**Table I: Enteral protein and energy requirements of a 1kg preterm infant compared to the nutritional content of unfortified and fortified mature human milk**

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| --- | --- |
| **ENTERAL PROTEIN AND ENERGY REQUIREMENTS** | **NUTRITIONAL CONTENT** |
| **HUMAN MILK, UNFORTIFIED (11)** | **HUMAN MILK, STANDARD FORTIFIED****(1g FM85/20mL MILK) (11,17)** |
| **Milk volume (mL)** | **Milk volume (mL)** |
| **Nutrient** | **Unit** | **AAP (14)** | **ESPGHAN (15)** | **150** | **180** | **200** | **150** | **180** | **200** |
| **PROTEIN (g/day)** | **3.4 to 4.2** | **3.5 to 4.0**  | **1.4 to 1.8** | **1.6 to 2.2** | **1.8 to 2.4** | **2.9 to 3.3** | **3.4 to 4.0** | **3.8 to 4.4** |
| **ENERGY** | **kcal/day****kJ/day \*** | **110 to 130****462 to 546** | **110 to 135****462 to 567** | **98 to 105****412 to 441** | **117 to 126****491 to 529** | **130 to 140****546 to 588** | **124 to 131****521 to 550** | **149 to 158****626 to 664** | **165 to 175****693 to 735** |
| **PROTEIN:ENERGY RATIO** | **g/100 kcal****g/100 kJ** | **2.6 to 3.8****0.6 to 0.9** | **3.2 to 3.6****0.8 to 1.0** | **1.3\*\* to 1.8\*\*\* (1.6\*\*\*\*)****0.3\*\* to 0.4\*\*\* (0.37\*\*\*\*)** | **2.2\*\* to 2.7\*\*\* (2.4\*\*\*\*)****0.5\*\* to 0.6\*\*\* (0.6\*\*\*\*)** |

\*4.2kJ/kcal used in conversion, \*\*Lowest protein and highest energy used in calculation, \*\*\*Highest protein and lowest energy used in calculation, \*\*\*\* Mid-values of protein and

energy used in calculation

**Table II: Outcomes of alternative human milk fortification intervention strategies**

| **ALTERNATIVE FORTIFICATION STRATEGY** | **STUDY** | **INTERVENTION** | **OUTCOMES IN TERMS OF IN-HOSPITAL GROWTH** | **OTHER OUTCOMES, INCLUDING ADVERSE EFFECTS** | **REFERENCE** |
| --- | --- | --- | --- | --- | --- |
| **Design** | **Sample** | **Initiation of standard fortification**  | **Initiation of alternative fortification**  | **Volume and type of milk** | **Type of fortifier and supplement** | **Growth parameter** | **p-value** |
| **Super-fortification**  | Randomised controlled trial: Moderate (MF) and Aggressive fortification (AG) compared to Standard fortification (SF) | **n** = 84 **GA** ≤32wk**BW** ≤1500g | **When volume of intake at:** 90 to 100 mL/kg/d**GA (weeks):** SF: 31MF: 30.5AG: 30.5(p=0.18)**W (g):**SF: 1106MF: 1066AG: 1097(p=0.73) | **When volume of intake at:** 150-170mL/kg**Day of life:**MF: 12 AG: 10 **Duration:**Until discharge from hospital | **Full volume (mL/kg/d):**SF: 155 ± 4.6MF: 154 ± 6AG: 156 ± 6.9(p=0.59)**Type:** Human milk (no indication if donor milk was used) | **Fortifier:**Eoprotin (Milupa, Germany) (Cow’s milk based) | W gain (g/d)W gain (g/kg/d)L at discharge (cm)HC (cm/wk) | 0.380.240.850.001 | **Feeding tolerance:** NS differences in feeding tolerance, residuals, abdominal distension, frequency of stooling1 Patient in MF group developed NEC**Biochemistry:**NS differences in S-urea, S- calcium, S-phosphorous, S-ALP Blood gas within normal range; no metabolic acidosis | 20 |
| **Adjustable fortification** (AF)  | Prospective observational intervention: SF plus additional protein supplement (based on weekly S-BUN levels) compared to **S**F (Historical control group) | **n**= 58 **GA** ≤32wk**BW** ≤1500g | **When volume of intake at:** 80mL/kg/d**Median age:**Day of life: 8 (for SF and AF) | **When volume of intake at:** not clear from article **Day of life:** 17 **Mean W (g):** 1501 (±252)**Duration:**At least two weeks (median duration 21d) | **Median volume (mL/kg/d):** SF: 141 (90-160)AF: 143.5 (125 -163)(p=0.135)**Type:**Exclusively fed mother’s own milk | **Fortifier:**Aptamil Eoprotin (Milupa, Germany)(Cow’s milk based)**Protein supplement:**Protifar (Nutricia, Netherlands) | W velocity (g/kg/d)L velocity(mm/d)HC velocity (mm/d)Daily growth index for W (%)Daily growth index for L(%)Daily growth index for HC(%)**Subgroup analysis of GA ≤ 28wk:**W velocity (g/kg/d)L velocity(mm/d)HC velocity (mm/d)Daily growth index for W (%)Daily growth index for L(%)Daily growth index for HC(%)  | 0.0530.008<0.0010.0260.0270.0030.1920.040.0040.090.0530.027 | **Feeding tolerance:** NS differences in “feeding interruption” (abdominal distention and/or GRV > 50% and/or vomiting)**Clinical outcome:** Similar between groups: NEC, BPD, ROP requiring laser treatment | 22 |
| **Adjustable fortification**  | Randomised controlled trial: Fortifier and additional protein supplement (based on twice-weekly S-BUN levels) compared to SF | **n**=32 **GA** ≤34wk**BW** ≤1700g | **When volume of intake at:** 90mL/kg/d | **When volume of intake at:** 150mL/kg/d **Day of life:** 19**Duration:**Until W of 2000g (at least 14 days) | **Full volume:** 150 to 160 mL/kg/d**Type:**Own mother’s milk or banked donor milk | **Fortifier:**FM85 (Nestle, Italy)**Protein supplement:**Pro-Mix (Corpak Medsystems, USA) | W gain (g/d)W gain (g/kg/d)L gain (mm/d)HC gain (mm/d) | < 0.01< 0.01> 0.05<0.05 | **Feeding tolerance:**NS differences in feeding intolerance as defined by: emesis, withholding of feeds, abdominal distentionNo study infant had NEC or systemic infection**Biochemistry:**S-albumin, S-creatinine and S-calcium: did not change significantlyS-BUN, S-phosphorous, S-ALP: NS increased | 24 |
| **Adjustable fortification**  | Randomized controlled trial: Fortifier and additional protein supplement (based on S-BUN level) compared to SF | **n**= 61 **GA**≤32wk**BW** 580 to 1250g | **When volume of intake at:** Full enteral feeding | **When volume of intake at:** Full enteral feeding**Duration:**Until discharge or transfer to other hospital or when >50% of milk taken directly from breast  | **Prescribed volume of intake:** 160mL/kg/d**Type:**Own mother’s milk and banked donor milk  | **Fortifier:**Aptamil**Protein supplement:**Protifar (Nutricia) | W gain (g/kg/d)L gain (cm/wk)HC gain (cm/wk)**In ELBW sub-group (W 580-980g; GA 23-30wk):**W gain (g/kg/d)Length gain (cm/wk)HC gain (cm/wk) | NSNSNS0.050.040.02 | **Feeding tolerance:**No information given**Biochemistry:**Significantly higher S-urea levelsNS lower pH levels Metabolic acidosis and increased S- creatinine: not more than previously seen | 23 |
| Target fortification (TF) | Prospective clinical trial: Fortifier plus additional protein, fat and carbohydrate supplements (based on human milk analysis)compared toSF (matched-paired groups of infants in the same neonatal unit) | **n**=10 *(*plus 20 for matched-pairs)**GA** <32w**BW** <1500g**n**=10 *(*plus 20 for matched-pairs)**GA** <32w**BW** <1500g | **When volume of intake at:** Not indicated | **When volume of intake at:** Step-wise introduction over a 3day period, full amount of target fort on day 4Volume of intake not indicated**Day of life:** 30**Duration:**Minimum of 3 consecutive weeks | **Feeding volume:** 147 ± 5mL/kg/d (TF)155±5mL/kg (SF)**Type:**Own mother’s milk | **Fortifier:**Similac (Abbott Nutrition, USA)**Supplements:****Protein:** Beneprotein (Nestle Health Care Nutrition, USA)**Fat:**Microlipid (Nestle Health Care Nutrition, USA)**Carbohydrate:**Polycose (Abbott Nutrition, USA) | W gain similar between groups but feeding volume in SF group significantly higher than in IF group (p<0.001)Linear relationship between milk intake and wt gain seen in IF group but not in SF group |  | **Feeding tolerance:**No feeding intolerance seen (GRV > 50% previous feeding volume; emesis; abdominal distention; decrease/delay/discontinuation of feeds)**Biochemistry:**S-TG,S- BUN,S- protein, S-albumin and glucose allwithin normal ranges No metabolic acidosis seen | 25 |
| **Target fortification** | Prospective randomised trial:Fortifier plus additional human milk cream supplement (based on human milk analysis)compared to SF | **n** =78**GA** **SF** 27.7±2.1**TF** 27.6±1.6 (p=0.88)**BW** 750 to 1250g | **When volume of intake at:** 100mL/kg/day or sooner | **When volume of intake at:** Once standard fortified feeds tolerated**Day of life:** Not indicated**Duration:**Until 36 weeks PMA or when weaned from fortification | **Feeding volume:**Not indicated**Type:**Own mother’s milk and pasteurised donor milk | **Fortifier:**Prolact+H2MF (Prolacta Bioscience, USA)**Supplement:****Fat:**Prolact CR (Prolacta Bioscience, USA) | W velocity (g/kg/d)L velocity(cm/wk)HC (cm/wk)W velocity from time BW regained (g/d)W velocity from time BW regained (g/kg/d)L velocity from birth (cm/wk)HC from birth (cm/wk) | 0.030.020.210.020.020.010.58 | No cases of NEC or death reportedNS in number of sepsis episodes | 26 |

AF: adjustable fortification, ALP: alkaline phosphatase, BPD: bronchopulmonary dysplasia, BUN: blood urea nitrogen, BW: birth weight, ELBW: extremely low birth weight, GA: gestational age, GRV: gastric residual volume, HC: head circumference, L: length,

n: sample size, NEC: necrotising enterocolitis, NS: non-significant, PMA: postmenstrual age, ROP: retinopathy of prematurity, SF: standard fortification, TF: target fortification, TG: serum triglycerides, W: weight, wk: weeks