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Early Phosphate-to-Amino Acid Provision and Refeeding Syndrome in Extremely Low Birth Weight Infants: A Systematic Review

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Abstract

Early high-amino acid parenteral nutrition is standard care for extremely low birth weight (ELBW) infants, but it has been linked to a neonatal form of refeeding syndrome (RFS) characterized by hypophosphatemia, often with hypercalcemia. This review aimed to synthesize recent evidence on the relationship between early phosphate and amino acid provision and RFS, hypophosphatemia, and related clinical outcomes in ELBW and extremely preterm infants.

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. PubMed, Scopus, CINAHL, and Embase were searched for original peer-reviewed studies first published online from 1 January 2021 to 19 September 2026, a window chosen to reflect parenteral nutrition practice after the 2018 European guidance on early phosphate provision. Eligible studies enrolled infants with a birth weight below 1000 g or a gestational age below 29 weeks, quantified early amino acid and/or phosphate provision, and reported RFS or hypophosphatemia. Risk of bias was assessed with the revised Cochrane risk-of-bias tool (RoB 2) and the Newcastle-Ottawa Scale, and findings were synthesized narratively.

Of 734 records, 425 were screened after duplicate removal, 72 full texts were assessed, and five studies comprising 782 unique infants (after accounting for overlapping trial participants) were included: one multicenter randomized controlled trial, a secondary two-year cohort analysis of that trial, two cohort studies, and one case-control study. Additional parenteral amino acids (1 g/day for five days) increased RFS from 15.7% to 24.4% (adjusted relative risk 1.64; 95% CI 1.09-2.47). In a before-after study in which phosphate, other electrolytes, and routine monitoring were introduced together from birth, RFS decreased from 11.9% to 2.9%, hypophosphatemia from 53.5% to 21.2%, and severe hypophosphatemia from 11.3% to 1.2%, despite a higher protein intake. First-week RFS and hypophosphatemia were associated with death or neurodisability at two years (adjusted odds ratios 1.96 and 1.74, respectively), and RFS severity was associated with postnatal growth failure and bronchopulmonary dysplasia. The randomized trial raised some concerns for bias, and three of four observational studies were at low risk of bias.

No included study evaluated a phosphate-to-amino acid ratio directly. The evidence is consistent with the hypothesis that RFS risk in ELBW infants reflects the balance between phosphate and amino acid supply rather than amino acid dose alone, and it supports existing guideline recommendations to provide phosphate from birth alongside amino acids, with first-week biochemical monitoring. Randomized trials of defined phosphate-to-amino acid ratios are needed.

Categories: Pediatrics
Keywords: amino acids, extremely low birth weight, hypophosphatemia, parenteral nutrition, phosphate, preterm infant, refeeding syndrome

Introduction And Background

Refeeding syndrome (RFS) was first characterized in malnourished adults as a potentially fatal shift of fluid and electrolytes that follows the reintroduction of nutrition, with hypophosphatemia as its biochemical hallmark [1]. The American Society for Parenteral and Enteral Nutrition (ASPEN) has since proposed consensus criteria that define RFS by a measurable decline in serum phosphorus, potassium, and/or magnesium after nutrition is started, graded by severity and by the presence of organ dysfunction [2]. These criteria were developed for adult and pediatric patients and have not been validated in preterm neonates. Neonates were long assumed to be protected from this disorder because nutrition is begun within hours of birth. This assumption was challenged in 2012, when RFS was described in a small-for-gestational-age

(SGA) micropreemie who developed bradycardia, respiratory failure, and hemolysis during early parenteral nutrition, and when severe first-week hypophosphatemia was reported in SGA extremely low birth weight (ELBW) infants [3,4].

Neonatal RFS differs from the classic adult syndrome in three respects. It does not follow prolonged starvation; instead, birth abruptly interrupts active placental transfer of amino acids, phosphate, and calcium during the period of most rapid fetal tissue and bone accretion, and anabolic parenteral nutrition begins within hours. Growth-restricted infants may additionally be born with depleted phosphate stores. Finally, hypophosphatemia in preterm infants is frequently accompanied by hypercalcemia, which is not a feature of adult RFS, so neonatal studies have often used composite or phosphate-based definitions rather than adult criteria [5,6]. ELBW infants, born weighing less than 1000 g, are particularly vulnerable to this sequence.

The proposed pathophysiology of neonatal RFS links amino acid supply directly to phosphate demand. Parenteral amino acids stimulate insulin secretion and protein synthesis, and each increment of lean tissue accretion requires intracellular phosphate and potassium. When the infusate supplies amino acids without proportionate phosphate, extracellular phosphate falls, phosphate is diverted away from bone, and calcium that can no longer be deposited accumulates in the serum. This model is supported mainly by observational biochemical data rather than direct measurement of mineral flux. A randomized trial of enhanced early nutrition in very low birth weight infants reported more electrolyte disturbances (hypophosphatemia, hypokalemia, and hypercalcemia), together with more septicemia, in the enhanced-nutrition arm [7]. Observational data in preterm infants further showed that initial amino acid intake was inversely associated with serum phosphate and positively associated with serum calcium, prompting a call to change the composition of early parenteral nutrition [8]. These disturbances are clinically important because phosphate is essential for adenosine triphosphate generation, tissue oxygen delivery, respiratory muscle function, and leukocyte activity.

The 2018 ESPGHAN/ESPEN/ESPR/CSPEN guidelines responded to these signals by recommending phosphate provision from the first days of parenteral nutrition in preterm infants and a calcium-to-phosphorus molar ratio below 1 during early parenteral nutrition [9]. Nevertheless, a review of RFS in the neonatal intensive care unit found wide variation in definitions, phosphate dosing, and monitoring practices [5]. It therefore remains uncertain whether RFS in ELBW infants is driven by amino acid dose itself or by a mismatch between amino acid and phosphate supply, and whether correcting this mismatch improves clinical outcomes. This systematic review aimed to synthesize recent original evidence on early phosphate and amino acid provision, considered jointly as a phosphate-to-amino acid balance, and its association with RFS, hypophosphatemia, and related clinical outcomes in ELBW and extremely preterm infants. Because no established measure of this balance exists, the two exposures were examined together rather than as a reported ratio.

Review

Materials and methods

Protocol and Reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. The protocol was not prospectively registered. Ethical approval was not required because only published data were analyzed.

Eligibility Criteria

Eligibility criteria were defined a priori using the population, intervention/exposure, comparator, outcomes, and study (PICOS) design framework (Table *1*). Only peer-reviewed original research articles were eligible. Studies of very low birth weight or very preterm populations were eligible only if they reported data separately for infants weighing less than 1000 g or born before 29 weeks of gestation. Electrolyte disturbances were defined as hypophosphatemia, hypokalemia, or hypomagnesemia, with hypercalcemia recorded where reported.

Domain	Inclusion criteria	Exclusion criteria
Population	Infants with birth weight <1000 g or gestational age <29 weeks receiving parenteral nutrition in the first week	Term or late-preterm infants; VLBW or very preterm cohorts without separate ELBW data
Intervention/exposure	Early (first-week) parenteral amino acid and/or phosphate provision: dose, protocol, randomized allocation, or measured intake	Mineral supplementation started after week 1; enteral-only regimens
Comparator	Lower vs higher amino acid intake; earlier/higher vs later/lower phosphate; infants with vs without RFS or hypophosphatemia	None
Outcomes	Primary: RFS or early hypophosphatemia. Secondary: electrolyte disturbances (low phosphate, potassium, or magnesium), sepsis, BPD, growth, mortality, neurodevelopment	Bone mineralization outcomes alone
Study design	RCTs and their secondary analyses; cohort, before-after, and case-control studies; peer-reviewed full texts first published online 1 January 2021 to 19 September 2026	Reviews, meta-analyses, case reports, conference abstracts, editorials, letters, protocols, preprints

TABLE 1: Eligibility criteria according to the PICOS framework

BPD: bronchopulmonary dysplasia; ELBW: extremely low birth weight; RCT: randomized controlled trial; RFS: refeeding syndrome; VLBW: very low birth weight; PICOS: population, intervention/exposure, comparator, outcomes, and study.

Information Sources and Search Strategy

PubMed, Scopus, CINAHL, and Embase were searched on 19 September 2026 for studies published from 1 January 2021 to 19 September 2026. Search terms combined three concepts, namely, the population (extremely low birth weight, very low birth weight, or preterm infants), the outcome (refeeding syndrome, hypophosphatemia, or phosphate/phosphorus), and the exposure (amino acids, protein, or parenteral nutrition), and were applied to titles and abstracts. Controlled vocabulary (MeSH, Emtree, and CINAHL Headings) was not used, so that an equivalent free-text strategy could be applied across all four databases and recently published records not yet indexed with controlled terms would be captured. Because this may reduce sensitivity, the reference lists of included studies were screened manually. The databases, limits, and numbers of records are summarized in Table *2*, and the complete search string for each database is presented line by line in the Appendix.

Database (platform)	Fields and limits	Records retrieved (n)
PubMed (MEDLINE)	Title/abstract [tiab]; publication date 2021/01/01 to 2026/09/19	314
Scopus (Elsevier)	TITLE-ABS; publication years 2021 to 2026	148
CINAHL (EBSCOhost)	TI/AB; published 20210101 to 20260919	138
Embase (Embase.com)	ti,ab; publication years 2021 to 2026	134
Total		734

TABLE 2: Databases searched, limits applied, and records retrieved

All databases were searched on 19 September 2026. Duplicate records (n = 309) were removed using EndNote (Clarivate, Philadelphia, PA, USA). Full search strings are given line by line in the Appendix.

The publication window was restricted to studies first published online from 1 January 2021 for two reasons. First, the 2018 ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommended phosphate provision from the start of parenteral nutrition [9], and studies published from 2021 onward were expected to reflect practice after a period of guideline implementation, which is the practice to which this review is intended to apply. Second, the earlier neonatal literature had been summarized in a 2021 review [5]. Eligibility was based on the date of first online publication rather than issue year. Consequently, earlier studies that would otherwise have been eligible [4,11-13], including the ProVIDe cohort analysis by Cormack et al., which was first published online in 2020 [14], were not included in the synthesis; they are considered in the Discussion, and the impact of

their exclusion is addressed under Limitations.

Study Selection

Records were imported into EndNote software (Clarivate, Philadelphia, PA, USA), and duplicates were removed. Two reviewers independently screened titles and abstracts and then assessed the full texts of potentially relevant reports against the eligibility criteria. Disagreements were resolved by discussion or, if necessary, by a third reviewer.

Data Extraction

Two reviewers independently extracted data using a piloted form, including first author, year, country, study design, population, sample size, amino acid and phosphate provision, comparator, definitions of RFS and hypophosphatemia, incidence of biochemical disturbances, clinical outcomes, and effect estimates with 95% confidence intervals. Adjusted estimates were preferred when available. Reports drawing on the same trial were identified by comparing trial name, sites, recruitment period, and authorship, and their participants were counted only once when the number of unique infants was calculated.

Risk-of-Bias Assessment

The randomized controlled trial was assessed with the revised Cochrane risk-of-bias tool (RoB 2) for the RFS outcome across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [15]. Judgments were visualized with the robvis tool [16]. Observational studies were assessed with the Newcastle-Ottawa Scale (NOS), which awards up to four points for selection, two for comparability, and three for outcome (cohort studies) or exposure (case-control studies) [17]. Total scores of 7-9, 4-6, and 0-3 were considered to indicate low, moderate, and high risk of bias, respectively. Because these cut-offs are a widely used convention rather than validated thresholds and a total score can mask domain-specific weaknesses [18], domain scores and the main study-specific limitation are reported alongside each total. Assessments were performed independently by two reviewers.

Data Synthesis

Phosphate-to-amino acid balance was not required to be reported as a ratio. Instead, each study was classified by how the balance changed: amino acid supply increased without a change in phosphate; phosphate supply increased relative to amino acid supply; or neither nutrient was manipulated, with RFS or hypophosphatemia examined as an exposure for later outcomes.

Meta-analysis was considered but not performed because no outcome was reported by two or more independent studies with a comparable exposure. The two studies that reported RFS as an outcome of nutrient provision examined opposite manipulations (additional amino acids in a randomized trial versus a multi-component phosphate protocol in a before-after study), reported different effect measures (adjusted relative risk versus adjusted odds ratio), and shared trial participants. The remaining studies used RFS as an exposure, applied different definitions, or examined different outcomes. Results were therefore synthesized narratively and grouped by exposure and by outcome. Effect estimates are presented as reported by the original authors, without pooling; relative risks and odds ratios were not combined or compared directly.

Results

Study Selection

The database search identified 734 records (PubMed, n = 314; Scopus, n = 148; CINAHL, n = 138; Embase, n = 134). After 309 duplicates were removed, 425 titles and abstracts were screened, of which 353 were excluded. All 72 reports sought for retrieval were obtained and assessed in full text. Of these, 67 were excluded because the population was not ELBW or born before 29 weeks or did not report data separately for this subgroup (n = 34), or because they were reviews or letters (n = 33). A recent descriptive study by Fialkowski et al. [19], first published online in July 2026, enrolled very low birth weight infants (<1500 g; mean gestational age 29.1 weeks) without reporting RFS or nutrient exposure separately for infants below 1000 g or 29 weeks, and was therefore excluded on population criteria. Five studies met all eligibility criteria and were included in the review (Figure *1*) [20-24].

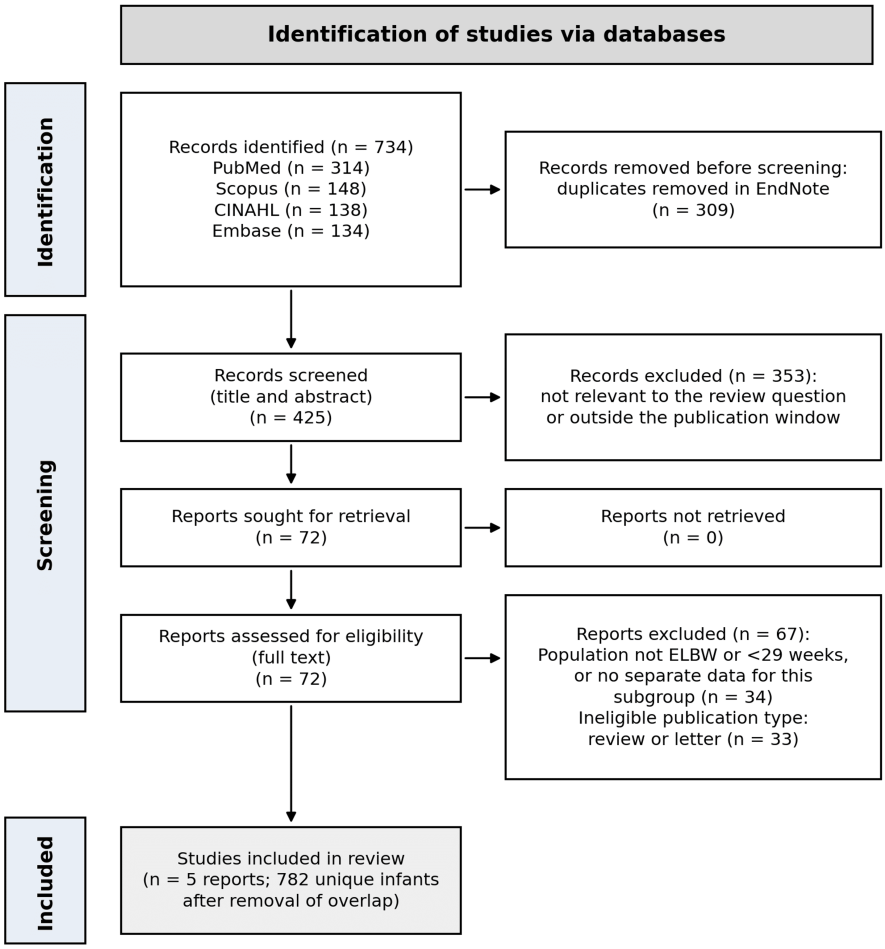


FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion

ELBW: extremely low birth weight; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Characteristics of Included Studies

The included studies comprised one multicenter, double-blind, placebo-controlled randomized controlled trial (ProVIDe) [20], a secondary two-year cohort analysis of the same trial [22], a retrospective before-after cohort study [23], a retrospective cohort study [24], and a retrospective matched case-control study [21]. The ProVIDe trial was conducted in New Zealand and Australia [20], the ProVIDe cohort analysis and the before-after study in New Zealand [22,23], the case-control study in Australia [21], and the remaining cohort in the United States [24]. Sample sizes ranged from 122 to 434 infants. All studies enrolled infants with a birth weight below 1000 g, except Fisher and Staub, who enrolled infants born before 29 weeks of gestation with average birth weights of 767 g in cases and 901 g in controls [21]. The characteristics of the included studies are summarized in Table *3*.

Study	Country	Design	Population (n)	Exposure	RFS/HP definition
Bloomfield et al., 2022 [20]	New Zealand, Australia	Multicenter double-blind RCT (ProVIDe)	BW <1000 g (434)	IV amino acids +1 g/day, days 1–5	Composite*
Fisher and Staub, 2024 [21]	Australia	Matched case-control	GA <29 weeks (141; 48/93)	Week-1 IV protein intake; hypophosphatemia	HP, study-specific threshold
Ford et al., 2025 [22]	New Zealand	Secondary cohort analysis of RCT	BW <1000 g (352)	Week-1 RFS and hypophosphatemia	Composite*
Wright et al., 2025 [23]	New Zealand	Retrospective before-after cohort	BW <1000 g (157; 72/85)	IV phosphate from birth (≤1.1 mmol/kg/day on day 1; ≤1.7 from day 3) plus monitoring	Composite*
Joung et al., 2026 [24]	United States	Retrospective cohort	BW <1000 g (122)	Early PN; SGA status; RFS severity	Graded RFS severity

TABLE 3: Characteristics of included studies

*Serum phosphate <1.4 mmol/L with serum calcium >2.8 mmol/L; severe hypophosphatemia, phosphate <0.9 mmol/L. BW: birth weight; GA: gestational age; HP: hypophosphatemia; IV: intravenous; PN: parenteral nutrition; RCT: randomized controlled trial; RFS: refeeding syndrome; SGA: small for gestational age.

Participants overlapped across three reports. The cohort (n = 352) of Ford et al. consisted entirely of ProVIDe participants [22], and the comparator cohort of Wright et al. (n = 72) was drawn from the ProVIDe placebo arm [23]. The number of unique infants was therefore calculated as the 434 randomized ProVIDe infants plus the non-overlapping cohorts of Wright et al. (n = 85), Fisher and Staub (n = 141), and Joung et al. (n = 122), giving 782 infants. Estimates from the three ProVIDe-derived reports are not statistically independent and were interpreted accordingly.

Amino Acid and Phosphate Exposures

None of the included studies expressed exposure as a phosphate-to-amino acid ratio. Two studies directly manipulated nutrient supply, in opposite directions. The ProVIDe trial randomized infants to an additional 1 g/day of parenteral amino acids for the first five days without a matched increase in phosphate, shifting the balance toward amino acids [20]. Wright et al. evaluated a protocol that replaced a phosphate-free starter solution with a concentrated solution containing phosphate, calcium, sodium, and potassium from birth, providing up to 1.1 mmol/kg/day of phosphate on day 1 and up to 1.7 mmol/kg/day from day 3, together with routine biochemical monitoring [23]. The early-phosphate cohort received an initial maximum protein intake approximately 25% higher than the comparator cohort, so phosphate supply increased relative to amino acid supply [23]. The remaining studies examined first-week intravenous protein intake [21] or the consequences of RFS arising under contemporary early parenteral nutrition [22,24], without manipulating either nutrient.

Definitions were harmonized only within the ProVIDe network: the three reports from this network used the same composite definition of RFS (Table 3) [20,22,23], whereas Fisher and Staub examined hypophosphatemia alone [21] and Joung et al. graded RFS severity rather than applying a binary definition [24]. Incidence figures are therefore not directly comparable across these groups.

Refeeding Syndrome and Electrolyte Disturbances

RFS and its biochemical components were common across all cohorts (Table 4). In the ProVIDe trial, RFS occurred in 42 of 172 infants (24.4%) who received additional amino acids and in 26 of 166 infants (15.7%) who received placebo [20]. In the before-after study, RFS during days 1-5 decreased from 8 of 67 infants (11.9%) to 2 of 70 (2.9%), hypophosphatemia from 38 of 71 (53.5%) to 18 of 85 (21.2%), and severe hypophosphatemia from 8 of 71 (11.3%) to 1 of 85 (1.2%) after phosphate was introduced from birth, whereas the incidence of hypercalcemia was unchanged (14.7% vs. 12.9%) [23]. In the United States ELBW cohort, hypophosphatemia occurred in 38.5%, hypokalemia in 19.7%, hypomagnesemia in 4.1%, hypercalcemia in 18.0%, and hyperglycemia in 49.2% of infants, and phosphate, potassium, and magnesium concentrations were significantly lower in SGA than in non-SGA infants throughout the first week [24]. In the case-control study, hypophosphatemia was present in 26% of infants with late-onset infection and in 15% of matched controls (P = 0.18) [21].

Study	Comparison	Outcome	Event rate	Estimate (95% CI)
Bloomfield 2022 [20]	Extra amino acids vs placebo	RFS	24.4% vs 15.7%	aRR 1.64 (1.09–2.47)
		Moderate-severe neurodisability	16.5% vs 8.6%	aRR 1.95 (1.09–3.48)
Fisher 2024 [21]	Sepsis cases vs controls	Hypophosphatemia	26% vs 15%	P = 0.18
	Week-1 IV protein intake	Late-onset sepsis	2.1 vs 2.3 g/kg/day	OR 0.90 (0.76–1.00)
Ford 2025 [22]	RFS vs none	Death or neurodisability	NR	aOR 1.96 (1.09–3.53)
	HP vs none	Death or neurodisability	NR	aOR 1.74 (1.09–2.79)
	Severe HP vs none	Death	NR	aOR 2.67 (1.41–5.00)
Wright 2025 [23]	Early vs standard phosphate	RFS (days 1–5)	2.9% vs 11.9%	aOR 0.21 (0.03–0.90)
		Hypophosphatemia	21.2% vs 53.5%	aOR 0.15 (0.06–0.33)
		Severe HP	1.2% vs 11.3%	aOR 0.07 (0.01–0.42)
		Probable late-onset sepsis	28.0% vs 62.5%	aOR 0.22 (0.11–0.44)
Joung 2026 [24]	Whole cohort (n = 122)	HP; hypercalcemia	38.5%; 18.0%	NR
	RFS severity	Growth <10th percentile; BPD	NR	P = 0.0004; P = 0.005

TABLE 4: Principal biochemical and clinical outcomes of the included studies

aOR: adjusted odds ratio; aRR: adjusted relative risk; BPD: bronchopulmonary dysplasia; HP: hypophosphatemia; IV: intravenous; NR: not reported; OR: odds ratio; RFS: refeeding syndrome.

Clinical Outcomes

Additional parenteral amino acids did not increase survival free from neurodisability at two years (47.8% vs. 49.8%) but were associated with more moderate-to-severe neurodisability and more patent ductus arteriosus [20]. In the two-year ProVIDe cohort analysis, first-week RFS and hypophosphatemia were each associated with death or neurodisability, and severe hypophosphatemia was associated with both death and neurodisability [22]. These estimates were adjusted for sex and SGA status, but not for gestational age or illness severity. Early phosphate provision was associated with lower rates of probable early-onset and late-onset sepsis, although culture-proven late-onset sepsis and patent ductus arteriosus did not differ significantly [23]. Because the comparator was a non-contemporaneous trial cohort and several practices changed together, these associations may be confounded. The severity of RFS was associated with weight below the 10th percentile at discharge and with bronchopulmonary dysplasia, despite less early weight loss [24]. These associations were reported as P values without adjusted effect estimates. Hypophosphatemia was not significantly associated with late-onset sepsis in the case-control study, whereas a higher first-week intravenous protein intake showed a borderline protective association [21].

The adjusted effect estimates for nutrient provision and for the downstream associations of first-week biochemical disturbances are displayed in Figure *2*. Relative risks and odds ratios are distinguished by marker and are shown on a common axis for orientation only. The estimate for amino acid supplementation lay above unity, those for early phosphate provision lay consistently below unity, and all estimates linking RFS or hypophosphatemia with death or neurodisability lay above unity.

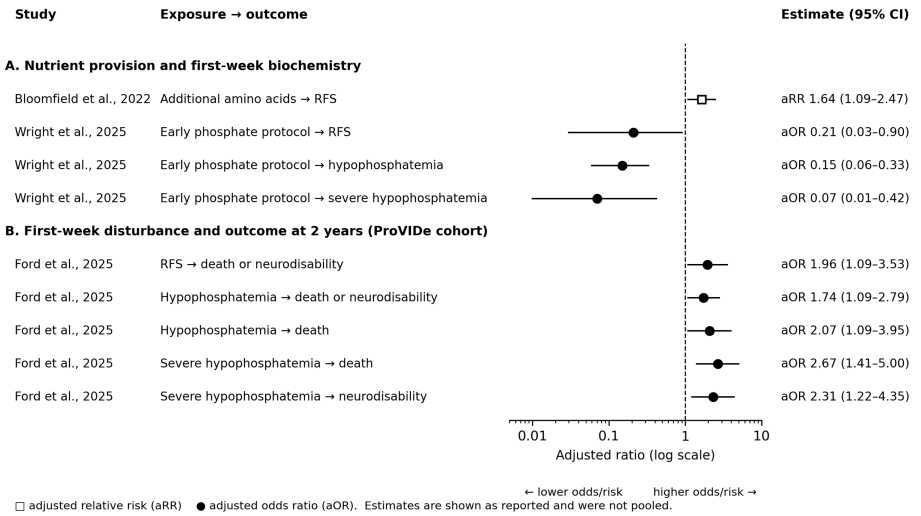


FIGURE 2: Adjusted effect estimates reported by the included studies

Squares, adjusted relative risk; circles, adjusted odds ratio. These measures are not interchangeable and were not pooled. Panel B estimates derive from a single cohort and are not independent. Data from Bloomfield et al. [20], Wright et al. [23], and Ford et al. [22]. aOR: adjusted odds ratio; aRR: adjusted relative risk; RFS: refeeding syndrome.

Risk of Bias

The ProVIDe trial was judged to be at low risk of bias for the randomization process, deviations from intended interventions, and measurement of the outcome, because allocation was randomized, the intervention and placebo were given double-blind, and RFS was based on objective laboratory values. Some concerns arose for missing outcome data, because biochemistry for the RFS outcome was available for 338 of 434 randomized infants, and for selection of the reported result, because RFS was analyzed post hoc. The overall judgment was therefore some concerns (Figure *3*) [20].

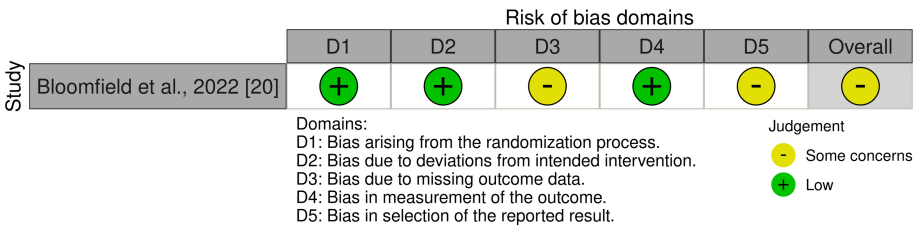


FIGURE 3: Risk-of-bias assessment of the randomized controlled trial using the RoB 2 tool

RoB 2: revised Cochrane risk-of-bias tool for randomized trials.

Among the four observational studies, three were at low risk of bias, with NOS scores of 7-8 [21,22,24], and one was at moderate risk of bias [23] (Table *5*). The before-after study by Wright et al. was downgraded because its comparator cohort was non-contemporaneous and drawn from a trial population, several nutrients and monitoring practices were changed simultaneously, and only infants who survived to day 5 with available biochemistry were analyzed [23].

Study	Selection (max 4)	Comparability (max 2)	Outcome/exposure (max 3)	Total; risk	Main limitation
Fisher and Staub, 2024 [21]	4	1	3	8/9; low	Partial control of confounding
Ford et al., 2025 [22]	4	2	2	8/9; low	Adjusted for sex and SGA only; incomplete 2-year follow-up
Wright et al., 2025 [23]	3	1	2	6/9; moderate	Historical trial comparator; co-interventions; day-5 survivors only
Joung et al., 2026 [24]	4	1	2	7/9; low	Limited adjustment; unadjusted outcome associations

TABLE 5: Risk-of-bias assessment of observational studies using the Newcastle-Ottawa Scale

Scores of 7–9 indicate low risk of bias, 4–6 moderate risk, and 0–3 high risk. SGA: small for gestational age.

Discussion

Principal Findings

This systematic review of five recent studies, including 782 unique ELBW or extremely preterm infants, identified a consistent pattern. RFS and hypophosphatemia were common in the first postnatal week; their risk increased when amino acid supply was raised without a matching increase in phosphate, and decreased when phosphate was supplied from birth, even though amino acid intake also rose. The only randomized evidence showed that an additional 1 g/day of parenteral amino acids increased RFS by approximately two-thirds in relative terms [20], whereas a protocol that introduced up to 1.1 mmol/kg/day of phosphate on day 1 was associated with an approximately fourfold lower incidence of RFS despite a higher initial protein intake [23]. Downstream, first-week RFS and hypophosphatemia were associated with death or neurodisability at two years, with postnatal growth failure and bronchopulmonary dysplasia, and, in one cohort, with probable sepsis [22-24]. These data are consistent with the hypothesis that the balance between phosphate and amino acid provision, rather than amino acid dose alone, contributes to early RFS risk. However, no study evaluated this balance directly, and the certainty of the two components differs: the amino acid effect is supported by randomized data, whereas the phosphate effect rests mainly on one before-after study with co-interventions. The balance concept should therefore be regarded as a biologically plausible hypothesis rather than an established independent determinant.

Amino Acid Supply

The amino acid component is well supported by earlier studies that fell outside the review period. Sung et al. reported that a change from low to high initial amino acid intake (3 g/kg/day) in 142 ELBW infants increased RFS-like electrolyte disturbances, and that severe hypophosphatemia affected 27% of SGA infants compared with 2% of appropriately grown infants even before the protocol change [13]. In an earlier secondary analysis of the ProVIDe trial, RFS affected 20% of infants; intravenous amino acid intake in the first week correlated negatively with serum phosphate and positively with serum calcium [14]. These findings are consistent with the earlier randomized trial of enhanced feeding and with the inverse amino acid-phosphate relationship described by Bonsante et al. [7,8]. The ProVIDe trial adds a causal dimension that observational data could not provide: random allocation to more amino acids, with phosphate supply unchanged, produced more RFS [20].

Phosphate Supply and Calcium

Wright et al. showed that adding phosphate, calcium, sodium, and potassium to the starter solution from birth was followed by large reductions in RFS, hypophosphatemia, and severe hypophosphatemia, even though the same protocol increased protein, lipid, and fluid intakes [23]. Because phosphate, other electrolytes, and routine monitoring were introduced simultaneously and the comparator was a non-contemporaneous trial cohort, these reductions cannot be attributed to phosphate alone; secular changes in practice and the selection of trial participants as controls may also have contributed. Comparable signals were reported earlier in broader preterm populations [25-27]: an equimolar calcium-to-phosphate ratio lowered peak calcium and raised plasma phosphate with an amino acid-enriched formulation [26], and sodium glycerophosphate from the first day reduced hypophosphatemia in infants weighing 1250 g or less [27]. The closest available approximation to a joint analysis comes from the earlier ProVIDe cohort, in which the adjusted odds of RFS fell by 70% for each 1 mmol/kg/day of intravenous phosphate and rose by 80% for each 1 g/kg/day of intravenous protein [14]. The ratio concept is therefore biologically coherent and

empirically consistent, although it has not been tested by randomizing infants to different phosphate-to-amino acid ratios.

Hypercalcemia did not decline after the Auckland protocol change (14.7% vs. 12.9%), whereas hypophosphatemia fell substantially [23]. The proposed explanation, that calcium accumulates in serum when phosphate is insufficient for its deposition in bone, is inferred from biochemical associations [8,26] rather than from direct measurement of bone mineral accretion in this period. Because the protocol increased calcium together with phosphate, the net calcium-to-phosphate balance may not have changed sufficiently to influence calcium concentrations, and a composite definition that requires both abnormalities may understate the benefit of phosphate provision. This interpretation is consistent with the ESPGHAN recommendation of a calcium-to-phosphorus molar ratio below 1 [9]. Future studies should report calcium and phosphate intakes together.

Small-for-Gestational-Age Status

In the United States ELBW cohort, phosphate, potassium, and magnesium concentrations were significantly lower in SGA than in non-SGA infants throughout the first week [24], consistent with SGA-specific risks reported earlier [4,11,13]. Growth-restricted infants enter postnatal life with depleted phosphate stores, so a given amino acid dose may generate a larger anabolic demand relative to available phosphate. In post hoc subgroup analyses of the ProVIDe trial, the numbers of infants with RFS were similar in the intervention and placebo groups within both SGA and non-SGA strata [20]. No included study reported a formal interaction test, and none was performed in this review; because the subgroups were small, effect modification by SGA status can neither be confirmed nor excluded. Closer biochemical monitoring of SGA ELBW infants is nevertheless prudent.

Clinical Outcomes and Confounding

In the ProVIDe cohort, first-week RFS nearly doubled the adjusted odds of death or neurodisability at two years, and severe hypophosphatemia was associated with more than twofold higher adjusted odds of both outcomes [22]. RFS severity was also associated with postnatal growth failure and bronchopulmonary dysplasia, although affected infants had less early weight loss [24]. Associations with sepsis were less consistent: probable sepsis declined after the Auckland protocol change, but culture-proven late-onset sepsis did not [23], and the case-control study found no significant association with late-onset infection [21]. Earlier cohorts linked severe hypophosphatemia with sepsis and greater respiratory and vasoactive support [28,29], and hypophosphatemia impairs phagocyte function [30]. However, lower gestational age, SGA status, and illness severity are associated both with RFS and with these outcomes. Ford et al. adjusted for sex and SGA status only [22], and Joung et al. reported unadjusted associations [24]; because this review extracted estimates as published, it could not adjust for these factors. Residual confounding is therefore likely, and these associations should not be interpreted as causal.

These findings do not imply that early amino acids should be withheld. In the ProVIDe trial, amino acid intake in the placebo group was already within recommended ranges, and additional amino acids conferred no benefit on survival free from neurodisability while increasing moderate-to-severe neurodisability, patent ductus arteriosus, and RFS [20]. Earlier data indicated that different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants [12], offering some reassurance that adjusting the balance need not compromise growth.

Definitions of Neonatal Refeeding Syndrome

The three ProVIDe-network reports used a composite of serum phosphate below 1.4 mmol/L and serum calcium above 2.8 mmol/L [20,22,23], whereas the ASPEN consensus defines RFS by declines in phosphorus, potassium, or magnesium without requiring hypercalcemia [2]. The ASPEN criteria were not designed around neonatal physiology, in which hypercalcemia is characteristic and nutrition starts without prior starvation, and they were therefore used in this review only as background; studies were included on the basis of their own neonatal definitions. Hypophosphatemia thresholds vary widely in the neonatal literature [5], and neonatal-specific risk criteria have been called for [6]. Grading RFS severity [24] may better capture dose-response relationships. A neonatal consensus definition with explicit thresholds and timing would enable meta-analysis.

Clinical Implications and Future Research

The recommendation to include phosphate in parenteral nutrition from the first day of life rests primarily on existing guidelines [9]; the included studies are consistent with it but provide low-certainty support because the main phosphate evidence is observational and confounded by co-interventions. Within that framework, any increase in protein intake should be accompanied by proportionate phosphate and potassium, and serum phosphate, calcium, and potassium should be monitored during the first week, particularly between days 3 and 7 [13,23], with particular vigilance in SGA infants. Organic phosphate salts can facilitate early calcium and phosphate delivery with a lower risk of precipitation [27], although their sodium load must be

considered [23]. No randomized trial has compared phosphate-to-amino acid or calcium-to-phosphate ratios in ELBW infants, and the roles of potassium, magnesium, and thiamine, outcomes beyond two years, and data from low- and middle-income settings remain largely unstudied. Adequately powered trials of balanced versus standard early parenteral nutrition, stratified by SGA status and using a common RFS definition, are needed.

Limitations

This review has several limitations. First, only five studies met the eligibility criteria, three of which drew on the ProVIDe population; the evidence base is therefore small and dominated by one research network. Second, the date restriction excluded several earlier studies, including a ProVIDe cohort analysis of 338 infants [14]; these were considered qualitatively, and because their findings were directionally consistent with the included evidence, their exclusion is unlikely to have changed the conclusions, although it reduced precision. Third, the search used free-text terms without controlled vocabulary, and the protocol was not registered, which may have reduced sensitivity and transparency. Fourth, only one study was randomized, and its RFS outcome was a post hoc analysis; the before-after design changed several nutrients and monitoring practices simultaneously, so the specific effect of phosphate cannot be isolated from co-interventions or secular trends. Fifth, definitions of RFS and hypophosphatemia, sampling times, and the reporting of mineral intakes differed across studies, which precluded meta-analysis, and the associations with clinical outcomes are subject to residual confounding by gestational age, SGA status, and illness severity. Finally, no included study expressed exposure as a phosphate-to-amino acid ratio; this balance was inferred from reported intakes and protocol changes.

Conclusions

In ELBW and extremely preterm infants, early RFS and hypophosphatemia are common and are associated with death, neurodisability, postnatal growth failure, and bronchopulmonary dysplasia, although residual confounding cannot be excluded. Randomized evidence shows that increasing parenteral amino acids without additional phosphate increases RFS, and observational evidence suggests that phosphate provision from the first day of life reduces RFS and hypophosphatemia even when protein intake increases. Although no study tested a phosphate-to-amino acid ratio directly, these findings support existing guideline recommendations to provide phosphate from birth alongside amino acids, to keep amino acid intake within current recommendations, and to monitor serum phosphate, calcium, and potassium during the first week, with particular attention to SGA infants. Randomized trials comparing defined phosphate-to-amino acid and calcium-to-phosphate ratios, using a standardized neonatal RFS definition and long-term outcomes, are needed.

Appendices

Database (platform); limits	Line	Search terms (title/abstract fields)
PubMed (MEDLINE); 2021/01/01 to 2026/09/19	#1	extremely[tiab] OR ELBW[tiab] OR "very low birth weight"[tiab] OR VLBW[tiab] OR micropremie*[tiab] OR preterm[tiab] OR premature[tiab]
	#2	refeeding[tiab] OR hypophosphatemia[tiab] OR hypophosphataemia[tiab] OR phosphate*[tiab] OR phosphorus[tiab]
	#3	amino[tiab] OR protein[tiab] OR "parenteral nutrition"[tiab] OR PN[tiab]
	#4	#1 AND #2 AND #3 (n = 314)
Scopus (Elsevier); 2021 to 2026	#1	TITLE-ABS(extremely OR elbw OR "very low birth weight" OR vlbw OR micropremie* OR preterm OR premature)
	#2	TITLE-ABS(refeeding OR hypophosphatemia OR hypophosphataemia OR phosphate* OR phosphorus)
	#3	TITLE-ABS(amino OR protein OR "parenteral nutrition" OR pn)
	#4	#1 AND #2 AND #3 AND PUBYEAR > 2020 (n = 148)
CINAHL (EBSCOhost); 20210101 to 20260919	#1	TI (extremely OR ELBW OR "very low birth weight" OR VLBW OR micropremie* OR preterm OR premature) OR AB (extremely OR ELBW OR "very low birth weight" OR VLBW OR micropremie* OR preterm OR premature)
	#2	TI (refeeding OR hypophosphatemia OR hypophosphataemia OR phosphate* OR phosphorus) OR AB (refeeding OR hypophosphatemia OR hypophosphataemia OR phosphate* OR phosphorus)
	#3	TI (amino OR protein OR "parenteral nutrition" OR PN) OR AB (amino OR protein OR "parenteral nutrition" OR PN)
	#4	#1 AND #2 AND #3 (n = 138)
Embase (Embase.com); 2021 to 2026	#1	extremely:ti,ab OR elbw:ti,ab OR 'very low birth weight':ti,ab OR vlbw:ti,ab OR micropremie*:ti,ab OR preterm:ti,ab OR premature:ti,ab
	#2	refeeding:ti,ab OR hypophosphatemia:ti,ab OR hypophosphataemia:ti,ab OR phosphate*:ti,ab OR phosphorus:ti,ab
	#3	amino:ti,ab OR protein:ti,ab OR 'parenteral nutrition':ti,ab OR pn:ti,ab
	#4	#1 AND #2 AND #3 AND (2021-2026)/py (n = 134)

TABLE 6: Full search strategy for each database

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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