Journal of Parenteral and Enteral Nutrition
Volume 45 Number 1
January 2021 65–78

DOI: 10.1002/jpen.1934
wileyonlinelibrary.com

Neonatal Refeeding Syndrome and Clinical Outcome in Extremely Low-Birth-Weight Babies: Secondary Cohort Analysis From the ProVIDe Trial

Barbara E. Cormack, MHSc[1,2]; Yannan Jiang, PhD[1]; Jane E. Harding, DPhil[1]; Caroline A. Crowther, MD[1]; Frank H. Bloomfield, PhD[1,2]; and for the ProVIDe Trial Group[1]

Abstract

Background: Refeeding syndrome (RS) following preterm birth has been linked to high intravenous (IV) protein intake in the presence of low electrolyte supply. In extremely low-birth-weight (ELBW) babies, we aimed to determine the incidence of RS and associations with birth characteristics and clinical outcomes. *Method:* Prospective cohort study of ELBW ProVIDe Trial participants in 6 New Zealand neonatal intensive care units. RS was defined as serum phosphate < 1.4 mmol.L^{-1} and total calcium > 2.8 mmol.L^{-1}. Relationships between RS and other factors were explored using 2-sample tests and logistic regression adjusted for sex, gestation, and birth-weight *z*-score. *Results:* Of 338 babies (mean [SD] birth-weight, 780 (134) g, gestational age, 25.9 [1.7] weeks), 68 (20%) had RS. Mortality was greater in babies with RS (32% vs 11%; $P < .0001$). More small- than appropriate-for-gestational-age babies developed RS (22% vs 8%; $P = .001$). Growth from birth to 36 weeks' corrected age was not different between babies who did and did not have RS. In logistic regression, the odds of RS decreased by 70% for each 1 mmol per kg^{-1}.d^{-1} IV phosphate intake (odds ratio [OR], 0.3; CI, 0.1–0.6; $P = .002$) and increased by 80% for each 1 g.kg^{-1}.d^{-1} IV protein intake (OR, 1.8; CI, 1.3–2.7; $P = .002$). *Conclusions:* Neonatal RS is common in this cohort of ELBW babies and is associated with increased morbidity and mortality. Optimizing phosphate and calcium intakes in IV nutrition solutions may reduce RS and its consequences. (*JPEN J Parenter Enteral Nutr.* 2021;45:65–78)

Keywords

amino acids; fluids-electrolytes/acid-base; hypophosphatemia; intraventricular hemorrhage; mortality; neonates; parenteral nutrition; preterm; proteins; refeeding syndrome

From the [1]Liggins Institute, University of Auckland, Auckland, New Zealand; and the [2]Newborn Services, Auckland City Hospital, Auckland, New Zealand.

Financial disclosure: The ProVIDe (Impact of protein intravenous nutrition on development) study was funded by the New Zealand Health Research Council (http://www.hrc.govt.nz 14/174), Cure Kids (www.curekids.org.nz; 3550 and 3580), Lotteries Grants Board (http://www.communitymatters.govt.nz; 3705291), A+ Trust (www.adhb.govt.nz; A+5854), Gravida: National Centre for Growth and Development, and the Nurture Foundation STF 13–19. B. E. Cormack was supported by a Gravida: National Centre for Growth and Development scholarship, the Neige Todhunter Award, the Yvonne A M Smith Charitable Trust grant, philanthropic donations to Liggins Institute, and the Starship Foundation. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest: None declared.

Received for publication April 9, 2020; accepted for publication May 19, 2020.

This article originally appeared online on July 4, 2020.

Corresponding Author:
Frank H. Bloomfield, PhD, Liggins Institute, University of Auckland, 85 Park Rd, Grafton, Auckland 1023, New Zealand.
Email: f.bloomfield@auckland.ac.nz

Clinical Relevancy Statement

This study shows refeeding syndrome (RS), which has been linked to high intravenous (IV) amino acid intake in the presence of low electrolyte supply, is common in extremely low-birth-weight babies and especially in babies who are small-for-gestational-age. In this cohort, RS was associated with a 3-fold increase in mortality, and severe hypophosphatemia with increased odds of intraventricular hemorrhage. Optimizing the phosphate and calcium content of IV solutions may decrease RS and its consequences.

Introduction

Extremely low-birth-weight (ELBW, birthweight < 1000 g) babies are born with very low stores of key nutrients, such as calcium, phosphate, iron, zinc, and vitamins, and little or no subcutaneous fat and glycogen stores because fetuses lay down these important nutrient stores during the third trimester of pregnancy.[1] Many preterm babies also are growth-restricted compared with their gestational age–matched intrauterine peers who go on to be born at term because of a suboptimal intrauterine environment that often accompanies preterm birth.[2] At any other stage of life, this physical state would be described as severe malnutrition. For these tiny babies, the immediate provision of appropriate intravenous (IV) and enteral nutrition is vital in preventing further depletion of nutrient stores and supporting rapid growth and development until they can breastfeed, but it also to brings potential dangers.

The presence of malnutrition followed by enteral or IV refeeding predisposes adults and children to a potentially fatal cluster of fluid and electrolyte disturbances known as refeeding syndrome (RS).[3] In preterm babies, it is proposed that this cluster of electrolyte disturbances is precipitated by the sudden supply of IV amino acids and glucose following a period of low nutrition, such as occurs with placental insufficiency or inadequate IV energy and protein intake for several days after birth. The supply of IV amino acids and glucose stimulates endogenous insulin secretion and the transfer of phosphate from bones into cells for energy and protein production.[4-6] Insufficient intake of electrolytes and vitamins to support the increased demand for phosphate, sodium, potassium, magnesium, and thiamin in particular then results in the characteristic biochemical disturbances of RS, usually within 2–5 days of refeeding.[3,7] These are hypophosphatemia, hypercalcemia, hypokalemia, hypomagnesemia, hyperglycemia, and thiamin deficiency. Hypercalcemia occurs because calcium is released from bone along with the phosphate needed to maintain serum phosphate concentrations. The first reports of associations between enhanced IV nutrition, hypophosphatemia, and hypercalcemia in preterm babies emerged in 2012–2013.[4,6,20] A series of cohort studies and case reports followed describing hypophosphatemia and other biochemical disturbances consistent with RS in preterm babies who were small-for-gestational-age (SGA) and/or born following maternal preeclampsia and who were thought to be triggered by early aggressive IV nutrition in the first week after birth,[6,8-17] including in randomized controlled trials.[18,19] The definition of hypercalcemia in these reports (>2.8 $mmol.L^{-1}$) is reasonably consistent[4,16,17,20]; however, the definition of hypophosphatemia varies between <1.1 to <1.6 $mmol.L^{-1}$ [4,9,12,14,16,17,21-23] and severe hypophosphatemia between <0.7 and <1.0 $mmol.L^{-1}$.[4,9,12-14,16,22,24] A clear, consistent definition of neonatal RS has not yet been established.

Neonatal RS has been associated with metabolic acidosis, hypernatremia, hypovolemia, ischemia, respiratory alkalosis, delayed full enteral feeding,[9,11] and clinical problems, such as sepsis[6] and chronic lung disease.[9] Possible mechanisms are shown in Figure 1. The hypernatremia that has been reported may be due to hypertonic dehydration accompanying the hypovolemia, a risk for all ELBW babies due to high rates of transepidermal water loss.

For many years, international-consensus preterm nutrition guidelines recommended the early initiation of high IV amino acid and energy intakes in combination with little or no sodium, potassium, calcium, and phosphate for the first 24–48 hours after birth.[25] The rationale for giving higher amino acids and energy was to prevent early nutrient deficits and subsequent growth faltering. Delayed electrolyte supplementation until after the onset of extracellular fluid contraction was thought to help prevent hyperkalemia and reduce the incidence of chronic lung disease. In fact, this combination may promote the subsequent development of neonatal RS (Figure 1). Recent 2018 European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) preterm IV nutrition guidelines[26,27] now recommend sodium, phosphate, and potassium supplementation in IV nutrition solutions from birth, although the authors acknowledge this recommendation is not based on level 1 evidence. Further investigation is needed to determine how common neonatal RS is and whether it influences important neonatal health outcomes.

The ProVIDe (impact of protein intravenous nutrition on development) Trial randomized 434 ELBW babies in 6 New Zealand (NZ) and 2 Australian neonatal intensive care units (NICUs) between 2014 and 2018 to receive either 1 $g.d^{-1}$ of IV amino acids or placebo (saline) in the first 5 days after birth, in addition to standard nutrition support. The primary outcome of the trial is survival free from neurodevelopmental disability at 2 years' corrected age (CA), expected to be available in 2021. Baseline nutrition intakes were not mandated, meaning that participants in both the intervention and placebo groups received a range of nutrient intakes because of the differences in nutrition policies and composition of IV nutrition solutions at each site. The

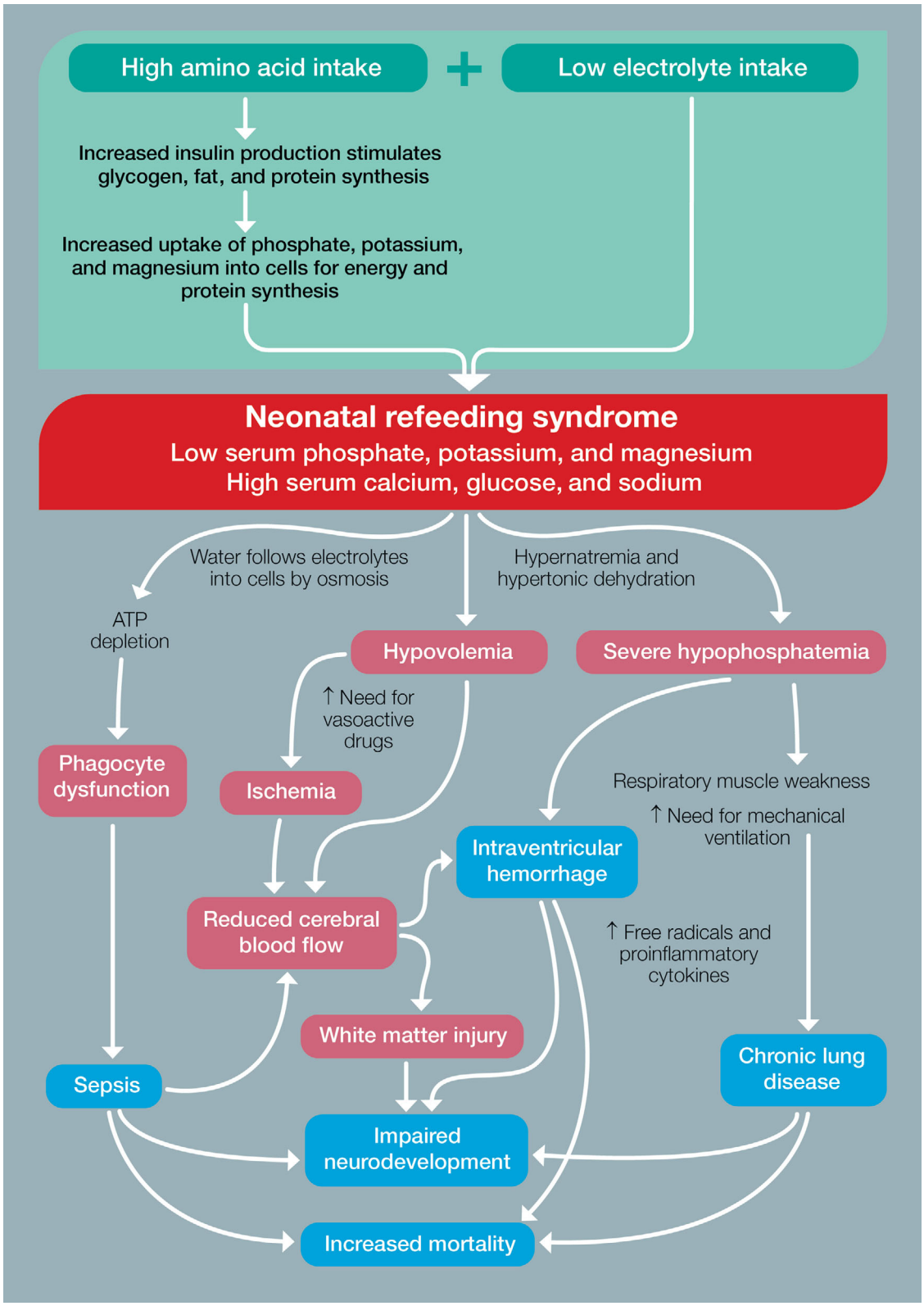

Figure 1. Proposed mechanisms for neonatal refeeding syndrome and effects on clinical outcomes.

aim of this blinded cohort analysis was to investigate the incidence of RS and relationships between RS and clinical outcomes, birth characteristics, growth, and nutrient intake.

Aims

To determine, in a cohort of ELBW babies cared for in NICUs with varied nutrition practices, the following:

1. The incidence of neonatal RS in the 5 days after birth
2. The associations between RS and
   a clinical outcomes
   b maternal and birth characteristics
   c growth to 36 weeks' CA
   d nutrition intakes

Participants and Methods

The cohort comprises ELBW babies participating in the ProVIDe trial (Australian New Zealand Clinical Trials Registry: ACTRN12612001084875), a multicenter, 2-arm, double-blind, parallel, randomized controlled trial. The Northern B Health and Disability Ethics Committee gave ethical approval for the study (No 13/NTB/84). Each participating site received institutional approval through local institutional review processes. Informed written consent was obtained for all participants from their parents or caregivers.

The ProVIDe study protocol has been published elsewhere.[28] Briefly, 434 participants were recruited from 6 NZ and 2 Australian sites and randomized at 1:1 ratio to receive either 1 $g.d^{-1}$ amino acid solution (TrophAmine, B Braun Medical, Irvine) or placebo (saline) via the umbilical arterial catheter (UAC) for the first 5 days after birth, in addition to standard IV nutrition. Inclusion criteria were placement of a UAC and birthweight < 1000 g. Exclusion criteria were admission to the NICU >24 hours after birth, congenital disorder affecting growth, inborn error of metabolism, danger of imminent death, multiple births of >2 babies, and known chromosomal or genetic abnormality. Survival that is free of neurodevelopmental disability at 2 years' CA is the primary outcome. Secondary outcomes are growth from birth to 36 weeks' at NICU discharge and at 2 years' CA; body composition at 36–42 weeks' CA and at 2 years' CA; and neonatal morbidity, length of stay, and nutrition intake. Protein intakes in both arms of the study were within current internationally reported ranges in observational studies.[29-31]

A subgroup of participants admitted to NZ recruiting centers had an additional arterial blood sample collected 24 hours after the intervention commenced (ie, 24–48 hours after birth) and again within 1 hour of the intervention ceasing, irrespective of the actual duration of the intervention. The blood sample (0.5 mL) was transported immediately to the site laboratory for analysis of serum urea, calcium, phosphate, total protein, and albumin concentrations. Routine daily biochemistry (pH [lowest], bicarbonate [lowest], base excess [most negative], lactate [highest], potassium [lowest], urea [highest], calcium [daily serum albumin concentration adjusted], and phosphate [lowest]) for the first 5 days after birth was collected for all trial participants at the 6 NZ and 2 Australian sites, either from blood gas analysis or from venous blood analyses. As the ProVIDe Trial is ongoing with a primary outcome at 2 years' CA, this cohort analysis was conducted without unblinding group allocation. We defined hypophosphatemia as serum phosphate < 1.4 $mmol.L^{-1}$, severe < 0.9 $mmol.L^{-1}$[6] and hypercalcemia as serum albumin concentration–adjusted calcium > 2.8 $mmol.L^{-1}$.[32] The formula used by all laboratories for serum albumin concentration–adjusted calcium was [Ca adjusted] = [Ca total] + 0.012 × (39.9 - [serum albumin concentration]).[33] Biochemistry consistent with neonatal RS was defined as the presence of both hypophosphatemia and hypercalcemia in the blood sample taken at the end of the intervention.

Data Collection

Nutrition intake and weight data were collected prospectively and used to estimate mean daily IV intakes of energy ($kcal.kg^{-1}.d^{-1}$), macronutrients (protein, fat, and carbohydrate, $g.kg^{-1}.d^{-1}$), electrolytes and thiamin ($unit.kg^{-1}.d^{-1}$), and enteral volume ($mL.kg^{-1}.d^{-1}$) from birth until 5 days of age. Intakes on the day of birth and, where relevant, day of death were excluded, as they did not represent a full 24-hour intake. Fluid and nutrient intakes included fluids from medication and serum albumin infusions but not from other transfused blood products. Weight-based nutrient intakes per day were calculated using the birth weight until the birth weight was surpassed, then calculated using the weight on the day nutrition information was collected or the most recent weight. Full enteral feeds were defined as the day when no further IV nutrition was given or 150 $mL.kg^{-1}.d^{-1}$ enteral feeds was reached. Protein intake was calculated from protein equivalent for IV amino acids.[34] Some of the standard IV solutions commenced after birth at each site contained no phosphate, potassium, magnesium, and chloride (Table 1). After 48–72 hours, a variety of other standard solutions of differing composition was given at varying volumes. Only 2 sites used the same standard solutions. Nutrient intakes were calculated using recommended values[34] and manufacturers' composition data.

Weight, length, and head circumference were measured at birth and at 36 weeks' CA and discharge (±10 days). Measurements were by trained staff using validated, repeatable methods: nonstretch, teflon measuring-head tapes (Seca, Protec Solutions Ltd, Wellington), and a Harpenden (Holtain Ltd, Dyfed, Wales) or similar neonatometer.

Fenton normative data were used to calculate *z*-scores.[35] As there are currently no birth length and head circumference data for babies born at <23 weeks in the Fenton

Table 1. Nutrition Composition Data Used for Calculations.

Site	Protein, g	Glucose, g	Energy, kcal	Sodium, mmol	Calcium, mmol	Phosphate, mmol	Potassium, mmol	Magnesium, mg	Chloride, mg
1	2.7	12.5	53	2.3	1.0	1.2	2.5	4.2	30.4
2	3.5	10.0	48	1.2	0.7	0.5	Nil	7.3	24.8
3	4.0	10.0	54	2.0	1.0	1.0	Nil	9.8	27.1
4	6.2	13.6	70	0.4	1.5	Nil	Nil	Nil	53.6
5	6.8	15.0	78	0.4	1.6	Nil	Nil	Nil	Nil
6	6.8	15.0	78	0.4	1.6	Nil	Nil	Nil	Nil

Composition per 100 mL of standard intravenous nutrition solutions used following admission at each site.

dataset, we examined INTERGROWTH fetal ultrasound data on head growth and determined relatively linear growth through 20–24 weeks' CA.[36] The rate of change in the Fenton length data was examined for 23–28 weeks and found to be less at the lower ages.[35] To extrapolate head and length measures to 22 weeks, the linear and decreasing rates of change trends were continued. SGA was based on the same dataset.[35]

Outcome Measures

Clinical outcome definitions were patent ductus arteriosus (diagnosed by echocardiography and with a clinical decision to treat); late-onset sepsis (>7 days after birth and defined as a positive bacterial culture in cerebrospinal fluid, urine, or blood with clinical signs of infection and with antibiotics for ≥5 days, with the intention of treating an infection or treatment for a shorter period if the patient died; if after 10 days of appropriate antibiotic therapy there was demonstration of sterile culture and then the same organism was cultured or if a different organism was cultured from a subsequent culture, this was considered an additional episode); severe intraventricular hemorrhage (IVH, grade 3 or higher, defined using the grading system from Papile et al)[37]; periventricular leukomalacia; chronic lung disease (need for oxygen at 36 weeks' postmenstrual age or 28 days after birth, if born after 32 weeks' gestation); retinopathy of prematurity (ROP, grades as per the International Classification of ROP)[38]; necrotizing enterocolitis, Bell stage 2 or higher),[39] and death prior to discharge from neonatal care.

Statistics

Participants' data were stored in a secure study database and imported to SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) for analysis. Assignment to intervention or placebo remained blinded, but actual total nutrient intakes were used and included amino acid intake from the intervention. To calculate nutrient intakes, only babies who had survived for ≥3 days after birth were included. Descriptive summaries are presented using median (interquartile range [IQR]) or mean (SD) as appropriate for continuous variables and number (%) for categorical variables. Two-sample *t*-test or Wilcoxon test was used to compare the distribution of continuous variables between groups, and the χ^2 test was used for categorical variables. Relationships between serum biochemistry and early nutrient intakes were tested using Spearman correlation coefficients. Logistic regression analysis was conducted for babies with and without RS, adjusted for gestational age at birth, birth weight *z*-score, and sex. The results were compared with and without site in the model. Statistical tests were 2-sided at a 5% significance level.

Results

For the 434 babies randomized in the ProVIDe Trial, mean (SD) gestational age at birth was 25.9 (1.7) weeks, birth weight was 780 (134) g, and 48 (11%) were SGA (Table 2.) Routine blood data were collected for all 434 trial babies, including 382 babies admitted to NZ hospitals. Additional samples, before and after the intervention, were collected on 371 and 356 NZ babies, respectively (Figure 2). Of these, 338 babies had both serum phosphate and serum albumin concentration–adjusted calcium measured after the intervention, and 68 (20%) babies met the RS criterion (Tables 3 and 4).

Mortality was 3-fold higher in babies with RS than in those without (22/68 (32.4%) vs 29/270 (10.7%); $P = .001$) and also differed widely amongst sites (range, 7%–27%, $P < .01$) (Table 5). The median (IQR) age at death was 28 (15, 67) days. There were no other differences in clinical outcomes in unadjusted or adjusted analyses between babies who did and did not have RS.

Development of RS was not associated with gestational age at birth, multiple birth, or maternal characteristics. Significantly more SGA than appropriate-for-gestational-age babies developed RS, and birth weight *z*-score was significantly lower in babies who developed RS (Table 2). More boys than girls met RS criteria, but this difference was not statistically significant (24.4% vs 16.5%; $P = .08$).

There were no differences between babies who did and did not have RS in *z*-score change for weight, length, or head

Table 2. Birth Characteristics and Neonatal Outcomes.

Characteristics	Total Cohort n = 434		NZ Cohort n = 338		NZ Cohort[a] Refeeding Syndrome n = 68		NZ Cohort[a] No Refeeding Syndrome n = 270		*P*
For baby	n		n		n		n		
Gestational age, wk	434	25.8 (1.6)	338	25.9 (1.6)	68	25.7 (1.8)	270	25.9 (1.6)	.42
Birthweight, g	434	775 (135)	338	780 (134)	68	713 (132)	270	796 (129)	**<.0001**
Birth weight *z*-score	434	−0.1 (0.9)	338	0.0 (0.9)	68	−0.4 (0.9)	270	0.1 (0.8)	**.0002**
Small-for-gestational-age	434	48 (11)	338	37 (11)	68	15 (22)	270	22 (8)	**.001**
Sex (male)	434	212 (49)	338	156 (46)	68	38 (56)	270	118 (44)	.07
Singleton	434	340 (78)	338	279 (83)	68	54 (79)	270	225 (83)	.45
For mother									
Cesarean delivery	434	234 (54)	338	181 (54)	68	39 (57)	270	142 (53)	.48
Antenatal corticosteroids (any)	434	410 (94)	338	320 (95)	68	63 (93)	270	257 (95)	.40
Maternal diabetes	434	24 (6)	338	20 (6)	68	5 (7)	270	15(6)	.57
Neonatal outcomes									
IVH ≥ grade 3	423	46 (11)	336	32 (10)	68	10 (15)	268	22 (8)	.10
Periventricular leukomalacia	418	9 (2)	333	7 (2)	66	2 (3)	267	5 (2)	.56
Patent ductus arteriosus	410	197 (48)	327	153 (47)	62	31 (50)	265	122 (46)	.57
Necrotizing enterocolitis	423	54 (13)	336	41 (12)	68	10 (15)	268	31 (12)	.48
Chronic lung disease	363	264 (73)	292	220 (75)	50	41 (82)	242	179 (74)	.23
ROP ≥ grade 3	376	60 (16)	300	45 (15)	54	9 (17)	246	36 (15)	.70
Culture-proven early onset sepsis	422	13 (3)	336	8 (2)	68	0	268	8 (3)	.15
Probable early onset sepsis	422	112 (27)	336	95 (28)	68	16 (24)	268	79 (29)	.33
Culture-proven late-onset sepsis	422	142 (34)	336	111 (33)	68	29 (43)	268	82 (31)	.06
Probable late-onset sepsis	422	182 (43)	336	156 (46)	68	30 (44)	268	126 (47)	.67
Death before NICU discharge	434	77 (18)	338	51 (15)	68	22 (32)	270	29 (11)	**<.0001**
Severe adverse outcome[b]	434	350 (81)	338	278 (82)	68	60 (88)	270	218 (81)	.15
Length of NICU stay, d	357	110 (35)	287	112 (34)	46	118 (39)	241	111 (33)	.21
Feeding									
Days to full enteral feeds[c]	388	21 (20)	314	21 (21)	58	25 (23)	256	21 (21)	.20
Growth									
Mean *z*-score change from birth to 36 weeks' corrected age									
Weight	344	−0.6 (0.8)	277	−0.6 (0.8)	48	−0.4 (0.9)	229	−0.6 (0.8)	.13
Length	323	−1.2 (1.1)	262	−1.2 (1.1)	42	−1.2 (1.4)	220	−1.2 (1.1)	.90
Head circumference	339	−0.9 (1.0)	273	−0.9 (1.0)	46	−1.0 (1.0)	227	−0.9 (1.0)	.90

Number of babies (%) or mean (SD), *P*-values in bold are <.05.
IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; NICU, neonatal intensive care unit; NZ, New Zealand.
[a]Refeeding syndrome was defined as hypophosphatemia (serum phosphate <1.4 mmol.L^{-1}) and hypercalcemia (calcium [total] >2.8 mmol.L^{-1}).
[b]Severe adverse outcome was defined as death; severe intraventricular hemorrhage (≥ grade 3 defined using the grading system from Papile et al)[37]; periventricular leukomalacia; chronic lung disease (need for oxygen at 36 weeks' postmenstrual age or 28 days after birth if born after 32 weeks' gestation); retinopathy of prematurity grades 3 and 4, as per the International Classification of Retinopathy of Prematurity [13]; and necrotizing enterocolitis (defined as Bell stage 2 or higher) [11].
[c]Full enteral feeds were defined as the day when no further intravenous nutrition was given or 150 mL.kg^{-1}.d^{-1} enteral feeds was reached.

circumference from birth to 36 weeks' CA, days to reach full enteral feeds, or length of NICU stay in unadjusted or adjusted analyses. Mean IV nutrient intakes for the first 5 days varied widely (Tables 1 and 6). Phosphate, calcium, and magnesium intakes were ≈50% of the 2018 ESPGHAN–recommended range in most sites (Figure 3). Mean week 1 IV amino acid intakes were negatively correlated with serum phosphate and positively correlated with serum calcium concentrations. These associations were stronger for phosphate than calcium (Figure 4). Serum calcium increased and phosphate decreased each day in the first 4 days after birth (Figure 5) and differed by site (Figure 6).

There was no significant association between RS and severe IVH in adjusted logistic regression. However, when also adjusted for site, babies in the lowest quintile of serum phosphate concentration (0.1–0.8 mmol.L^{-1}) had 5 times the odds of severe IVH (odds ratio [OR], 5.3; CI, 1.4–21.0; $P = .02$), and those in the highest quintile of serum phosphate concentration of 1.7–2.6 mmol.L^{-1} had 90% lower odds of severe IVH (OR, 0.1; CI, < 0.1–0.6; $P = .02$) compared with

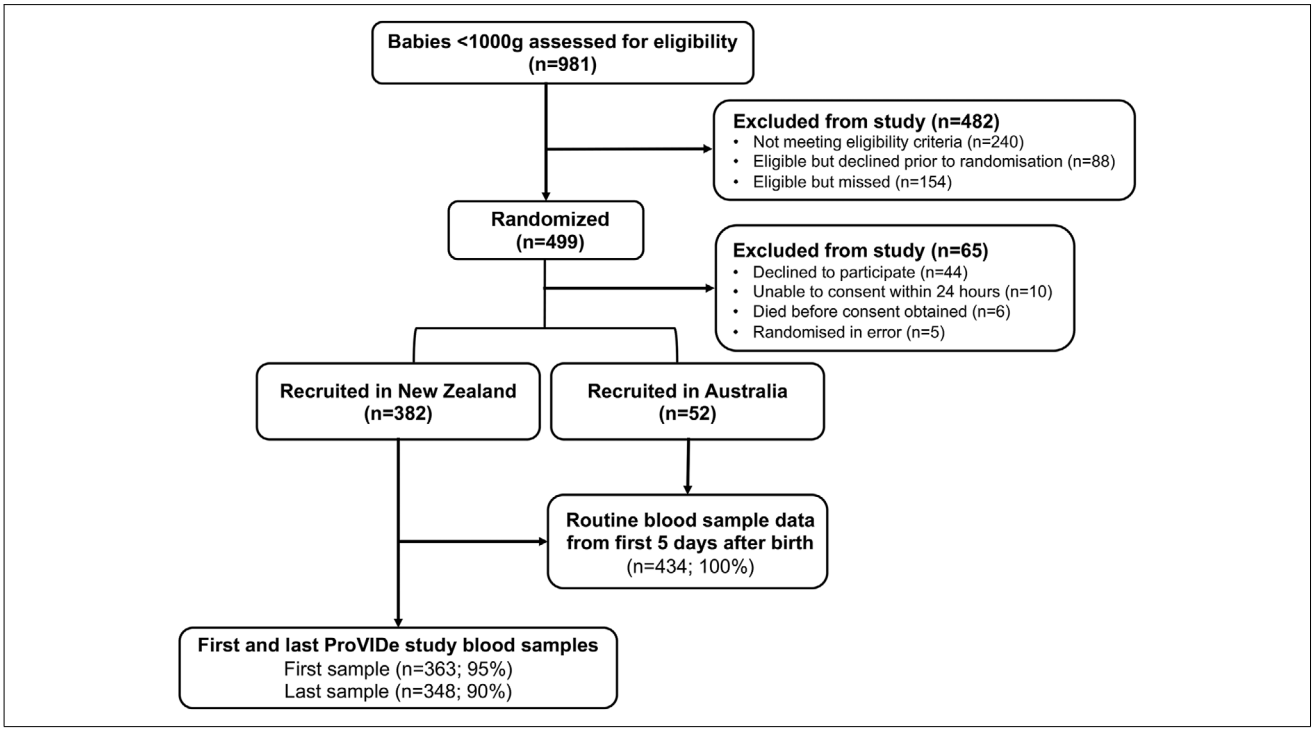

Figure 2. ProVIDe STROBE flow diagram. ProVIDe, impact of Protein intravenous nutrition on development; STROBE, Strengthening The Reporting of Observational studies in Epidemiology.

Table 3. Serum Biochemistry in the First Week After Birth.

Parameter	First blood sample n = 371	Last blood sample n = 356
Calcium, adjusted for serum albumin, mmol.L^{-1}	2.2 (0.2)	2.7 (0.3)
Phosphate, mmol.L^{-1}	1.7 (0.5)	1.3 (0.5)
Total protein, g.L^{-1}	40.5 (4.9)	42.9 (3.5)
Serum albumin, g.L^{-1}	21.5 (3.0)	22.2 (3.6)
Urea, mmol.L^{-1}	10.8 (3.6)	11.5 (6.0)
Time after birth sample taken, d	1.3 (0.4)	4.9 (1.0)

Mean (SD).

babies who had a serum phosphate in the middle quintile of 1.2–1.4 mmol.L^{-1}, although these confidence intervals are wide. In logistic regression across quintiles (adjusted for gestational age at birth, birth weight *z*-score, and sex), babies with a serum phosphate concentration in the lowest quintile of 0.1–0.8 mmol.L^{-1} were more likely to die before NICU discharge (OR, 2.7; CI, 1.0–7.3; $P = .047$) compared with those in the middle quintile of 1.2–1.4 mmol.L^{-1}. Babies with a serum calcium in the highest quintile of 2.9–3.9 mmol.L^{-1} had nearly 5 times the odds of death before NICU discharge (OR, 4.9; CI, 1.8–13.3; $P = .002$) compared with babies in the middle quintile of 2.7–2.7 mmol.L^{-1}. When also adjusted for site, only serum calcium remained significant (OR, 4.2; CI, 1.5–11.9; $P = .007$).

Babies who developed RS had significantly higher intakes of energy, amino acid, glucose, and lipid and lower intakes of phosphate, calcium, and sodium (Table 6). In adjusted logistic regression (without site), the odds of RS increased by 60% for every 10 kcal.kg^{-1}.d^{-1} higher IV intake of energy (OR, 1.6; CI, 1.1–2.1; $P = .005$) and also increased for each 1 g.kg^{-1}.d^{-1} of IV amino acid (OR, 1.8; CI, 1.3–2.7; $P = .002$), IV fat (OR, 2.1; CI, 1.2–3.9; $P = .02$), and IV carbohydrate (OR, 1.2; CI, 1.1–1.4; $P = .01$). However, the odds of RS decreased by 30% for each additional 1 mmol.kg^{-1}.d^{-1} of sodium (OR, 0.7; CI, 0.5–0.9; $P = .002$) and by 70% for each additional 1 mmol.kg^{-1}.d^{-1} phosphate (OR, 0.3; CI, 0.1–0.6; $P = .002$) and calcium (OR, 0.3; CI, 0.1–0.8; $P = .01$). When also adjusted for site, only IV amino acid intake remained significant (OR, 2.1; CI, 1.3–3.4; $P = .001$). The IV phosphate intake in the first 2 days was lower in babies who had RS than in those who did not (mean [SD], 0.3 [0.5] vs 0.4 [0.4] mmol.kg^{-1}.d^{-1}); $P = .08$), although not significant. In adjusted analyses (without site), each extra 1 mmol.kg^{-1}.d^{-1} phosphate in the first 2 days after birth reduced the odds of RS by 50% (OR, 0.5; CI, 0.3 to <1.0; $P = .04$).

In adjusted regression analyses (without site), the odds of developing RS decreased by 70% for babies with mean IV protein intakes for the first 5 days in the lowest quintile of

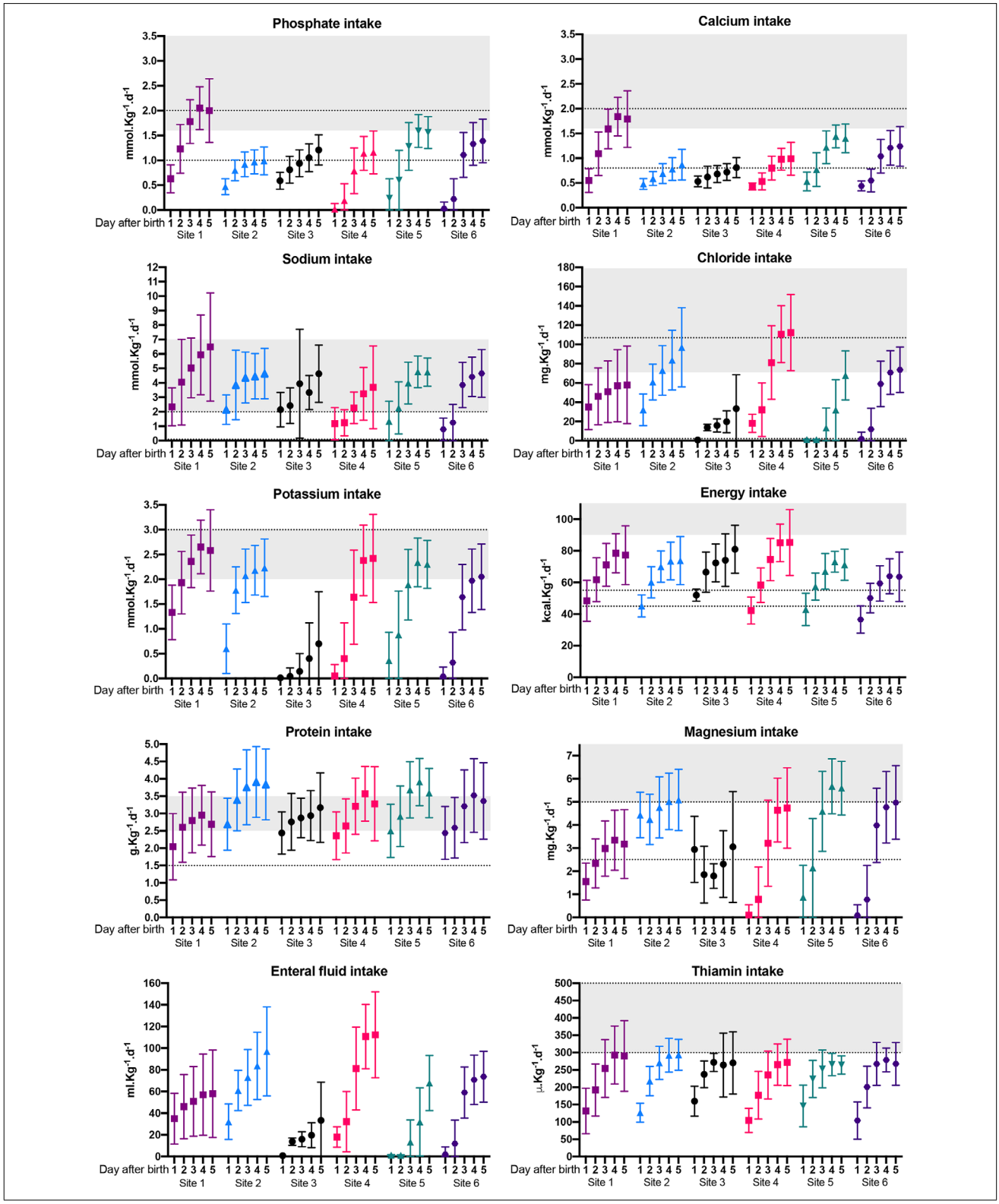

Figure 3. Intravenous nutrition intakes from days 1–5 at each New Zealand site. Data are mean and SD. The dotted black lines and shaded area show ESPGHAN 2018–recommended intakes for day 1 and week 1, respectively.[26,27,54,55] Site 1, n = 70. Site 2, n = 53. Site 3, n = 14. Site 4, n = 73. Site 5, n = 40. Site 6, n = 88. European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

Table 4. Last Blood Sample Serum Biochemistry in the First Week After Birth.

Parameter	Neonatal refeeding syndrome[a]				
	Yes n = 68		No n = 270		*P*
Last blood sample	n		n		
Calcium, adjusted for serum albumin, mmol.L^{-1}	68	3.1 (0.3)	270	2.6 (0.2)	**<.0001**
Phosphate, mmol.L^{-1}	68	0.8 (0.3)	270	1.4 (0.4)	**<.0001**
Total protein, g.L^{-1}	68	40.4 (5.3)	267	42.5 (5.3)	**.004**
Serum albumin, g.L^{-1}	68	21.0 (3.3)	270	22.7 (3.5)	**.0002**
Urea, mmol.L^{-1}	66	11.0 (6.4)	269	11.4 (5.9)	.62
Ammonia, *u*mol.L^{-1}	62	69.4 (31.9)	252	69.7 (77.2)	.96

Mean (SD). *P*-values in bold are <.05.

Table 5. Last Blood Sample Serum Biochemistry in the First Week After Birth, by Site.

Last blood sample	Site 1 n = 70	Site 2 n = 53	Site 3 n = 14	Site 4 n = 73	Site 5 n = 40	Site 6 n = 88	All n = 338
Hypophosphatemia[a]	22 (31%)	41 (77%)	4 (29%)	68 (93%)	27 (64%)	45 (51%)	207 (61%)
Severe hypophosphatemia[b]	5 (7%)	13 (25%)	3 (21%)	41 (56%)	6 (15%)	10 (11%)	78 (23%)
Hypercalcemia[a]	12 (17%)	9 (17%)	2 (14%)	34 (47%)	6 (15%)	14 (16%)	77 (23%)
Refeeding syndrome[a]	9 (13%)	9 (17%)	1 (7%)	32 (44%)	6 (15%)	11 (13%)	68 (20%)
IVH ≥ grade 3	8 (12%)[c]	2 (4%)[d]	3 (21%)	8 (11%)	7 (18%)	4 (5%)	32 (10%)[e]
Died before discharge	5 (7%)	9 (17%)	3 (21%)	20 (27%)	6 (15%)	8 (9%)	51 (15%)
Proportion of babies who died before discharge who had RS in the first week	0/5 (Nil)	2/9 (22%)	1/3 (33%)	17/20 (85%)	2/6 (33%)	0/8 (Nil)	22/51 (43%)

Number of babies (%) or mean (SD).
IVH, intraventricular hemorrhage.
[a]Refeeding syndrome was defined as hypophosphatemia (serum phosphate < 1.4 mmol.L^{-1}) and hypercalcemia (calcium [total] > 2.8 mmol.L^{-1}).
[b]Severe hypophosphatemia < 0.9 mmol.L^{-1}.
[c]IVH ≥ grade 3 (denominator site 1, n = 69).
[d]Site 2, n = 52.
[e]All, n = 336.

Table 6. Early Intravenous Nutrition Intake in Babies Who Did and Did Not Have Neonatal Refeeding Syndrome.

	Neonatal refeeding syndrome[a]		
Nutrients in 5 days	Yes (n = 68)	No (n = 270)	*P*
Energy, kcal.kg^{-1}.d^{-1}	66 (9)	63 (10)	**.01**
Glucose, g.kg^{-1}.d^{-1}	10.0 (2.2)	9.3 (2.0)	**.01**
Amino acid, g.kg^{-1}.d^{-1}	3.3 (0.8)	3.0 (0.7)	**.001**
Lipid, g.kg^{-1}.d^{-1}	2.1 (0.4)	2.0 (0.5)	**.02**
Phosphate, mmol.kg^{-1}.d^{-1}	0.8 (0.4)	1.0 (0.4)	**.002**
Calcium, mmol.kg^{-1}.d^{-1}	0.9 (0.3)	1.0 (0.3)	**.01**
Sodium, mmol.kg^{-1}.d^{-1}	3.0 (1.4)	3.5 (1.5)	**.01**
Potassium, mmol.kg^{-1}.d^{-1}	1.5 (0.6)	1.5 (0.6)	.22
Magnesium, mmol.kg^{-1}.d^{-1}	3.0 (1.3)	3.2 (1.1)	.14
Chloride, mg.kg^{-1}.d^{-1}	58 (22)	55 (24)	.35
Thiamin, *u*g.kg^{-1}.d^{-1}	224 (41)	227 (43)	.49

Mean (SD). N = 338. *P*-values in bold are <.05.
[a]Neonatal refeeding syndrome was defined as hypophosphatemia (serum phosphate < 1.4 mmol.L^{-1}) and hypercalcemia (calcium [total] > 2.8 mmol.L^{-1}).

1–2.4 compared with the middle quintile of 2.8–3.2 g.kg^{-1}.d^{-1} (OR, 0.3; CI, 0.1–0.9; $P = .03$) and tripled for IV phosphate intakes in the 2 lowest quintiles of 0–0.6 mmol.kg^{-1}.d^{-1} (OR, 3.2; CI, 1.2–8.3; $P = .02$) and 0.7–0.8 mmol.kg^{-1}.d^{-1} (OR, 3.0; CI, 1.2–7.9; $P = .03$) compared with the middle quintile of 0.9–1.0 mmol.kg^{-1}.d^{-1}.

Serum total protein and albumin concentrations were significantly lower in babies with RS than in those without RS (Table 4). Those with severe hypophosphatemia also had significantly lower concentrations of total protein (mean [SD], 40.0 [0.6] vs 42.4 [0.3] g.L^{-1}; $P = .0007$) and serum albumin (21.1 [0.4] vs 22.5 [0.2] g.L^{-1}; $P = .002$) than those with serum phosphate concentrations ≥0.9 mmol.L^{-1}. Patent ductus arteriosus was more common in babies with serum protein concentrations <40 g.L^{-1} (70.1% vs 29.9%; $P < .0001$) and hypoalbuminemia (<25 g.L^{-1}) (54.7% vs 45.4%; $P < .0001$).

In routine blood tests in the total cohort, median serum calcium concentration increased and phosphate concentration decreased each day in the first 4 days after

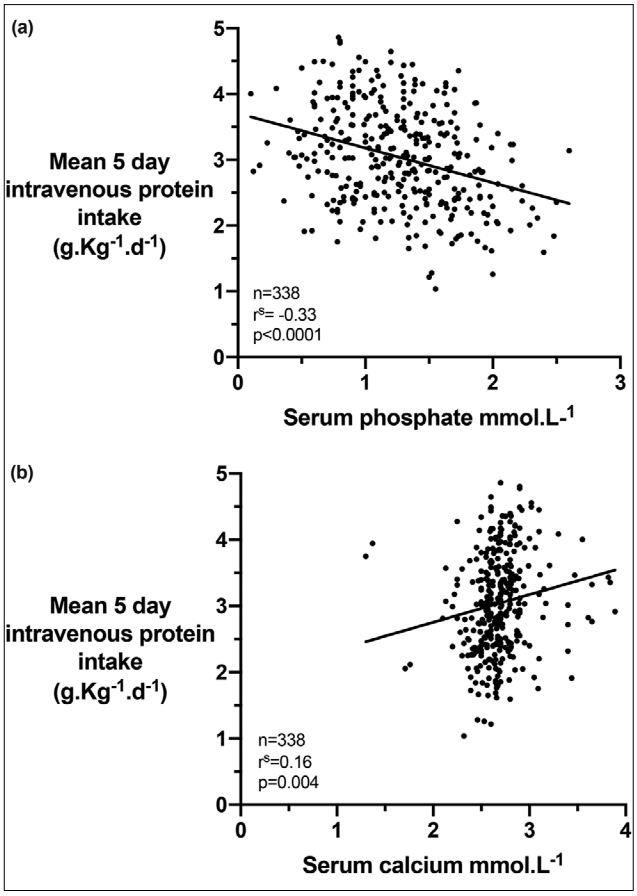

Figure 4. Correlation between mean week 1 intravenous protein intake and (A) serum phosphate and (B) serum calcium (serum albumin adjusted).

birth (Figure 6). Potassium, pH, lactate, base excess, and bicarbonate concentrations all fell in the first 4 days after birth and urea concentrations increased. Serum phosphate and calcium were not routinely measured in some sites.

Discussion

We report, in a large prospective cohort, that RS is common in ELBW babies (particularly in SGA babies), varies by hospital and nutrition practice, and is associated with a 3-fold greater mortality rate compared with babies who do not develop RS. Death mostly occurred some weeks later, rather than RS being a marker of imminent death.

Our finding that RS was more likely in SGA babies and those with a LBW *z*-score (as found previously by others[9-12,40]) is not surprising, as some SGA babies are growth-restricted because of inadequate placental transport of nutrients, including amino acids, glucose and phosphorus, leading to chronic fetal malnutrition.[2,41,42] Umbilical artery resistance index, a marker of placental function in preterm babies, has been associated with hypophosphatemia.[11] If followed by generous amino acid and energy supply in the absence of adequate electrolyte intake, this may lead to RS (as seen in malnourished children and adults[43]) because amino acid intake increases endogenous insulin production and the demand for electrolytes because of the transfer of phosphate and potassium into cells for energy production and synthesis of glycogen, fat, and protein.[29]

Electrolyte disturbances consistent with RS have been described previously in smaller preterm cohorts and reported to be associated with sepsis,[6] hyperglycemia,[23] chronic lung disease,[23] enhanced nutrition intakes,[6] and lower phosphate intakes.[24,44] Similarly, intrauterine growth–restricted piglets fed an enteral feed containing 50% more protein than standard sow milk without additional electrolytes developed RS symptoms, and 32% died.[45]

We found that severe hypophosphatemia was associated with a 5-fold increased rate of severe IVH. It is possible that this association is a consequence rather than cause, with IVH inducing a sudden intracellular shift of phosphate. However, severe hypophosphatemia also causes thrombocytopenia and impaired clotting processes.[46] Although the potential role of coagulopathy in the development of IVH is unclear, a recent study in 122 preterm babies reported that concentrations of factor V (a coenzyme needed for coagulation) at birth correlated with IVH and were lower in hypophosphatemic babies.[47] In ELBW babies, 1 small study found twice the rate of severe IVH in those with severe hypophosphatemia (<0.7 mmol.L^{-1}) compared with those without (37% vs 18%; $P = .48$, n = 82), although this was not significant.[24] In the same study, there was also a trend towards higher mortality in the babies with severe hypophosphatemia compared with those without severe hypophosphatemia (42% vs 18%; $P = .06$, n = 82).

We did not find convincing evidence of increased sepsis in babies with RS, with no difference in rates of early onset sepsis in babies with and without RS. However, there was a trend for higher rates of late-onset sepsis in babies with RS (29/68 (43%) vs 82/268 (31%); $P = .06$), consistent with a previous report.[6] Severe hypophosphatemia leads to depletion of adenosine triphosphate (ATP) and phagocyte dysfunction, thereby increasing the risk of sepsis.[6,48] The mean phosphate intakes in our cohort were similar to those in the trial of increased protein intake from birth (3.5 vs 2 g.kg^{-1}.d^{-1} amino acid) by Moltu et al, in which a higher incidence of septicemia was observed in the intervention group (63% vs 29%), but amino acid intakes on the day after birth in our cohort were closer to those of the control group in Moltu's trial, potentially explaining the lower rate of severe hypophosphatemia and sepsis in our cohort.

We also report that serum total protein and albumin concentrations were significantly lower in babies with severe hypophosphatemia, and hypoalbuminemia and hypoproteinemia previously have been reported to be associated with

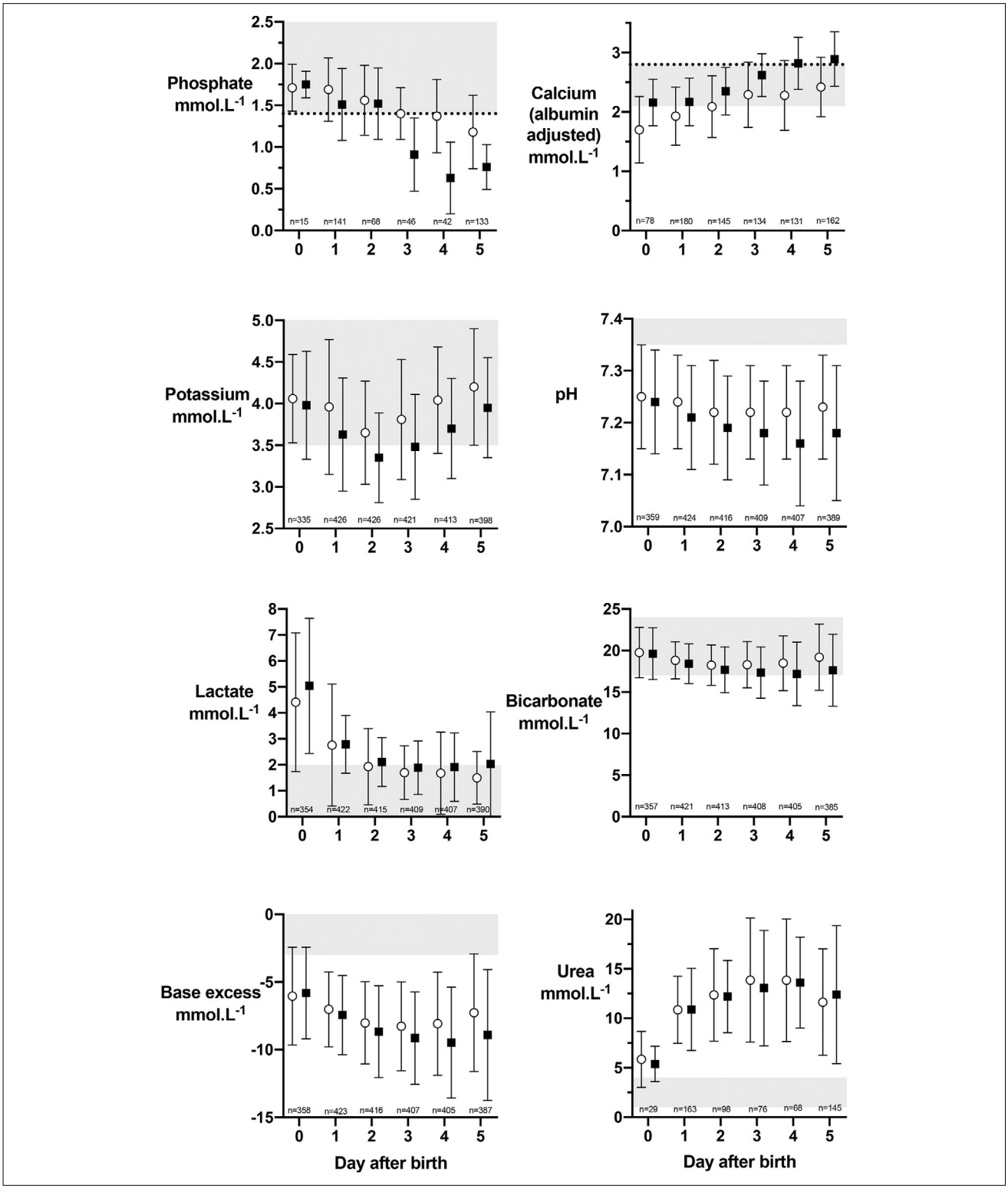

Figure 5. Biochemistry in the first 5 days after birth in babies with and without refeeding syndrome (RS). The black square shows participants with RS, and the open circle shows those without. Data are the median and interquartile range of the highest or lowest recorded value in each baby on each day (see Methods) from samples collected routinely for clinical care rather than from samples at prespecified times, according to the trial protocol. The shaded area shows the local laboratory normal reference range. For phosphate and calcium, the dotted line shows the criterion used in the definition of neonatal RS.

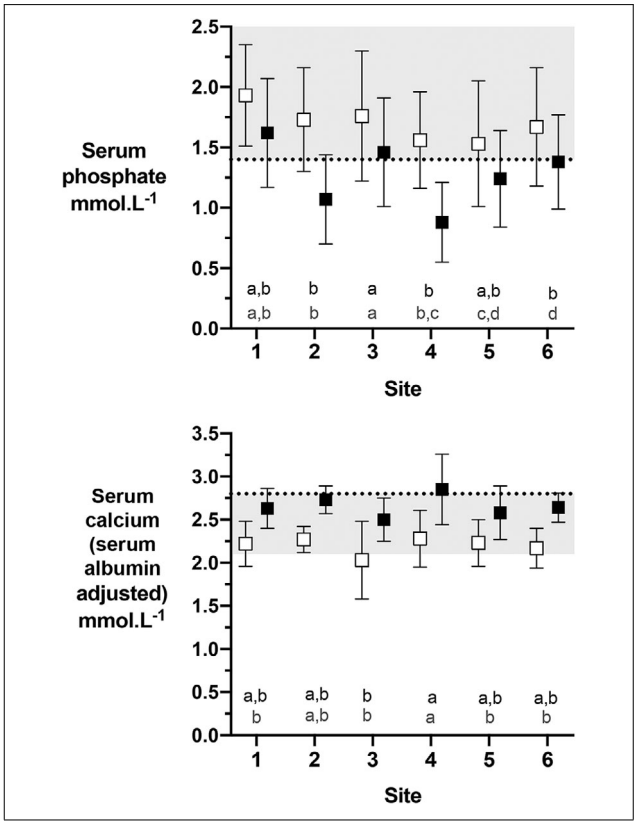

Figure 6. ProVIDe study serum phosphate and calcium concentrations at each site. Data are mean and SD. Serum phosphate: open box, first sample (n = 336); closed box, last sample (n = 348); Serum calcium: open box, first sample (n = 351); closed box, last sample (n = 342). The shaded area shows the local laboratory normal reference range. The dotted line shows refeeding syndrome criteria. Sites not sharing the same letter were significantly different. Black letters relate to first sample, gray letters to last sample. ProVIDe, Impact of protein intravenous nutrition on development.

higher rates of death and/or severe IVH in very preterm babies and very LBW babies.[49,50] However, although statistically lower, the mean concentrations of serum albumin and protein in babies with RS were only ≈2 g.L^{-1} lower than in those without RS.

Mean IV phosphate, calcium, and magnesium intakes in our cohort were significantly lower than 2018 ESPGHAN–recommended intakes at most sites but broadly similar to intakes reported by others,[6,8,11,12] even in more recent studies.[16,23] The IV amino acid intakes in our cohort are higher in the first 2 days than those reported in similar cohorts[6,8,11,12,16,20,40,51] but similar to intakes in more recent reports on this topic.[13-15,17,21,23,24] We found RS was more likely in babies with IV amino acid intakes close to the ESPGHAN 2018–recommended range of 2.5–3.5 g.kg^{-1}.d^{-1} [52] but 3 times more likely when mean IV phosphate intake was lower than recommended.[27] For rapidly growing preterm babies, an estimated 0.33 mmol of phosphate is needed for every 1 g amino acid because phosphate is an essential component of the nucleic acids, ATP, and membrane phospholipids needed for lean tissue accretion.[53] Therefore, ≈0.7 mmol.kg^{-1}.d^{-1} phosphate would be needed for 2 g.kg^{-1}.d^{-1} amino acid on the day of birth. In our cohort, only 2 sites supplied ≥0.6 mmol.kg^{-1}.d^{-1} phosphate on day 1, and these were also the only 2 sites where mean serum phosphate concentrations were >1.6 mmol.L^{-1}. Our study adds to accumulating evidence that high IV amino acid intake, combined with low electrolyte intake in the first few days after preterm birth, is associated with RS.[3,4,6,7,9-18,22] Our findings support the ESPGHAN 2018 recommendation of 0.8–2.0 mmol.kg^{-1}.d^{-1} IV phosphate on day 1 followed by 1.6–3.5 mmol.kg^{-1}.d^{-1} IV phosphate in week 1 and also the routine monitoring of calcium and phosphate in the first 5 days after birth, especially for SGA ELBW babies.[27]

Strengths and Limitations

The main strengths of our study are this is the first large multicenter prospective cohort study to report the incidence of neonatal RS and severe hypophosphatemia in ELBW babies receiving different IV standard nutrition solutions and a range of IV amino acid and electrolyte intakes. Data collection was prospective, and blood samples were taken as part of a randomized trial with standardized processes. Although causality cannot be inferred from these data, they provide useful information to help guide the composition of early neonatal IV nutrition. This is an ELBW cohort for whom the clinical team elected to insert a UAC, and a potential limitation is the extent to which findings in this cohort are generalizable. Other limitations are that we did not measure serum magnesium and thiamin, and the documentation of exact intakes of additional IV electrolytes was not part of the ProVIDe Trial protocol. Additionally, routine blood sampling was not consistent across sites.

Conclusions

Neonatal RS is common in this cohort of ELBW babies and is associated with substantially increased mortality. Severe hypophosphatemia is associated with substantially increased IVH. SGA babies are at greatest risk. Enhanced monitoring of phosphate and other electrolytes in the first week after birth may be advisable. The composition of IV nutrition solutions is related to RS rates, indicating that optimizing the phosphate and calcium content of these solutions may reduce neonatal RS, severe IVH, and mortality throughout the NICU course.

Acknowledgments

We thank all the babies and their families for being part of the ProVIDe study. The authors sincerely thank the ProVIDe

investigators and research nurses at each recruitment center for their support, recruitment, and oversight of data collection: Roland Broadbent and Frances McCaffrey, Dunedin Hospital, Dunedin; Adrienne Lynn, Carole Spencer, Nicola Ellis, and Trish Graham, Christchurch Women's Hospital, Christchurch; Michael Hewson, Harshad Patel, Mel Gibson, and Natalie Wilkes, Wellington Regional Hospital, Wellington; Arun Nair, Deborah Harris, Nicola Streifler, Stephanie Edwards, Rebecca Sisterson, Kimberly Akehurst, Waikato Hospital, Hamilton; Mike Meyer, Aiza de Monteverde, Audrey Yu, Cristina Tapnio, and Tanith Alexander, KidzFirst, Middlemore Hospital, Auckland; Barbara Cormack and Sabine Huth, Auckland City Hospital, New Zealand; Helen Liley and Suzanne Bates, Mater Health Services, Brisbane; Sue Jacobs, Brenda Argus, and Emily Twitchell, The Royal Women's Hospital, Melbourne, Australia. We thank all the newborn services staff at Auckland City Hospital, Waikato Hospital, Wellington Hospital, Christchurch Women's Hospital, Dunedin Hospital, Mater Health Services, and The Royal Women's Hospital; the ProVIDe Trial Steering Group: Frank Bloomfield (Chair), Caroline Crowther, Jane Harding, Yannan Jiang, Barbara Cormack; Data Monitoring Committee: Peter Davis (Chair), Greg Gamble, David Knight, and Maria Makrides; Safety Monitoring Committee: Carl Kuschel (Chair), Brian Darlow, and Chris McKinley; Trial Coordinators: Ellen Campbell, Kelly Fredell, and Isabelle Lee; and data management and web randomization provided by the Clinical Data Research Hub, Liggins Institute, University of Auckland.

Statement of Authorship

B. E. Cormack and F. H. Bloomfield equally contributed to the conception and design of the research; J. E. Harding, Y. Jiang, and C. A. Crowther contributed to the design of the research; B. E. Cormack, F. H. Bloomfield, J. E. Harding, and Y. Jiang contributed to the acquisition and analysis of the data; B. E. Cormack, F. H. Bloomfield, J. E. Harding, Y. Jiang, and C. A. Crowther contributed to the interpretation of the data; and B. E. Cormack and F. H. Bloomfield drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Kovacs CS. Maternal mineral and bone metabolism during pregnancy, lactation, and post-weaning recovery. *Physiol Rev*. 2016;96(2):449-547.
2. Cooke RW. Conventional birth weight standards obscure fetal growth restriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(3):F189-192.
3. Solomon SM, Kirby DF. The refeeding syndrome: a review. *J Parenter Enteral Nutr*. 1990;14(1):90-97.
4. Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants it is time to change the composition of the early parenteral nutrition. *PLoS One*. 2013;8(8):e72880.
5. Hakan N, Aydin M, Dilli D, Zenciroglu A, Okumus N. Transient hyperinsulinemia may be responsible from electrolyte abnormalities of refeeding syndrome seen in very low birth weight infants with intrauterine growth-restriction. *J Perinatol*. 2014;34(3):247.
6. Moltu SJ, Strommen K, Blakstad EW, et al. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia. a randomized, controlled trial. *Clin Nutr*. 2013;32(2):207-212.
7. Skipper A. Refeeding syndrome or refeeding hypophosphatemia. *Nutr Clin Pract*. 2012;27(1):34-40.
8. Christmann V, de Grauw AM, Visser R, Matthijsse RP, van Goudoever JB, van Heijst AF. Early postnatal calcium and phosphorus metabolism in preterm infants. *J Pediatr Gastroenterol Nutr*. 2014;58(4):398-403.
9. Ross JR, Finch C, Ebeling M, Taylor SN. Refeeding syndrome in very-low-birth-weight intrauterine growth-restricted neonates. *J Perinatol*. 2013;33(9):717-720.
10. Mizumoto H, Mikami M, Oda H, Hata D. Refeeding syndrome in a small-for-dates micro-preemie receiving early parenteral nutrition. *Pediatr Int*. 2012;54(5):715-717.
11. Igarashi A, Okuno T, Ohta G, Tokuriki S, Ohshima Y. Risk factors for the development of refeeding syndrome-like hypophosphatemia in very low birth weight infants. *Dis Markers*. 2017;2017:9748031.
12. Boubred F, Herlenius E, Bartocci M, Jonsson B, Vanpee M. Extremely preterm infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia. *Acta Paediatr*. 2015;104(11):1077-1083.
13. Pajak A, Krolak-Olejnik B, Szafranska A. Early hypophosphatemia in very low birth weight preterm infants. *Adv Clin Exp Med*. 2018;27(6):841-847.
14. Mulla S, Stirling S, Cowey S, et al. Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(5):F451-F455.
15. Sung SI, Chang YS, Choi JH, et al. Increased risk of refeeding syndrome-like hypophosphatemia with high initial amino acid intake in small-for-gestational-age, extremely-low-birthweight infants. *PLoS One*. 2019;14(8):e0221042.
16. Bustos Lozano G, Hidalgo Romero A, Melgar Bonis A, Ureta Velasco N, Orbea Gallardo C, Pallas Alonso C. [Early hypophosphataemia in at risk newborns. frequency and magnitude]. *An Pediatr (Barc)*. 2018;88(4):216-222.
17. Senterre T, Abu Zahirah I, Pieltain C, de Halleux V, Rigo J. Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 2015;61(4):491-498.
18. Morgan C, Green J. Hyperalimentation and electrolyte requirements in very preterm infants: a randomised controlled parenteral nutrition study. *Clin Nutr*. 2014;33(1):S7.
19. Uthaya S, Liu X, Babalis D, et al. Nutritional evaluation and optimisation in neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition. *Am J Clin Nutr*. 2016;103(6):1443-1452.
20. Ichikawa G, Watabe Y, Suzumura H, Sairenchi T, Muto T, Arisaka O. Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth. *J Pediatr Endocrinol Metab*. 2012;25(3-4):317-321.
21. Moe K, Beck-Nielsen SS, Lando A, Greisen G, Zachariassen G. Administering different levels of parenteral phosphate and amino acids didÂ not influence growth in extremely preterm infants. *Acta Paediatr*. 2015;104(9):894-899.

22. Brener Dik PH, Galletti MF, Fernandez Jonusas SA, Alonso G, Mariani GL, Fustinana CA. Early hypophosphatemia in preterm infants receiving aggressive parenteral nutrition. *J Perinatol*. 2015;35(9):712-715.
23. Al-Wassia H, Lyon AW, Rose SM, Sauve RS, Fenton TR. Hypophosphatemia is prevalent among preterm infants less than 1,500 grams. *Am J Perinatol*. 2019;36(13):1412-1419.
24. Yang SM, Noh OK, Lee J. Late and insufficient phosphorus supplementation is associated with early severe hypophosphatemia in extremely low birth weight infants with early amino acid administration. *Perinatology* 2018;29(1):13-29.
25. Tsang RC, Uauy R, Koletzko B, Zlotkin SH. Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines. 2nd ed. Cincinnati: Digital Education.; 2005.
26. Jochum F, Moltu SJ, Senterre T, Nomayo A, Goulet O, Iacobelli S. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: fluid and electrolytes. *Clin Nutr*. 2018;37(6):2344-2353.
27. Mihatsch W, Fewtrell M, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: calcium, phosphorus and magnesium. *Clin Nutr*. 2018;37(6):2360-2365.
28. Bloomfield FH, Crowther CA, Harding JE, Conlon CA, Jiang Y, Cormack BE. The ProVIDe study: the impact of protein intravenous nutrition on development in extremely low birthweight babies. *BMC Pediatr*. 2015;15(1):100.
29. Moltu SJ, Blakstad EW, Strommen K, et al. Enhanced feeding and diminished postnatal growth failure in very-low-birth-weight infants. *J Pediatr Gastroenterol Nutr*. 2014;58(3):344-351.
30. Cormack BE, Bloomfield FH. Increased protein intake decreases postnatal growth faltering in ELBW babies. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(5):F399-404.
31. Loui A, Buhrer C. Growth of very low birth weight infants after increased amino acid and protein administration. *J Perinat Med*. 2013;41(6):735-741.
32. Rigo J, Pieltain C, Viellevoye R, Bagnoli F. Calcium and phosphorus homeostasis: pathophysiology In: Buonocore G, Bracci R, Weindling M, eds. *Neonatology: A practical approach to neonatal diseases*. Rome Springer-Verlag Italia; 2012:333-353.
33. James MT, Zhang J, Lyon AW, Hemmelgarn BR. Derivation and internal validation of an equation for albumin-adjusted calcium. *BMC Clin Pathol*. 2008;8:1, 12.
34. Cormack BE, Embleton ND, van Goudoever JB, Hay WW, Jr., Bloomfield FH. Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. *Pediatr Res*. 2016;79(6):810-820.
35. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:1, 59.
36. Papageorghiou AT, Ohuma EO, Altman DG, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet*. 2014;384(9946):869-879.
37. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92(4):529-534.
38. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.
39. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. *Ann Surg*. 1978;187(1):1-7.
40. Bonsante F, Iacobelli S, Chantegret C, Martin D, Gouyon JB. The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant. *Eur J Clin Nutr*. 2011;65(10):1088-1093.
41. Fenton TR, Lyon AW, Rose MS. Cord blood calcium, phosphate, magnesium, and alkaline phosphatase gestational age-specific reference intervals for preterm infants. *BMC Pediatr*. 2011;11:1, 76.
42. Gaccioli F, Lager S. Placental nutrient transport and intrauterine growth restriction. *Front Physiol*. 2016;7:40.
43. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ*. 2008;336(7659):1495-1498.
44. Dreyfus L, Fischer Fumeaux CJ, Remontet L, et al. Low phosphatemia in extremely low birth weight neonates: A risk factor for hyperglycemia? *Clin Nutr*. 2016;35(5):1059-1065.
45. Jamin A, D'Inca R, Le Floc'h N, et al. Fatal effects of a neonatal high-protein diet in low-birth-weight piglets used as a model of intrauterine growth restriction. *Neonatology*. 2010;97(4):321-328.
46. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition*. 2001;17(7-8):632-637.
47. Hochart A, Nuytten A, Pierache A, et al. Hemostatic profile of infants with spontaneous prematurity: can we predict intraventricular hemorrhage development? *Ital J Pediatr*. 2019;45(1):113.
48. Craddock PR, Yawata Y, VanSanten L, Gilberstadt S, Silvis S, Jacob HS. Acquired phagocyte dysfunction. *N Engl J Med*. 1974;290(25):1403-1407.
49. Morris I, McCallion N, El-Khuffash A, Molloy EJ. Serum albumin and mortality in very low birth weight infants. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(4):F310-312.
50. Iacobelli S, Bonsante F, Lacoutiere C, et al. Hypoproteinemia on the first day of life and adverse outcome in very preterm infants admitted to the neonatal intensive care unit. *J Perinatol*. 2012;32(7):520-524.
51. Morgan C, McGowan P, Herwitker S, Hart AE, Turner MA. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. *Pediatrics*. 2014;133(1):e120-128.
52. van Goudoever JB, Carnielli V, Darmaun D, Sainz de Pipaon M, ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids. *Clin Nutr*. 2018;37(6):2315-2323.
53. Pieltain C, Rigo J. Early mineral metabolism in very-low-birth-weight infants. *J Pediatr Gastroenterol Nutr*. 2014;58(4):393.
54. Bronsky J, Campoy C, Braegger C, ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Vitamins. *Clin Nutr*. 2018;37(6):2366-2378.
55. Joosten K, Embleton N, Yan W, Senterre T. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Energy. *Clin Nutr*. 2018;37(6):2309-2314.