

3.2 ANTHROPOMETRIC ASSESSMENT: [26, 29]

Each infant's intra-uterine growth status should be determined at birth by plotting his weight-, length- and head circumference for gestational age on the perinatal growth chart. (See Appendix A, p 47)

a) Determination of gestational age. [29]
If the duration of pregnancy is unknown, gestational age can be assessed in newborns by means of the Ballard-gestational determination method. (See Appendix B, p 48)

b) Classification according to birth weight[3, 92]:

Low Birth Weight (LBW):	<2.5 kg
Very Low Birth Weight (VLBW):	<1.5 kg
Extremely Low Birth Weight (ELBW):	<1,0 kg

Large for gestational age (LGA):	>90th percentile
Appropriate for gestational age (AGA):	10th – 90th percentile
Small for gestational age (SGA):	<10th percentile

c) Classification of intra uterine growth restriction according to all 3 anthropometrical indicators[3]: (i.e. Weight, Height, Head circumference)

Symmetrical growth restriction: Birth weight, height and head circumference all fall below the 10th percentile.

Prognosis of symmetrical growth restriction (GR): Always poor.

Asymmetrical growth restriction: Only one or two of the above-mentioned indicators fall below the 10th percentile.

Prognosis of asymmetrical growth restriction (GR): Good, if head circumference falls within the normal percentiles (10th – 90th), but:

Poor, if head circumference falls below the 10th percentile.

The prognosis does not refer to a prediction of life or death, but rather to an increased risk of complications due to the prematurity, as well as a diminished quality of life due to neuro-developmental delays. A suboptimal head circumference measurement at 8 months of age has been independently associated with decreased intellectual quotients, cognitive functioning skills and behavioral problems at school age.[98]

d) Evaluation of growth rate: [34, 35, 91]

Ideal rate of weight gain[3]:   15 g/ kg / day (At 2-3 weeks after birth.)

According to Lubchenco and associates, between 24 and 36 weeks of gestation an infant who grows at the 50th percentile, gains 14.5g/kg/day.

Expect an initial weight loss of 5-15% of birth weight during the first week of life, due to loss of lung fluid, passage of urine and meconium, energy produced for maintenance of body temperature as well as insensible fluid losses.

Birth weight should be regained at 10-14 days after birth in both preterm and term infants.

Ideal length accretion rate: 0,8 – 1,0 cm / week

Accurate length measurements are difficult to obtain.[91]

Ideal head circumference accretion rate: 0,5 – 0,8 cm / week

Alterations in head circumference measurements will occur from birth to week one of life due to head molding and edema. Head circumference measurements should be done weekly while the infant remains in hospital.[91]

e) Evaluation of skin folds and Mid-upper Arm Circumference[91]

As skinfolds and mid-upper arm circumference (MAC) measurements are not sensitive reflections of dietary adequacy, their routine use is not recommended in premature infants. These measurements are generally not used for routine clinical care, but may be of use in growth studies, although there are limited standards available. Weight and length are recommended as routine proxy for dietary adequacy.

f) Catch up growth[3, 91, 95, 96]:

The potential for catch-up growth is determined by the etiology of the poor fetal growth. Those infants who had the insult late in gestation due to placental insufficiency or uterine restrictions will grow well when provided with appropriate nutrition. Those infants who had an early perinatal insult related to congenital infection or genetic disorders will remain small in physical size.[95, 96]

There is growing evidence that severely IUGR infants in utero undergo physiological adaptations that can produce fetal, neonatal and potentially adult adverse consequences and that trying to "over-feed" these infants to attain catch up growth, may lead to acute metabolic disturbances and actually promote adult disease.[17] Experimental studies have furthermore shown that slower and leaner rates of growth are associated with less adult morbidity and longer life spans.[69]

Recent epidemiological evidence indicates that obesity, insulin resistance, glucose intolerance, diabetes mellitus, plasma lipid abnormalities and cardiovascular disease are more common among adults who were born smaller secondary to intra-uterine growth restriction.[17] This phenomenon has been named the "catch-up growth" hypothesis.[69, 104, 105] Limited markers exist however to accurately differentiate the more severe IUGR subpopulation of SGA infants at birth.[17]

Catch up growth must ideally be achieved at 2 years (max 3 years) of age. Recent research has found that by 20 years of age females have caught up in weight, height and Body Mass Index (BMI). Males however remain smaller than men who were born at term.[97]

To evaluate catch up growth effectively: use **corrected age**.
Adjustment of age in premature infants **older than 40 weeks**:
Chronological age – (40 – gestational age at birth) = Corrected age
Example: For a 10 month old infant born at 32 weeks gestation:
10 months chronological age – (40 – 32 weeks) = 8 months corrected age.

g) Techniques for assessing body proportion[50]

Body proportion in the preterm infant may be assessed by techniques such as the ponderal index and the ratio of mid-upper arm circumference (MAC) to head circumference (HC). The MAC : HC ratio probably has limited applicability in assessing body proportion in hospitalized premature infants as no published standards exists for this population group.
The ponderal index (weight divided by length^3) appears to have potential for longitudinal assessment of body proportion in preterm infants.

h) Growth charts[3, 31, 32, 93]

During the first 98 days of life, the Ehrenkrantz growth chart may be used to assess weight progress. This chart longitudinally depicts daily weight changes and actual growth curves for 1660 infants who were born with a weight of 501 – 1500g. These infants received care in 12 neonatal Intensive Care Units for various neonatal medical problems. Charts are also available for length, head circumference and mid-upper arm circumference. The growth chart recommended by most for use in assessing the premature infant, is Fenton's updated version (2003) of the 1976 Babson and Benda growth chart. (See Appendix A, p 47) On the latter growth chart SGA and LGA is defined as two standard deviations from the mean birth weight.

i) Assessment of growth in premature infants post-discharge [14]

There is a lack of clear standards for evaluation of the growth of premature infants after discharge from the hospital.

The following proposed growth rates are recommended as a guideline for the evaluation of growth following discharge: [14]

	First 3 months post-discharge	3 – 12 months post-discharge
Weight gain	25 – 30 g/day	10 – 15 g/day
Length gain	0.7 – 1.0 cm/week	0.4 – 0.6 cm/week

3.3 BIOCHEMISTRY [3, 5, 14, 15, 26, 39, 46, 47, 48, 49, 50, 91]:

See Appendix C (p49 - 50) for the Normal Blood Values for the neonate.
During the first week of life, serum electrolytes, glucose, creatinine and urea nitrogen are monitored daily or more frequently while values are abnormal.[91]
In case of Parenteral Nutrition (PN) administration: the following tests must be done on a routine basis in preterms requiring TPN for > 5 days.
A   Electrolytes, urea and creatinine: 2-3 times / week
B   Calcium, Magnesium and Albumin: once / week
C   Full Blood Count: once / week
D   Blood glucose (capillary):   once / day
E   Cholesterol and Triglycerides: once/ week (To check lipid tolerance.) [91]
F   Direct Bilirubin: once/week (To detect cholestasis.)[91]
G   Serum Alanine Aminotransferase   once/week (To evaluate hepatic function.) [91, 101]

As these blood parameters stabilize, they can be examined twice weekly for those infants receiving parenteral nutrition and as needed for infants on enteral feeds.[101]

The following biochemical indicators are important for evaluation of the adequacy of nutrient intake [14, 15, 26, 118]:

Biochemical Indices	Values indicating deficiency	Interpretation
Serum urea	<1.8 mg/dL	Insufficient nutrient intake (especially protein)
Serum total protein*	< 44g/L	Insufficient nutrient intake (especially protein)
Serum pre-albumin*	<10 mg/dL	Insufficient nutrient intake (especially protein)
Serum retinol binding protein*	<1.05 mg/dL (Children's values = ½ adult values until puberty. Adult values = 2.1 – 6.4 mg/dL)[118]	Insufficient nutrient intake (especially protein)
Serum alkaline phosphatase	>450 IU/L	Insufficient nutritional intake of calcium, phosphorus and subsequent decreased bone mineral deposition
Serum phosphate	<4.5 mg/dL(<1.45 mmol/L)	Insufficient phosphate intake

*: Note that the levels of the indicated indices are also influenced by the infant's gestational age, acute inflammatory reaction, illness, level of stress, Vitamin A and Zinc status.[3,46] A simultaneous measurement of one or more of the acute-phase proteins should be included when these indices are measured.[46]

Albumin:
Serum Albumin has long been used as a measure of protein status. However the long half-life (±12.5 - 21 days)[48] of this protein limits its usefulness in assessing nutritional status.[46] Normal albumin levels remains undefined for the premature infant, with albumin levels increasing significantly with gestational age (e.g mean serum albumin= 19g/L for <30 weeks gestational age to a mean of 31g/L at term).[39, 47, 50]

Hypoalbuminaemia occurs in a number of clinical situations, including prematurity, the acutely sick infant, respiratory distress syndrome, chronic lung disease, necrotizing enterocolitis, hydrops fetalis [see Glossary (p 3) for definition] and oedema.[39]

Intravenous albumin administration for the treatment of hypoalbuminaemia: There is a lack of evidence from randomized trials to either support or refute the routine use of albumin infusion for premature infants with a low albumin level.[39]

Pre-albumin (Transthyretin), Transferrin and Retinol-binding protein[46, 47, 48]:
Plasma pre-albumin, retinol-binding protein and transferrin concentrations were found to be reliable indicators of protein nutritional status in healthy, growing VLBW infants due to their short half-life of ±2 days[48, 49, 50] for pre-albumin and 12 hours[50] for retinol-binding protein respectively. To appropriately determine protein nutritional status as well as assessment of adequacy of nutritional rehabilitation in premature infants, it is suggested that, simultaneous to the determination of the plasma concentrations of the aforementioned proteins, one or more of the acute-phase proteins (e.g. serum C-reactive protein [half-life: 5 -7 hours], $_1$-antichymotrypsin) must also be evaluated.[46, 50]

Identification of the presence of osteopenia and rickets:
A decreased serum phosphate, accompanied by an increased alkaline phosphatase.

3.4 CLINICAL FEATURES [4, 33]:

- General appearance: Preterms look small and lean due to the presence of very little subcutaneous fat.
- They have a thin skin, with a yellow colour, if neonatal jaundice is present. Normal skin colour depends on the gestational age and range from transparent to pink.
- Lanugo might be present. (Lanugo is fine black hair which is present at a specific stage of gestation.)
- Rib retraction will be present if the preterm is suffering from respiratory distress.
- Underdeveloped eyes, ears, areola and genitalia.
- The creases on the soles of the preterm's feet might be absent.
- Reduced spontaneous activity and tone.
- Craniotabes (Non-rachitic craniotabes is at times present in the immediate post-natal period and tends to disappear before rachitic softening of the scull would appear. The latter usually occur within the 2nd to 4th month of life.[33])
- Poor muscle tone

Refer to the New Ballard Score in Appendix B (p 48) for a description of the clinical features present at the different gestational weeks.

3.5   DIETARY THERAPY

3.5.1 Background information:

Metabolic reserves and stomach capacity [4]
Premature infants have very little metabolic reserves as most of the reserves are laid down during the third trimester.

E.g.: A 1000 g baby has ± 1% fat stores, compared to a 3500 g baby's ± 16% fat stores.
A 1000 g appropriate-for-gestational-age infant has glycogen and fat reserves of ± 110 kcal/kg, which will last ± 4 days when he is only receiving water.
(Such an infant's basal metabolic needs are 50 kcal/kg/day)
In comparison a 3000 g infant has glycogen and fat reserves, which will last him for ± 32 days when he is only receiving water.

In newborns, the normal stomach capacity is ±5ml/kg, which amounts to:

5 ml for a 1000 g baby and

12 – 15 ml for a 2500 g baby.

3.5.2 Fluid recommendation:

Progression of feeds: Recommended to progress with 20 ml/kg/day in the premature infant to prevent an increased risk for the development of Necrotising Enterocolitis.[18, 26]

Factors to consider before initiating or increasing the volume of the enteral feeds[3, 38]

CATEGORY	FACTORS
Perinatal	Birth asphyxia
Respiratory	Stability of ventilation, blood gases, apnea, bradycardia, cyanosis
Medical	Vital signs (heart rate, respiratory rate, blood pressure, temperature
Gastro-intestinal	Anomalies (gastroschisis, omphalocele), patency, GI tract function (abdominal distension present, bowel sounds present, volume of gastric aspirate, passage of meconium), risk of necrotizing enterocolitis
Procedure	Pending intubation, extubation or surgery

VOLUMES OF ENTERAL AND INTRAVASCULAR FLUID ADMINISTRATION (ml/kg/day)[5]

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
800-1000g														
Total	110	120	130	140	150	150	150	150	150	150	150	150	150	150
Enteral	0	10	20	30	40	50	60	80	90	100	110	120	140	150
Intravenous	110	110	110	110	110	100	90	70	60	50	40	30	10	0
1-1.65kg														
Total	75	90	110	120	130	140	150	150	150	150	150	150		
Enteral	0	10	20	30	40	50	60	80	100	120	140	150		
Intravenous	75	80	90	90	90	90	90	70	50	30	10	0		
1.65-1.8kg														
Total	60	80	100	110	120	130	140	150	150					
Enteral	0	10	20	40	60	90	120	140	150					
Intravenous	60	70	80	70	60	40	20	10	0					
1.8-2.2kg														
Total	60	80	100	120	130	150	150							
Enteral	0	30	50	70	90	120	150							
Intravenous	60	50	50	50	40	30	0							
>2.2kg														
Total	50	75	100	125	150	150								
Enteral	0	30	60	90	120	150								
Intravenous	50	45	40	35	30	0								

Additional volumes: (These volumes are additional to the above-mentioned fluid recommendations)

Overhead heater or incubator: Give 10% fluid extra (ie. 15 ml extra on 150ml/kg/day)
Phototherapy: Give 10% fluid extra (i.e. 15 ml extra on 150 ml/kg)
Maximum enteral fluid prescription for most preterm infants = 180 ml/kg/day.

The above-mentioned table serves just as a guideline. Evaluate the hydration status and fluid administration of each baby individually. One clinical sign indicative of peripheral circulation is testing for capillary filling time. A capillary filling time of <2-3 seconds indicate normal hydration status. It is good clinical practice to confirm/ evaluate hydration status by testing for at least one other clinical sign of hydration.
Fluid restriction may be considered in cases of PDA, BPD, excessive oedema, congestive heart failure, renal failure or cerebral oedema.

3.5.3 Parenteral nutrition (Refer to Protocol on PN administration in Paediatrics)

For the VLBW infant, parenteral nutrition should be initiated within 24 hours of life (if practical) to promote energy intake, glucose homeostasis, establishment of nitrogen balance and prevention of essential fatty acid deficiency.[99]

PN is mostly provided in conjunction with minimal enteral feeding or while enteral feeding is still being increased to the recommended levels.[45]

The goal of PN in the premature and LBW infant is to provide sufficient macro- and micronutrients for prevention of a negative energy and nitrogen balance.

It is therefore recommended that intravenous fluid must consist at least partially of parenteral nutrition from day 1 in all VLBW premature infants.

PN must be given in all instances where a preterm infant will be kept Nil per Os (NPO) for more than 3 days.

3.5.4 Enteral nutrition of the premature infant

3.5.4.1 Goals:
> In early postnatal life the goal is to provide sufficient energy intake to at least match rates of energy expenditure in order to preserve body energy stores.[17]
> In the stable, growing period the goal is to increase energy intake as quickly as possible, to achieve adequate growth (i.e. 15g/kg/day).[17, 91]

3.5.4.2 General assessment to determine whether the gastro-intestinal tract is ready to receive feeds:
> - No abdominal distention present
> - No signs of peritonitis
> - No bile-containing nasogastric drainage
> - Signs of peristaltic activity i.e. passage of meconium or the presence of bowel sounds
> - No signs of gastro-intestinal bleeding
> - No signs of abdominal obstruction, i.e. bile-stained/ coffee-ground/ frank blood vomiting
> - Gastric aspirate of less than 2 ml/kg before a feed.*
>
> *: A note on gastric residuals[91]: Gastric residuals or aspirates often are present, but what exactly constitutes an unacceptable volume is difficult to define. Residuals may be due to immature intestinal motor activity.[94] Some infants have small aspirates no matter what the feeding volume, and yet are tolerating the feeds.[100] With bolus feeds a residual of up to 50% of the feeding volume or 1.5 times the hourly rate for continuous feeding is often accepted.[101] A fixed volume of 2-3 ml/residual has also been used.[102] Mucus residuals are not a concern and are present in the infant recovering form lung disease. Undigested breast milk or infant milk formula may indicate that the infant:
> - is receiving a too large feeding volume,
> - not tolerating the infant milk formula,
> - has poor gastro-intestinal motility, or
> - has NEC or intestinal obstruction.[91]

3.5.4.3 Frequency of feeds for the healthy/ uncomplicated premature infant: [26]

Weight of baby	Frequency of feeds
< 1,8 kg	2 hourly bolus
1,8 – 2,5 kg	3 hourly bolus
> 2,5 kg and older than 4 weeks	4 hourly bolus

Indications for the use of continuous infusion of enteral feeds:
Continuous infusion may be considered in case of severe respiratory distress or hypoglycaemia or intolerance to bolus feeds.

Consider intermittent constant infusion over a one-hour period with a one-hour rest period between feeds.

Maximum hanging time of a continuous milk feed administered via a pump: 4 hours [30]

Ad libitum or demand/semi-demand feeding versus scheduled interval feeding:[41]

(See Glossary on page 6 for the definitions of the above terminology.)

Semi-demand feeding is associated with better weight gain and earlier discharge. The problem with this type of feeding is that it requires close monitoring for pre-determined visual cues, which is very labour intensive. Current evidence therefore is insufficient to guide clinical practice with regards to whether feeding preterm infants in response to their own hunger cues is better than feeding set volumes of milk at pre-defined intervals. A large randomized controlled trial is needed.

3.5.4.4 Route of feeding: [8]

Tube feeding via the orogastric route if < 33-34 weeks gestational age (or while sucking and swallowing is still uncoordinated), because:
- A stable sucking rhythm is achieved from 34 weeks' gestation.
  (Swallowing develops from 12 – 14 weeks gestation.
  Sucking is initiated in-utero from 15 – 18 weeks gestation.
  Extra-uterine mouthing activity starts from 27 – 28 weeks gestational age, but is disorganized.)
- All infants are predominantly nasal breathers for the first 2 – 3 months of life.
  To prevent respiratory distress, occlusion of the nasal route must be avoided during this time period.

Transpyloric versus gastric tube feeding:[43]
(Transpyloric refers to the naso/ oro duodenal and –jejunal routes)

A recent review by Cochrane did not find any evidence of benefit, but did find evidence of adverse effects of transpyloric feeding in preterm infants. Feeding via the transpyloric route **cannot** be recommended for preterm infants or neonates (even up to one year of age).

3.5.4.5 Type of feed: [26, 34, 50]

Feeding options to consider in hospital in order of preference:

1) Fortified breastfeeding or expressed breast milk   Fortified pasteurised own breast milk (In case of HIV exposure)
2) Fortified Donor Breast Milk DBM (pasteurised)   (See Appendix E (p 52 – 53) for indications for DBM administration)
3) Preterm infant milk formula   (See Appendix F1, p 54-55) (When medically   indicated.)

  : "Preterm" formula is designed for premature infants. These are calorie-enriched (±80kcal/100ml) and variable protein- and mineral-enriched to support intra-uterine nutrient accretion rates. It is suggested that a preterm infant milk formula should contain calcium and phosphorus at a minimum approximate level of 75mg/100ml and 42 mg/100ml respectively (if fed at 180ml/kg/day).[53, 54]

Feeding options NOT recommended for feeding of premature infants:

Semi-elemental   (and elemental) infant milk formula
Cow's milk based term infant milk formula#
Soy based term formula
Home prepared formula*

  : Semi-elemental (and elemental) infant milk formula is not suitable for use in the preterm infant due to the fact that its' composition is based on the nutrient needs of a term infant.
(See Appendix F2 (p 56) for a discussion on the use of semi-elemental infant milk formula in the premature infant.)
#: A "term" infant milk formula is based on the composition of mature human milk and designed for term infants. The typical energy content is ±68kcal/100ml. The protein concentration is approximately 1.5g/100ml and the calcium and phosphorus content ±50mg/100ml and 30mg/100ml respectively.[52]
*: A home prepared formula refers to a feed compiled from mixing commercial products such as unmodified cow's, goats, sheep or soy milk powder, sugar and oil.

3.5.4.6 Fortification of human milk:

Research confirms the necessity of fortification of EBM for preterm infants. [1, 2, 3, 20]
A multi-nutrient fortifier, providing an additional ± 0,7g protein/ 100ml EBM and an additional of 5 – 18 kcal energy/ 100ml EBM is the recommendation. [2]
Together with energy and protein, the fortification of EBM with calcium, phosphorus, sodium, potassium and chloride, are recommended.

The addition of multi-nutrient fortifiers to human milk has been shown to result in short-term improvements in weight gain and increments in both length and head circumference in the premature infant. Despite the absence of evidence of long-term benefit and insufficient evidence to be reassured that there are no deleterious effects, it is unlikely that future studies evaluating fortification of human milk in comparison with no fortification will be conducted. Further research is however needed to improve the composition of the current commercial human milk fortifiers to ensure that optimal growth and feeding tolerance is achieved. [17, 57]

Comments on types of fortifiers available [20, 34]:
Liquid and powdered fortifiers are available.
Powdered fortifiers:
An advantage of powdered fortifiers is that it does not dilute the human milk provided. A possible disadvantage might be the fact that the powdered fortifier is added to undiluted breast milk, where some nutrients (particularly protein and calcium) may be oversupplied depending on the specific breast milk's content of these nutrients.[34]
Liquid fortifiers:
It is suggested that the use of a liquid fortifier is reserved for situations where the mother is unable to provide sufficient milk to meet her infant's needs.
A disadvantage of liquid fortifiers: Mixing preterm mother's milk with an equal volume of liquid fortifier dilutes the constituents, such as nutrients, growth factors and anti-infective factors found in human milk,

Tolerance and safety considerations for human milk fortification:

- The use of fortified human milk is not associated with feeding intolerance, as manifest by abdominal distension, vomiting, changes in stool frequency or volume gastric aspirate compared to control-supplement human milk. Compared with infants fed preterm formulae, infants fed fortified human milk had similar tolerance to feeding.[22]
- Like any powdered milk product, powdered fortifiers are not guaranteed micro-biologically sterile, although their use is not associated with increased rates of neonatal infection. [34]
- Bacterial colony counts increase over time of storage of fortified human milk. When fortified human milk was tested under simulated nursery conditions, bacterial colony counts were not significantly different after 20 hours' storage at incubator temperature. The overall increase in bacterial colony counts by 24 hours was small. This data do not suggest that changes are necessary regarding the current practice^ of how fortifiers are used in nurseries, but caution is suggested when human milk are handled. Continued surveillance of milk preparation methods is recommended. [21]
  (^: The current practice used most often is to mix the amount of fortifier with the volume of breast milk encompassing one single feed just before the feed is given.)
- In all cases of fortification: Individual packaging for single feed administration is the ideal, e.g. a sachet with the correct amount of fortifier that can be added to a single feed of 10 - 20 ml EBM.
- It is recommended that the fortifier-milk mixture is well-shaken to ensure that all the nutrients are available for absorption.[34]

See Appendix G (p 57) for a nutrient analysis of different breast milk fortifiers. (Similac HMF and Nutriprem BMF are not currently available in South Africa.)

3.5.4.7 Minimal enteral feeding (Trophic Feeding) [19, 40, 91]
A lack of enteral nutrients may diminish gastro-intestinal functional and structural integrity by diminishing hormonal growth of intestinal mucosa, lactase activity, nutrient absorption or motor maturation. These problems may then compromise later feeding tolerance and growth and prolong hospital stay. The practice of providing trophic feedings (small volume feedings that provide minimal calories) additional to parenteral nutrition for some period after birth, was developed as a strategy to enhance the functional maturation of the gastro-intestinal tract, without increasing the risk of necrotizing enterocolitis. Trophic feedings can consist of human milk or premature infant milk formula and it is suggested to commence with 1ml every 2 - 4 hours in infants weighing less than 1 kg.[19] The latter volume is gradually increased until 10 – 20ml/kg/day is given, usually for a period of 4 – 7days. Feedings can be advanced when the infant's condition has stabilized.[91]

The following table summarizes the main benefits of the provision of trophic feeds to the premature infant.

Benefits of Trophic Feeding[91]

1. Feeding:
    • Improved feeding tolerance
    • Achieve full per os feedings sooner

2. Gastro-intestinal:
    • Increased plasma gastrin
    • Decreased intestinal transit time
    • More mature intestinal motor pattern
    • Increased calcium, copper and phosphorus retention

3. Clinical:
    • Decreased serum bilirubin and days of phototherapy
    • Decreased incidence of cholestasis
    • Lower serum alkaline phosphatase activity levels

4. Decreased length of stay (in hospital)

A recent Cochrane review evaluated 11 trials on this topic and concluded that "despite plausible rationale and the suggested benefits of the initial use of trophic feedings in this meta-analysis it is unclear whether trophic feedings are beneficial relative to no feedings or advancing feedings for high-risk infants".[40] A large multi-centre trail of trophic feedings is needed among ELBW infants.[40]

3.5.5 A comparison of the parenteral and enteral nutritional needs of the stable, growing VLBW and ELBW premature infant

Two successive periods are described in the clinical nutrition of premature infants, namely:
1) The early adaptive or "transition" period, which lasts from birth to the second week of life, and
2) The "stable-growing" period, which last up to discharge from the neonatal unit.[17]

Protein intake and protein to energy ratio are the main determinants of growth and body composition during the stable, growing period. Nutritional deprivations arise in the early adaptive period as well as from several neonatal events and illness; therefore additional recommendations are suggested to promote early catch-up growth before discharge. These recommendations are indicated in the following table and are in line with previous guidelines from other Committees (AAP, ESPGHAN, CPS LSRO/ASNS).[17]

Suggested enteral and parenteral protein intake during the transition period:[17]

Protein intake during the transition period:[17]
To achieve a zero nitrogen balance: • 0.75 g/kg/day in healthy, growing preterm infants (if on enteral feeding providing 110kcal/kg/day)) • 1.0 – 1.5 g/kg/day during the first days of life when energy supply is limited (parenteral feeding when only "maintenance" energy intake of 50 – 60kcal/kg/day is provided)[17, 34] • 1.5 – 2.0 g/kg/day during the first days of life if concomitant catabolic conditions are present
To achieve a positive nitrogen balance: • 2.5 – 3.0 g/kg/day during the first days of life when energy supply is limited (i.e. ±50 - 60kcal/kg/day)
Progressive increase in energy and protein supplies up to recommended values for conceptional age[17, 34]

See Appendix L (p 70) for calculations on the minimum volume parenteral and enteral feed required to achieve zero nitrogen balance.

Knowing that SGA infants are born with a body composition that is decreased in protein and fat content relative to AGA infants, most clinicians currently recommend increased protein and energy intakes per kg body weight compared to normally grown infants in order to achieve catch-up growth.[103] The following table indicates the revised recommended protein intake and protein: energy ratio (PER) for stable, growing preterm infants according to post-conceptional age and the need for catch-up growth:[17]

Post-conceptional age	Without need for catch-up growth (AGA)	With need for catch-up growth (SGA)
26 – 30 weeks: 16 – 18 g/kg/d Lean Body Mass 14% protein retention	3.8 – 4.2 g/kg/day PER: ~3.3 NPE: 125 – 139kcal/kg/day (TE: 140 -156kcal/kg/day)	4.4 g/kg/day PER: ~3.4 NPE: 125 – 139kcal/kg/day (TE: 143 -157kcal/kg/day)
30 – 36 weeks: 14 – 15 g/kg/d Lean Body Mass 15% protein retention	3.4 – 3.6 g/kg/day PER: ~2.8 NPE: 95 – 101kcal/kg/day (TE: 109 -115kcal/kg/day)	3.8 – 4.2 g/kg/day PER: ~3.3 NPE: 125 – 139kcal/kg/day (TE: 140 -156kcal/kg/day)
34 – 40 weeks: 13 g/kg/d Lean Body Mass 17% protein retention	2.8 – 3.2 g/kg/day PER: 2.4 – 2.6 NPE: 67 – 83kcal/kg/day (TE: 78 -96kcal/kg/day)	3.0 – 3.4 g/kg/day PER: 2.6 - 2.8 NPE: 78 – 95kcal/kg/day (TE: 90 -109kcal/kg/day)

Abbreviations: PER = Protein: Energy Ratio, NPE: Non-Protein Energy, TE: Total Energy

The following two tables indicate the recommended parenteral and enteral nutrient intakes of stable,growing VLBW and ELBW premature infants. Do note that these recommendations serve only as guidelines and individual assessment is still indicated.

A COMPARISON OF THE PARENTERAL AND ENTERAL NUTRITIONAL NEEDS OF THE STABLE, GROWING ELBW PREMATURE INFANT[17]

Nutrient	Unit	Parenteral	Enteral	
		(per kg/day)	Per kg/day	Per 100 kcal
Water	ml	140 - 180	160 - 220	107 - 169
Energy	**kcal**	**105 - 115**	**130 - 150**	**100**
Protein	**g**	**3.5 - 4.0**	**3.8 - 4.4**	**2.5 - 3.4**
Carbohydrate	g	13 - 17	9 - 20	6.0 - 15.4
Fat	g	3 - 4	6.2 - 8.4	4.1 - 6.5
Linoleic (Ω 6)	mg	340 - 800	700 - 1680	467 - 1292
Linolenic (Ω 3)	mg	1 - 4% of cal	1 - 4% of cal	110 - 440
C18:2 / C18:3		5 - 15 : 1	5 - 15 : 1	5 - 15 : 1
Arachidonic acid	mg	14	28	22
Docosahexaenoic acid	mg	11	21	16
Vitamin A (ug)	IU	700 – 1500 (210-450)	700 – 1500 (210-450)	467 – 1154 (140-346)
Vit A in lung disease#	IU	1500 - 2800	1500 – 2800 (450-840)	1250 - 2333
Vitamin D	IU	40 - 160 (max 400)	150-400 (aim 400)	100 - 308
Vitamin E	IU	2.8 - 3.5 (max 7)	6 - 12 (max 25)	4 – 9.2
Vitamin K	ug	10	8 - 10	5.3 - 7.7
Vitamin C	mg	15 - 25	18 - 24	12 – 18.5
Thiamin (B1)	ug	200 - 350	180 - 240	120 - 185
Riboflavin (B2)	ug	150 - 200	250 - 360	167 - 277
Niacin (B3)	mg	4 - 6.8	3.6 - 4.8	2.4 - 3.7
Piridoxine (B6)	ug	150 - 200	150 - 210	100 - 162
Pantothenate	mg	1 - 2	1.2 - 1.7	0.8 - 1.3
Biotin	ug	5 - 8	3.6 - 6	2.4 - 4.6
Folate	ug	56	25 - 50	17 – 38
Vitamin B_{12}	ug	0.3	0.3	0.2 - 0.23
Sodium	mg	69 – 115 (161*)	69-115 (up to 161*)	46 - 88
Potassium	mg	78 - 117	78 - 117	52 - 90
Chloride	mg	107 - 249	107 - 249	71 - 192
Calcium	mg	60 - 80	100 - 220	67 - 169
Phosphorus	mg	45 - 60	60 - 140	40 - 108
Magnesium	mg	4.3 - 7.2	7.9 - 15	5.3 - 11.5
Iron	mg	0.1 - 0.2	2 - 4	1.33 - 3.08
Zinc	ug	400	1000 - 3000	667 - 2308
Copper	ug	20	120 - 150	80 - 115
Selenium	ug	1.5 - 4.5	1.3 - 4.5	0.9 - 3.5
Chromium	ug	0.05 - 0.3	0.1 - 2.25	0.07 - 1.73
Manganese	ug	1.0	0.7 - 7.5	0.5 - 5.8
Molybdenum	ug	0.25	0.3	0.20 - 0.23
Iodine	ug	1.0	10 - 60	6.7 - 46.2
Taurine	mg	1.88 - 3.75	4.5 - 9.0	3.0 – 6.9
Carnitine	mg	~2.9	~2.9	~1.9 - 2.2
Inositol	mg	54	32 - 81	21 - 62
Choline	mg	14.4 - 28	14.4 - 28	9.6 - 21.5

*: May require up to 160mg/kg/day in case of late hyponatremia.[17]

#: Reference for this recommendation: nr 18

Conversion factors[3]:

Vit A: 3.33 IU = 1µg retinol;

Vit D:1 IU = 0.025µg cholecalciferol (Vit D_3) ;

Vit E: 1.49IU = 1 mg d-   tocoferol

A COMPARISON OF THE PARENTERAL AND ENTERAL NUTRITIONAL NEEDS OF THE STABLE, GROWING VLBW PREMATURE INFANT [17]

Nutrient	Unit	Parenteral	Enteral	
		(per kg/day)	Per kg/day	Per 100 kcal
Water	ml	120 - 160	135 - 190	104 - 173
Energy	**kcal**	**90 - 110**	**110 - 130**	**100**
Protein	**g**	**3.2 - 3.8**	**3.4 - 4.2**	**2.6 - 3.8**
Carbohydrate	g	9.7 - 15	7 - 17	5.4 - 15.5
Fat	g	3 - 4	5.3 - 7.2	4.1 - 6.5
Linoleic (Ω 6)	mg	340 - 800	600 - 1440	462 - 1309
Linolenic (Ω 3)	mg	1 - 4% of cal	1 - 4% of cal	110 - 440
C18:2 / C18:3		5 - 15 : 1	5 - 15 : 1	5 - 15 : 1
Arachidonic acid	mg	14	24	22
Docosahexaenoic acid	mg	11	18	16
Vitamin A (ug)	IU	700 – 1500 (210-450)	700 – 1500 (210-450)	538 – 1364 (162-409)
Vit A in lung disease#	IU	1500 - 2800	1500 – 2800 (450-840)	1250 - 2333
Vitamin D	IU	40 - 160 (max 400)	150-400 (aim 400)	115 - 364
Vitamin E	IU	2.8 - 3.5 (max 7)	6 - 12 (max 25)	4.6 - 10.9
Vitamin K	ug	10	8 - 10	6.2 - 9.1
Vitamin C	mg	15 - 25	18 - 24	13.8 – 21.8
Thiamin (B1)	ug	200 - 350	180 - 240	138 - 218
Riboflavin (B2)	ug	150 - 200	250 - 360	192 - 327
Niacin (B3)	mg	4 - 6.8	3.6 - 4.8	2.8 - 4.4
Piridoxine (B6)	ug	150 - 200	150 - 210	115 - 191
Pantothenate	mg	1 - 2	1.2 - 1.7	0.9 - 1.5
Biotin	ug	5 - 8	3.6 - 6	2.8 - 5.5
Folate	ug	56	25 - 50	19 - 45
Vitamin B_{12}	ug	0.3	0.3	0.23 - 0.27
Sodium	mg	69 – 115 (161*)	69-115 (up to 161*)	53 - 105
Potassium	mg	78 - 117	78 - 117	60 - 106
Chloride	mg	107 - 249	107 - 249	82 - 226
Calcium	mg	60 - 80	100 - 220	77 - 200
Phosphorus	mg	45 - 60	60 - 140	46 - 127
Magnesium	mg	4.3 - 7.2	7.9 - 15	6.1 - 13.6
Iron	mg	0.1 - 0.2	2 - 4	1.54 - 3.64
Zinc	ug	400	1000 - 3000	769 - 2727
Copper	ug	20	120 - 150	92 - 136
Selenium	ug	1.5 - 4.5	1.3 - 4.5	1.0 - 4.1
Chromium	ug	0.05 - 0.3	0.1 - 2.25	0.08 - 2.05
Manganese	ug	1.0	0.7 - 7.5	0.5 - 6.8
Molybdenum	ug	0.25	0.3	0.23 - 0.27
Iodine	ug	1.0	10 - 60	7.7 - 54.5
Taurine	mg	1.88 - 3.75	4.5 - 9.0	3.5 - 8.2
Carnitine	mg	~2.9	~2.9	~2.2 - 2.6
Inositol	mg	54	32 - 81	25 - 74
Choline	mg	14.4 - 28	14.4 - 28	11.1 - 25.5

*: May require up to 160mg/kg/day in case of late hyponatremia.[17]

#: Reference for this recommendation: nr 18

Conversion factors[3]:

Vit A: 3.33 IU = 1µg retinol;

Vit D:1 IU = 0.025µg cholecalciferol (Vit D_3) ;

Vit E: 1.49IU = 1 mg d- tocoferol

3.5.6 PRACTICAL IMPLEMENTATION OF ENTERAL NUTRITION FOR THE PREMATURE AND LOW BIRTH WEIGHT INFANT [3, 13, 17, 26, 30]

The volume of EBM provided, is gradually increased during the first 2 weeks of life (with increments of 10 – 20 ml/kg/day) until a volume of 150 - 180 ml/kg is reached. (See fluid regimen on page 15.)

3.5.6.1 Macronutrient requirements that must be met when full enteral feeds are given for stable, growing premature infants: [3, 13, 17, 26, 34, 36]

Nutrient	Daily Recommendation (ranges included)
Energy	110 – 150 kcal/kg/d
Protein	3,4 – 4,4 g/kg/d [Ideally 10.2 – 12.4% of Total Energy (TE)]
Fat	5,3 - 8,4 g/kg/d [Ideally 40 – 50% of TE] Linoleic acid (omega-6): 600 – 1680 mg/kg/d [3 – 5% of TE] Linolenic acid (omega-3): 1% of TE
Carbohydrate	7 – 20 g/kg/d [Ideally 40 - 50% of TE]

Comments on macronutrient provision:

Energy:

For a healthy, growing premature infant, the recommended energy intake is 110 - 130 kcal/kg/day.

For the ELBW infant at least 130 kcal/kg/day of enteral intake seems necessary to achieve a positive energy balance of 25 – 30kcal/kg/day. Up to 150kcal/kg/day may be required to achieve an energy balance closer to that of a healthy, growing, more mature premature infant.[17]

When a preterm infant milk formula is provided at the recommended fluid range of 150 – 180ml/kg/day, the energy requirement is reached in most cases and further energy supplementation is rarely indicated.

Protein:

Protein supplementation of human milk in relatively well premature infants results in increases in short-term weight gain, linear and head growth. Urea levels are increased but remain within the normal range. There is still an absence of data evaluating long-term effects and adverse effects of protein supplementation. As supplementation of human milk with multiple components (such as found in fortifiers) is common practice, further research should concentrate on the modification and refinement of available fortifiers.[55]

Excessive protein intakes have been reported to result in adverse neuro-developmental outcomes and are associated with evidence of metabolic stress such as acidosis and elevated blood urea concentrations.[56]

When a preterm infant milk formula is provided at the recommended fluid range of 150 – 180ml/kg/day, the protein requirement is reached in most cases and further protein supplementation is not indicated.

Fat:

Long-chain poly-unsaturated fatty acids (LCPUFA)[26, 34]:

Controversy exists on whether the dietary provision of the longer-chain derivatives of linoleic and linolenic acids, namely arachidonic (AA) (20:4, 6) and docosa-hexaenoic (DHA) (22:6, 3) acid can be regarded as essential at any period of development. There seem to be advantages with respect to visual and neurodevelopmental outcome for premature infants, but not all authors have made recommendations for their addition to preterm formula. [26] (When added, the ideal ratio of AA: DHA is 2: 1.)

Medium Chain Triglycerides (MCT):

MCT'S are known to be absorbed without the need for initial cleavage in the gut and may therefore be more readily used by the preterm infant.[51] Theoretically MCT should lead to improved fat absorption although no consistent advantage with respect to fat or nitrogen balance has been found. [27] The MCT content of breast milk is very low. Results of recent studies furthermore show that growth is not improved with the use of MCT's and no support exists for its' routine use in preterm infant milk formula.[36]

Fat supplementation of breast milk:

A Cochrane review on fat supplementation of breast milk for promotion of growth in premature infants found insufficient evidence to make recommendations for practice.[51]

Carbohydrate:

The minimum intravenous glucose supply needed to maintain adequate energy for the brain is ±9mg/min/kg. Caution is advised when high levels of carbohydrates are given for the premature infant. To prevent hyperglycemia and other associated complications (eg high osmotic load) the upper range for glucose administration in the premature infant is 12mg glucose/min/kg.

The addition of carbohydrate supplements to human milk in preterm infants has not been studied sufficiently to make recommendations for practice.[58]

3.5.6.2   Fortification:

Fortification of the breast milk may be started when full oral feeds are reached, i.e. 150 ml/kg or between 120 - 150 ml/kg in case of fluid restriction.

On day one of fortification: Add the amount of fortifier as per manufacturer's prescription to the breast milk. (A note of caution: Always check that the energy jump does not exceed the recommended 10-15 kcal/kg/day. It is therefore necessary in some instances to commence with half the recommended amount of fortifier on the first day of fortification).
If no signs of feeding intolerance occurred on day 1, the full dosage of fortifier is added on day 2 (if only half the dosage was prescribed on day 1).
Continue with this fortification if an adequate rate of weight gain (15g / kg / day) is maintained.
Regular adjustments to the milk volume are recommended, especially if the growth rate slows down or is still not ideal. Increasing the prescribed volume of milk, while still adhering to the upper limits for fluid (200 – 220ml/kg/day) and the macronutrients (as indicated in the tables in section 3.5.5), is recommended.

Duration of fortification:
Fortification should continue until the infant is feeding effectively from the breast (± 34 – 38 weeks gestational age) and thriving, with all the biochemical indices having normalised, or until around 1.8 – 2,5kg.[26, 34]

Fortification when the infant is already being breastfed:
It is recommended that the mother expresses 10 - 20ml breast milk in a sterilized cup prior to a breastfeeding session. The prescribed single dosage of fortifier is then thoroughly mixed with the breast milk and fed to the infant with the cup. Ad libitum breastfeeding is then resumed. This process is repeated with every breastfeeding session or for at least 6 – 8 sessions of the day, whichever is most appropriate and feasible.

Supplementation of preterm infant milk formula:
Further supplementation of preterm infant milk formula is rarely indicated.
Refer to the clinical guideline on "Supplementation of Infant milk formula" for further guidelines on the correct procedure for the supplementation of infant milk formula:

If insufficient weight-gain velocity persists:
Ensure that the infant is actually receiving the full prescribed enteral feed.
If the above is true: Consider medical problems, such as anaemia, hypoglycemia, hyponatremia, hypothermia, acute inflammatory response and/ or sepsis as the cause of the infant's poor growth.

3.5. 7 MICRONUTRIENT SUPPLEMENTATION [23, 24, 26, 34]

Micronutrients are provided through the following supplementation:

- **Multivitamin Syrup (eg Vidaylin®)**: 0,3 – 0,6 ml/d
  Supplementation commences only when full enteral feeds are provided, due to the high osmolality of the multivitamin supplement.
- Omit supplementation if the fortifier contains sufficient amounts of vitamins. (See Appendix G (p 57) for the different breast milk fortifiers available.)
- Omit supplementation if the preterm infant milk formula contains sufficient amounts of vitamins. (See Appendix F (p 54 – 55) for the different preterm infant milk formulas available.)

- **Iron** [23, 24, 26]: 2 – 4 mg elemental Iron / kg / day
  (Fe-lactate drops are used: 0,1 ml = 2,5 mg Fe)
  Iron supplementation is initiated when full volume (i.e. 120 – 150ml/kg) enteral feeds are reached, and only in the **absence of any signs of infection.**
  The dosage of total iron to be administered is based on the infants' birth weight, i.e.:
  Birth weight: < 1,0 kg   : give 4 mg elemental Fe / kg / day
  Birth weight: 1,0 - 1,5 kg: give 3 mg elemental Fe / kg / day
  Birth weight: 1,5 - 2,5 kg: give 2 mg elemental Fe / kg / day
  Maximum amount of elemental iron allowed: **15 mg / day**
  (Include the iron content of the milk the infant is receiving.)

- **Folic acid**: 2,5 mg / day
  Omit supplementation if the fortifier contains a sufficient amount of folic acid.
  Multivitamin syrup contains no folic acid due to its instability in a liquid.

  The abovementioned supplementation of a multivitamin plus folic acid and iron supplementation must continue for the first year of life.[34]

- **Vitamin D**: 400 IU/day, from when full oral feeds are provided until discharge.
  Little is known about the capacity of VLBW premature infants with a gestational age of <28 weeks to absorb or hydroxylate Vitamin D. During the stable-growing period, regardless of the infant's birth weight, a Vitamin D intake of 400 IU/day is needed to achieve a normal serum 25-OH Vitamin D concentration, without increasing the risk of toxic effects.[34] It is thus recommended that the breast milk plus fortifier or preterm formula must provide 400IU. Additional Vitamin D supplementation must only provide the deficit.
  Omit supplementation if the fortifier contains sufficient amounts of vitamin D.
  (See Appendix G [p 57] and H [p 58 – 61])
  Omit supplementation if the preterm infant milk formula contains a sufficient amount of Vitamin D. (See Appendix F [p 54 – 55] for the different preterm infant milk formulas available.)

- **Vitamin K$_1$**: Routinely supplemented in all neonates directly after birth.
  Prophylactic dosage: 0.5 – 1mg (A once-off intramuscular administration)
  In case of a bleeding tendency: give 1 – 2mg (Intravenously).[5]

- **Zinc**: Is not routinely supplemented.
  Consider zinc supplementation only when the infant is not growing optimally, i.e. at <15 g/kg/day.
  Dosage: 0,5 mg elemental Zn sulfate or Zn gluconate /kg / day.

Give only a short course (i.e. a 2 - 4 week period) of zinc supplementation, because zinc is a heavy metal which may cause brain- and liver damage if given in too high dosages. Excessive zinc supplementation is furthermore known to interfere with copper absorption.[119]

See Appendices H1 and H2 (p 58 - 61) , for a complete nutrient analysis of 150 ml/kg EBM + the different fortifiers currently commercially available in South Africa, with comments on the need for additional supplementation.

3.5.8 DETERMINATION OF RENAL LOAD OF THE FEED [12]

Determination of Potential Renal Solute Load (PRSL) and Renal Solute Load (RSL):
See Appendix I (p 62) for the formulas used to determine PRSL and RSL respectively. Satisfactory margins of safety for the abovementioned:
PRSL = 20 – 26mOsm/100 kCal or 200 -233 mOsm/Liter
Upper limit: 30 – 35mOsm/100 kCal
PRSL > 39mOsm/100 kCal places the infant at risk of hypertonic dehydration.
RSL = 133 – 173 mOsm/ Liter

3.5.9 THE USE OF PRE- AND PROBIOTICS IN THE PREMATURE AND LBW INFANT (See Appendix J, p 63 - 65)

3.5.10 EVALUATION OF THE USE OF CONDITIONALLY ESSENTIAL NUTRIENTS IN THE PREMATURE INFANT (See Appendix K, p 66 - 69)

3.5.11 KANGAROO MOTHER CARE (KMC) [1, 25, 44]

KMC is defined as skin-to-skin contact between a mother and her newborn, frequent and exclusive or near-exclusive breastfeeding, and early discharge from hospital.
It is recommended that all mothers of premature infants do KMC for at least 8 hours / day until their infant has a gestational age of 40 weeks or weighs at least 2,0 kg.
Mothers of infants not able to suckle yet should begin expressing their milk within the first 24 – 48 hours after delivery. They should receive the proper instructions about the correct methods for the collection, storage and handling of their breast milk.[1]

Advantages of KMC:

- Better temperature regulation.
- More even heart rate with less bradycardia.
- Less apnoea and periodic breathing, better oxygenation, less oxygen needed.
- Stimulation of the production and release of surfactant.
- Improved lactation (skin contact stimulate oxytocin release) and let-down reflex.
- Better growth rate in premature infants and earlier hospital discharge.
- Less nosocomial infections (skin contact improves the production of antibodies in the mother which are then transferred to the infant via the breast milk).
- Less crying. (Crying hinders lung function, increases intracranial pressure and initiate a cascade of stress reactions.)
- Fathers can do it as well! Good for emotional bonding between parent and child.

A recent Cochrane meta-analysis concluded that compared to conventional care, KMC appears to reduce severe infant morbidity without any serious deleterious effect reported, but there is still insufficient evidence to recommend its routine use in LBW infants. Due to serious concerns about the methodological quality of the included trials, the credibility of the positive findings with KMC is weakened; therefore more research (well-designed randomized controlled trials) is needed.[44]

3.5.12 IMPORTANT POINTS TO CONSIDER BEFORE DISCHARGE [3, 15, 17, 91]

Determination of a premature and LBW infant's readiness for discharge:
- Must be breastfeeding successfully. (Commence unfortified *ad libitum* breastmilk one week prior to discharge to help with the feeding transition from hospital to home. Refer to the next paragraph* on the initiation of breastfeeding in the premature infant.)
- Infants must continue to gain weight at the recommended rate of 15g/kg/day.
- Infants are currently discharged from a weight of 1.8 kg.
- Infant must be stable with regards to all vital signs, i.e. normal heart rate, body temperature and respiration rate without any episodes of apnoea.
- Infant must be able to maintain body temperature when nursed in an open crib and while being kangaroo cared.
- The mother must feel empowered and confident to handle and care for her infant at home.
- Social circumstances of the mother/family.
- A follow-up appointment must be given upon discharge to ensure continued monitoring and evaluation of the premature infants' progress.

* Initiation of breastfeeding in the premature infant:
Breastfeeding success requires not only adequate milk supply from the mother, but also adequate oral feeding skills from the infant. The use of behaviorally-based criteria is recommended to assess the infant's readiness for breastfeeding. Observations of oral activity in the infant, sucking on the feeding tube, rooting reflex during KMC sessions and brief periods of active or alert states provide a better assessment of when to initiate breastfeeding. The infant must furthermore be able to grasp and hold the breast tissue while sucking is initiated.[17]

Estimating milk intake from the breast:
Milk intake can be evaluated more accurately by test-weighing, a procedure in which a clothed infant is weighed on an electronic scale immediately before and after breastfeeding.[17, 106]

From the aforementioned it is clear that weight alone is not the determining factor for deciding when the premature infant is ready for discharge. All of the abovementioned criteria must be achieved before discharge.

3.5.13 POST-DISCHARGE NUTRITION RECOMMENDATIONS[15, 26]

Little data about the optimal or recommended nutrient intake for a premature infant post-discharge is available.

Feeding options to consider at discharge in order of preference

1) Breastfeeding *ad libitum*, at least 8 times/ 24 hours (i.e. 3 hourly)
2) Preterm infant milk formula
3) Preterm discharge infant milk formula: Not currently available in SA*.
4) In case of HIV exposed infants: A term infant milk formula is provided (as per Prevention of Mother to Child Transfer (PMTCT) protocol)

Supplementation of a multivitamin supplement plus iron must be prescribed upon discharge from the hospital and continued for the first year of life. During the post-discharge period the recommendation for Vitamin D intake remains at 400 IU/day. [34] Supplementation of the latter is then only warranted if the multivitamin supplement does not provide 400 IU of Vitamin D.

*: If breastfeeding is not possible it is worth noting that "nutrient enriched" post-discharge infant milk formulas may be used. Unfortunately none of these specialized infant milk formulas are currently available in South Africa. These nutrient enriched post-discharge formulas may be used until around 6-9 months or once catch-up growth has been achieved, whichever is sooner. Preliminary evidence shows that premature infants (especially ELBW) who have illnesses (such as BPD) or conditions necessitating complicated medical care may benefit from prolonged feeding with formula with a higher nutrient concentration during the post-discharge period.[34]

There have been few studies which evaluated the adequacy of standard term formula in meeting the micronutrient needs of the premature infant and more research in this area is needed. Until more evidence becomes available, the use of iron-fortified term infant milk formula are recommended for premature infants upon discharge and must be continued until 12 months corrected age.[34] Iron status should be adequately maintained; thus iron supplementation is usually not required.

The introduction of complementary food [26]
Factors to consider when deciding on the time to commence with the introduction of complementary food for a LBW infant are:
1) The degree of prematurity
2) The chronological age, and
3) The developmental level.

It is suggested that the introduction of complementary food does not take place prior to 40 weeks (i.e. term) gestational age and not before the infant weighs at least 5,0 kg. One formula that may be used to determine the appropriate age for complementary food introduction, is to add half the number of weeks of prematurity to 16 weeks, e.g.:

Formula: 16 weeks + ½ (40-gestational age at birth) [26]

E.g. for a preterm born at 30 weeks:
16 weeks + ½ (40 – 30 weeks)
= 16 + 5 weeks
= 21 weeks ~ 5 months

Complementary food should not be introduced before 16 weeks post-delivery (chronological age).
The suggested upper limit for the introduction of complementary food is 7 months post-delivery (chronological age).
Once weaning has started, it should proceed according to the usual guidelines recommended for term infants.

3.6. FOLLOW-UP OF THE PREMATURE AND LOW BIRTH WEIGHT INFANT POST-DISCHARGE [25]

Premature infants must be seen for evaluation of weight gain at the nearest appropriate health care facility (i.e. regional baby clinic of community health centre) within 3 days of discharge from hospital.
Follow-up intervals thereafter depend on the maturity, gestational age at birth and the weight of the infant.
A medical doctor should see the infant within 10 days after discharge from hospital.
Blood tests should be carried out according to clinical indications to ensure that the infant does not have a zinc deficiency, iron-deficiency anaemia or early rickets.[34]
All premature infants should have an appointment for follow-up booked prior to discharge.[91]

3.7 IMMUNISATIONS

The full dosage of all immunisations must be given according to chronological age.

3.8 TREATMENT OF THE COMPLICATIONS ASSOCIATED WITH PREMATURITY

3.8.1 Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD) [4, 6]

Definition: A disorder primarily of prematurity, manifested clinically by respiratory distress and pathologically by pulmonary hyaline membranes and atelectasis.[4] (atelectasis: See Glossary on page 6.)

Etiology: Lack of pulmonary surfactant at birth.
Most often occurs in infants born before 36 weeks' gestation.
RDS also found in infants of diabetic mothers and in case of prolonged rupture of membranes (PROM).

Treatment:

Medical: Natural/ Exogenous surfactant (i.e. Curosurf)
Oxygen therapy (by hood, nasal cannula, continuous positive airway pressure (CPAP) or ventilatory support).

Dietary: Little information that specifically addresses nutritional requirements for newborn infants with acute respiratory disorders is available.[17]

3.8.2 Broncho Pulmonary Displasia (BPD) / Chronic Lung Disease (CLD)[4, 5, 26]

Definition: A chronic lung disorder in infants who have been treated for respiratory distress with intermittent mandatory ventilation. At 28 days of age, they will have x-ray changes characteristic of respiratory distress and an ongoing need for oxygen support. These infants usually required ventilation for > 3 days in their first week of life.[4, 5]

Etiology: Lung injury due to CPAP or high inspired oxygen concentrations, endotracheal intubation or barotrauma.

Treatment:

Medical: Relative fluid restriction to prevent pulmonary oedema.[17]
Oxygenation must be maintained in the chronic disease phase.
Medication such as: Aminophylline or caffeine (acts as a respiratory stimulant).
Diuretics (for prevention of pulmonary congestion).

Dietary: Restrict fluid moderately: 120 – 150 ml/kg/day.
Failure to thrive is a major complication of BPD, which is in part caused by increased energy expenditure for work of breathing and lung repair.
Energy requirements in BPD may be increased by as much as 25% above basal needs.[17, 107]
Increase caloric density of the breast milk or formula provided to 80 – 100 kcal/100ml.
Milk may be supplemented with:
Breast milk: Breast milk fortifier. Always build up any fortification gradually, not increasing with more than 10 – 15 kcal/kg/day.
Preterm infant milk formula will usually provide nutrients within the prescribed enteral recommendations, even where a mild fluid restriction (i.e 130 – 150ml/kg) is prescribed.

Important:
There is no evidence to support supplementing breast milk or infant milk formulas with carbohydrates or lipids to achieve improved growth or respiratory function in preterm or term infants with acute or chronic respiratory problems. [17]

Many infants with CLD show growth failure resistant to nutritional intervention, and other factors, such as anaemia, sodium depletion (if on diuretics) or the effect of inadequate oxygen therapy must be considered. Growth rates in infants with BPD are limited more by protein deficiency than non-protein caloric intake. Higher protein intakes also may prove more valuable in supporting protein synthesis and growth of respiratory muscles, although there is no specific evidence for this.[17]

With all feeding options implemented:
Always ensure that the protein percentage remains between 10.2 – 12.4% (i.e. 3.4 – 4.4 g/kg/d) of the total energy (ideally 110 - 150 kcal/kg/d) provided.

Micronutrients: Very important to provide enough anti-oxidants especially vitamin A (± 2000 IU Vitamin A / day).

Recently a trial was conducted by the NICHD Neonatal Research Network on the administration of supplemental Vitamin A to ELBW preterm infants (n= >800) at risk of BPD development. The trial showed that a dose of 5000 IU Vitamin A administered intramuscularly for the first weeks of life, reduced the incidence of BPD at 36 weeks post-conceptional age from 62% to 55% (p<0.03) without any evidence of Vitamin A toxitiy.[108]

In the hospital the infants are supplemented with pediatric multi-vitamin syrup at a dosage of 0.3 - 0.6 ml/ day, which provides 2500 – 5000 IU of Vitamin A. The breast milk fortifier may contribute a further 434 – 620 IU Vitamin A /100ml breast milk, depending on the commercial fortifier used. It is concluded that the current feeding regimen will provide in nearly all preterm and LBW infants' Vitamin A requirements.

Folic acid: 2.5 mg/day
Vitamin D: Only supplemented if the feed does not provide ±400 IU/day
Minerals: Minerals are not routinely supplemented, except:
Iron, which is prescribed from full oral feeds and in the absence of any signs of infection.

Longterm complications: Children who had BPD as an infant, are at an increased risk of lower respiratory tract infections, especially viral infections.[4]

3.8.3 Patent Ductus Arteriosus (PDA)[4]

Definition: Failure of the fetal communication between the pulmonary artery and the aorta to close. [4]

Treatment:
Medical: Moderate fluid restriction (120 – 150 ml/kg/day).
Oxygenation must be optimal.
Medication: Diuretics and Ibuprofen®.
If the above mentioned method of therapy is ineffective, surgery is performed when clinically indicated (PDA ligation).

Dietary: No studies have determined optimal feeding practices in infants with PDA.[17]

In cases of mild fluid restriction, supplementation may be indicated if the infant does not gain weight at a rate of 15 g/kg/day.

3.8.4 Necrotizing Enterocolitis (NEC) [3, 16, 17, 59]

Definition: An acquired disease primarily of preterm or sick neonates. Mucosal or even deeper intestinal necrosis is present most commonly in the terminal ileum, with the colon and the proximal small bowel involved less frequently. The necrosis begins in the mucosa and may progress to involve the full thickness of the bowel wall, resulting in perforation. Associated sepsis occurs in a third of these infants.

Etiology: Unknown. NEC probably represents a common pathological response which is triggered by a variety of risk factors acting singly or in combination. The risk factors include immaturity, hypoxia, ischemia, disruption of mucosal integrity, infection, bacterial translocation, formula feeding, agressive advancement of enteral feeding, hypertonic feeding, polycythemia, milk protein allergy, exchange transfusions and the presence and use of umbilical catheters.[3, 16, 17, 59] Link of PDA with NEC: Decreased blood flow and subsequent hypo-perfusion of the gut has been implicated as an etiological factor in the increased incidence of NEC seen with PDA.[17]

An additional risk factor of enteral feeding in the pathophysiology of NEC is the malabsorption of carbohydrates. Carbon-dioxide, short-chain fatty acids and hydrogen gas are produced when carbohydrates are fermented by the intestinal flora. Distention and increased intra-luminal pressure from gas formed by fermented malabsorbed carbohydrates from enteric bacteria can slow down mucosal blood flow.[111]

Recommended feeding strategies for the prevention of NEC:[16, 17]
1) There is no evidence that brief or prolonged exclusive parenteral nutrition will prevent NEC.
2) Studies to date have not included sufficient numbers of patients to conclusively demonstrate that minimal enteral feedings or a specific rate of nutritive advance of enteral feedings either increase or decrease the incidence of NEC. No specific feeding strategy can therefore be recommended to prevent NEC.
3) Avoid hyperosmolar feedings and medications.
4) Breast milk may be preventative for the development of NEC.

Symptoms: Expect NEC in any infant with:
1) A gastric aspirate of more than 2 ml/kg plus:
2) Abdominal distension
3) Diarrhoea (especially if bloody) or occult bloody stools.
4) Vomiting

Radiological: Pneumotosis intestinalis. (Gas in the bowel wall)[3, 16]

Treatment:

Medical:
1) Screen for infection
2) Repeated abdominal X-rays (when clinically indicated)
3) Repeated hemoglobin and hematocrit determinations (when clinically indicated)
4) Keep infant null per mouth (NPM) with orogastric tube in situ for drainage of gastric aspirates
5) Start Antibiotics

6) A maximum of 3 days of intravenous fluid (Neonatalyte) may be given. If still kept NPM after 3 days, commence with total parenteral nutrition.
7) Measure abdominal circumference daily in case of severe abdominal distension.
8) Daily clinical examination of abdomen for signs of oedema, distension and discolourization.
9) Surgery when clinically indicated.

Management of NEC based on the Bell Classification system:[5, 109]

Stage	Clinical findings	Radiological findings	Treatment
I: Presumed NEC	-Mild abdominal distension -Feeding intolerance -Vomiting	Non-specific: -Sausage shaped bowel loops -Asymmetrical bowel loops -Thickened bowel wall -Possible ascites	-NPM for ± 3 - 5 days -IV fluids -Antibiotics (for at least 2 - 7 days: An individualized approach is followed.)
II: Classic / Confirmed NEC (Medical NEC)	As above plus : -GIT Bleeding -Bile-stained vomiting -Severe abdominal Distension	-Pneumatosis Intestinalis ± Portal gas -Obvious persistent bowel loops (ileus)	-Amount of days NPM depends on the severity of the NEC. -TPN ± minimal enteral feeding (of breast milk) -± Surgery -Antibiotics (according to clinical response: ± 7-10 days)
III: Progressive / Fulminating NEC (Surgical NEC)	-Haemodynamically unstable -Shocked picture with "shocked lung" -Clotting diathesis	-Pneumatosis Intestinalis -± Portal gas -Obvious persistent bowel loops (ileus) -Pneumoperitonium -Impending or proven intestinal perforation	-Amount of days NPM depends on the severity of the NEC. -TPN ± minimal enteral feeding (of breast milk) -Surgery -Antibiotics (according to clinical response: ± 7-10 days)

Dietary therapy post NEC:
- Breast milk (including pasteurized own or donor breast milk) is the first choice. If breast milk is not available, a preterm infant milk formula may be considered.[17] An elemental infant milk formula is indicated in cases of Short Bowel Syndrome.[17] A recent study showed that when milk-intolerant infants were returned to infant milk formulas containing milk proteins, reoccurrences of NEC with pneumatosis intestinalis were seen.[110]
- Increase enteral feeds gradually with increments of 10 – 20 ml/kg/day.
- Minimal enteral feeding is a safe approach that would not be contra-indicated while the infant is on ventilatory support, using umbilical catheters, or receiving drugs such as Indomethacin® or Dopamine®.[16] The practice of keeping the infant NPO for several weeks after birth and nourished only by the parenteral route, is known to cause atrophy of the intestinal mucosa and results in overall delayed development of absorptive function, motility, exocrine hormone secretion and shifts intestinal inflammatory cytokines and chemokines over the anti-inflammatory mediators.[112]
- When the infant is receiving full enteral feeding, supplementation/fortification must be considered for the attainment of adequate catch up growth. The same principles for supplementation/fortification apply as mentioned under section 3.5.6.2.

3.8.5 Short Bowel Syndrome (SBS):
(Refer to the Clinical Guideline on the Management of Short Bowel Syndrome)

3.8.6 Congenital Heart Defects:
(Refer to Clinical Guideline on Congenital Heart Disease)

3.8.7 Gastro-oesophageal Reflux;

Definitions: Gastro-oesophageal Reflux (GER) is defined as the spontaneous return of gastric contents into the esophagus.[60, 61] Gastro-oesophageal Reflux Disease (GERD) is defined as a spectrum of diseases that can best be defined as the symptoms and signs of oesophageal or adjacent organ injury secondary to the reflux of gastric contents into the oesophagus, the oral cavity or airways.[60, 65]

Etiology: GER is a disease of immaturity of the gastro-intestinal tract. GER is therefore commonly found in premature infants, neonates and infants <6 months old, with problems such as: a short oesophagus, gastro-oesophageal sphincter mechanism which is not fully developed, or a small stomach capacity.[60, 64]

The volume of diet ingested by a normal infant (on a per kg basis) which allows for tripling of their weight in their first year, is large and can easily overwhelm the gastric capacity. The latter is the reason why premature infants, neonates and infants need 6 to 12 small, frequent feeds during the day. In comparison with adults, infants need on a kcal per kg basis, 2.5 times more energy. A large volume is thus needed to provide their caloric needs.[66]

There is an interrelationship and interdependency between GER and respiratory disease in infants and children. GER can be a causal factor

in respiratory disease through aspiration of refluxed material. It is further postulated that the presence of acid reflux in the oesophagus may cause an increased amount of mucus produced in the lungs and possibly change the upper and lower airway dynamics.[60]

GER is frequently seen in conditions such as broncho-pulmonary displasia (BPD), cystic fibrosis, cerebral palsy or respiratory infections, where the forced expiration causes increased abdominal pressure. The presence of obesity and constipation may lead to increased abdominal pressure, resulting in GER.[60]

Several medications commonly used in the treatment of central apnoea in premature infants, such as Theophylline (Aminophylline) and caffeine have the side effect of lowering lower oesophageal sphincter tone. Theophylline can furthermore increase gastric acid production.[60]

Indwelling oro- or naso-gastric tubes may cause reflux by lowering lower oesophageal sphincter tone.[60]

Food allergy to foods such as cow's milk may result in secondary GER.[60]

Exposure to passive cigarette smoking may provoke GER by causing lower oesophageal sphincter relaxation.

Diagnosis: GER is diagnosed by taking a patient history (including nutrition), anthropometric and clinical evaluation, as well as conducting appropriate studies or tests, e.g. a video fluoroscopy (indicates the type of swallowing dysfunction present), Ph-studies or multiple electronic conductivity.

Symptoms:[60]

GER (No associated complications)	GERD (With associated complications)
• Consistent weight gain	• Weight loss or inadequate weight gain
• Content during and after feedings	• Crying and fussy during and after feedings
• No respiratory complications	• Respiratory problems such as aspiration, recurrent pneumonia, chronic stridor, wheezing
• Regurgitation# of partially digested milk	• May have blood tinged emesis
• Quiet after feedings	• Irritable after feedings
• No anaemia	• Anaemia may be present

\# (Regurgitation is defined as the passage of refluxed gastric contents into the oral pharynx.[65])

In summary the common clinical signs of GERD are divided into 3 major categories, i.e.:
- Regurgitation and malnutrition
- Oesophagitis
- Respiratory complications[60]

Treatment:

- **Lifestyle changes**: Parental reassurance that GER is a common problem of digestive immaturity that usually resolves with time.
  Avoidance of any passive smoking exposure definitely helps in alleviating the symptoms of GER.[63]

  Postural therapy: Left-lateral positioning is a safer and more effective alternative to prone positioning.[60, 62] It is however considered unethical to recommend prone positioning as a first line measure to reduce regurgitation, due to the higher incidence of sudden infant death syndrome (SIDS) in babies sleeping in the prone position.[60]

  Pharmacotherapy:
  No ideal pharmacological agent exists for the treatment of GERD. Refer to Clinical Guideline on GER for further information on the pharmacological therapy recommended.)

  Dietary: Breastfeeding or expressed breast milk remains the feed of choice for infants younger than 6 months.
  The beneficial role of the use of thickened feeds in the neonatal period is not well known and therefore not used in the treatment of reflux in premature infants.
  The efficacy of smaller, more frequent feeds has not been proven by all, but it was found that a greater volume given per feed worsens GER. The recommendation of smaller, more frequent feeds is therefore still practiced.[60, 62] Changing from bolus to (intermittent) constant infusion may also be considered, especially where the infant is still ELBW.

  Surgical: Surgical intervention is only considered when non-pharmacological and pharmacological measures fail to control the GERD. Indications for surgical intervention include severe failure to thrive, reflux-induced aspiration and pneumonia, oesophagitis, Barrett's oesophagitis and acute life-threatening events.[60] A fundoplication (Nissen- or Thal fundoplication) is the surgical procedure that is performed most often in the treatment of GERD.[60, 63]

(Refer to Clinical Guideline on Gastro-oesophageal Reflux for a more comprehensive overview.)

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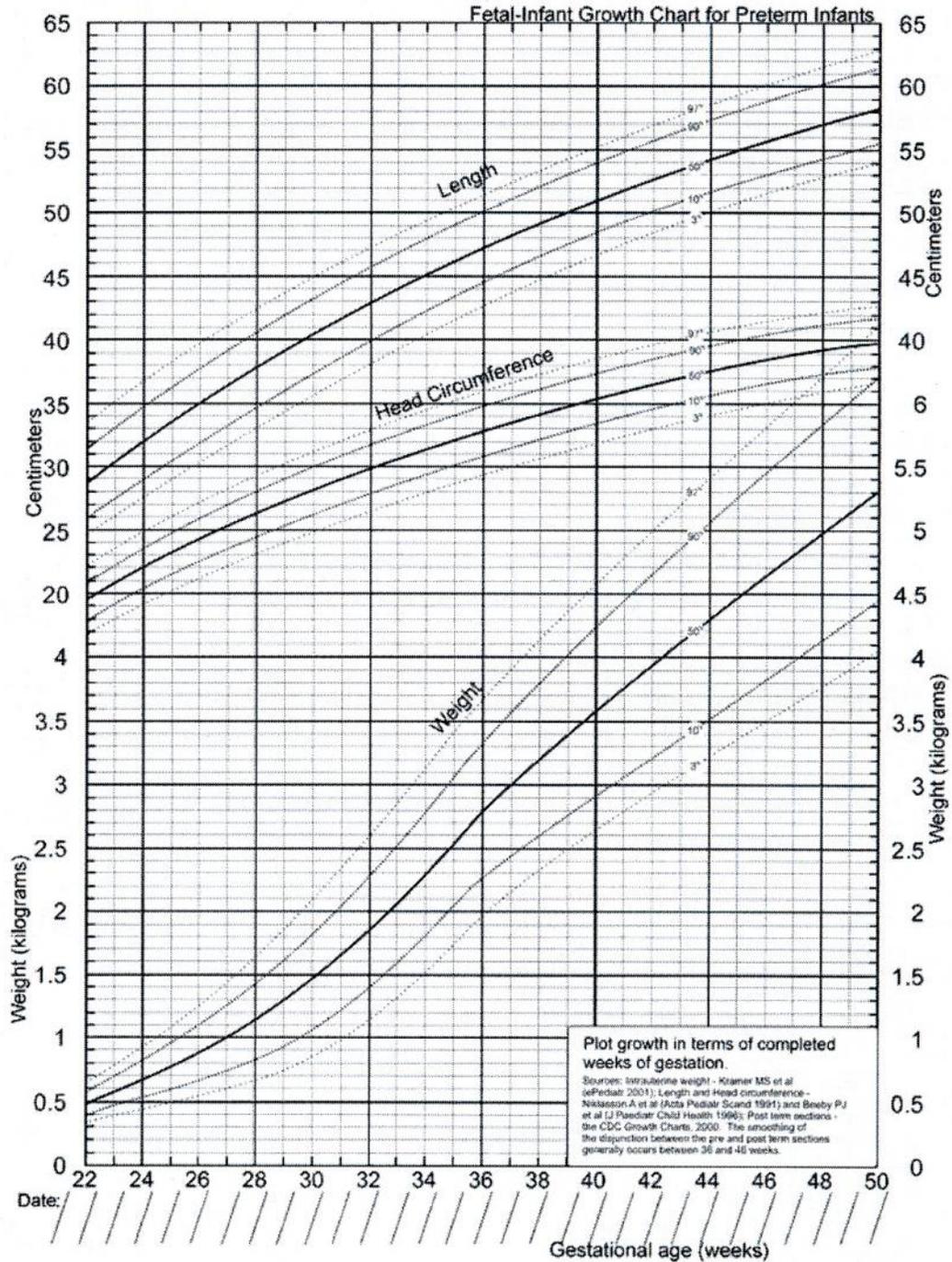
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5. APPENDICES
APPENDIX A: FENTON'S PERINATAL GROWTH CHART[93]

Ref: Fenton Tanis[i]. *BMC Pediatrics* 2003,

Fetal-Infant Growth Chart for Preterm Infants

Plot growth in terms of completed weeks of gestation.

Sources: Intrauterine weight - Kramer MS et al (ePediatr 2001); Length and Head circumference - Niklasson A et al (Acta Pediatr Scand 1991) and Beeby PJ et al IJ Paediatr Child Health 1996); Post term sections - the CDC Growth Charts, 2000. The smoothing of the disjunction between the pre and post term sections generally occurs between 36 and 46 weeks.

[i] Fenton Tanis R: A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. *BMC Pediatrics* 2003, 3:13

NEW BALLARD MATURATIONAL SCORE[29]

TYGERBERG HOSPITAAL

DEPARTEMENT PEDIATRIE

NEW BALLARD SCORE - PERINATALE GROEIKAART

Neuromuscular Maturity

	-1	0	1	2	3	4	5
Posture							
Square Window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm Recoil		180°	140°-180°	110°-140°	90-110°	<90°	
Popliteal Angle	180°	160°	140°	120°	100°	90°	<90°
Scarf Sign							
Heel to Ear							

Physical Maturity

	-1	0	1	2	3	4	5
Skin	sticky friable transparent	gelatinous red, transculent	smooth pink, visible veins	superficial peeling &/or rash few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	
Plantar Surface	*heel-toe 40-50mm:-1 <40mm:-2	>50mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole	
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1 - 2mm bud	raised areola 3 - 4mm bud	full areola 5 - 10mm bud	
Eye/Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff	
Genitals male	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae	
Genitals female	clitoris prominent labia flat	prominent clitoris small labia minora	prominent clitoris enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora	

Maturity Rating

score	weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

* Length

Pediatrie 11.2 (11)

APPENDIX C

Normal Blood Values for the Neonate [5]

Biochemistry:

Component	Unit	Normal range
Serum Sodium	mmol/l	135 – 145
Serum Potassium	mmol/l	3.6 – 6.7
Serum Chloride	mmol/l	95 – 115
Anion Gap	mmol/l	7 – 18
Serum Calcium	mmol/l	1.9 – 2.7
Serum Magnesium	mmol/l	0.8 – 1.1
Serum Phosphate	mmol/l	1.6 – 2.8
Serum Glucose	mmol/l	2.5 – 6.7
Serum Urea	mmol/l	Day 0-2 : 2-11 Day >2 : 1.8 – 5
Serum Creatinine	mmol/l	Preterm : Day 0 – 2 : 60 – 140 Day >2 : 30 – 90 Term : Day 0 – 2 : 40 – 113 Day > 2 : 15 - 60
Serum Osmolarity	g/l	270 – 290
Serum Protein	g/l	44 – 62
Serum Albumin	g/l	25 - 45
Serum Aspartate Transaminase (AST)	U/l	0 - 200
Serum Alanien Transaminase (ALT)	U/l	0 - 265
Serum Lactic Dehydrogenase (LDH)	U/l	100 – 1750
Serum Gamma Glutamyl Transpepdidase (GGT)	U/l	0 – 50
Serum Alkaline Phosphatase (ALP)	U/l	30 – 550
Serum Total Bilirubin	mmol/l	< 17

Blood Gases:

Component	Unit	Normal range
Pa O_2	kPa	Preterm : 8 – 10 Term : 8 - 12
Pa CO_2	kPa	4.5 – 6
Sa O_2	%	Preterm : < 35 weeks and on Oxygen therapy : 86 – 90 (92) > 35 weeks and on Oxygen therapy: 94 - 96
CO_2 Content	mmol/l	18 – 27
pH		7.33 – 7.45

Normal Blood Values for the Neonate [5]
(Continued)

Thyroid Function:

Component	Unit	Normal range
Serum Thyroid Stimulating Hormone (TSH)	mU/l	Umbilical Cord : 0.5 – 20 Day 3 – 7 : <25 Day 8 – 14 : < 10 Day > 15 : 0.4 - 4
Free Serum Thyroxine (T4)	pmol/l	Day 8 – 30 : 12 – 30 > Day 30 : 9.7 - 25

Haematology:

Component	Unit	Normal Range
Haemoglobin	g/dl	14 – 20
Haematocrit	%	42 – 60
Red Cell Count	X 10^{12}/l	5.2 – 5.8
Mean Corpuscular Volume (MCV)	fl	98 – 120
Platelets	X 10^9/l	150 – 300
Reticulocytes :	%	Day < 2 : 2 – 7 Day 2 – 6 : 1 – 3 Day $\geq$ 7 : < 1
	Absolute	Day < 2 : 100 – 250 Day $\geq$ 7 : 0 – 50
White Cell Count (WCC)	X10^9/l	Day < 7 : 9 – 30 Day > 7 : 5 – 20
Neutrophils	%	Day < 7 : 60 Day > 7 : 45
Partial Thromboplastin Time (PTT)	secs	Preterm : < 70 Term : < 55±10
INR		< 1.3
Thrombin Time	secs	10 – 16
Fibrinogen	mg/dl	150 – 300

Additional determinants:

Component	Unit	Normal Range
C-Reactive Protein (CRP)	mg/l	< 10
Alpha-1 Antitrypsin	g/l	1.04 – 2.36
G_6 PD Hb	U/10^{12} Rbc	118 – 145
Ammonia	umol/l	10 – 47
Insulin (during hypoglycemia)	µU/l	< 5

APPENDIX D

A COMBINED COMPARISON OF THE PARENTERAL AND ENTERAL NUTRITIONAL NEEDS OF THE STABLE, GROWING VLBW AND ELBW PREMATURE INFANT [17]

Nutrient	Unit	Parenteral	Enteral	
		(per kg/day)	Per kg/day	Per 100 kcal
Water	ml	120 - 180	135 - 220	104 - 173
Energy	**kcal**	**90 - 115**	**110 - 150**	**100**
Protein	**g**	**3.2 - 4.0**	**3.4 - 4.4**	**2.5 - 3.8**
Carbohydrate	g	9.7 - 17	7 - 20	5.4 - 15.5
Fat	g	3 - 4	5.3 - 8.4	4.1 - 6.5
Linoleic (Ω 6)	mg	340 - 800	600 - 1680	462 - 1309
Linolenic (Ω 3)	mg	1 - 4% of cal	1 - 4% of cal	110 - 440
C18:2 / C18:3		5 - 15 : 1	5 - 15 : 1	5 - 15 : 1
Arachidonic acid	mg	14	24 - 28	22
Docosahexaenoic acid	mg	11	18 - 21	16
Vitamin A (ug)	IU	700 – 1500 (210-450)	700 – 1500 (210-450)	467 – 1364 (140-409)
Vit A in lung disease#	IU	1500 - 2800	1500 – 2800 (450-840)	1250 - 2333
Vitamin D	IU	40 - 160 (max 400)	150-400 (aim 400)	100 - 364
Vitamin E	IU	2.8 - 3.5 (max 7)	6 - 12 (max 25)	4 - 10.9
Vitamin K	ug	10	8 - 10	5.36 - 9.1
Vitamin C	mg	15 - 25	18 - 24	12 – 21.8
Thiamin (B1)	ug	200 - 350	180 - 240	120 - 218
Riboflavin (B2)	ug	150 - 200	250 - 360	167 - 327
Niacin (B3)	mg	4 - 6.8	3.6 - 4.8	2.4 - 4.4
Piridoxine (B6)	ug	150 - 200	150 - 210	100 - 191
Pantothenate	mg	1 - 2	1.2 - 1.7	0.8 - 1.5
Biotin	ug	5 - 8	3.6 - 6	2.4 - 5.5
Folate	ug	56	25 - 50	17 - 45
Vitamin B_{12}	ug	0.3	0.3	0.2 - 0.27
Sodium	mg	69 – 115 (161*)	69-115 (up to 161)	46 - 105
Potassium	mg	78 - 117	78 - 117	52 - 106
Chloride	mg	107 - 249	107 - 249	71 - 226
Calcium	mg	60 - 80	100 - 220	67 - 200
Phosphorus	mg	45 - 60	60 - 140	40 - 127
Magnesium	mg	4.3 - 7.2	7.9 - 15	5.3 - 13.6
Iron	mg	0.1 - 0.2	2 - 4	1.33 - 3.64
Zinc	ug	400	1000 - 3000	667 - 2727
Copper	ug	20	120 - 150	80 - 136
Selenium	ug	1.5 - 4.5	1.3 - 4.5	0.9 - 4.1
Chromium	ug	0.05 - 0.3	0.1 - 2.25	0.07 - 2.05
Manganese	ug	1.0	0.7 - 7.5	0.5 - 6.8
Molybdenum	ug	0.25	0.3	0.20 - 0.27
Iodine	ug	1.0	10 - 60	6.7 - 54.5
Taurine	mg	1.88 - 3.75	4.5 - 9.0	3.0 - 8.2
Carnitine	mg	~2.9	~2.9	~1.9 - 2.6
Inositol	mg	54	32 - 81	21 - 74
Choline	mg	14.4 - 28	14.4 - 28	9.6 - 25.5

*: May require up to 160mg/kg/day in case of late hyponatremia.[17]

#: Reference for this recommendation: nr 18

Conversion factors[3]:

Vit A: 3.33 IU = 1µg retinol;

Vit D:1 IU = 0.025µg cholecalciferol (Vit D_3) ;

Vit E: 1.49IU = 1 mg d- tocoferol

APPENDIX E1

INDICATIONS FOR THE USE OF DONOR BREAST MILK

- Premature infants (<1,8 kg and/or <35 weeks gestation) who are unable to receive their own mother's milk due to one of the following reasons:

  1) Mothers with a disease treated/ controlled with medication contra-indicated for breastfeeding, eg:

     - Certain chemotherapeutic agents, such as cyclophosphamide, doxorubicin and methotrexate.
     - Androgens or immune-suppressant medication, such as cyclosporine.
     - Anti-psychotropic agents (such as Lithium containing medication), sedatives, most anti-depressants and anti-psychotic agents.
     - Radiopharmaceuticals (such as Copper 64, Gallium 67, Indium 111, Iodide 123, 125, 131, radio-active Sodium and Tegnetium 99, ergot and related agents, phenindione, chloramphenicol, phenielbutasone, atropine, thiouracil and mercurates).

  2) Mothers who are HIV positive and are not able to produce breast milk, e.g. stage IV HIV (AIDS) (CD4 count < 200).

  3) Mothers who are alcohol and/or drug addicts to drugs such as amphetamine, cocaine, heroin, marijuana, phencyclidine and tik.

  4) Infants who are for adoption.

  5) Maternal death during or after labour.

In all other cases own mother's milk must be provided to the infants.
HIV positive mothers who are able to express breast milk are encouraged to express and pasteurize their own breast milk.
Formula milk may only be used with the consent of a doctor or dietitian and then only in cases such as post gastro-intestinal tract surgery with impaired gut function, galactosemia and other inborn errors of metabolism.

EvW/Donor Milk Indications: Mar 2006

APPENDIX E2

PROTOCOL FOR THE HANDLING AND DISTRIBUTION OF PASTEURIZED DONOR BREAST MILK IN THE NEONATAL UNIT AND -WARDS

1. Before administration of donor breast milk, consent must be obtained from the mother, or father, or legal guardian of the baby for the use of donor milk for feeding their baby. If none of the above individuals are available, the applicable hospital's protocol must be observed and consent for the use of donor milk must be obtained from the relevant stated hospital representative. Cognizance must be taken of possible medical-legal implications of the use of donor breast milk.

2. Only donors with a confirmed negative HIV test result are accepted and used. (The HIV test must have been performed in the preceding 3 months.)

3. Only pasteurized fresh (non-frozen) or pasteurized frozen donor breast milk may be used.

4. All donor milk received in the ward must be clearly labeled with the donor's code and the date on which the sample was issued from the milk kitchen.
   As soon as the donor milk arrives in the ward, the name and file number of the recipient baby must be recorded on every container of donor milk received.

5. The same guidelines for the handling of breast milk apply as described in the document compiled by Profs Kirsten, Forder and Cotton ("Guidelines to prevent contamination during expression and storage of breast milk"). The following are the applicable guidelines for the hygienic handling of fresh or frozen pasteurized donor breast milk:

   • Storage containers: Only sterile glass or hard plastic containers must be used for storage of the milk. Plastic bags may not be used, due to the difficult sealing thereof and also due to the risk of contamination.
   Milk containers must be provided with caps that ensure airtight sealing.
   • Fresh (unfrozen) pasteurized donor milk may be refrigerated at 4°C for a maximum period of 24 hours.
   • On ward level: Pasteurized milk that is not used within 24 hours of refrigeration must be discarded.
   • Thawing of frozen pasteurized donor milk may be done by holding the lower part of the milk container under lukewarm water, or by putting the milk container in a bucket with warm water, or by letting the milk thaw overnight in the refrigerator (4°C).
   • The temperature of the thawed milk may not exceed body temperature (37°C).
   • Milk may not be thawed in the washbasin (due to the risk of contamination), and also not in the microwave oven (due to the risk of overheating of the milk).
   • Frozen milk that has been thawed may be refrigerated for a maximum period of 24 hours after which it must be thrown away (re-freezing is not allowed).
   • Milk that has been heated before a feed must be thrown away if all of it was not used.
   • Before every feed two nursing personnel must check that the recipient baby's name and file number corresponds to the name and file number as indicated on the donor milk container.

Donor milk protocol: March 2006

APPENDIX F1

COMPARISON OF THE NUTRIENT COMPOSITION OF PREMATURE INFANT MILK FORMULAS (per 100 kcal)

	Enteral Recommen-dation / 100 kcal[17]	Nenatal with LCP'S (Cow & Gate)	Prenan + LCPUFA (Nestlé)	Prenan (Nestlé)	Similac special care (Ross / Abbott)	S26 LBW Gold (Wyeth)
Volume providing 100 kcal	125 - 167	125	125	125	148	125
Fat (g)	**5.0 - 7.0**	**5.5**	**5.25**	**4.88**	**5.43**	**5.4**
MCT (g)	No Recomm		1.58	1.85	2.75	0.83
Linoleic acid (18:2) (n-6) (g)	0.44 - 1.7	0.69	0.71	0.64	0.71	0.67
Linolenic acid (18:3) (n-3) g	0.1 - 0.44	0.08	0.08	0.05	N/A	N/A
Docosahexaenoic acid (22:6) (n-3) (mg)	No Recomm	20	16.3	N/A	N/A	N/A
Arachidonic acid (20:4) (n-6) (mg)	No Recomm	30.0	5	N/A	N/A	N/A
n-6 /n- 3 ratio	5:1 - 10:1	9:1	9:1	12.5:1	N/A	N/A
Total Protein (g)	**3.0 - 3.16**	**3.0**	**2.9**	**2.9**	**2.71**	**2.4**
Whey (g)	1.8 - 1.9	1.8	2.24	2.03	1.65	1.44
Casein (g)	1.2 - 1.26	1.2	0.63	0.87	1.1	0.96
Whey : Casein ratio	60 / 40	60 / 40	77 / 23	70 / 30	60 / 40	60 / 40
Carbohydrate (g)	**3.16 - 9.5**	**9.75**	**10.75**	**11.4**	**10.3**	**10.5**
Lactose (g)	3.16 - 9.5	7.5	7.0	8.6	N/A	5.25
Maltodextrin (g)	No Recomm	2.25	3.75	2.8	N/A	5.25
Other Polysaccharides (g)	No Recomm	-	-	-	-	-
Prebiotic oligosaccharides (g)	No Recomm	-	-	-	-	-
Energy (kcal)	**100**	**100**	**100**	**100**	**100**	**100**
(kJ)	420	420	420	420	420	420
Energy concentration (kcal/ml)	**0.73 - 0.83**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**
Vit A (I.U.)	583 - 1250	941	350	306	1250	366
(ug)	175 - 375	282.4	105	91.8	375	109.8
Of which beta-carotene (ug)	No Recomm	50	N/A	N/A	N/A	N/A
Vit D (I.U.)	125 - 333	249	100	100	150	73.2
(ug)	3.13 - 8.33	6.23	2.5	2.5	3.8	1.83
Vit E (I.U.)	5 - 10	5.6	2.5	2.0	4.0	2.2
Vit K (ug)	6.66 - 8.33	8.2	8.0	12.0	4	9.8
Vit C (mg)	15 - 20	20	16.25	16.1	37.6	13.4
Thiamine (B1) (mg)	0.15 - 0.2	0.2	0.07	0.06	0.25	0.146
Riboflavin (B2) (mg)	0.2 - 0.3	0.25	0.15	0.13	0.62	0.245
Niacin (B3) (mg)	3 - 4	3	1.0	1.0	5	1.0
Biotin (ug)	3 - 5	3.7	2.25	2.25	37	2.9

COMPARISON OF THE NUTRIENT COMPOSITION OF
PREMATURE INFANT MILK FORMULAS (per 100 kcal) (CONT.)

	Enteral Recommen-dation / 100 kcal[17]	Nenatal with LCP'S (Cow & Gate)	Prenan + LCPUFA (Nestlé)	Prenan (Nestlé)	Similac special care (Ross / Abbott)	S26 LBW Gold (Wyeth)
Folic acid (ug)	21 - 42	60	70	58.8	37	58.5
Pantothenic acid (mg)	1 - 15	1.2	0.45	0.5	1.9	0.55
Vitamin B6 (mg)	0.125 - 0.175	0.2	0.08	0.125	0.25	0.088
Vitamin B12 (ug)	0.25	0.25	0.3	0.25	0.55	0.37
Choline	12 - 23.4	13	15	7.5	10	-
Myo-inositol (mg)	27 - 67.5	37	6.5	4.5	5.63	-
Taurine (mg)	3.75 - 7.5	6.9	8	8.0	5.3	-
Carnitine (mg)	2.4	2.5	2.13	1.625	0	-
Calcium (mg)	100 - 192	124	124	100	180	97.5
Phosphorus (mg)	50 - 117	62	67.5	65	100	52
Ca : P04 ratio	2:1 - 1.6:1	2:1	1.83:1	1.54:1	1.8:1	1.9:1
Magnesium (mg)	6.6 - 12.5	12	10	11	12	9.8
Potassium (mg)	65 - 100	94	107.5	107.5	129	104
Sodium (mg)	38 - 58	40	36.3	36.3	43	42.7
Chloride (mg)	59 - 89	60	70	57.5	81	73
Iron (mg)	1.67	1.1	1.5	1.5	0.4	1
Copper (ug)	100 - 125	100	100	90	250	100
Iodine (ug)	25 - 50	31	25	10	6	12.2
Manganese (ug)	6.3	12	7	6.9	12	12.2
Zinc (mg)	0.833	0.9	0.8	0.75	1.5	1
Selenium (ug)	1.08 - 2.5	2.4	2	-	1.8	-
Chromium (ug)	0.083 - 0.42	-	-	-	-	-
Molibdenum (ug)	0.25	-	-	-	-	-
Energy distribution						
Protein as % of total energy	**10 - 20**	**12**	**11.5**	**11.5**	**11**	**9.5**
Fat as % of total energy	**40 - 50**	**49**	**46.5**	**43.5**	**48**	**48.5**
Carbohydrate as % of total energy	40 - 50	39	42	45	41	42
Renal Solute Load (mOsm/L) (acc. to formula*)(2)	133-173	197 (186)	142.43 (183)	139.62 (180)	149 (149)	163
Potential Renal Solute Load: (mOsm/L)(formula #)	< 233	[200]	[200.7]	[197]	262 [177]	[176]
Osmolality (mOsm/kg water)	<300	N/A	N/A	N/A	235	295
Osmolarity (mOsm/l water)	<300	260	N/A	N/A	211	260
Price / 100 kcal (Tender: 7/9/03 - 6/9/04)		**R 5.42**	**R 2.22**	**R 0.91**	**R9.45**	**R 2.62**

Abbreviations used: NA: Not Available

APPENDIX F2

A DISCUSSION ON THE USE OF SEMI-ELEMENTAL INFANT MILK FORMULA IN THE PREMATURE INFANT

Since 1994 several researchers have investigated the nutritional adequacy of a semi-elemental (i.e. extensively hydrolyzed) infant milk formula in preterm infants.[72] Research mostly focused on the proposed allergy preventative or improved absorptive capacity of the semi-elemental infant milk formula.

From an allergy-preventative perspective the use of an extensively hydrolyzed formula in the preterm infant has no scientific basis.[71] The latter was confirmed by another researcher who did not find any articles in the literature concerning the efficacy of hydrolyzed formula in cow's milk allergy prevention in preterm infants. [72]

The use of a semi-elemental feed for a premature infant was recently investigated. Twenty-one preterm infants (1750g, 34weeks) were randomly fed a hydrolyzed protein or an ordinary preterm formula. Blood and amino acid concentrations before the start and after 14 and 28 days were analyzed. The researchers found a slower rate of weight gain in the infants receiving the hydrolyzed formula. These infants also showed a higher renal excretion of essential amino acids at 14 days. The researchers concluded that the protein hydrolysate did not involve any nutritional advantage.[70]

Hydrolyzed formula could however have a positive role in the early feeding of VLBW infants but several concerns exist about their nutritional adequacy. Further investigations addressing protein and mineral metabolism, as well as long-term effects, including neuro-developmental, are needed.[72]

APPENDIX G

BREAST MILK FORTIFIERS
(Indicated as dosages to be added to 100ml of breasmilk)

	Similac Human Milk Fortifier (0.9g x 4 sachets) (Abbott)	FM 85 (5g) (Nestlé)	Nutriprem Breastmilk Fortifer (2,1g x 2 sachets) (Cow + Gate)
FAT (g)	0,36	0,2	0
Linoleic acid (18:2) (Ω6) (g)	-	-	
Linolenic acid (18:3) (Ω3) (g)	-	-	
PROTEIN EQUIVALENT (g)	1,0	1,0	0,7
Whey (g)	1,0	1,0	0,42
Casein (g)	-	-	0,28
CARBOHYDRATE (g)	1,8	3,35	2,0
Lactose (g)	-	-	
Maltodextrin (g)	-	3,35	
ENERGY (kcal)	14	18	10
ENERGY (kJ)	58.8	74	44
ENERGY DISTRIBUTION			
Protein as % of total energy	28	21	27
Fat as % of total energy	22	9	-
Carbohydrate as % of total energy	50	70	77
Renal solute load (mOsm/3.6g, 5g or 4.2g respectively)		6.43	
Potential renal solute load: (mOsm/3.6g, 5g or 4.2g respectively)		8.14	
Calcium (mg)	117	75	60
Phosphorus (mg)	67	45	40
Magnesium (mg)	7.0	2.4	6,0
Sodium (mg)	15	20	6,0
Potassium (mg)	63	42	4,0
Chloride (mg)	38	17	7,0
Zinc (mg)	1.0	0.8	0,30
Copper (μg)	170	40	26
Iron (mg)	0,35	1.3	
Iodine (μg)	-	15	11,0
Manganese (μg)	7.2	1.5	6,0
Selenium (μg)	-	1.5	
Vitamin A (IU) and (ug)	620 and (186)	500 and (150)	434 and (130)
Vitamin D (IU)	120	100	200
Vitamin E (IU) and (mg)	3.2 and (2.13)	4.5 and (3)	3,8 and (2.53)
Vitamin K (μg)	8.3	4.0	6,30
Vitamin C (mg)	25	10	12
Vitamin B1 (μg)	233	50	0,130
Vitamin B2 (μg)	417	100	170
Vitamin B3 (mg)	3.57	0.8	2,5
Biotin (μg)	26	3.0	2,5
Folic acid (μg)	23	40	50
Pantothenic acid (mg)	1.5	0.04	0,75
Vitamin B6 (μg)	211	50	110
Vitamin B12 (μg)	0.64	0.1	0,2

FULL ANALYISIS OF THE NUTRIENT COMPOSITION OF BREAST MILK
+ FM 85, AND A COMPARISON WITH THE COMBINED ENTERAL RECOMMENDATIONS
FOR A ELBW AND VLBW PREMATURE INFANT [17] (adapted)

NUTRIENT	Per 150 ml EBM	7.5 g FM 85	0.3 ml Vidaylin	150 ml EBM + 7.5g FM85 + 0.3 ml Vidaylin	Enteral Recommen-dations per 100 kCal [17]	% of Enteral Recommen-dation provided (average %)
Fat (g)	5.3	0.3		5.6	4.1 - 6.5	86 - 137 (112)
Protein Equivalent (g)	2.4	1.5		3.9	2.5 - 3.8	102 - 156 (129)
Whey (g)	1.68	1.5		3.18		
Casein (g)	0.72	0		0.72		
Carbohydrate (g)	10.95	5.03		15.98	5.4 - 15.5	103 - 296 (200)
Maltodextrin (g)		4.8		4.8		
Energy (kcal)	100.5	27		127.5	100	127.5 (128)
(kJ)	420	111		531	420	
Calcium (mg)	37.95	112.5		150.45	67 - 200	75 - 225 (150)
Phosphorous (mg)	22.05	67.5		89.55	40 - 127	71 - 224 (148)
Ca: PO4 ratio	1.7 : 1	1.7 : 1		0	1.6:1 - 2.1:1	W/R*
Magnesium (mg)	5	3.6		8.6	5.3 - 13.6	63 - 162 (113)
Sodium (mg)	43.95	30		73.95	46 - 105	70 - 161(116)
Potassium (mg)	73.95	63		136.95	52 - 106	129 - 263 (196)
Chloride (mg)	88.95	25.5		114.45	71 - 226	51 - 161(106)
Iron (mg)	0.135	1.95		2.085	1.33 - 3.64	57 - 157(107)
Zinc (mg)	0.56	1.2		1.76	0.67 - 2.73	64 - 263 (164)
Copper (ug)	57	60		117	80 - 136	86 - 146 (116)
Iodine (ug)	27	22.5		49.5	6.7 - 54.5	91 - 739 **(415)**
Manganese (ug)	0.54	2.25		2.79	0.5 - 6.8	41 - 558 **(300)**
Selenium (ug)		2.25		2.25	0.9 - 4.1	55 - 250 (153)
Chromium (ug)					0.07 - 2.05	
Molibdenum (ug)					0.2 - 0.27	
Choline (mg)					9.6 - 25.5	
Inositol (mg)					21 - 74	
Taurine (mg)					3.0 - 8.2	
Carnitine (mg)					~1.9 - 2.6	
Vit A (I.U.)	72	750	2500	3322	467 - 1364	244 - 711 **(478)**
Vit A (in lung disease)(I.U.)	72	750	2500	3322	2250 - 2333	142 - 148 (145)
D (I.U.)	12	150	200	362	100 - 364	100 - 362 **(231)**
E (I.U.)	0.6	4.5		5.1	4 - 10.9	50 - 128 (89)
K (ug)	3	6		9	5.63 - 9.1	99 - 160 (130)
C (mg)	6.75	15	25	46.75	12 - 21.8	214 - 389 **(302)**
Thiamin (B1) (mg)	0.014	0.075	0.75	0.839	0.12 - 0.22	381 - 699 **(540)**
Riboflavin (B2) (mg)	0.041	0.15	0.6	0.791	0.17 - 0.33	240 - 465 **(353)**
Niacin (B3) (mg NE)	0.3	1.2	5	6.5	2.4 - 4.4	148 - 271 **(210)**
Biotin (ug)	0.8	4.5		5.3	2.4 - 5.5	96 - 221 (159)
Folic acid (ug)	4.95	60		64.95	17 - 45	144 - 382 **(263)**
Pantothenic acid (mg)	0.3	0.6		0.9	0.8 - 1.5	60 - 113 (87)
Vit B6 (mg)	0.009	0.075	0.25	0.334	0.1 - 0.19	176 - 334 **(255)**
Vit B12 (ug)	0.03	0.15		0.18	0.2 - 0.27	67 - 90 (79)

Energy Distribution						
Protein as % of TE	9.5	21		12	9.0 - 12.0	Adequate
Fat as % of TE	47.2	9		39	40 - 50	Low Normal
Carbohydrate as % of TE	43.3	70		49	40 - 50	High Normal
RSL (mOsm/L)	106			171	133 - 173	High Normal
PRSL (mOsm/L)	138			234	200 - 233	High Normal
Price (R / 150 ml EBM)						

Abbreviations: * W/R: Within Recommendation, TE: Total Energy, RSL : Renal Solute Load, PRSL: Potential Renal Solute Load

AUTHOR'S COMMENTS: With the proposed feeding regimen the premature infant will receive all the nutrients in sufficient amounts (when the averaged percentage of the nutrient provided is compared with the enteral recommendation). A few nutrients is provided at very high levels of more than 200% of the enteral recommendation. Of these nutrients, the water-soluble vitamins are not problematic. (The applicable vitamins are not known to cause toxicity). Of the minerals and trace elements only Iodine and Manganese will be provided at extremely high levels, due to the wide range regarded as the enteral recommendation for these two trace elements. Iron content is sufficient and necessitates a discussion on the need for further iron supplementation in hospital (The risk for iron overload might now become an issue). Potential renal solute load is at the high level of normal and therefore renal function must be monitored.

FULL ANALYSIS OF THE NUTRIENT COMPOSITION OF BREAST MILK + SIMILAC HUMAN MILK FORTIFIER (HMF) AND A COMPARISON WITH THE COMBINED ENTERAL RECOMMENDATIONS FOR A ELBW AND VLBW PREMATURE INFANT
[17(adapted)]

NUTRIENT	Per 150 ml EBM	5.4 g Similac HMF	150 ml EBM + 5.4g Similac HMF	Enteral Recommen-dations per 100 kCal [17]	% of Enteral Recommendation provided (average %)
Fat (g)	5.3	0.54	5.84	4.1 - 6.5	90 - 142 (116)
Protein Equivalent (g)	2.4	1.5	3.9	2.5 - 3.8	102 - 156 (129)
Whey (g)	1.68		1.68		
Casein (g)	0.72		0.72		
Carbohydrate (g)	10.95	2.7	13.65	5.4 - 15.5	88 - 253 (171)
Maltodextrin (g)			0		
Energy (kcal)	100.5	21	121.5	100	121.5 (122)
(kJ)	420	88.2	508.2	420	121.5 (122)
Calcium (mg)	37.95	175.5	213.45	67 - 200	107 - 319 **(213)**
Phosphorous (mg)	22.05	100.5	122.55	40 - 127	96 - 306 **(201)**
Ca: PO4 ratio	1.7 : 1	1.75 : 1	1.7 : 1	1.6:1 - 2.1:1	W/R*
Magnesium (mg)	5	10.5	15.5	5.3 - 13.6	114 - 292 **(203)**
Sodium (mg)	43.95	22.5	66.45	46 - 105	63 - 144 (104)
Potassium (mg)	73.95	94.5	168.45	52 - 106	159 - 324 **(242)**
Chloride (mg)	88.95	57	145.95	71 - 226	65 - 206 (136)
Iron (mg)	0.135	0.525	0.66	1.33 - 3.64	18 - 50 **(34)**
Zinc (mg)	0.56	1.5	2.06	0.67 - 2.73	75 - 307 (191)
Copper (ug)	57	255	312	80 - 136	229 - 390 **(310)**
Iodine (ug)	27	0	27	6.7 - 54.5	50 - 403 **(227)**
Manganese (ug)	0.54	10.8	11.34	0.5 - 6.8	167- 2268**(1218)**
Selenium (ug)				0.9 - 4.1	
Chromium (ug)				0.07 - 2.05	
Molibdenum (ug)				0.2 - 0.27	
Choline (mg)				9.6 - 25.5	
Inositol (mg)				21 - 74	
Taurine (mg)				3.0 - 8.2	
Carnitine (mg)				~1.9 - 2.6	
Vit A (I.U.)	72	930	1002	467 - 1364	73 - 215 (144)
Vit A (in lung disease)(I.U.)	72	930	**1002**	2250 - 2333	43 - 45 **(44)**
D (I.U.)	12	180	**192**	100 - 364	53 - 192 (123)
E (I.U.)	0.6	4.8	5.4	4 - 10.9	50 - 135 (93)
K (ug)	3	12.45	15.45	5.63 - 9.1	170 - 274 **(222)**
C (mg)	6.75	37.5	44.25	12 - 21.8	203 - 369 **(286)**
Thiamin (B1) (mg)	0.014	0.35	0.364	0.12 - 0.22	165 - 303 **(234)**
Riboflavin (B2) (mg)	0.041	0.626	0.667	0.17 - 0.33	202 - 392 **(297)**
Niacin (B3) (mg NE)	0.3	5.355	5.655	2.4 - 4.4	129 - 236 (183)
Biotin (ug)	0.8	39	39.8	2.4 - 5.5	724 - 1658 **(1191)**
Folic acid (ug)	4.95	34.5	39.45	17 - 45	88 - 232 (160)
Pantothenic acid (mg)	0.3	2.25	2.55	0.8 - 1.5	170 - 319 **(245)**
Vit B6 (mg)	0.009	0.317	0.326	0.1 - 0.19	172 - 326 **(249)**
Vit B12 (ug)	0.03	0.96	0.99	0.2 - 0.27	367 - 495 **(431)**

Energy Distribution					
Protein as % of TE	9.5	28	12.7	9.0 - 12.0	High Normal
Fat as % of TE	47.2	22	42.8	40 - 50	W/R
Carbohydrate as % of TE	43.3	50	44.5	40 - 50	W/R
RSL (mOsm/L)	106		**180**	133 - 173	**Too High**
PRSL (mOsm/L)	138		**250**	200 - 233	**Too High**
Price (R /150ml EBM)					

Abbreviations: * W/R: Within Recommendation, TE: Total Energy, RSL : Renal Solute Load, PRSL: Potential Renal Solute Load

AUTHOR'S COMMENTS: With the proposed feeding regimen the premature infant will receive all the nutrients in sufficient amounts (when the averaged percentage of the nutrient provided is compared with the enteral recommendation). A few nutrients are provided at very high levels of more than 200% of the enteral recommendation. Of these nutrients, the water-soluble vitamins are not problematic, but the extremely high Biotin content seems inappropriate. (None of these vitamins are known to cause toxicity however.) The amount of Vitamin A provided will be insufficient for the preterm with lung disease. Additional Vitamin A supplementation must be considered in such cases. Vitamin D is provided at a sufficient level, when compared to the enteral recommendation and the need for additional Vitamin D supplementation in the hospital seems unnecessary. Overall it seems as if routine vitamin supplementation would not be required when Similac HMF are added to the EBM. Of the minerals and trace elements only Copper and Manganese will be provided at very high levels, due to the wide range regarded as the enteral recommendation for these two trace elements. Iron content is provided at a low level of a third of the recommendation, which is acceptable, but will necessitate further iron supplementation.
Renal Solute Load and Potential Renal Solute Load are both at levels higher than the recommended range due to the high electrolyte content of the fortifier; therefore sufficient fluid must be provided and renal function monitored on a regular basis.

APPENDIX I

Calculation of Potential Renal Solute Load and Renal Solute Load: [12]

Potential Renal Solute Load (PRSL):
Formula:
PRSL = Nitrogen/28 + Sodium (mmol/Liter) + Chloride (mmol/Liter) + Potassium (mmol/Liter) + available Phosphorus (mmol/Liter)
PRSL is expressed in mOsm/Liter

Additional information for calculation purposes:
Nitrogen = ([g Protein/Liter ÷ 6.25) x 1000] / 28

Available Phosphorus is assumed to be total phosphorus of milk-based formulas and two-thirds of the phosphorus of soy-based formulas. (Phytate phosphorus which accounts for about one third of total phosphorus in isolated soy protein-based formulas is largely unabsorbed and thus not relevant to the calculation of PRSL.[12])

Molecular weights of respective electrolytes:
Sodium = 23mg/ mmol
Chloride = 35 mg/ mmol
Potassium = 39 mg/ mmol
Phosphorus = 31 mg/ mmol

Renal Solute Load (RSL):
Formula:
RSL = (g Protein/Liter x 4) + Sodium (mmol/ Liter) + Chloride (mmol/ Liter) + Potassium (mmol/ Liter)
RSL expressed in mOsm/ Liter

Prediction of RSL from PRSL[12]:
RSL $_{(est)}$ = PRSL – (0.9 X gain)
RSL and PRSL are expressed in mOsm/day
Gain refers to grams of weight gained per day

APPENDIX J

THE USE OF PRE- AND PROBIOTICS IN THE PREMATURE AND LBW INFANT

Definitions:
Prebiotics are non-absorbable, non-digestible food ingredients (fructans, e.g. fructo-oligosaccharides and inulin) that may benefit the host by acting as substrates for probiotics.[75, 85, 86,]
Probiotics are live non-pathogenic bacteria that exist naturally and colonize the gastro-intestinal tract, where it carries a health benefit to the host through the prevention of disease.[75, 80, 86]
Synbiotics: when both pre-and probiotics are added to dietary products such as infant milk formula.[85]

The bacterial species mostly used for induction of the probiotic effect are lactobacilli and bifidobacteria, which form part of the normal intestinal microflora of a human being.[85] Human milk contain more than 130 different oligosaccharides at a concentration of 15 – 23 g/L in colostrums and 8 – 12 g/L in transitional and mature milk.[87, 88]

Advantages of Prebiotics[89, 90]

- May lead to increased resistance to (mainly gastro-intestinal) pathogens
- Modulates the systemic immune response and allergy risk
- Improved bowel function and laxative effect
- Enhanced calcium bio-availability and bone mineralization.

Advantages of Probiotics[74, 75]

- May improve intestinal immunoregulation
- Improves mucin production
- Produces anti-bacterial agents
- Stimulates Ig-A production
- Prevents mucosal adherence of pathogens
- Decrease mucosal permeability
- Produces anti-inflammatory cytokines

Proposed mechanisms of action: [74, 79, 80]
Probiotics may contribute to the establishment of normal non-pathogenic flora through:
1) prevention of the adherence of bacterial and viral pathogens to the enterocyte,
2) local production of antimicrobial products,
3) changing the intestinal lumen pH (to the ideal range of 5.5 – 5.8) through the production of lactate and potential microbicidal highly-active short chain fatty acids which may inhibit the growth of pathogenic micro-organisms,
4) stimulation of the immune system,
5) modification of toxin receptors through enzymatic mechanisms.

Specific features required of probiotics:
- Must be able to survive gastric acidity
- Must be able to colonize the GIT
- Must be able to produce factors such as bacteriocins, which can inhibit the growth of pathogenic bacteria.[80]
  (*Bacteriocins are proteins or protein complexes with bactericidal activities directed against species that are closely related to the producer bacterium.[80])
- The probiotic species , Lactobacille and Bifidobacteria are gram-positive bacteria with a more rapid growth velocity than gram negative bacteria.[84]

The following table indicates commercial probiotics which have previously been used in the premature infant:

Product	Probiotic present	Manufacturer	Type of studies where used
Infloran	Lactobacillus acidophilus Bifidobacterium infantis	Berna Biotech Ltd (Berne, Switzerland)	Randomized clinical trial, where probiotics were given prophylactic to VLBW infants. NEC incidence decreased from 5.3% to 1.1% (Relative risk reduction of 79%)[76]
	Lactobacillus GG		A prospective randomized clinical trial in 585 VLBW infants. The relative risk for NEC in the infants receiving probiotics was half of that of the control group (1.4% vs 2.8%). This difference was not statistically significant. Recommend the provision of more than one probiotic agent.[77]
	Bifidobacterium breve		Double-blind randomized controlled study in >150 VLBW infants. Results: Found high levels of colonization. No adverse effects could be attributed to the probiotic administration. Improved weight gain observed.[78]

Conclusion from the above-mentioned research:
In most recent studies on probiotic administration in premature infants, no adverse effects were reported. Early probiotic supplementation in premature infants is theoretically sound and associated with minimal risk. It is however still necessary to work with caution when any new and potentially infective agent is used in VLBW infants.[80, 81] The latter is confirmed by three reported cases where Lactobacillus GG caused bacteraemia. (Lactobacillus Casei GG naturally forms part of human GIT microflora and has been shown to be advantageous in the clinical outcome of enterally-fed premature infants.[84]) It may thus be that probiotics do have pathogenic potential, but the risk for the latter is still regarded as low.[84]

Comments on the use of probiotics in the premature infant:
- Necrotising enterocolitis remains a major cause of morbidity and mortality in premature infants. Although the pathogenesis of NEC remains unclear, prevention strategies are continually being investigated. One such an emerging strategy is the use of pre- and probiotics for the prevention of NEC.[75] Given the relationship between the development of a monoflora and impending NEC, probiotic administration may be a way of protecting

the VLBW neonate against colonization of the GIT with potential pathogens through artificial strengthening of the diversity of the intestinal microflora.[74]

- The safety aspects and effectiveness of the use of probiotics in the premature infant requires further research. Premature infants, especially those treated under intensive care conditions, often have an abnormal pattern of gut colonization, and their gut flora may contain only small amounts of lactobacilli and bifidobacteria which are considered the target micro-organisms for oligosaccharide supplementation.[85]

- Literature confirms that the prophylactic use of probiotics in premature infants with the following defects or problems must be avoided:
  - Congenital or acquired immunological deficiencies
  - Congenital heart disease
  - Gastro-intestinal tract impairment due to ileus, mucositis, diarrhoea, presumed or confirmed NEC.

- The first bacteria to colonize the previously sterile GIT of the neonate, originates from the mother. It is suggested that the administration of probiotics to the mother shortly before labour, may contribute to the early colonization of the neonate's GIT.[82]

Recommendations for pre and probiotic use in the premature infant:
The agent used must be the least virulent probiotic, and have a favourable antibiotic susceptibility profile.

Prebiotic supplementation in addition to probiotics must be investigated in the premature infant. Prebiotics selectively stimulate the growth or activity of certain probiotic bacteria in the colon.[83] The oligosaccharides present in human milk are classified as prebiotics. When prebiotics are added to the diet a marked increase in the concentrations of bifidobacterium and corresponding decrease in bacteriodes ensue. Human milk, as opposed to formula, is rich in oligosaccharides. Feeding with human milk leads to the colonization of the GIT with Lactobacillus and Bifidobacterium species, which reduces the risk of NEC. This might be a contributing factor to the protective effect of human milk against NEC, confirming the preferred use of human milk for the premature infant.[73, 80]

The use of Saccharomyces and Bacillus Species as probiotic agents must be avoided, as they have been associated with invasive disease in target populations. In contrast to the aforementioned, population-based studies indicate that rates of invasive disease by lactobacilli are extremely low.[74]

Lactobacillus Casei is the only probiotic which have shown effectivity when used as a preventative therapy and may thus be regarded as a bio-therapeutic agent. (A bio-therapeutic agent is defined as a micro-organism with proven medical effect and therefore regarded as a medication.[83]) When micro-organisms are considered for preventative use, it is recommended that micro-organisms which normally inhibits the human GIT must be tested first.[84]

The ESPGHAN Committee on Nutrition has concluded in 2004 that there is no published evidence of clinical benefits of adding prebiotic oligosaccharides to dietetic products for infants. Combinations of oligosaccharide mixtures and dosages need to be fully evaluated with respect to both safety and efficacy before their use in infant products could be recommended. Future trials should define optimal quantity and types of oligosaccharides with prebiotic function, optimal dosages and duration of intake, as well as short- and long term benefits and safety. No general recommendation on the use of oligosaccharide supplementation in infancy as either a prophylactic or therapeutic measure, can be made.[85]

APPENDIX K

EVALUATION OF CONDITIONALLY ESSENTIAL NUTRIENTS AND THE USE OF OTHER DIETARY FACTORS IN THE PREMATURE INFANT

ARGININE:

Functions in the premature infant: [17, 59, 67, 68]
In early life arginine plays an important regulatory role in priming the urea cycle and in the activation of the carbamoyl-phosphate synthetase.
It is also a precursor for creatine synthesis, which is important for muscle and brain energy utilization.
Arginine is a precursor of guanidine nitrogen, which is necessary for the formation of nitric oxide, a potent endothelial relaxing factor. Nitric oxide acts as an intracellular signal that leads to smooth muscle relaxation. Inadequate concentration of nitric oxide leads to vasoconstriction of the intestinal vessels, which might lead to ischemia and a predisposition to NEC. Due to its volatile nature, nitric oxide cannot be delivered to the gut in its intact form. An indirect method of achieving adequate concentration is by supplementing substrates such as arginine, as the latter is a precursor of nitric oxide.
Arginine furthermore enhances cellular immune mechanisms, in particular, T-cell activity.

Dietary content: [67]
Human milk provides ±0,3mmol/kg/d while infant milk formulas have up to 5 times that amount. An infant on TPN will receive ±1-2 mol/kg/d. Arginine salts, may provide an additional load of arginine as the former is used in antibiotics to improve solubility and stability of the medication.

Toxicity: [67]
Toxicity has been demonstrated in children receiving 20 – 30 times the customary daily dietary arginine intake.
Arginine may be toxic in infants with liver failure.
Since arginine is a potent stimulator of insulin, excess intake may promote hypoglycemia.

Suggested intakes: [67, 68, 59]
The recommended minimum and maximum concentrations of arginine in preterm infant milk formula are 72mg/100kcal and 104mg/kcal respectively.[68] Caution is advised with arginine supplementation in view of the known toxicity from excessive intakes, the high intakes from TPN and antibiotics and the lack of demonstrated benefit in human trials.

A Cochrane review on arginine supplementation for the prevention of necrotising enterocolitis in preterm infants concluded that there is insufficient data at present to support a practice recommendation for arginine supplementation for prevention of NEC, but this could be an important avenue for further research (Cochrane)

CARNITINE: [17]

Functions in the premature infant: [17]
Play an important role in the oxidation of long-chain fatty acids.

Dietary content: [17]
Both breast milk and infant milk formula contain carnitine, but it is not routinely provided in parenteral nutrition solutions.

Suggested intakes:[17]
There is no evidence to support the routine supplementation of parenterally fed neonates with carnitine.

CHOLINE:

Functions in the premature infant:[67]
Choline is an important component of phospholipids, e.g. phosphatidylcholine, which are constituents of all cell membranes.
Choline synthesis and sufficiency in vivo is dependant on folate, vitamin B12, methionine and phosphatidyl etanolamine interaction.
Dietary intake contributes a substantial amount of choline.

Deficiency: [67]
Choline deficiency in humans has not been firmly established as a clinical syndrome.

Dietary content: [67]
Human milk and formulas provide varying amounts of free choline and choline-containing phospholipids.
Mature breast milk contains ±75 –110umol/100ml, while cow's milk based infant milk formulas contain 40 – 150umol/100ml. Soy based infant milk formulas do contain choline at al level of ±120umol/100ml.

Toxicity: [67]
Toxicity related to choline has not been reported in infants.

Suggested intakes: [67]
Based on human milk content (aim for 100 – 150umol/100ml).

CYSTEINE

Functions in the premature infant:[67]
Cysteine is an important amino acid component of most proteins.
It is a precursor to taurine.

Toxicity: [67]
Toxicity related to cysteine has not been linked to clinical abnormalities in term infants.
Many preterm infants (especially preterms <1250g at birth) who receive parenteral nutrition regimens, supplemented with cysteine hydrochloride develop metabolic acidosis.
Appropriate monitoring for signs of acidosis or initiation of base therapy is warranted in these cases.

Dietary content: [67]
Human milk protein contains ± 17mg cysteine/g protein.
Bovine milk protein contains 8mg/g on average, ranging from 22mg/g protein for whey fraction to 3mg/g protein for the casein fraction.
As cysteine is unstable and only partially soluble in an aqueous solution, no parenteral amino acid mixture contains appreciable amounts of cysteine.

Suggested intakes: [67]
For term and preterm infants fed human milk or infant milk formula, an intake of 0,2 – 0,5mmol cysteine equivalents/kg/day (i.e. 0.13 – 0.33mmol cysteine equivalents/100ml of 24kcal/30ml formula) is suggested.

If the premature infant is receiving an infant milk formula, a whey-predominant formula is preferred.

As TPN solutions do not contain cysteine, the latter is regarded as conditionally essential when the premature infant is only receiving TPN. A dose of 0.5 – 1.0 mmol cysteine/kg/day (i.e. 0.4 – 0.8mmol/100ml) is suggested in the latter. Caution is advised when feeding small infants weighing <1.250kg.

GLUTAMINE

Functions in the premature infant: [67]
Glutamine is a fuel for lymphocytes and intestinal epithelial cells.
Glutamine may contribute to gastro-intestinal cell metabolism and is thought to become essential during times the body experiences stress.[113]

Toxicity: [67]
Toxicity can be expected, because the byproduct formed from high concentrations of glutamine, y-aminobutyric acid (GABA), plays an inhibitory role in central nervous system function.
Glutamate, a derivative of glutamic acid used as a flavour enhancer also serves as a neurotransmitter but high concentrations has neurotoxic potential.
Glutamine is unstable during autoclaving and is thus omitted from parenteral nutrition solutions. Glutamine is however found in TPN solutions, in the form of peptides.

Suggested intakes: [67]
Although abundant in human milk, glutamine is not currently used in amino acid solutions due to its instability in an aqueous solution.[114] All studies showing positive effects have furthermore been performed in animal models or adult humans, with doses vastly in excess of that expected from human milk.
There is currently no quantitative information about either immune function or gut mucosal function to enable recommendations for enteral or parenteral glutamine supplementation for term or preterm infants.

INOSITOL:

Functions in the premature infant: [67]
Act as growth factors for several human cells.
Inositol metabolites are part of multiple transmembrane signalling processes.
Helps with activation of cell surface enzymes (e.g. Na/K ATPase) and receptors.
Modulate cell proliferation.
Inositol-containing glycophospholipids are rich in arachidonic acid and thus serve as a readily available pool for eicosanoid synthesis.
Chiro-inositol may play an integral role in insulin mediation.
Inositol may increase surfactant availability through increased synthesis, release or recycling.
Inositol may furthermore have a positive effect on oxygen-induced retinal and lung damage through its effect of cell differentiation or on free-radical protection.

Deficiency: [67]
No human deficiency syndrome has been described.

Toxicity: [67]
Toxicity is related to inositol's diuretic effect when excessive amounts are given. The latter produces large fluid losses, which could result in dehydration.

Dietary content: [67]
Mature human milk provides 1 – 2mmol/l (18 – 36mg/100ml) and infant milk formula 0.2 – 0.8mmol/l (4-15mg/100ml), while parenteral nutrition provides about 0.1mmol/l (1.8mg/100ml).

Suggested Intakes: [67]
The suggested intake is based on human milk content.
Preterm infant milk formula and/or TPN should contain 1 – 2,5mmol/l.
Additional, information on efficacy is needed before inositol supplementation can be recommended for all preterm infants with respiratory distress.

NUCLEOTIDES AND NUCLEIC ACIDS

Functions in the premature infant: [67]
Play a role in the modulation of normal immune response.
Play a role in the development of the gastro-intestinal tract.
Play a role in lipoprotein metabolism.

Dietary content: [67]
Free nucleotides in human milk range from 5 – 8mg/100ml. Total nucleic acids from the cells present in human milk can add up to 30mg/dL
Thus, in total, human milk can contribute 20 – 25% of daily nucleotide needs, which amounts to ±160mg/kg/day. Unsupplemented milk-based infant milk formula contains <1mg/100ml.

Toxicity: [67]
Toxicity relates primarily to the normal catabolic end product of nucleotides, i.e. uric acid.
Chronic excessive intake could result in a uric acid nephropathy or increased free-radical generation.
No evidence of toxicity has been observed with the use of nucleotide-supplemented formula at levels similar to those found in human milk.

Suggested intakes: [67]
No recommendation for the inclusion of nucleotides in preterm infant milk formula or in TPN solutions can be made at this stage, although at present some infant milk formulas in Europe and the USA are supplemented with the major free nucleotides to mimic human milk content. Further studies to show efficacy and safety will be required before nucleic acids can be recommended for routine inclusion into infant milk formula.

APPENDIX L

CALCULATION OF THE MINIMUM VOLUME PARENTERAL OR ENTERAL FEED REQUIRED TO ACHIEVE ZERO NITROGEN BALANCE

An example of the minimum TPN prescription required to achieve zero nitrogen balance and prevent catabolism:
A 1000g infant requires:
Protein: 1.0 - 2.0 g/kg/day and
Energy: 50 – 60 kcal/kg/day.
The above is provided with a volume range of 50 - 100ml Isotec® (ITN 1601N Solution which contains: 0.33g Nitrogen and 60kcal per 100ml)
The lower end of the range will provide 1.0 g protein/kg but only 30kcal energy/kg, while the upper range provides 2.0g protein/kg and 60kcal energy/kg.
On the lower range, the addition of intravenous maintenance fluid, e.g Neonatelyte (NNL) will provide an additional 20kcal per 50ml NNL, which will then provide sufficient energy to achieve zero nitrogen balance.

Compared to:
An example of the minimum Enteral prescription required to achieve zero nitrogen balance and prevent catabolism:
A 1000g infant requires:
Protein: 1.0 - 2.0 g/kg/day and
Energy: 50 – 60 kcal/kg/day.
The above is provided with a volume range of 75 - 150ml Breast milk (if breast milk composition is regarded as 1.1 – 1.5g protein and 67kcal per 100ml). The lower end of the range provides 1.0 g protein/kg and 50kcal energy/kg.

OR:
The above is provided with a volume range of 45 - 90ml Prenan® (with a composition of: 2.3g protein and 80kcal per 100ml). The lower end of the range will provide 1.0 g protein/kg but only 36kcal energy/kg.

OR:
The above is provided with a volume range of 55 - 110ml Similac Special Care Advance® (with a composition of 1.8g protein and 67kcal per 100ml).
The lower end of the range will provide 1.0 g protein/kg but only 37kcal energy/kg.
For both Prenan® and Similac Special Care Advance®:
On the lower range, the addition of intravenous maintenance fluid, e.g Neonatelyte (NNL) will provide an additional 20kcal per 50ml NNL, which will then provide sufficient energy to achieve zero nitrogen balance.

Medication frequently used in the neonate with possible nutrient interactions:[115, 116, 117]

Aminophylline[115, 116]
Description: A combination of theophylline with ethylendiamine, which enhances theophylline absorption in the stomach.
Indications: Used prophylactically in all VLBW infants, for prevention of apnoeic attacks.
For the relief of bronchospasm.
May improve respiratory muscle contractility.
Route of administration: Intravenous or orally.
Adverse effects: Allergy to ethylendiamine.
Neonates should be monitored for apnoea, tachycardia, jitteriness, irritability, gagging and vomiting.
Use with caution in neonates as plasma clearance may be decreased and there is a possibility of increased serum concentrations and/or toxicity. Serum levels must be obtained once a steady state has been achieved.
Drug-nutrient interactions: Hyperglycemia has been reported in preterm infants.

Caffeine[5, 117]
Indications: Used prophylactic in all VLBW infants, for prevention of apnoeic attacks.
For the relief of bronchospasm.
May improve respiratory muscle contractility.
Start with aminophylline and switch to caffeine as soon as the infant is receiving at least 50% of his total daily fluid requirements as milk feeds. Caffeine has a more favorable therapeutic index than aminophylline.[117]
Route of administration: Intravenous or orally
Adverse effects: Restlessness, irritability, nausea, vomiting, diarrhea. Functional cardiac symptoms, e.g. arrythmia/ tachycardia; thus recommended to monitor heart rate.
Drug-nutrient interactions: Hyperglycaemia, increased urinary calcium excretion.

Dexamethazone[115, 116, 117]
Description: A anti-inflammatory glucocorticoid (steroid).
Indications: Anaphylaxis and management of allergic and inflammatory disorders.
May be administered before labour to improve lung maturity and to prevent respiratory distress syndrome in premature neonates (<34 weeks gestational age).
Broncho-Pulmonary Displasia
Post-extubation stridor
Proposed mechanism of action: Enhanced production of surfactant and anti-oxidant enzymes, decreased bronchospasm, decreased pulmonary and bronchial edema and fibrosis, improved Vitamin A status and decreased responses of inflammatory cells and mediators in the injured lung.
Route of administration: Oral or Intravenous
Adverse effects: Neuropsychiatric reactions, gastro-intestinal disturbances, fluid and electrolyte disturbances, hypertension, susceptibility to infections and leucocytosis, adrenocortical suppression, somatic and lung growth suppression and hypertrophic myocardiopathy.
Drug-nutrient interactions: May cause sodium and water retention and hypokalemia.
Hypocalcemia due to increased calcium excretion may cause osteopenia.
Hypertriglyceridemia and hyperglycemia may occur with high doses..
Growth inhibition may occur due to increased protein catabolism with a potential loss of muscle tissue.

Curosurf[117]
Description: A modified porcine-derived minced lung extract that contains phospholipids,
neutral lipids, fatty acids and surfactant-associated proteins.
Indications: Used for treatment and prevention of neonatal respiratory distress syndrome.
Route of administration: Inhalation
Adverse effects and drug-nutrient interactions: None reported.

Ibuprofen[116]
Description: An anti-inflammatory and anti-rheumatic product.
Indications: Analgesia in a wide range of conditions.
Used for closure of symptomatic PDA.
Route of administration: Oral
Adverse effects: Gastric effects ranging from mild irritation to erosion, peptic ulceration and
bleeding. Hypersensitivity reactions, e.g. bronchospasm, skin rash, pruritis,
urticaria and angioedema. Central nervous system effects: headache, dizziness,
drowsiness, depression. Nephrotoxicity and renal insufficiency. Hepatic
dysfunction. Haematological disorders, e.g. hemolytic anemia is rarely found.
Drug-nutrient interactions: Fluid and sodium retention.

Antibiotics[5, 117]
Indications: *Amikacin*: Treatment of infections caused by gram-negative bacilli that are
resistant to other aminoglycosides.
Amphoteracin B: Systemic fungal infections.
Gentamicin: Treatment of infections caused by aerobic gram-negative bacilli,
such as Pseudomonas, Klebsiella and Escherichia Coli.
Meropenem: Treatment of pneumococcal meningitis and other serious infections
caused by susceptible gram-negative organisms resistant to other antibiotics.
Nystatin: Treatment of mucocutaneous candidal infections.
Vancomycin: Drug of choice for serious infections caused by methicillin-resistant
staphylococci and penicillin-resistant pneumococci.
Drugs of choice for:
Respiratory distress: HMD: Penicillin G
Pneumonia: Penicillin G and Gentamicin (or Amikacin)
Septicaemia: Penicillin G and Gentamicin (or Amikacin)
Meropenem for multi-resistant Klebsiella
Vancomycin for resistant Staphylococcus
Meningitis: Penicillin G or Ampicillin for Group B Streptococcus or Listeria
Claforan (Cefotaxime) for gram negative or no organism
Meropenem for multi-resistant Klebsiella
Acyclovir for Herpes
Amphoteracin B for fungi, e.g. Candida
Route of administration: All Intravenous
Adverse effects: *Amikacin and Gentamicin*: Ototoxicity, neuromuscular weakness and
respiratory failure.
Amphoteracin B: Anemia, thrombocytopenia, nausea, vomiting, fever/chills.
Meropenem: Diarrhoea, nausea, vomiting, rash. May cause inflammation at
the injection site.
Nystatin: Possible skin rash when applied topically.
Vancomycin: Nephrotoxicity, ototoxicity, rash, hypotension, neutropenia,
phlebitis.
Drug-nutrient interactions: *Amikacin and Gentamicin*: Renal tubular dysfunction may occur,
which may result in increased urinary sodium, calcium and magnesium
losses.
Amphoteracin B: Hypokalemia

Anti-retrovirals:

Nevirapine [116]
Description: A non-nucleoside antiretroviral agent.
Indications: Use only in combination with zidovudine in the treatment of neonates born to HIV-infected women who have had no therapy during pregnancy.
Inhibits HIV-1 replication by selectively interfering with viral reverse transcriptase without requiring intracellular metabolism. It also inactivates cell-free virions in the genital tract and breast milk. Synergistic antiviral activity occurs when administered with zidovudine (AZT)
Route of administration: Oral
Adverse effects: No toxicity yet reported in neonates.
Drug-nutrient interactions: None yet reported.

Lamivudine (3TC) [116]
Description: A nucleoside analog.
Indications: Inhibits HIV-1 replication by interfering with viral reverse transcriptase. It also inactivates cell-free virions in the genital tract and breast milk.
Route of administration: Oral or Intravenously
Adverse effects: Anemia, neutropenia.
Drug-nutrient interactions: None yet reported.

Zidovudine [116]
Description: A nucleoside analog.
Indications: Inhibits HIV-1 replication by interfering with viral reverse transcriptase. It also inactivates cell-free virions in the genital tract and breast milk.
Route of administration: Oral or Intravenously
Adverse effects: Anemia, neutropenia.
Drug-nutrient interactions: None yet reported.