EtD 14. Should higher parenteral protein (>4 g/kg/day) vs. Lower parenteral protein be used for preterm infants and what is the recommended protein intake by postnatal age?

POPULATION:	Preterm infants requiring parenteral nutrition
INTERVENTION:	Higher parenteral protein (>4 g/kg/day)
COMPARISON:	Lower parenteral protein (≤4 g/kg/day)
MAIN OUTCOMES:	**Critical outcomes** Mortality Neurodevelopmental impairment Faltering growth/body composition **Important but not critical** Adverse effects Fully breastfed or breastmilk feeding at hospital discharge Time to full enteral feeds Duration of initial hospital stay Sepsis: proven or suspected Bronchopulmonary dysplasia Necrotizing enterocolitis Retinopathy of prematurity Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Less important for decision making** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation - patient perspective
BACKGROUND:	Preterm infants have high protein requirements due to their limited protein stores at birth and their rapid growth needs. Many extremely preterm infants face biochemical disturbances after birth, growth faltering and neurodevelopmental impairments during infancy and childhood, and long-term risks for cardio-metabolic diseases. For the smallest preterm infants, parenteral nutrition plays a critical role in mitigating these risks, with protein being a key nutrient supporting growth and development. Early adequate protein delivered parenterally, enhances tissue growth and promotes neurodevelopment. However, too much parenteral protein can lead to metabolic acidosis, hyperammonaemia, elevated blood urea refeeding syndrome and impaired neurodevelopment. Too little protein can result in protein deficiency, faltering growth, altered body composition and impaired neurodevelopment. Despite its importance, the optimal protein intake remains uncertain. Studies have explored intakes ranging from 2.3 to 4.5 g/kg/day, with many recommending higher intakes of 3.5–4.5 g/kg/day to support growth and development. Studies focusing on the impact of protein intake on both short-term outcomes as well as long-term growth, body composition and neurodevelopment are critical in guiding evidence-based practices.

CONFLICT OF INTERESTS:	The following Systematic Review on Protein (Das, S. et al) co-authors are on the Guideline Development Group: Barbara Cormack, Luling Lin and Frank Bloomfield and supervised the first author. Frank Bloomfield and Barbara Cormack were the ProVIDe trial investigators.

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A 2024 systematic review [1] reported that seven guidelines (ESPGPR/CSPEN [critically ill neonate] guidelines, 2021; NICE 2020; Irish Society for Clinical Nutrition and Metabolism, 2020; Australasian neonatal parenteral nutrition consensus update, 2017; Turkish Neonatal Society, 2019, Portuguese Neonatal Society; ESPGHAN [parenteral] 2018) recommended a gradual increase of parenteral protein intake, ranging between 1.0–3.0 g/kg/day for the first 2 days and up to 4.0 g/kg/day subsequently. The upper limit of recommended parenteral protein intakes varied, including a maximum of 3.5 g/kg/day (strong recommendations, very low to high certainty of evidence) [ESPGHAN [critically ill neonate] guidelines, 2021; Turkish Neonatal Society, 2019]; 4 g/kg/day weak to strong recommendations, very low to high certainty of evidence) [NICE 2020; Australasian Neonatal Parenteral Nutrition Consensus Update, 2017; Turkish Neonatal Society, 2019] and >3.5 g/kg/day only as part of clinical trials (weak recommendation, low certainty of evidence) [ESPGHAN [critically ill neonate] guidelines, 2021]. **NSW 2022 (1) commence parenteral protein within the first 24 hours of birth (2) commence parenteral protein at 2 g/kg/day and (3) incrementally increase protein to a maximum 4 g/kg/day by day 3-5 of life in preterm neonates.The 2022 consensus noted the latest ESPGHAN 2018 recommendation of maximum 3.5 g/kg/day of parenteral protein and NICE 2020 recommendations of maximum 4 g/kg/day.** **ESPGHAN 2018** R 3.1 In preterm infants the parenteral protein supply should start on the first postnatal day with at least 1.5 g/kg/day to achieve an anabolic state. (strong recommendation) R 3.2 In preterm infants the parenteral protein intake from postnatal day 2 onwards should be between 2.5 and 3.5 g/kg/day and should be accompanied by non-protein intakes >65 kcal/kg/day and adequate micronutrient intakes. (strong recommendation) R 3.3 In preterm infants, parenteral protein intakes above 3.5 g/kg/day should only be administered as part of clinical trials (conditional recommendation) Other data for this question comes from a systematic review by Osborn *et al* [2] and a relevant Aotearoa New Zealand randomised trial by Bloomfield *et al* [3]. **Higher versus parenteral protein**	

	Mortality: RCT: No significant reduction in deaths with higher parenteral protein (13 fewer per 1,000; 41 fewer to 22 more); or early parenteral protein (1 g extra per day for 5 days) versus placebo (14 fewer per 1,000; 70 fewer to 66 more) [Critical]. **Neurodevelopmental impairment**: RCT: No events reported for deafness. No significant effect Bayley III score at ≥ 18 months (MD 3 points higher; 2.52 lower to 8.52 higher) and Bayley III psychomotor score at ≥18 months for higher dose of parenteral protein (MD 3 points higher; 6.41 lower to 12.41 higher); no significant effect on autism for higher dose of parenteral protein (0 fewer per 1,000; 58 fewer to 853 more); no significant reduction in survival without neurodisability (25 fewer per 1,000; 104 fewer to 70 more); little or no difference in blindness (1/61 (0.36%) vs. 1/63 (0.6%)) and deafness (6/161 (3.7% vs. 2/163 (1.2%)) [Critical]. **No faltering growth/body composition**: RCT: Very large reduction in infants with weight <10th centile (144 fewer per 1,000; 244 fewer to 17 fewer); reduction in postnatal faltering growth at discharge [weight 2 SD below mean] (20 fewer per 1,000; 170 fewer to 200 more); no significant reduction in postnatal faltering growth post discharge (95 fewer per 1,000; 188 fewer to 90 more); fewer days to regain birthweight (MD 1.14 days lower; 1.73 lower to 0.56 lower). No significant effect on weight gain to discharge (MD 0.76 g/kg/day higher; 0.02 lower to 1.54 higher), weight change z score at discharge (MD 0.01 points higher; 0.33 lower to 0.36 higher); weight z score at discharge (MD 0.16 points higher; 0.02 lower to 0.33 higher). Small increase in head circumference to discharge (MD 0.09 cm/week higher; 0.06 higher to 0.13 higher). No significant increase in head circumference change z score to discharge (MD 0.18 points higher; 0.15 lower to 0.5 higher); head circumference z score at discharge (MD 0.04 points higher; 0.18 lower to 0.26 higher); weight z score at discharge (Adj MD 0.09 points higher; 0.08 lower to 0.26 higher); length z score at discharge (Adj MD 0.07 points higher; 0.13 lower to 0.26 higher); length z score at discharge (MD 0.12 points higher; 0.14 lower to 0.38 higher); nor head circumference z score at discharge (Adj MD 0.02 points higher; 0.16 lower to 0.2 higher)[Critical]. **Adverse effects**: RCT: Hyperglycaemia (plasma glucose >8.3 mmol/L). Very large reduction in hyperglycaemia (78 fewer per 1,000; 129 fewer to 10 fewer) [Important]. **Fully breastfed or breastmilk feeding at hospital discharge**: RCT: 87/201 (43.3%) fully breastfed or breastmilk feeding at discharge with higher parenteral protein and 82/207 (39.6%) with lower protein [Important]. **Time to full enteral feeds:** RCT: No significant effect on time to full enteral feeds with higher parenteral protein (MD 0.2 days lower; 1.1 lower to 0.7 higher) [Important]. **Sepsis:** RCT: No significant effect in late onset sepsis with higher parenteral nutrition (9 fewer per 1,000; 45 fewer to 38 more) [Important]. **Necrotising enterocolitis (NEC):** RCT: No significant effect on NEC with higher parenteral protein (0 fewer per 1,000; 23 fewer to 34 more) [Important]. **Retinopathy of prematurity**: RCT: Very large reduction in retinopathy of prematurity with higher parenteral protein (81 fewer per 1,000; 114 fewer to 10 fewer). No significant effect on retinopathy of prematurity for early parenteral protein (1 g extra per day for 5 days) versus placebo (0 fewer per 1,000; 59 fewer to 96 more) [Important]. Osborn *et al* also reported on five relevant subgroup analyses [2]. These are summarised below: **1. Higher versus lower parenteral protein intake at commencement of parenteral nutrition (>1 to ≤2 g/kg/day; >2 to ≤3 g/kg/day; >3 g/kg/day)** **Mortality**: RCT: No difference in mortality to discharge (RR 0.78, 95% CI 0.45 to 1.36; n = 433; studies = 6) and no subgroup differences: P = 0.79, I2 = 0% [Critical]. **Neurodevelopmental impairment**: RCT: No difference in neurodevelopmental disability at two years (RR 1.04, 95% CI 0.48 to 2.23; n = 201; studies = 2); subgroup difference was significant: P = 0.02, I2 = 81.2%. Neither study reported a significant difference (high intake >2 to ≤ 3 g/kg/day; very high intake >3 g/kg/day). A single study commencing 3.6 g/kg/day versus 2.4 g/kg/day on day 2 to 6 reported no difference in cerebral palsy (RR 5.00, 95% CI 0.61 to 41.11; n = 90). No difference in developmental delay at ≥ 18 months (RR 1.04, 95% CI 0.35 to 3.11; n = 201; studies = 2); and no subgroup difference; P = 0.53, I2 = 0%. No infants were reported with blindness or deafness [Critical].

	No faltering growth/body composition: RCT: Reduction in postnatal faltering growth at discharge (RR 0.74, 95% CI 0.56 to 0.97; n = 203; studies = 3) and no subgroup differences. No difference in days to regain birthweight (MD 0.43, 95% CI -0.51 to 1.37; n = 303; studies = 6) and no subgroup difference; P = 0.06, I2 = 64.2%. No difference in weight gain to discharge (MD 1.05, 95% CI -0.55 to 2.66; n = 140; studies = 2) and no subgroup difference; P = 0.34; I2 = 0%. A single study commencing 3.6 g/kg/day versus 2.4 g/kg/day on day 2 to 6 reported no difference in head circumference growth to discharge (MD 0.03, 95% CI -0.03 to 0.09; n = 96) and no difference in head circumference change z-score up to one month (MD 0.00, 95% CI -0.36 to 0.36; n = 96). No difference in head circumference change z-score up to discharge (MD 0.18, 95% CI -0.15 to 0.50; n = 207; studies = 2) and no subgroup difference; P = 0.10, I2 = 62.7%. No difference in head circumference change z-score up to discharge (MD 0.25, 95% CI -0.14 to 0.64; n = 201; studies = 2) and no subgroup difference; P = 0.16, I2 = 50.1%. A single study commencing 3.6 g/kg/day versus 2.4 g/kg/day on day 2 to 6 reported no difference in weight gain change z-score up to one month (MD -0.20, 95% CI -0.62 to 0.22; n = 96). No difference in weight gain change z-score up to discharge (MD 0.01, 95% CI -0.33 to 0.36; n = 207; studies = 2) and no subgroup difference; P = 0.17; I2 = 48%. No difference in weight gain change z-score post-discharge (MD 0.13, 95% CI -0.26 to 0.52; n = 201; studies = 2) and no subgroup difference; P = 0.17, I2 = 47.1% [Critical]. **Time to full enteral feeds**: RCT: No difference by commencement intake in days to full enteral feeds (MD -0.22, 95% CI -1.60 to 1.17; n = 196; studies = 4); no subgroup differences: P = 0.88, I2 = 0% [Important]. **Adverse effects**: RCT: A single study of infants receiving very high amino acid intake (> 3 g/kg/day) reported no difference in hyperglycaemia (RR 1.47, 95% CI 0.85 to 2.53; n = 42). A single study reported no difference in hypoglycaemia among infants commencing on high amino acid intake at 3 g/kg/day (RR 1.68, 95% CI 0.83 to 3.41; n = 123) [Important]. **Sepsis**: RCT: No difference in late-onset sepsis (RR 0.94, 95% CI 0.65 to 1.38; n = 319; studies = 5) and no subgroup difference; P = 0.93, I2 = 0% [Important]. **Necrotising enterocolitis (NEC)**: RCT: No difference in NEC (RR 0.96, 95% CI 0.45 to 2.03; n = 340; studies = 5) and no subgroup difference; P = 0.18, I2 = 44% [Important]. **Bronchopulmonary dysplasia**: RCT: No difference in bronchopulmonary dysplasia (RR 1.32, 95% CI 0.86 to 2.02; n = 202; studies = 4) and no subgroup difference; P = 0.90, I2 = 0% [Important]. **Retinopathy of prematurity**: RCT: A reduction in retinopathy of prematurity (RR 0.44, 95% CI 0.21 to 0.93; n = 269; studies = 4) and no subgroup difference; P = 0.76, I2 = 0%. Studies commencing with high protein intake (>2 to ≤3 g/kg/day) found a reduction in retinopathy of prematurity (RR 0.36, 95% CI 0.14 to 0.95; n = 198; studies = 2) whereas the study commencing at low protein intake (>1 to ≤ 2g/kg/day) and the study commencing at very high parenteral protein intake (3.5 g/kg/day) reported no differences in retinopathy of prematurity [Important]. **2. Higher versus lower protein intake at maximal intake of parenteral nutrition sub grouped by maximal intake (high amino acid intake (>3 to ≤4 g/kg/day) versus low protein intake (>2 to ≤3 g/kg/d) at maximal intake of parenteral nutrition** **Mortality:** RCT: No difference in mortality to discharge (RR 0.94, 95% CI 0.57 to 1.55; n = 292; studies = 2) [Critical]. **No faltering growth/body composition**: RCT: One trial reported an increase in head circumference growth to one month (MD 0.13 cm/week, 95% CI 0.05 to 0.20; n = 135); an increase in head circumference change z-score to one month (MD 0.37, 95% CI 0.15 to 0.59; n = 135). One trial reported a reduction in days to regain birthweight (MD -3.60 days, 95% CI -5.88 to -1.32; n = 114) [Critical]. **Time to full enteral feeds**: RCT: One trial reported an increase in days to full enteral feeds (MD 4.00 days, 95% CI 1.01 to 6.99; n = 114) [Important]. **Sepsis**: RCT: One trial reported no difference in late-onset sepsis (RR 0.94, 95% CI 0.63 to 1.41; n = 127) [Important]. **Necrotising enterocolitis (NEC)**: RCT: No difference in NEC (RR 0.76, 95% CI 0.37 to 1.59; n = 241; studies = 2) [Important]. **Bronchopulmonary dysplasia:** RCT: No difference in bronchopulmonary dysplasia (RR 1.10, 95% CI 0.92 to 1.31; n = 241; studies = 2) [Important]. **Retinopathy of prematurity**: RCT: One trial reported no difference in severe retinopathy of prematurity (RR 2.71, 95% CI 0.75 to 9.75; n = 127) [Important].

	3. Higher versus lower protein intake at commencement and maximal intake of parenteral nutrition, subgrouped by commencement intake (Very low protein intake (≤1 g/kg/day); Low protein intake (>1 to ≤2 g/kg/day); High protein intake (>2 to ≤3g/kg/day); Very high protein intake (>3 g/kg/day)) **Mortality**: RCT: No difference in mortality to discharge (RR 0.97, 95% CI 0.66 to 1.42; n= 567; studies = 5) and no subgroup difference; P = 0.32, I2 = 13.8% [Critical]. **Neurodevelopmental impairment**: RCT: A single study of low amino acid intake (>1 to ≤2 g/kg/day) reported no difference in cerebral palsy (RR 3.00, 95% CI 0.35 to 25.87; n = 32), or blindness (RR 2.00, 95% CI 0.20 to 19.91; n = 32). A single study commencing with high parenteral protein intake (2.5 g/kg/d) reported no difference in developmental delay (RR 3.25, 95% CI 0.35 to 30.19; n = 100) [Critical]. **No faltering growth/body composition**: RCT: A reduction in days to regain birthweight (MD -1.86, 95% CI -2.79 to -0.93; n = 496; studies = 5) and no subgroup difference; P = 0.80, I2 = 0%. One study of commencing on high protein intake (>2 to ≤3 g/kg/day) reported no difference in weight gain to discharge (MD 0.60 g/kg/d, 95% CI -0.34 to 1.54; n = 114). Two studies commencing on high protein intake (>2 to ≤3 g/kg/day) reported an increase in head circumference change to discharge (MD 0.11 cm/week, 95% CI 0.07 to 0.15; n = 182) [Critical]. **Time to full enteral feeds**: RCT: A reduction in days to full enteral feeds with a significant subgroup effect by commencement intake (MD -1.08, 95% CI -2.42 to 0.25; n = 431; studies = 5). Two studies commencing on high protein intake (>2 to ≤3 g/kg/day) reported a reduction in days to full enteral feeds (MD -3.32, 95% CI -5.39 to -1.25; n = 158). Studies commencing with low parenteral protein intake (>1 to ≤2 g/kg/day) and very high parenteral protein intake (>3 g/kg/day) reported no difference in days to full enteral feeds [Important]. **Adverse effects:** RCT: A reduction in hyperglycaemia (RR 0.54, 95% CI 0.36 to 0.82; n = 463; studies = 4) and no subgroup difference; P = 0.55, I2 = 0%. No difference in hypoglycaemia (RR 1.03, 95% CI 0.70 to 1.50; n = 253; studies = 2) and no subgroup difference; P = 0.76, I2 = 0%. **Sepsis**: RCT: No difference in late-onset sepsis (RR 0.96, 95% CI 0.72 to 1.29; n = 772; studies = 8) and no subgroup difference; P = 0.70, I2 = 0% [Important]. **Necrotising enterocolitis (NEC)**: RCT: No difference in NEC (RR 1.14, 95% CI 0.63 to 2.07; n= 683; studies = 6) and no subgroup difference; P = 0.43, I2 = 0%. [Important] **Bronchopulmonary dysplasia:** RCT: No difference in bronchopulmonary dysplasia (RR 0.81, 95% CI 0.55 to 1.19; n = 376; studies = 4) and no subgroup difference; P = 0.13, I2 = 58% [Important]. **Retinopathy of prematurity:** RCT: No difference in severe retinopathy of prematurity in infants commencing on low parenteral protein intake (2 g/kg/day) (RR 1.24, 95% CI 0.49 to 3.09; n = 166; studies = 2). One study of high parenteral protein intake reported no cases of severe retinopathy of prematurity [Important]. **4. Higher versus lower parenteral protein intake at commencement and maximal intake of parenteral nutrition subgrouped by maximal intake (Low protein intake (>1 to ≤2 g/kg/day); High protein intake (>2 to ≤3g/kg/day); Very high protein intake (>3 g/kg/day))** **Mortality**: RCT: No difference in mortality to discharge (RR 0.97, 95% CI 0.66 to 1.42; n = 567; studies = 5) and no subgroup difference; P = 0.40, I2 = 0% [Critical]. **Neurodevelopmental impairment**: RCT: One study (n = 32) of high maximal protein intake (4 g/kg/day) reported no difference in cerebral palsy (RR 3.00, 95% CI 0.35 to 25.87) or blindness (RR 2.00, 95% CI 0.20 to 19.91). One study of high maximal protein intake (4 g/kg/day) reported no difference in developmental delay (RR 3.25, 95% CI 0.35 to 30.19; n = 100) [Critical]. **No faltering growth/body composition**: RCT: A reduction in days to regain birthweight (MD -1.86, 95% CI -2.79 to -0.93; n = 496; studies = 5) and no subgroup difference; P = 0.67, I2 = 0%. One study of high protein intake (>3 to ≤4 g/kg/day) reported no difference in weight gain to discharge (MD 0.60 g/kg/day, 95% CI -0.34 to 1.54; n = 114). Two studies of high maximal protein intake (>3 to ≤4 g/kg/day) reported an increase in head circumference growth to discharge (MD 0.11, 95% CI 0.07 to 0.15; n = 182) [Critical]. **Time to full enteral feeds**: RCT: Five studies of high maximal protein intake (>3 to ≤4 g/kg/day) reported a reduction in days to full

	enteral feeds (MD -1.08, 95% CI -2.42 to 0.25; n = 431) [Important]. **Adverse effects:** RCT: A reduction in hyperglycaemia (RR 0.54, 95% CI 0.36 to 0.82; n = 463; studies = 4) and no subgroup difference; P = 0.28, I2 = 15.8%. No difference in hypoglycaemia (RR 1.03, 95% CI 0.70 to 1.50; n = 253; studies = 2) and no subgroup difference; P = 0.76, I2 = 0% [Important]. **Sepsis:** RCT: No difference in late-onset sepsis (RR 0.96, 95% CI 0.72 to 1.29; n = 772; studies = 8) and no subgroup difference; P = 0.55, I2 = 0% [Important]. **Necrotising enterocolitis (NEC)**: RCT: Six studies of high maximal protein intake (>3 to ≤4 g/kg/day) reported no difference in NEC (RR 1.14, 95% CI 0.63 to 2.07; n = 683) [Important]. **Bronchopulmonary dysplasia**: RCT: Four studies of high maximal protein intake (>3 to ≤4 g/kg/day) reported no difference in bronchopulmonary dysplasia (RR 0.81, 95% CI 0.55 to 1.19; n = 376) [Important]. **Retinopathy of prematurity**: RCT: Three studies of high maximal amino acid intake (>3 to ≤4 g/kg/day) reported no difference in severe retinopathy of prematurity (RR 1.24, 95% CI 0.49 to 3.09; n = 280) [Important]. 5. **Higher versus lower parenteral protein intake in parenteral nutrition, very preterm or low birthweight infants (Studies that enrolled infants ≤1500 g and/or at ≤32 weeks' gestation).** **Mortality**: RCT: No difference in mortality (RR 0.90, 95% CI 0.69 to 1.17; n = 1407; studies = 14). **Neurodevelopmental impairment:** RCT: No difference in neurodevelopmental disability at two years (RR 1.04, 95% CI 0.48 to 2.23; n = 201; studies = 2). No difference in cerebral palsy (RR 4.00, 95% CI 0.89 to 17.97; n = 122; studies = 2) or in developmental delay (RR 1.35, 95% CI 0.52 to 3.53; n = 301; studies = 3) or in blindness (RR 2.00, 95% CI 0.20 to 19.91; n = 122; studies = 2). One study reported no difference in infants with deafness in either group. **No faltering growth/body composition**: RCT: A reduction in postnatal faltering growth at discharge (RR 0.74, 95% CI 0.56 to 0.97; n = 203; studies = 3). One study reported no difference in faltering at two years (RR 0.66, 95% CI 0.33 to 1.32; n = 111). A significant reduction in days to regain birthweight (MD -0.78, 95% CI -1.46 to -0.11; n = 800; studies = 10). A reduction in weight gain to one month (MD -1.50, 95% CI -2.56 to -0.44; n = 373; studies = 4) and no difference in weight gain to discharge (MD 0.72, 95% CI -0.09 to 1.52; n = 254; studies = 3). A reduction in linear growth to one month (MD -0.16, 95% CI -0.26 to -0.06; n = 245; studies = 2). No difference in head circumference growth to one month (MD 0.01, 95% CI -0.04 to 0.06; n = 476; studies = 4) and an increase in head circumference growth to discharge (MD 0.08, 95% CI 0.05 to 0.12; n = 182; studies = 2). One study reported no difference in weight change in z-score to one month (MD -0.20, 95% CI -0.62 to 0.22; n = 96). No difference in weight change in z-score to discharge (MD 0.01, 95% CI -0.33 to 0.36; n = 207; studies = 2) and no difference in weight change in z-score post-discharge (MD 0.13, 95% CI -0.26 to 0.52; n = 201; studies = 2). An increase in head circumference change in z-score to one month (MD 0.27, 95% CI 0.08 to 0.46; n = 231; studies = 2). No difference in head circumference change in z-score to discharge (MD 0.18, 95% CI -0.15 to 0.50; n = 207; studies = 2) and no difference in head circumference change in z-score post-discharge (MD 0.25, 95% CI -0.14 to 0.64; n = 201; studies = 2). **Time to full enteral feeds:** RCT: No difference in days to full enteral feeds (MD -0.19, 95% CI -1.07 to 0.70; n = 778; studies = 11). **Adverse effects**: RCT: A reduction in hyperglycaemia (RR 0.66, 95% CI 0.45 to 0.96; n = 409; studies = 4). No difference in hypoglycaemia (RR 1.17, 95% CI 0.84 to 1.63; n = 376; studies = 3). **Sepsis**: RCT: No difference in late-onset sepsis (RR 0.96, 95% CI 0.79 to 1.18; n = 1255; studies = 15). **Necrotising enterocolitis (NEC)**: RCT: No difference in NEC (typical RR 1.00, 95% CI 0.68 to 1.47; n = 1301; studies = 14). **Bronchopulmonary dysplasia: RCT**: No difference in bronchopulmonary dysplasia (RR 1.04, 95% CI 0.89 to 1.23; n = 819; studies = 10). **Retinopathy of prematurity:** RCT: A reduction in retinopathy of prematurity (RR 0.44, 95% CI 0.21 to 0.93; n = 269; studies = 4).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lower parenteral protein	Risk difference with higher parenteral protein

Mortality: RCT: higher versus lower protein intake assessed with: Mortality to hospital discharge	1407 (13 RCTs)	⨁◯◯◯ Very low[a,b,c]	**RR 0.90** (0.69 to 1.17)	Study population	
				131 per 1,000	**13 fewer per 1,000** (41 fewer to 22 more)
Mortality: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Death	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 0.93** (0.64 to 1.34)	Study population	
				194 per 1,000	**14 fewer per 1,000** (70 fewer to 66 more)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: neurodevelopmental disability	201 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	**RR 1.04** (0.48 to 2.23)	Study population	
				118 per 1,000	**5 more per 1,000** (61 fewer to 145 more)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Developmental delay at ≥ 18 months	301 (3 RCTs)	⨁◯◯◯ Very low[a,e]	**RR 1.35** (0.52 to 3.53)	Study population	
				45 per 1,000	**16 more per 1,000** (22 fewer to 115 more)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Cerebral palsy	122 (2 RCTs)	⨁◯◯◯ Very low[a,f]	**RR 4.00** (0.89 to 17.97)	Study population	
				33 per 1,000	**98 more per 1,000** (4 fewer to 556 more)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Blindness	122 (2 RCTs)	⨁◯◯◯ Very low[f,g,h]	**RR 2.00** (0.20 to 19.91)	Study population	
				16 per 1,000	**16 more per 1,000** (13 fewer to 310 more)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Deafness	90 (1 RCT)	⨁◯◯◯ Very low[h,i,j]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Bayley III motor development at ≥ 18 months	105 (2 RCTs)	⨁◯◯◯ Very low[a,e]	-	The mean neurodevelopmental impairment: RCT: higher versus lower amino acid intake: Bayley III Motor Development score was **79.8 points**	MD **4.18 lower** (8.53 lower to 0.17 higher)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Bayley score at ≥ 18 months	100 (1 RCT)	⨁◯◯◯ Very low[e,i,j]	-	The mean neurodevelopmental impairment: RCT: higher versus lower amino acid intake: Bayley score was **94 points**	MD **3 higher** (2.52 lower to 8.52 higher)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Bayley II psychomotor score at ≥ 18 months	32 (1 RCT)	⨁◯◯◯ Very low[f,i,j]	-	The mean neurodevelopmental impairment: RCT: higher versus lower amino acid intake: Bayley II Psychomotor score was **64 points**	MD **3 higher** (6.41 lower to 12.41 higher)
Neurodevelopmental impairment: RCT: higher versus lower parenteral protein intake assessed with: Autism	32 (1 RCT)	⨁◯◯◯ Very low[f,i,j]	**RR 1.00** (0.07 to 14.64)	Study population	
				63 per 1,000	**0 fewer per 1,000** (58 fewer to 853 more)
Neurodevelopmental impairment: RCT: early parenteral	408		**Adj RR 0.95**	Study population	

protein intake (1 g extra per day for 5 days) versus placebo assessed with: Survival without neurodisability	(1 RCT)	⨁⨁⨁◯ Moderate[b]	(0.79 to 1.14)	498 per 1,000	**25 fewer per 1,000** (104 fewer to 70 more)
Neurodevelopmental impairment: RCT: early parenteral protein intake (1 g extra per day for 5 days) versus placebo assessed with: Neurodisability	327 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.16** (0.90 to 1.50)	Study population	
				374 per 1,000	**60 more per 1,000** (37 fewer to 187 more)
Neurodevelopmental impairment: RCT: protein assessed with: Blindness	324 (1 RCT)	⨁⨁⨁◯ Moderate[h]	not estimable	Study population	
				6 per 1,000	**6 fewer per 1,000** (6 fewer to 6 fewer)
Neurodevelopmental impairment: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Deafness	324 (1 RCT)	⨁⨁⨁◯ Moderate[h]	not estimable	Study population	
				12 per 1,000	**12 fewer per 1,000** (12 fewer to 12 fewer)
Neurodevelopmental impairment: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Cerebral palsy	324 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.47** (0.64 to 3.39)	Study population	
				55 per 1,000	**26 more per 1,000** (20 fewer to 132 more)
Neurodevelopmental impairment: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Bayley III Cognitive score at 2 years	321 (1 RCT)	⨁◯◯◯ Very low[b,k,h]	-	The mean neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo: Bayley III cognitive score was **96 points**	Adj MD **2.13 lower** (5.29 lower to 1.02 higher)
Neurodevelopmental impairment: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Bayley III Motor score at 2 years	321 (1 RCT)	⨁◯◯◯ Very low[eb,h,k]	-	The mean neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo: Bayley III Motor score was **96 points**	Adj MD **1.88 lower** (4.9 lower to 1.14 higher)
Neurodevelopmental impairment: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Bayley III Language score at 2 years	321 (1 RCT)	⨁⨁◯◯ Low[h,k]	-	The mean neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo: Bayley III Language score was **93 points**	Adj MD **3.86 lower** (7.43 lower to 0.29 lower)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Weight <10th centile	203 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.74** (0.56 to 0.97)	Study population	
				554 per 1,000	**144 fewer per 1,000** (244 fewer to 17 fewer)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Postnatal faltering growth at discharge (weight 2 SD below mean)	114 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**RR 0.96** (0.66 to 1.40)	Study population	
				500 per 1,000	**20 fewer per 1,000** (170 fewer to 200 more)
Faltering growth/body composition: RCT: higher versus lower parenteral protein assessed with: Postnatal faltering growth post-discharge.	111 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.66** (0.33 to 1.32)	Study population	
				281 per 1,000	**95 fewer per 1,000** (188 fewer to 90 more)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Days to regain birthweight	950 (13 RCTs)	⨁⨁◯◯ Low[a,j]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **12.49 days**	MD **1.14 lower** (1.73 lower to 0.56 lower)

Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Weight gain to discharge (g/kg/day)	291 (4 RCTs)	⨁⨁⨁◯ Moderate[a]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **19.33 days**	MD **0.76 higher** (0.02 lower to 1.54 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Weight change z score at discharge	207 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **-0.3 points**	MD **0.01 higher** (0.33 lower to 0.36 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Weight z score at discharge	352 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **-1.67 points**	MD **0.16 higher** (0.02 lower to 0.33 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Linear growth cm/week	245 (2 RCTs)	⨁⨁◯◯ Low[d]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **0.7 cm/week**	MD **0.16 lower** (0.26 lower to 0.06 lower)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Head circumference to discharge (cm/week)	315 (4 RCTs)	⨁◯◯◯ Very low[a,d]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **0.8 cm/week**	MD **0.09 higher** (0.06 higher to 0.13 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Head circumference change z score to discharge	207 (2 RCTs)	⨁◯◯◯ Very low[a,b,j]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **0.2 points**	MD **0.18 higher** (0.15 lower to 0.5 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Head circumference z score at discharge	354 (3 RCTs)	⨁◯◯◯ Very low[a,b,j]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **-1.2 points**	MD **0.04 higher** (0.18 lower to 0.26 higher)
Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Weight z score at discharge	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **0**	Adj MD **0.09 higher** (0.08 lower to 0.26 higher)
Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Weight z score at 2 years	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **-0.05 points**	Adj MD **0.19 lower** (0.41 lower to 0.02 higher)
Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Length z score at discharge	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **0**	Adj MD **0.07 higher** (0.13 lower to 0.26 higher)
Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Length z score at 2 years	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **-0.41 points**	Adj MD **0.16 lower** (0.4 lower to 0.08 higher)
Faltering growth/body composition: RCT: higher versus lower parenteral protein intake assessed with: Length z score at discharge	228 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth/body composition: RCT: higher versus lower amino acid intake was **-2.25 points**	MD **0.12 higher** (0.14 lower to 0.38 higher)

Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Head circumference z score at discharge	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **-0.55 points**	Adj MD **0.02 higher** (0.16 lower to 0.2 higher)
Faltering growth/body composition: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Head circumference z score at 2 years	434 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo was **0.13 points**	Adj MD **0.26 lower** (0.53 lower to 0.002 higher)
Adverse effects: RCT: higher versus lower parenteral protein intake assessed with: Hypoglycaemia	376 (3 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.17** (0.84 to 1.63)	Study population	
				238 per 1,000	**40 more per 1,000** (38 fewer to 150 more)
Adverse effects: RCT: higher versus lower parenteral protein intake assessed with: Hyperglycaemia (plasma glucose > 8.3 mmol/L)	505 (5 RCTs)	⨁⨁◯◯ Low[a,j]	**RR 0.69** (0.49 to 0.96)	Study population	
				253 per 1,000	**78 fewer per 1,000** (129 fewer to 10 fewer)
Adverse effects: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Refeeding syndrome	338 (1 RCT)	⨁⨁◯◯ Low[i,g]	**Adj RR 1.64** (1.09 to 2.45)	Study population	
				157 per 1,000	**100 more per 1,000** (14 more to 227 more)
Fully breastfed or breastmilk feeding at hospital discharge: RCT: early protein (1 g extra per day for 5 days) versus placebo assessed with: Exclusively breastfed or breastmilk fed	408 (1 RCT)	⨁◯◯◯ Very low[a,h]	not estimable	Study population	
				396 per 1,000	**396 fewer per 1,000** (396 fewer to 396 fewer)
Time to full enteral feeds: RCT: higher versus lower parenteral protein intake assessed with: Days to full enteral feeds	778 (11 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean time to full enteral feeds: RCT: higher versus lower amino acid intake was **16.75 days**	MD **0.19 lower** (1.07 lower to 0.7 higher)
Time to full enteral feeds: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Days after birth full enteral feed was reached	377 (1 RCT)	⨁⨁⨁◯ Moderate[b]	-	The mean time to full enteral feeds: RCT: early amino acid (1 g per day for 5 days) versus placebo was **16.6 days**	Adj HR **0.86 higher** (0.69 higher to 1.06 higher)
Duration of initial hospital stay - not measured	-	-	-	-	-
Sepsis: proven or suspected: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Culture proven late onset	422 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.19** (0.91 to 1.56)	Study population	
				308 per 1,000	**58 more per 1,000** (28 fewer to 172 more)
Sepsis: proven or suspected: RCT: higher versus lower parenteral protein intake assessed with: Late onset sepsis	1255 (15 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 0.96** (0.79 to 1.18)	Study population	
				213 per 1,000	**9 fewer per 1,000** (45 fewer to 38 more)
Bronchopulmonary dysplasia: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo	363 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.10** (0.96 to 1.24)	Study population	
				696 per 1,000	**70 more per 1,000** (28 fewer to 167 more)

Bronchopulmonary dysplasia: RCT: higher versus lower parenteral protein intake assessed with: Bronchopulmonary dysplasia at ≥ 36 weeks' PMA	819 (10 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.04** (0.89 to 1.23)	Study population	
				353 per 1,000	**14 more per 1,000** (39 fewer to 81 more)
Necrotising enterocolitis: RCT: higher versus lower parenteral protein intake	1301 (13 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.00** (0.68 to 1.47)	Study population	
				73 per 1,000	**0 fewer per 1,000** (23 fewer to 34 more)
Necrotising enterocolitis: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo assessed with: Bell stage ≥II	423 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.06** (0.65 to 1.74)	Study population	
				124 per 1,000	**7 more per 1,000** (44 fewer to 92 more)
Retinopathy of prematurity: RCT: higher versus lower parenteral protein intake	269 (4 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.44** (0.21 to 0.93)	Study population	
				144 per 1,000	**81 fewer per 1,000** (114 fewer to 10 fewer)
Retinopathy of prematurity: RCT: early parenteral protein (1 g extra per day for 5 days) versus placebo	376 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**Adj RR 1.00** (0.63 to 1.60)	Study population	
				160 per 1,000	**0 fewer per 1,000** (59 fewer to 96 more)
Anaemia of prematurity - not measured	-	-	-	-	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-

a. Downgraded one level for concerns of risk of bias
b. Downgraded one level for imprecision as confidence intervals cross the line of no effect
c. Downgraded one level as funnel plot suggested publication/reporting bias
d. Downgraded two levels for inconsistency with I2>80%
e. Downgraded two levels for imprecision with very wide confidence intervals crossing the line of no effect
f. Downgraded three levels for imprecision with extremely wide confidence intervals crossing the line of no effect
g. Downgraded for imprecision due to low event rates
h. Downgraded one level for indirectness as evidence is based on a single study
i. Downgraded one level for imprecision due to wide confidence intervals
j. Downgraded one level for inconsistency with I2 >50% but <80%
k. Downgraded one level for imprecision as a result of low sample size

Desirable effects for Māori

In the Aotearoa New Zealand randomised trial, the ProVIDe trial (5), 102 of the 434 enrolled preterm infants (24%) were pēpi Māori. The study investigated whether an additional 1 gram of parenteral amino acids daily for 5 days improved neurodevelopmental outcomes in extremely low birthweight infants. Pēpi Māori were well represented in both the intervention and placebo groups. The trial found no overall benefit in survival without neurodisability at 2 years and suggested a possible increase in moderate-to-severe neurodisability in the intervention group.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Higher versus lower parenteral protein** **Neurodevelopmental impairment**: RCT: Higher dose of parenteral protein showed no significant effect on neurodevelopmental disability (5 more per 1,000; 61 fewer to 145 more); on developmental delay at ≥18 months (16 more per 1,000; 22 fewer to 115 more); cerebral palsy (98 more per 1,000; 4 fewer to 556 more); blindness (16 more per 1,000; 13 fewer to 310 more); Bayley III Motor development score at ≥18 months (MD 4.18 points lower; 8.53 lower to 0.17 higher); Bayley III Cognitive score at 2 years (Adj MD 2.13 lower; 5.29 lower to 1.02 higher), the Bayley III Motor score at 2 years (Adj MD 1.88 lower; 4.9 lower to 1.14 higher). There was a reduction in Bayley III Language score at 2 years (Adj MD 3.86 lower; 7.43 lower to 0.29 lower). No significant increase in neurodisability (60 more per 1,000; 37 fewer to 187 more); or in cerebral palsy (26 more per 1,000; 20 fewer to 132 more) [Critical]. **Faltering growth/body composition:** RCT: Small reduction in linear growth with higher dose of parenteral nutrition (MD 0.16 cm/week lower; 0.26 lower to 0.06 lower). No significant effect on weight z score at 2 years (Adj MD 0.19 points lower; 0.41 lower to 0.02 higher); length z score at 2 years (Adj MD 0.16 points lower; 0.4 lower to 0.08 higher) or head circumference z score at 2 years (Adj MD 0.26 points lower; 0.53 lower to 0.002 higher) [Critical]. **Adverse effects**: RCT: No significant increase in hypoglycaemia with higher parenteral protein (40 more per 1,000; 38 fewer to 150 more). Very large increase in refeeding syndrome (100 more per 1,000; 14 more to 227 more) [Important]. **Time to full enteral feeds:** RCT: Small increase in time to full enteral feeds with higher parenteral protein (Adj HR 0.86 days higher; 0.69 higher to 1.06 higher) [Important]. **Sepsis:** RCT: No significant increase in culture proven late onset sepsis with higher parenteral nutrition (58 more per 1,000; 28 fewer to 172 more). [Important] **Bronchopulmonary dysplasia**: RCT: No significant increase in bronchopulmonary dysplasia (70 more per 1,000; 28 fewer to 167 more) or bronchopulmonary dysplasia (14 more per 1,000; 39 fewer to 81 more) with higher parenteral protein [Important]. **Necrotising enterocolitis (NEC)**: RCT: No significant effect on NEC with higher parenteral protein (7 more per 1,000; 44 fewer to 92 more) [Important]. **Undesirable effects for Māori** No additional evidence available	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Moderate to very low certainty of evidence overall	

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality: RCT: higher versus lower amino acid intake assessed with: Mortality to hospital discharge	CRITICAL	⨁◯◯◯ Very low

Mortality: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Death	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: neurodevelopmental disability	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Developmental delay at ≥ 18 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Cerebral palsy	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Blindness	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Deafness	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Bayley motor development at ≥ 18 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Bayley III score at ≥ 18 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Bayley psychomotor score at ≥ 18 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: higher versus lower amino acid intake assessed with: Autism	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placeboassessed with: Survival without neurodisability	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Neurodisability	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Blindness	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Deafness	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Cerebral palsy	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Bayley III Cognitive score at 2 years	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Bayley III Motor score at 2 years	CRITICAL	⨁⨁⨁◯

		Moderate
Neurodevelopmental impairment: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Bayley III Language score at 2 years	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Weight < 10th centile	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Postnatal growth failure at discharge (weight 2 SD below mean)	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Postnatal growth failure post discharge.	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Days to regain birthweight	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Weight gain to discharge (g/kg/day)	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Weight change z score at discharge	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Weight z score at discharge	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Linear growth cm/week	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Head circumference to discharge (cm/week)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Head circumference change z score to discharge	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Head circumference z score at discharge	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Weight z score at discharge	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Weight z score at 2 years	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Length z score at discharge	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Length z score at 2 years	CRITICAL	⨁⨁⨁◯ Moderate

Faltering growth/body composition: RCT: higher versus lower amino acid intake assessed with: Length z score at discharge	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Head circumference z score at discharge	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Head circumference z score at 2 years	CRITICAL	⨁⨁⨁◯ Moderate
Adverse effects: RCT: higher versus lower amino acid intake assessed with: Hypoglycaemia	IMPORTANT	⨁⨁◯◯ Low
Adverse effects: RCT: higher versus lower amino acid intake assessed with: Hyperglycaemia (plasma glucose > 8.3 mmol/L)	IMPORTANT	⨁⨁◯◯ Low[a,l]
Adverse effects: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Refeeding syndrome	IMPORTANT	⨁⨁◯◯ Low
Fully breastfed or breastmilk feeding at hospital discharge: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Exclusively breastfed or breastmilk fed	IMPORTANT	⨁◯◯◯ Very low
Time to full enteral feeds: RCT: higher versus lower amino acid intake assessed with: Days to full enteral feeds	IMPORTANT	⨁⨁◯◯ Low
Time to full enteral feeds: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Days after birth full enteral feed was reached	IMPORTANT	⨁⨁⨁◯ Moderate
Duration of initial hospital stay - not measured	IMPORTANT	-
Sepsis: proven or suspected: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Culture proven late onset	IMPORTANT	⨁⨁⨁◯ Moderate
Sepsis: proven or suspected: RCT: higher versus lower amino acid intake assessed with: Late onset sepsis	IMPORTANT	⨁⨁◯◯ Low
Bronchopulmonary dysplasia RCT: early amino acid (1 g per day for 5 days) versus placebo	IMPORTANT	⨁⨁⨁◯ Moderate
Bronchopulmonary dysplasia: RCT: higher versus lower amino acid intake assessed with: Bronchopulmonary dysplasia at ≥ 36 weeks' PMA	IMPORTANT	⨁⨁◯◯ Low
Necrotizing enterocolitis: RCT: higher versus lower amino acid intake	IMPORTANT	⨁⨁◯◯ Low
Necrotising enterocolitis: RCT: early amino acid (1 g per day for 5 days) versus placebo assessed with: Bell stage ≥II	IMPORTANT	⨁⨁⨁◯ Moderate
Retinopathy of prematurity: RCT: higher versus lower amino acid intake	IMPORTANT	⨁⨁⨁◯ Moderate

Retinopathy of prematurity: RCT: early amino acid (1 g per day for 5 days) versus placebo	IMPORTANT	⨁⨁⨁◯ Moderate
Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds - not measured	NOT IMPORTANT	-

Certainty of evidence for Māori
No additional evidence available

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Probably no important uncertainty or variability **Values for Māori** No additional research available.	

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	**Higher versus lower parenteral protein - moderate certainty evidence** Reduction in faltering growth/body composition (weight <10th centile), retinopathy of prematurity Uncertain effect on mortality, neurodevelopmental impairment, faltering growth/body composition, sepsis, NEC, bronchopulmonary dysplasia, retinopathy of prematurity Increase in neurodevelopmental impairment (Lower Bayley III Language score at 2 years), increase in time to full enteral feeds, **Higher versus lower parenteral protein - low certainty evidence** Reduced days to regain birthweight, reduced hyperglycaemia Reduction in linear growth Increase in adverse effects (refeeding syndrome) Uncertain effect on faltering growth/body composition, adverse effects (hypoglycaemia), time to full enteral feeds, sepsis, bronchopulmonary dysplasia, NEC **Higher versus lower parenteral protein - very low certainty evidence**	

	Reduction in faltering growth/body composition (Increase in head circumference) Uncertain effect on mortality, neurodevelopmental impairment, faltering growth/body composition, fully breastfed or breastmilk feeding at hospital discharge **Balance of effects for Māori** No additional evidence

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Costs for PN:** Additional protein (amino acids) added to a standard parenteral nutrition solution has a minimal effect on the total cost of the solution. **Resourcing for Māori** No additional evidence available	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	The certainty of resource requirements is high. **Certainty of evidence of required resources for Māori** No additional evidence available	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention	None of the evidence reported on cost-effectiveness of different intravenous protein intakes. **Cost effectiveness for Māori** No additional evidence available	

○ Varies ● No included studies	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	**Equity for Māori** Influenced by the effects of colonisation, pēpi Māori are more likely to be born preterm, have more sepsis and neurodisability, both of which are associated with parenteral nutrition practices, and fewer survive. Thus, implementing standardised parenteral nutrition practices in Aotearoa New Zealand will contribute to achieving equitable health outcomes for preterm pēpi Māori and their whānau. **Equity for Pacific families** Implementing standardised parenteral nutrition practices in Aotearoa New Zealand will contribute directly to reducing health disparities for all ethnicities and underrepresented groups. **Equity for underrepresented groups** Understanding the importance of parenteral protein may be difficult for parents with language or health literacy barriers. If explanations are lacking, these families may disengage or feel mistrust. Equity requires culturally appropriate communication and consistent clinical practice to ensure all infants receive adequate protein regardless of background.	

Acceptability
Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is probably acceptable. Acceptability for Māori is unknown	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	A specified parenteral protein intake would not be difficult to implement if there were clear guidance and protocols available.	

○ Varies ○ Don't know	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

References

1. Meiliana, M.; Alexander, T.; Bloomfield, F.H.; Cormack, B.E.; Harding, J.E.; Walsh, O.; Lin, L. Nutrition guidelines for preterm infants: A systematic review. *JPEN J. Parenter. Enteral Nutr.* **2024**, *48*, 11-26, doi:10.1002/jpen.2568.
2. Osborn, D.A.; Schindler, T.; Jones, L.J.; Sinn, J.K.; Bolisetty, S. Higher versus lower amino acid intake in parenteral nutrition for newborn infants. *Cochrane Database Syst. Rev.* **2018**, *3*, CD005949, doi:10.1002/14651858.CD005949.pub2.
3. Bloomfield, F.H.; Jiang, Y.; Harding, J.E.; Crowther, C.A.; Cormack, B.E.; ProVIDe Trial Group. Early amino acids in extremely preterm infants and neurodisability at 2 years. *N Engl J Med* **2022**, *387*, 1661-1672, doi:10.1056/NEJMoa2204886.

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