**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: 31  MF: 30.5  AG: 30.5  (p=0.18)  **W (g):**  SF: 1106  MF: 1066  AG: 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 ± 4.6  MF: 154 ± 6  AG: 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) | 0.38  0.24  0.85  0.001 | **Feeding tolerance:**  NS differences in feeding tolerance, residuals, abdominal distension, frequency of stooling  1 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  (%) | 0.053  0.008  <0.001  0.026  0.027  0.003  0.192  0.04  0.004  0.09  0.053  0.027 | **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 distention  No study infant had NEC or systemic infection  **Biochemistry:**  S-albumin, S-creatinine and S-calcium: did not change significantly  S-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) | NS  NS  NS  0.05  0.04  0.02 | **Feeding tolerance:**  No information given  **Biochemistry:**  Significantly higher S-urea levels  NS 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 to  SF (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 4  Volume 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 all  within 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) | 0.03  0.02  0.21  0.02  0.02  0.01  0.58 | No cases of NEC or death reported  NS 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