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Early versus Late Parenteral Nutrition in Critically Ill Term Neonates: a Post-hoc Subgroup analysis of the PEPaNIC multicentre randomised controlled trial

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Abstract

Background Recent RCTs showed that withholding parenteral nutrition for one week of critical illness (Late-PN) was superior to early (<24-48h) initiation in children and adults. Neonates are considered more susceptible to macronutrient deficits. We investigated the impact of withholding PN for one week in critically ill term neonates.

Methods This pre-planned secondary analysis of the PEPaNIC-study investigated 209 neonates (studied in overlapping age-groups <4wk, <1wk, and <1day) randomised to Early-PN or Late-PN. Primary endpoints were new infections and time-to-live PICU discharge. Secondary efficacy endpoint was time-to-live weaning from mechanical ventilation. Safety outcomes were 90-day mortality and hypoglycaemic incidents during the intervention. Independent associations between doses of individual macronutrients and efficacy endpoints were investigated with multivariable Cox proportional hazard analyses.

Findings Among <4wk-neonates, Late-PN increased the likelihood of earlier live discharge from PICU (adjusted-HR 1.61 (1.19-2.20); $p=0.0021$) and earlier live weaning from mechanical ventilation (adjusted-HR 1.62 (1.19-2.21); $p=0.0020$), but did not significantly affect risk of infection. Among <1wk-neonates, Late-PN decreased risk of infections, and increased likelihood of earlier live discharge from PICU and earlier live weaning from mechanical ventilation. Benefits were also observed among <1day-neonates. Among <4wk-neonates (adjusted-OR 3.05 (1.27-7.35); $p=0.013$) and <1wk-neonates, Late-PN increased risk of hypoglycaemia. No effect on mortality was observed in any age-group. Increasing doses of amino acids, not glucose or lipids, decreased the likelihood of earlier live discharge from PICU and earlier live weaning from mechanical ventilation.

Interpretation In critically ill term neonates, withholding PN for one week was clinically superior to Early-PN regarding short-term outcome. However, withholding PN for one week increased the risk of developing hypoglycaemia, necessitating long-term follow-up of the children before Late-PN can be uniformly applied in this vulnerable patient group.

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Introduction

Recent multicentre randomised controlled trials showed that withholding parenteral nutrition (PN) to supplement insufficient enteral nutrition (EN) in the first week in the intensive care unit (ICU) is superior to initiating PN early (<24-48h) from a clinical and health-economic perspective, both in adults and in children.¹⁻⁴ Pre-planned secondary analyses suggested that the early administration of amino acids rather than of glucose or lipids was associated with the harm caused by early supplementation of PN.^{5,6} In these trials, there appeared to be an age-dependent effect, with the largest benefit of withholding PN observed in children and term neonates.^{1,3} However, withholding supplemental PN in neonates for a week, especially amino acids, contradicts with current advice.⁷ Neonates are susceptible to accumulate macronutrient deficits because of limited glycogen and fat stores combined with increased energy and protein requirements to sustain growth. Therefore, recommendations for macronutrient intake are higher for neonates than for older children and adults and early supplementation with PN is often more aggressively promoted.⁷ Concerns raised by experts regarding withholding PN in neonates primarily focussed on the risk of developing hypoglycaemia and amino acid deficits.⁸⁻¹⁰

In this secondary analysis of the PEPaNIC study, we investigated the efficacy and safety of withholding supplemental PN for one week in all neonates enrolled in the PEPaNIC trial. We analysed the impact for patients younger than four weeks (<4wk), younger than one week (<1wk) and younger than one day (<1day). Considering the major concerns raised by experts in the field, we further investigated the impact in neonates who did not tolerate any enteral nutrition during the first week in the paediatric ICU (PICU). Finally, we investigated whether early amino acid administration may be associated with harm in neonates as has been observed in children.

Methods

Patients and randomisation

This pre-planned secondary analysis included critically ill term-newborns (gestational age ≥ 37 weeks) to children aged 28 days from three PICUs in Belgium, The Netherlands and Canada, who participated in the PEPaNIC trial (Supplementary_appendix, figure_S1).³ The study protocol has been reported in detail elsewhere.^{3,11} Briefly, 1440 critically ill children (term-newborn to 17-years) with a medium to high risk of malnutrition were randomly assigned to withholding supplemental PN in the first week in

PICU (Late-PN) or initiating PN within 24 hours (Early-PN). In both groups, EN was initiated as soon as possible and increased according to local protocols. In patients randomised to Early-PN, PN was initiated within 24 hours after PICU admission to supplement EN if this provided less than 80% of target to reach the local age- and weight-specific caloric targets. PN was provided in a dose and composition that varied according to local guidelines and was not provided as an all-in-one product. In patients assigned to Late-PN, PN was withheld during the first week in PICU. To match the fluid administration of the Early-PN group, taking into account the volume of EN delivered, a mixture of dextrose 5% and saline was provided. To prevent refeeding syndrome, patients from both groups received intravenous micronutrients (trace elements, minerals, and vitamins) early in similar amounts, until EN reached 80% of caloric targets. For patients from both groups who were still in the PICU after a week and who were not yet receiving 80% of the caloric target enterally, PN was administered to reach the targets. If a central venous line was not/no longer in place for clinical purposes, any required PN was delivered via a peripheral line.

Blood glucose control with insulin for neonates differed according to local protocols. In Leuven, insulin infusion was started in all neonates to target blood glucose concentrations of 2.7-4.4 mmol/L. In Rotterdam, all neonates received insulin infusion to target blood glucose concentrations of 4.0-8.0 mmol/L. In Edmonton, patients received insulin infusion when blood glucose levels exceeded 10.0 mmol/L. Blood glucose levels were checked hourly after every change in macronutrient intake or insulin administration until three consecutive blood glucose measurements were within the normal range.^{3,11}

This secondary analysis investigated the impact of withholding PN for one week in three overlapping age groups of critically ill term neonates (<4wk, <1wk, and <1day). Neonates with “no or minimal EN” were defined as those who stayed in PICU for at least seven days, and were unable to receive EN or had only received trophic feeding (<40 ml/day) during the first week, with a maximum of 80 ml/week.

Outcome assessors and investigators not directly involved in PICU were blinded to treatment allocation.

The institutional ethical review boards of the participating centres in Leuven (ML8052), Rotterdam (NL38772.000.12) and Edmonton (Pro00038098) approved the study, which was performed in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained from the parents or legal guardians.

110

111 *Outcome measurements*

112 Primary efficacy endpoints were incidence of PICU-acquired infections and duration of PICU
113 dependency (expressed as crude number of days and as likelihood of earlier live discharge from
114 PICU). Secondary efficacy outcomes were duration of mechanical ventilation (crude number of days
115 and likelihood of earlier live weaning), maximum plasma urea concentration, duration of hospital stay
116 (crude number of days and likelihood of earlier live discharge from hospital) and direct healthcare
117 costs.⁴ The assessment of PICU-acquired infections was based on an *a priori* drafted protocol, which
118 makes use of prescribed antibiotics and clinical infection and inflammation data
119 (Supplementary_appendix, methods_S1).^{3,11} PICU dependency was defined as 'requiring or at risk for
120 requiring vital organ support'. Secondary safety endpoints were incidence of hypoglycaemia (plasma
121 glucose level <40 mg/dl (2.2 mmol/l)), time-to-recovery from hypoglycaemia, death during the first
122 week, PICU mortality, hospital mortality and 90-day mortality. Time-to-recovery from hypoglycaemia
123 could be analysed only in Belgian neonates (n=60), because the exact time of glucose measurements
124 had not been recorded by bedside glucometers used in other centres. Total direct healthcare costs
125 were explored from a hospital perspective, in Belgian and Dutch study populations, as these
126 healthcare systems are reasonably comparable.⁴

127

128 *Statistical analysis*

129 Data were analysed based on intention-to-treat, for the whole group of <4w-neonates and <1wk-
130 neonates. The main outcomes were also analysed separately in neonates younger than 24 hours
131 (<1day-neonates) and in neonates who had received no or minimal EN during the first week. The
132 original PEPaNIC-trial was a priori statistically powered to detect a difference in new infections as
133 observed in the adult EPaNIC-trial¹ and stratified for age according to age groups <1 year and ≥ 1year.
134 As the sample size of the present study depended on the number of neonates included in the
135 PEPaNIC-trial, we planned to perform a retrospective power analysis based on observed differences
136 for risk of new infection as primary endpoint, rather than performing an *a priori* sample size calculation.

137

138 Variables are reported as frequencies (%), mean (±SD) or median (IQR) as appropriate. The
139 multivariable analyses included logistic and linear regression for dichotomous and continuous

outcomes, respectively, and Cox proportional hazard analysis for time-to-event outcomes with data censored at 90 days. A competing risk analysis was used for duration outcomes with data of non-survivors censored at 91 days. Multivariable analyses were adjusted for predefined baseline risk factors being centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group (medical, surgical-cardiac or surgical-other) and weight-for-age Z-scores on admission, and in a sensitivity analysis also for age in the <4wk-neonates.^{12,13} Results are reported as odds ratio (OR), hazard ratio (HR) or Beta (β) and corresponding 95% confidence intervals (CI). No corrections were made for multiple testing.

To investigate which macronutrient may explain potential harm, we analysed the independent associations between average daily total doses of each macronutrient class up to each of the first seven days in PICU and clinical outcomes with use of multivariable Cox proportional hazard analysis censored at 90 days, adjusted for the predefined baseline risk factors listed above. This method has previously been described in detail.⁶ Briefly, as the PEPaNIC trial investigated the effect on outcome of Late-PN versus Early-PN over the first 7 days after admission to the PICU, with doses titrated differently for each macronutrient as crude grams per kilogram per day, we analysed independent associations between clinical outcomes and average daily total doses of each macronutrient up to each of the 7 days for all <4wk-neonates and <1wk-neonates who were still in the PICU on these respective days (Supplementary_appendix, methods_S2). Associations of each of these average doses with likelihood of acquiring a new infection (with left-truncation) and with likelihood of earlier live discharge from PICU and likelihood of earlier live weaning from mechanical ventilation were studied. No corrections for multiple comparisons were done in this explanatory analysis.

Two-sided p-values <0.05 were considered statistically significant. Analyses were performed with SPSS Statistics version 21 (IBM, Armonk, NY, USA) or JMP®Pro-13.1 (SAS Institute, Cary, NC).

Role of the funding source

The funding sources have had no role in the collection, analysis or interpretation of data, nor in the writing of the paper.

The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patients

This study included 209 term <4wk-neonates (of 917 screened for eligibility), of which 145 <1wk-neonates, of which 45 <1day-neonates (Supplementary_appendix, figure_S1). Macronutrient intake per day up to day 7 in the PICU, illustrating protocol adherence, is shown in the supplementary appendix (table_S1). In the <4wk-neonates and <1wk-neonates, the PIM2 score was significantly higher in the Early-PN groups than in the Late-PN groups, reflecting a higher risk of mortality (table_1). In the <1day-neonates, the Early-PN group had a significantly higher PELOD score than the Late-PN group (table_1). Furthermore, in <1day-neonates, the Early-PN group contained a higher proportion of patients with congenital diaphragmatic hernia and a lower proportion of patients with gastroschisis than the Late-PN group (Supplementary_appendix, table_S2). In the subgroup of neonates without EN, baseline characteristics were similar, but with similar disproportionate distribution of diagnoses (Supplementary_appendix, table_S3, table_S4).

Primary outcomes

In univariable analysis, Late-PN reduced the risk of acquiring a new infection with an absolute 14.4% in <4wk-neonates, 21.7% in <1wk-neonates and 45.3% in <1day-neonates (all $p \leq 0.02$, table_2-4). In multivariable analysis, the impact of Late-PN versus Early-PN on the odds of acquiring a new infection was only maintained when focusing on the youngest neonates, with an adjusted OR of 0.54(0.27-1.08); $p=0.082$ in <4wk-neonates, of 0.36(0.15-0.83); $p=0.017$ in <1wk-neonates and of 0.10(0.01-0.64); $p=0.015$ in <1day-neonates (tables_2-4). Statistical power (one-tailed test, alpha 0.05) retrospectively calculated for the observed differences in risk of new infection in univariable analysis was 79.6%, 92.3%, and 95.4% for <4wk-neonates, <1wk-neonates and <1-day-neonates, respectively. Starting from the observed risk of new infection in the Early-PN group, the minimally demonstrable versus observed absolute risk reduction (one-tailed) with Late-PN for new infections in the PICU, accepting an alpha of 0.05 and a power of 80%, would be -14.5% versus -14.4% in the <4wk-neonates, -18.1% versus -21.7% in the <1wk-neonates, and -36.5% versus -45.3% in the

<1day-neonates. Late-PN also shortened the duration of PICU dependency with a median 2 days in the <4wk-neonates and <1wk-neonates, with a higher likelihood of an earlier live discharge at any time (<4wk-neonates HR 1.61(1.19-2.20), p=0.0021; <1wk-neonates HR 1.68(1.16-2.46), p=0.0063)(table_2-3). Further adjustment for age in the <4wk-neonates did not impact the main outcomes (Supplementary_appendix, table_S5, table_S7).

Secondary outcomes

Mortality was similar for Early-PN and Late-PN in all age groups (table_2-4). The risk of experiencing an episode of hypoglycaemia was significantly higher with Late-PN as compared to Early-PN in <4wk-neonates and in <1wk-neonates (23.4% versus 14.3%; OR 3.05(1.27-7.35), p=0.013 and 23.6% versus 13.7%; OR 3.57(1.23-10.35), p=0.019)(table_2-3). Further adjustment for age in the <4wk-neonates did not impact the main safety outcomes (Supplementary_appendix, table_S5, table_S7).

In total, 83 hypoglycaemic episodes were further analysed (Supplementary_appendix, table_S6). None of these episodes was symptomatic, and 94% were found during insulin administration. Time-to-recovery from hypoglycaemia was equally fast in both treatment groups after a median of approximately 58 minutes, and in 84% of the cases at the first glucose check.

In all age groups, the need for mechanical ventilation was shorter with Late-PN, with a higher likelihood of being weaned alive from the ventilator at any time than with Early-PN (table_2-4). In <4wk-neonates and <1wk-neonates, plasma urea concentrations and direct healthcare costs were lower with Late-PN as compared with Early-PN (table_2-3).

Neonates without enteral intake

In total, 38 neonates (18%) who stayed in the PICU for at least 7 days had received no or minimal EN during the first week. This group consisted predominantly of neonates younger than 1 week (n=33, 87.0%) and most prominent diagnosis groups were abdominal surgery (n=20, 52.6%), and cardiac surgery (n=15, 39.5%). The proportion of patients who received no or minimal EN due to a contraindication (defined as "EN was prohibited during at least 3 days") was 61% in the Early-PN group versus 47% in the Late-PN group (p=0.39). The main outcomes among neonates without enteral intake differed from the entire group of neonates with a high incidence of new infections, longer stay in the PICU, longer dependency on mechanical ventilation and a higher 90-day mortality. Given the

severity of illness scores and risk of mortality on admission, these neonates should be considered as more severely ill (table_5, Supplementary_appendix table_S3). In this group of neonates withholding PN increased the likelihood of earlier live weaning from mechanical ventilation (HR 2.55(1.09-5.96), $p=0.031$) and increased the risk of hypoglycaemia (univariable_OR 5.43(1.24-23.86), $p=0.033$). The impact of Late-PN versus Early-PN on other main outcomes followed the same direction as in the total group of neonates, but the analysis was limited in power due to the small number of subjects (table_5).

Macronutrients

Associations of average total doses of the three individual macronutrients administered up to each of the first seven days in PICU with the efficacy endpoints time to first new infection acquired in the PICU, time to live discharge from the PICU and the time to live weaning from ventilatory support were assessed for <4wk-neonates and <1wk-neonates. The multivariable models showed no significant association of the average doses of any of the individual macronutrients with the likelihood of acquiring a new infection (figure_1A). In <4wk-neonates, higher average doses of amino acids were associated with a significantly lower likelihood of earlier live PICU discharge from day two to five (HR 0.56-0.71, $p\leq 0.04$). In <1wk-neonates, a similar association reached significance for doses up to day three, four, and seven (HR 0.42-0.70, $p\leq 0.04$)(figure_1B). Higher average doses of amino acids were also associated with a lower likelihood of earlier live weaning from mechanical ventilation from day three onwards in <4wk-neonates (HR 0.44-0.66, $p\leq 0.01$)(figure_1C). A similar association was observed in the <1wk-neonates, with significance reached for average doses administered from day four, six and seven (HR 0.32-0.58, $p\leq 0.03$)(figure_1C). No association was observed between the average doses of glucose and any of the efficacy endpoints. Higher average doses of lipids tended to be associated with a higher likelihood of an earlier live discharge reaching significance at day seven in both <4wk-neonates (HR 1.66 (1.11-2.52), $p=0.015$) and <1wk-neonates (HR 2.00 (1.15-3.45), $p=0.013$). Higher average doses of lipids were also associated with a higher likelihood of an earlier live weaning from mechanical ventilation in the <4wk-neonates (up to day 6 and 7; HR 1.46-1.73, $p<0.05$) and <1wk-neonates (up to day 7; HR 2.10(1.17-3.93), $p=0.016$)(figure_1B and figure_1C).

Discussion

Withholding supplemental PN for one week in critically ill *term* neonates was superior to Early-PN from a clinical and health-economic perspective. It resulted in fewer nosocomial infections in <1wk-neonates and in a shorter dependency on intensive care and mechanical ventilation for all age groups. The benefits of Late-PN were irrespective of centre, disease severity, risk of mortality, diagnosis and nutritional status upon admission. Among the <1day-neonates the benefits and large treatment effects observed should be interpreted with the small sample size and differences in diagnoses in consideration, although the direction of the effect was also consistently in favour of Late-PN. Taking statistical power into consideration, benefits of withholding PN during critical illness were also observed for term neonates, in agreement with findings for older children and adults.^{1,3} This observation contrasted with concerns that have been raised by experts.⁸⁻¹⁰ A pathophysiological explanation would help support these clinical findings and abate remaining concerns. Underlying mechanisms of the clinical benefits of withholding PN cannot be determined by our study and remain speculative. However, a role for better activation of autophagy, a process essential for innate immunity, cellular damage control and preservation of endogenous energy supply during critical illness, appeared plausible.^{14,15} It has been shown in mice fetuses that autophagy activation is low in utero, but rises shortly after birth to bridge the time from trans-placental nutrient supply to suckling.¹⁶ Whereas autophagy is activated during fasting, both during the physiologic transition from foetal to neonatal life as well as during critical illness-related anorexia, it is inhibited with Early-PN.^{14,15} While neonates can rely on a strong autophagy response, they can also fall back on another adaptation process that makes them resilient to fasting. During the third trimester, fetuses accumulate brown adipose tissue, which contains much more and larger mitochondria than white adipose tissue.¹⁷ Mitochondria are necessary for efficient production of ketone bodies as fuel for the brain during (physiological) lower levels of glucose after birth. Thus, efficient ketone body production and upregulated autophagy could provide strategies to manage a macronutrient deficit during acute critical illness in the neonatal period. Such resilience to a macronutrient deficit might also explain why the results in the group of critically ill term neonates incapable of receiving any EN during the first week appeared to point to the same direction of benefit from Late-PN. However, the small number of patients does not allow us to draw any firm conclusions. Also safety aspects need to be considered. Regarding the main safety concerns, we found that Late-PN did not significantly affect mortality. However, Late-PN increased the incidence of hypoglycaemia,

which necessitates caution when Late-PN is applied to this vulnerable patient group. Neonates receiving no or minimal EN had the highest risk for developing hypoglycaemia. Increased awareness in neonates under Late-PN, especially with no or minimal EN and neonates who are receiving insulin, remains warranted. Symptomatic, prolonged and recurrent hypoglycaemia may have serious short-term harmful effects in neonates.¹⁸ However, long-term consequences of brief episodes of asymptomatic hypoglycaemia reported in previous studies in preterm neonates and healthy newborns are contradictory and remain a subject of debate.¹⁹⁻²² Critically ill infants and children examined 4 years after a large RCT on glycaemic control did not show negative effects of hypoglycaemia on neurocognitive functioning.²³ Real-time continuous glucose monitoring was unavailable in all centres and unnoticed hypoglycaemic periods up to one hour thus cannot be excluded. Whether the hypoglycaemic incidents in the Late-PN group affect long-term neurocognitive outcome has to be established. A long-term follow-up of the patients is currently ongoing.

In line with a secondary analysis of all children included in the PEPaNIC trial⁶, we found in a similar explanatory analysis that higher amounts of amino acids, rather than glucose or lipids, were associated with prolonged need of mechanical ventilation and intensive care in critically ill term neonates as well, a population that required mechanical ventilation and intensive care for a longer time than the older patients in the PEPaNIC trial. Current advice for amino acid intake is based on studies investigating nitrogen balance as outcome measure.^{24,25} Based on (exclusively preterm) neonatal research, amino acid intake in neonates is advised to be started as soon as possible after birth to avoid the metabolic derangement caused by the interruption of continuous feeding that is present *in utero*.²⁶ Higher amounts of amino acids indeed result in positive nitrogen balances and anabolic state, though at the cost of higher urea concentrations and higher amino acid oxidation rates.²⁷⁻²⁹ Furthermore, no long-term beneficial effects of early high amino acid administration were found.³⁰ Thus, optimal amino acid administration in preterm neonates is under debate.³⁰ Although findings in preterm neonates cannot be extrapolated to term neonates, they raise questions about the presumed beneficial effect of early high amounts of amino acids in critically ill term neonates. In that regard, our present data call for caution, as higher amino acid doses appeared to be associated with delayed recovery and with higher plasma urea concentrations, urging the need for addressing causality in an adequately powered RCT.

One strength of our study is the randomised design in a large group of critically ill neonates. Another asset is the clinically relevant outcome measures, unique for nutritional studies in this population. Important limitations are the lack of power in some of the sub-analyses, and the observational design of the explanatory macronutrient dose analyses. Another major limitation was that the baseline characteristics differed between the randomization groups. However, we corrected for this during the multivariable analyses. A final limitation is the lack of data on (long-term) growth.

In conclusion, withholding PN, while administering micronutrients during the first week of critical illness, is superior to early initiation of PN from a short-term clinical and health-economic perspective, also in term neonates. However, withholding PN for one week increased the risk of developing hypoglycaemia, necessitating frequent monitoring of blood glucose levels. Long-term effects of hypoglycaemia need to be investigated before Late-PN can be uniformly applied in this vulnerable patient group.

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Authors' contributions: EvP, KJ, IV and SV designed the protocol for this secondary analysis of the PEPaNIC study. EvP, SV, IV and GVdB wrote the statistical analysis plan and performed the statistical analyses. EvP, IV, SV and KJ interpreted the results and wrote the manuscript. PW designed the database, supervised and monitored data entry, checked the database for accuracy and exported the data for statistical analysis. All authors approved the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests:

The authors declared no conflicts of interest

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Early versus Late Parenteral Nutrition in Critically Ill Term Neonates: a Post-hoc Subgroup analysis of the PEPaNIC multicentre randomised controlled trial

Table 1 Baseline characteristics

	4w-neonates			1w-neonates			1-day neonates		
	Early PN (n=98)	Late PN (n=111)	P-value*	Early PN (n=73)	Late PN (n=72)	P-value*	Early PN (n=28)	Late PN (n=17)	P-value*
Male – No. (%)	58 (59.2)	62 (55.9)	0.63	45 (61.6)	39 (54.2)	0.36	20 (71.4)	10 (58.8)	0.38
Age at randomisation - median days (IQR)	2 (0-8)	3 (1-13)	0.036	1 (0-3)	2 (1-3)	0.26	-	-	-
Gestational Age (weeks) - mean (SD)	38.4 (1.35)	38.6 (1.55)	0.23	38.3 (1.2)	38.7 (1.4)	0.10	38.3 (0.84)	37.6 (1.00)	0.022
Birth Weight (gram) - mean (SD)	3193 (538)	3238 (510)	0.54	3162 (496)	3193 (496)	0.70	3109 (504)	3065 (424)	0.83
Weight-for-age Z-score - mean (SD)^	-0.43 (1.18)	-0.46 (1.07)	0.83	-0.29 (1.06)	-0.35 (1.05)	0.75	-0.40 (1.03)	-0.17 (0.91)	0.32
PELOD score – median (IQR)	12.5 (12-32)	12 (12-31)	0.19	13 (12-32)	12 (12-22)	0.067	12 (12-21)	12 (12-12)	0.010
PIM2 score – mean (SD)	-1.71 (1.79)	-2.30 (1.77)	0.016	-1.63 (1.87)	-2.33 (1.77)	0.021	-1.74 (1.79)	-2.35 (1.89)	0.28
Risk of mortality (%) - median (IQR)#	9.9 (4.8-41.7)	6.7 (3.0-20.4)	0.011	9.9 (5.0-44.1)	5.6 (3.0-21.5)	0.021	9.0 (5.3-15.2)	5.6 (3.2-28.1)	0.18
Diagnostic group – no (%)			1.00			0.62			0.84
Medical	25 (25.5)	28 (25.2)		13 (17.8)	12 (16.7)		4 (14.3)	3 (17.6)	
Surgical cardiac	34 (34.7)	39 (35.1)		23 (31.5)	18 (25.0)		3 (10.7)	1 (5.9)	
Surgical other	39 (39.8)	44 (39.6)		37 (50.7)	42 (58.3)		21 (75.0)	13 (76.5)	
Mechanical ventilation on admission – no. (%)	95 (96.9)	102 (91.9)	0.14	70 (95.9)	65 (90.3)	0.21	28 (100)	15 (88.2)	0.14
Haemodynamic support on admission – no. (%)	52 (53.1)	54 (48.6)	0.58	40 (54.8)	32 (44.4)	0.25	15 (53.6)	6 (35.3)	0.56

*Proportions: Chi square test (Fisher's exact test if necessary), means: independent t-test, medians: Mann-Whitney U test; ^neonates <1 week: birthweight-for-gestational age Z-score ¹², neonates ≥1 week: weight-for-age Z-score ¹³; #based on PIM2 score =((exp (PIM2))/(1+exp (PIM2)))*100%
 PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, range 0-71, with higher scores indicating more severe illness, PIM2 = Paediatric Index of Mortality 2, higher score reflecting a higher risk of mortality.

Table 2 Outcomes of <4wk-neonates

	Early PN (n=98)	Late PN (n=111)	Univariable OR, HR or β	P-value [^]	OR, HR or β , adjusted for baseline risk factors*	P-value*
<i>Efficacy endpoints</i>						
PICU-acquired infections – No. (%)	30 (30.6)	18 (16.2)	0.44 (0.22-0.85)	0.020	0.54 (0.27-1.08)	0.082
Airway	9 (9.2)	6 (5.4)		0.42		
Bloodstream	8 (8.2)	2 (1.8)		0.048		
Urinary tract	3 (3.1)	1 (0.9)		0.34		
Central nerve system	1 (1.0)	0 (0.0)		0.47		
Soft Tissue	2 (2.0)	2 (1.8)		1.00		
Others	0 (0.0)	1 (0.9)		1.00		
Duration of PICU dependency — median days (IQR)	7 (3.75-15.75)	5 (3-9)	1.71 (1.27-2.30)	0.0066	1.61 (1.19-2.20)	0.0021
Duration of mechanical ventilatory support — median days (IQR)	5 (3-13)	3 (2-6)	1.69 (1.26-2.27)	0.0021	1.62 (1.19-2.21)	0.0020
Highest plasma level of urea – median mg/dl (IQR)	43 (32-56.75)	33 (20.25-43)	-15.7 (-22.3;-9.10)	<0.0001	-13.4 (-19.6;-7.1)	<0.0001
Duration of hospital stay — median days (IQR)	18 (9-32.3)	14 (9-29)	1.47 (1.09-1.99)	0.43	1.38 (1.02-1.88)	0.037
Direct healthcare costs (€) – mean (SD)~	62 260 (110 820)	36 380 (39 100)	-25 880 (-48 110;-3 640)	0.030	-22 971 (-45 603;-339)	0.047
<i>Safety endpoints</i>						
Death during first week – no. (%)	6 (6.1)	2 (1.8)	0.28 (0.06-1.43)	0.15	0.71 (0.09-5.61)	0.74
90-day mortality – no. (%)#	15 (15.3)	6 (5.4)	0.32 (0.12-0.85)	0.018	0.41 (0.13-1.30)	0.13
Hypoglycaemia (blood glucose <40 mg/dl (<2.2 mmol/l)) during first week – no. (%)	14 (14.3)	26 (23.4)	1.84 (0.90-3.76)	0.11	3.05 (1.27-7.35)	0.013

[^]Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test

*Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, OR and HR are shown for late PN versus early PN; ~Only of Dutch and Belgian patients (Early PN n=98, Late PN n=110); # all non-surviving patients died in PICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality. PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU=Paediatric Intensive Care Unit.

Table 3 Outcomes of <1wk-neonates

	Early PN (n=73)	Late PN (n=72)	Univariable OR, HR or β	P-value [^]	OR, HR or β , adjusted for baseline risk factors*	P-value*
<i>Efficacy endpoints</i>						
PICU-acquired infections – No. (%)	26 (35.6)	10 (13.9)	0.29 (0.13-0.66)	0.0036	0.36 (0.15-0.83)	0.017
Airway	8 (11.0)	5 (6.9)		0.56		
Bloodstream	7 (9.6)	1 (1.4)		0.063		
Urinary tract	2 (2.7)	0 (0.0)		0.50		
Central Nervous System	1 (1.4)	0 (0.0)		1.00		
Soft Tissue	2 (2.7)	1 (1.4)		1.00		
Others	0 (0.0)	1 (1.4)		0.50		
Duration of PICU dependency — median days (IQR)	7 (3.5-19)	5 (3-9)	1.87 (1.31-2.67)	0.016	1.69 (1.16-2.46)	0.0063
Duration of mechanical ventilatory support — median days (IQR)	4 (3-14)	3 (2-6)	1.78 (1.25-2.54)	0.015	1.61 (1.10-2.35)	0.014
Highest plasma level of urea – median mg/dl (IQR)	43 (32-59)	33 (21.5-44)	-18.6 (-26.9;-10.2)	<0.0001	-15.1 (-22.9;-7.3)	0.00020
Duration of hospital stay — median days (IQR)	21 (10-37)	18.5 (11-35.5)	1.45 (1.01-2.01)	0.99	1.29 (0.88-1.88)	0.19
Direct healthcare costs (€) – mean (SD)~	67 000 (111 720)	37 760 (30 430)	-29 250 (-56 210;-2 280)	0.034	-29 760 (-58 200;-1 320)	0.040
<i>Safety endpoints</i>						
Death during first week –no. (%)	6 (8.2)	1 (1.4)	0.16 (0.02-1.34)	0.12	0.47 (0.04-5.83)	0.56
90-day mortality – no. (%)#	12 (16.4)	3 (4.2)	0.22 (0.06-0.82)	0.026	0.31 (0.07-1.44)	0.13
Hypoglycaemia (blood glucose <40 mg/dl (<2.2 mmol/l)) during first week after randomisation – no. (%)	10 (13.7)	17 (23.6)	1.95 (0.82-4.61)	0.14	3.57 (1.23-10.45)	0.019

[^]Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test

*Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, OR and HR are shown for late PN versus early PN; # all non-surviving patients died in PICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality.

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU=Paediatric Intensive Care Unit.

Table 4 Main outcomes of 1day-neonates

	Early PN (N=28)	Late PN (N=17)	Univariable HR or OR	P-value[^]	Adjusted HR or OR[*]	P-value[*]
PICU-acquired infections – No. (%)	16 (57·1)	2 (11·8)	0·10 (0·02-0·52)	0·0041	0·10 (0·01-0·64)	0·015
Duration of PICU dependency - median days (IQR)	15 (7·5-35·75)	6 (4-14·5)	2·11 (1·09-4·09)	0·036	1·95 (0·93-4·12)	0·078
Duration of mechanical ventilatory support — median days (IQR)	12 (5·75-31)	4 (2-12·5)	2·24 (1·16-4·32)	0·0086	2·63 (1·23-5·63)	0·013
90-day mortality – no. (%)	4 (14·3)	1 (5·9)	0·38 (0·04-3·67)	0·64		
Hypoglycaemia (blood glucose <40 mg/dl (<2·2 mmol/l)) during first week after randomisation – no. (%)	2 (7·1)	2 (11·8)	1·73 (0·22-13·61)	0·63		

[^]Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test

^{*}Adjusted for centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, OR and HR are shown for late PN versus early PN

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU=Paediatric Intensive Care Unit.

Table 5 Main outcomes of neonates who received no or only minimal EN

	Early PN	Late PN	Univariable HR or OR	P-value[^]	Adjusted HR or OR[*]	P-value[*]
	N=23	N=15				
PICU-acquired infections – No. (%)	16 (69·6)	7 (46·7)	0·38 (0·10-1·47)	0·19	0·57 (0·10-3·41)	0·54
Duration of PICU dependency - median days (IQR)	19 (13-33)	17 (9-31)	1·58 (0·75-3·34)	0·46	1·83 (0·79-4·24)	0·16
Duration of mechanical ventilatory support — median days (IQR)	17(9-33)	11 (5-20)	1·83 (0·87-3·86)	0·068	2·55 (1·09-5·96)	0·031
90-day mortality – no. (%)	7 (30·4)	2 (13·3)	0·35 (0·06-1·99)	0·23		
Hypoglycaemia (blood glucose <40 mg/dl (<2·2 mmol/l)) during first week after randomisation – no. (%)	4 (17·4)	8 (53·3)	5·43 (1·24-23·86)	0·033		

[^]Proportions: Fisher's exact test , means: independent t-test, medians: Mann-Whitney U test

^{*}Adjusted for centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, OR and HR are shown for late PN versus early PN

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU=Paediatric Intensive Care Unit

Figure 1. Association of average total macronutrient doses up to each of the first seven days in PICU with clinical outcome

PICU=Paediatric Intensive Care Unit. For each of the first seven days in the PICU, associations of average daily doses of the individual macronutrients up to that day with likelihood of (A) acquiring a new infection in the PICU, (B) earlier live PICU discharge, and (C) earlier live weaning from mechanical ventilation are shown as hazard ratios and 95 % CIs per gram per kg added. These results were obtained after adjustment for centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group and weight-for-age Z-scores on admission. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio less than one. N represents the number of patients still in the PICU on the day of analysis.

Figure 1

Early versus Late Parenteral Nutrition in Critically Ill Term Neonates: a Post-hoc Subgroup analysis of the PEPaNIC multicentre randomised controlled trial

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Supplementary material

SUPPLEMENTARY APPENDIX METHODS

Methods S1. Protocol for scoring of infections

Methods S2. Stepwise transformation of the given doses of glucose, lipid, and amino acids and association with clinical outcome

SUPPLEMENTARY APPENDIX FIGURES

Supplementary Figure S1: Consort flow diagram

SUPPLEMENTARY APPENDIX TABLES

Supplementary Table S1:

S1a: Average macronutrient administration for up to each of the first seven days in PICU to neonates up to four weeks old

S1b: Average macronutrient administration for up to each of the first seven days in PICU to neonates up to one week old

S1c: Average macronutrient administration for up to each of the first seven days in PICU to neonates younger than one day

Supplementary Table S2: Diagnoses of <1day-neonates

Supplementary Table S3: Baseline characteristics of neonates needing intensive care for at least 7 days who did not receive EN in the first week in PICU

Supplementary Table S4: Admission diagnoses of neonates needing intensive care for at least 7 days who did not receive EN in the first week in PICU

Supplementary Table S5: Outcomes of <4wk-neonates, with further adjustment for age

Supplementary Table S6: Episodes of hypoglycaemia

Supplementary Table S7: Multivariable linear regression analysis determining significant and independent associations between baseline risk factors and outcomes

References for the supplementary appendix

Supplementary Methods S1. Protocol for scoring of infections

1. Data export All patients receiving antimicrobial agents were identified by the data manager, who provided an export of all patient numbers with all the information on antimicrobial agents given as well as the duration of such treatment.

2. Identification of patients with infections The infectious disease specialists, who were blinded for treatment allocation, selected all patients receiving antimicrobial agents for more than 48h, after excluding all patients who received prophylaxis. Each patient who fulfilled the criteria for infection, as well as the type of infection, was identified as such based on thorough review of the medical record. Patients for whom antimicrobials were initiated prior to PICU admission or within the first 48 hours of admission while the criteria for infection were fulfilled, were labelled as “having an infection upon admission”. When antimicrobial agents were initiated after randomization and beyond the first 48 hours in the PICU, and were given for more than 48 hours while the criteria for infection were fulfilled, the patient was labelled as “having a new infection”.¹

Supplementary Methods S2: Stepwise transformation of the given doses of glucose, lipid, and amino acids and association with clinical outcome

In a first step, doses of glucose, lipid, and amino acids as the crude grams per kilogram per day that were given on each of the first seven days in PICU were used to calculate average doses of glucose, lipid, and amino acids administered up to each of the first seven days in PICU for all patients who were still in PICU on these respective days.

In a second step, associations of these average doses up to each of the first seven days in PICU with the clinical endpoints (time to the first new infection acquired in the PICU, the time to live discharge from PICU accounting for mortality as a competing risk, and the time to live weaning from mechanical ventilatory support) were determined with Cox proportional hazard analyses, adjusting for centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group and weight-for-age Z-scores on admission.

This procedure was performed for total doses and repeated for enteral doses and parenteral doses of glucose, lipid, and amino acids.

Supplementary Figure S1: Consort flow diagram

DNR denotes do not resuscitate, and ICU Intensive Care Unit

Supplementary table S1A: Average macronutrient administration for up to each of the first seven days in PICU to neonates up to four weeks old

Route	Dose up to day	N	Glucose		Amino acids		Lipids	
			Early PN	Late PN	Early PN	Late PN	Early PN	Late PN
Total dose (g/kg)	1	209	4.64 (2.73-7.10)	1.71 (1.29-2.72)	1.14 (0.00-1.57)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	200	6.44 (4.63-8.87)	2.34 (1.94-3.86)	1.64 (0.98-2.04)	0.00 (0.00-0.18)	0.71 (0.09-1.20)	0.00 (0.00-0.31)
	3	178	7.14 (5.40-9.71)	2.88 (2.22-4.42)	1.77 (1.37-2.15)	0.04 (0.00-0.42)	1.34 (0.60-2.08)	0.12 (0.00-0.80)
	4	149	7.82 (5.50-10.71)	3.27 (2.42-4.84)	1.91 (1.63-2.15)	0.06 (0.00-0.50)	1.81 (1.19-2.59)	0.13 (0.00-1.29)
	5	121	8.16 (5.93-11.27)	3.78 (2.65-5.30)	1.97 (1.76-2.16)	0.10 (0.00-0.54)	2.31 (1.59-2.94)	0.26 (0.00-1.37)
	6	105	8.50 (6.11-11.33)	4.04 (3.03-6.30)	2.01 (1.80-2.21)	0.16 (0.02-0.77)	2.63 (1.90-3.11)	0.40 (0.05-1.78)
	7	87	8.56 (6.45-11.33)	4.37 (3.29-6.00)	1.99 (1.85-2.26)	0.24 (0.04-0.71)	2.84 (2.05-3.41)	0.71 (0.09-1.45)
Enteral dose (g/kg)	1	209	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	200	0.00 (0.00-0.00)	0.00 (0.00-0.44)	0.00 (0.00-0.00)	0.00 (0.00-0.07)	0.00 (0.00-0.00)	0.00 (0.00-0.22)
	3	178	0.00 (0.00-0.61)	0.17 (0.00-1.65)	0.00 (0.00-0.10)	0.03 (0.00-0.28)	0.00 (0.00-0.34)	0.08 (0.00-0.78)
	4	149	0.11 (0.00-1.60)	0.21 (0.00-2.41)	0.01 (0.00-0.30)	0.03 (0.00-0.38)	0.04 (0.00-0.71)	0.11 (0.00-1.28)
	5	121	0.30 (0.00-2.13)	0.48 (0.00-2.66)	0.05 (0.00-0.33)	0.09 (0.00-0.47)	0.15 (0.00-1.06)	0.23 (0.00-1.37)
	6	105	0.45 (0.00-2.07)	0.75 (0.10-3.57)	0.08 (0.00-0.41)	0.13 (0.02-0.61)	0.22 (0.00-1.02)	0.39 (0.05-1.78)
	7	87	0.37 (0.00-2.99)	1.28 (0.03-2.86)	0.06 (0.00-0.56)	0.23 (0.01-0.49)	0.21 (0.00-1.36)	0.71 (0.02-1.45)
Parenteral dose (g/kg)	1	209	4.58 (2.68-7.03)	1.70 (1.22-2.58)	1.11 (0.00-1.57)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	200	5.97 (4.08-8.45)	2.09 (1.63-2.83)	1.60 (0.87-2.02)	0.00 (0.00-0.00)	0.52 (0.00-0.94)	0.00 (0.00-0.00)
	3	178	6.22 (4.21-9.04)	2.14 (1.67-2.94)	1.65 (1.28-2.10)	0.00 (0.00-0.00)	0.97 (0.27-1.78)	0.00 (0.00-0.00)
	4	149	5.82 (3.99-10.08)	2.33 (1.74-3.14)	1.78 (1.25-2.05)	0.00 (0.00-0.00)	1.25 (0.49-2.13)	0.00 (0.00-0.00)
	5	121	6.09 (4.13-10.13)	2.36 (1.95-3.24)	1.83 (1.41-2.06)	0.00 (0.00-0.00)	1.64 (0.85-2.46)	0.00 (0.00-0.00)
	6	105	6.34 (3.95-10.44)	2.41 (1.92-3.43)	1.85 (1.42-2.06)	0.00 (0.00-0.00)	1.85 (0.91-2.53)	0.00 (0.00-0.00)
	7	87	6.52 (3.66-10.33)	2.45 (1.89-3.57)	1.88 (1.15-2.04)	0.00 (0.00-0.03)	1.91 (0.86-2.73)	0.00 (0.00-0.01)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses (except on day 2), of glucose, amino acids, and lipids were significantly different for patients in the early PN and late PN groups. N indicates the number of patients still in PICU on the day of analysis.

Supplementary table S1b: Average macronutrient administration for up to each of the first seven days in PICU to neonates up to one week old

Route	Dose up to day	N	Glucose		Amino acids		Lipids	
			Early PN	Late PN	Early PN	Late PN	Early PN	Late PN
Total dose (g/kg)	1	145	4.55 (2.72-6.88)	1.71 (1.17-2.41)	1.23 (0.00-1.60)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	136	5.98 (4.31-8.37)	2.27 (1.90-3.20)	1.76 (0.97-2.04)	0.00 (0.00-0.07)	0.67 (0.09-1.00)	0.00 (0.00-0.09)
	3	119	6.76 (4.89-9.14)	2.53 (2.12-3.61)	1.85 (1.36-2.13)	0.00 (0.00-0.09)	1.26 (0.60-2.01)	0.00 (0.00-0.15)
	4	104	6.80 (5.06-10.57)	2.98 (2.34-3.85)	1.92 (1.63-2.15)	0.00 (0.00-0.11)	1.71 (1.20-2.52)	0.00 (0.00-0.26)
	5	86	7.03 (5.57-10.24)	3.41 (2.56-4.13)	1.95 (1.76-2.15)	0.03 (0.00-0.15)	2.29 (1.65-2.87)	0.09 (0.00-0.40)
	6	74	7.44 (5.73-10.87)	3.77 (2.82-4.52)	1.98 (1.80-2.20)	0.05 (0.00-0.23)	2.66 (1.91-3.11)	0.16 (0.00-0.58)
	7	62	7.79 (6.30-10.88)	4.24 (2.82-4.90)	1.98 (1.86-2.21)	0.12 (0.03-0.40)	2.87 (2.08-3.35)	0.15 (0.04-0.89)
Enteral dose (g/kg)	1	145	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	136	0.00 (0.00-0.00)	0.00 (0.00-0.15)	0.00 (0.00-0.00)	0.00 (0.00-0.02)	0.00 (0.00-0.00)	0.00 (0.00-0.07)
	3	119	0.00 (0.00-0.23)	0.00 (0.00-0.25)	0.00 (0.00-0.04)	0.00 (0.00-0.04)	0.00 (0.00-0.11)	0.00 (0.00-0.13)
	4	104	0.00 (0.00-0.58)	0.00 (0.00-0.44)	0.00 (0.00-0.09)	0.00 (0.00-0.06)	0.00 (0.00-0.28)	0.00 (0.00-0.23)
	5	86	0.13 (0.00-0.86)	0.15 (0.00-0.71)	0.02 (0.00-0.14)	0.02 (0.00-0.11)	0.07 (0.00-0.49)	0.07 (0.00-0.40)
	6	74	0.21 (0.00-1.49)	0.28 (0.00-1.08)	0.04 (0.00-0.26)	0.04 (0.00-0.20)	0.12 (0.00-0.73)	0.16 (0.00-0.58)
	7	62	0.21 (0.00-1.93)	0.21 (0.03-1.80)	0.04 (0.00-0.36)	0.03 (0.00-0.33)	0.12 (0.00-1.02)	0.11 (0.00-0.89)
Parenteral dose (g/kg)	1	145	4.54 (2.72-6.88)	1.71 (1.13-2.37)	1.23 (0.00-1.60)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	136	5.97 (4.17-8.37)	2.15 (1.78-2.96)	1.76 (0.95-2.03)	0.00 (0.00-0.00)	0.61 (0.00-1.00)	0.00 (0.00-0.00)
	3	119	6.40 (4.24-9.04)	2.28 (1.96-3.02)	1.76 (1.34-2.11)	0.00 (0.00-0.00)	1.09 (0.55-1.94)	0.00 (0.00-0.00)
	4	104	6.61 (4.50-10.38)	2.46 (2.08-3.20)	1.83 (1.58-2.05)	0.00 (0.00-0.00)	1.48 (0.86-2.32)	0.00 (0.00-0.00)
	5	86	6.17 (4.60-9.83)	2.56 (2.12-3.37)	1.88 (1.67-2.06)	0.00 (0.00-0.00)	1.81 (1.29-2.56)	0.00 (0.00-0.00)
	6	74	6.34 (4.30-10.36)	2.62 (2.19-3.73)	1.89 (1.68-2.05)	0.00 (0.00-0.00)	1.96 (1.09-2.66)	0.00 (0.00-0.00)
	7	62	6.52 (4.46-9.79)	2.76 (2.31-3.79)	1.90 (1.61-2.06)	0.00 (0.00-0.04)	2.07 (1.39-2.93)	0.00 (0.00-0.04)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses, of glucose, amino acids, and lipids were significantly different for patients in the early PN and late PN groups, except for the lipid dose on day 1. N indicates the number of patients still in PICU on the day of analysis.

Supplementary table S1c: Average macronutrient administration for up to each of the first seven days in PICU to neonates younger than one day

Route	Dose up to day	N	Glucose		Amino acids		Lipids	
			Early PN	Late PN	Early PN	Late PN	Early PN	Late PN
Total dose (g/kg)	1	45	3.16 (2.07-4.55)	1.71 (0.81-2.67)	0.00 (0.00-0.51)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	44	4.61 (3.51-5.54)	2.11 (1.82-3.15)	0.88 (0.68-1.22)	0.00 (0.00-0.03)	0.70 (0.46-0.94)	0.00 (0.00-0.05)
	3	41	5.11 (4.20-6.05)	2.39 (2.12-3.53)	1.35 (1.22-1.66)	0.00 (0.00-0.11)	1.55 (0.99-1.99)	0.00 (0.00-0.00)
	4	37	5.52 (4.61-6.61)	2.66 (2.37-3.11)	1.65 (1.50-1.91)	0.00 (0.00-0.02)	2.03 (1.32-2.51)	0.00 (0.00-0.00)
	5	34	5.91 (4.84-7.05)	3.07 (2.44-3.92)	1.87 (1.67-1.96)	0.00 (0.00-0.08)	2.58 (1.92-2.81)	0.00 (0.00-0.04)
	6	32	6.34 (5.22-7.63)	3.46 (2.76-4.63)	1.94 (1.78-2.07)	0.02 (0.00-0.24)	2.68 (2.06-2.98)	0.04 (0.00-0.63)
	7	30	6.86 (5.73-8.13)	4.00 (2.83-5.49)	1.97 (1.90-2.18)	0.04 (0.00-0.68)	2.93 (2.18-3.26)	0.07 (0.00-1.79)
Enteral dose (g/kg)	1	45	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	44	0.00 (0.00-0.00)	0.00 (0.00-0.11)	0.00 (0.00-0.00)	0.00 (0.00-0.02)	0.00 (0.00-0.00)	0.00 (0.00-0.05)
	3	41	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	4	37	0.00 (0.00-0.24)	0.00 (0.00-0.00)	0.00 (0.00-0.04)	0.00 (0.00-0.00)	0.00 (0.00-0.12)	0.00 (0.00-0.00)
	5	34	0.00 (0.00-0.26)	0.00 (0.00-0.07)	0.00 (0.00-0.05)	0.00 (0.00-0.01)	0.00 (0.00-0.14)	0.00 (0.00-0.04)
	6	32	0.00 (0.00-0.45)	0.08 (0.00-1.25)	0.00 (0.00-0.08)	0.01 (0.00-0.21)	0.00 (0.00-0.23)	0.04 (0.00-0.63)
	7	30	0.06 (0.00-0.91)	0.00 (0.00-3.65)	0.01 (0.00-0.20)	0.00 (0.00-0.65)	0.04 (0.00-0.42)	0.00 (0.00-1.76)
Parenteral dose (g/kg)	1	45	3.16 (2.07-4.55)	1.71 (0.81-2.48)	0.00 (0.00-0.51)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	2	44	4.30 (3.48-5.42)	2.00 (1.58-3.11)	0.88 (0.67-1.22)	0.00 (0.00-0.00)	0.65 (0.02-0.90)	0.00 (0.00-0.00)
	3	41	4.82 (4.02-6.05)	2.34 (1.96-3.00)	1.35 (1.21-1.65)	0.00 (0.00-0.00)	1.42 (0.55-1.97)	0.00 (0.00-0.00)
	4	37	4.80 (4.14-6.61)	2.50 (2.08-2.85)	1.65 (1.48-1.83)	0.00 (0.00-0.00)	1.96 (0.82-2.50)	0.00 (0.00-0.00)
	5	34	5.22 (4.14-7.05)	2.56 (2.29-3.15)	1.78 (1.67-1.96)	0.00 (0.00-0.00)	2.33 (0.83-2.80)	0.00 (0.00-0.00)
	6	32	5.63 (4.21-7.43)	2.69 (2.11-3.57)	1.91 (1.73-2.07)	0.00 (0.00-0.00)	2.48 (0.96-2.91)	0.00 (0.00-0.00)
	7	30	6.26 (4.94-7.87)	2.78 (1.89-4.19)	1.95 (1.83-2.16)	0.00 (0.00-0.04)	2.43 (0.96-3.10)	0.00 (0.00-0.00)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses, of glucose, amino acids, and lipids were significantly different for patients in the early PN and late PN groups, except for the protein and lipid dose on day 1. N indicates the number of patients still in PICU on the day of analysis.

Supplementary table S2. Diagnoses of <1day-neonate

Diagnosis	Early PN (n=28)	Late PN (n=17)	P-value
Surgical			
Abdominal / Thoracic surgery			
Congenital Diaphragmatic Hernia	17 (60·7%)	5 (29·3%)	0·041
Gastroschisis	3 (10·7%)	6 (35·3%)	0·045
Other	1 (3·6%)	2 (11·8%)	0·30
Cardiac surgery	3 (10·7%)	1 (5·9%)	0·58
Non-surgical			
Cardiac	3 (10·7%)	1 (5·9%)	0·58
Other	1 (3·6%)	2 (11·8%)	0·30

PN=parenteral nutrition

Supplementary table S3. Baseline characteristics of neonates needing intensive care for at least 7 days who did not receive EN in the first week in PICU

	Early PN (n=23)	Late PN (n=15)	P-value
Male – No. (%)	15 (65·2)	19 (66·7)	0·93
Age at randomisation - median days (IQR)	0 (0-5)	1 (0-6)	0·48
Gestational Age (weeks) – median (IQR)	38 (38-39)	38 (37-39)	0·54
Birth Weight (gram) – median (IQR)	3100 (2777-3500)	3080 (2700-3330)	0·33
Weight z-score - mean (SD)^	-0·56 (-1·30;0·41)	-0·85 (-1·26-0·01)	0·73
PELOD score – median (IQR)	21 (12-32)	22 (12-32)	1·00
PIM2 score – median (IQR)	-1·95 (-2·36;-0·00)	-0·77 (-2·90;-0·08)	0·70
Risk of mortality (%) - median (IQR)#	12·4 (8·6-50·0)	31·6 (5·2-48·0)	0·70
Diagnostic group – no (%)			0·76
Medical	2 (8·7)	1 (6·6)	
Surgical cardiac	8 (34·8)	7 (46·7)	
Surgical other	13 (56·5)	7 (46·7)	
Mechanical ventilation on admission – no. (%)	23 (100)	15 (100)	-
Haemodynamic support on admission – no. (%)	18 (78·3)	19 (66·7)	0·43

PN=parenteral nutrition; ^neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³;#based on PIM2 score =((exp (PIM2))/(1+exp (PIM2)))*100%

Supplementary table S4. Admission diagnoses of neonates needing intensive care for at least 7 days who did not receive EN in the first week in PICU

Diagnosis	Early PN (n=23)	Late PN (n=15)	P-value
Surgical			
Abdominal / thoracic surgery			
Congenital Diaphragmatic Hernia	12 (52.2%)	3 (20.0%)	0.047
Gastroschisis	1 (4.3%)	3 (20.0%)	0.12
Other	0 (0.0%)	1 (6.7%)	0.21
Cardiac surgery	8 (34.8%)	7 (46.7%)	0.46
Non-surgical			
Cardiac	2 (8.7%)	0 (0.0%)	0.24
Other	0 (0.0%)	1 (6.7%)	0.21

PN=parenteral nutrition

Supplementary table S5. Outcomes of <4wk-neonates, with further adjustment for age

	Early PN (n=98)	Late PN (n=111)	Univariable OR, HR or β	P-value [^]	OR, HR or β , adjusted for baseline risk factors*	P-value*
<i>Efficacy endpoints</i>						
PICU-acquired infections – No. (%)	30 (30·6)	18 (16·2)	0·44 (0·22-0·85)	0·020	0·55 (0·27-1·10)	0·092
Airway	9 (9·2)	6 (5·4)		0·42		
Bloodstream	8 (8·2)	2 (1·8)		0·048		
Urinary tract	3 (3·1)	1 (0·9)		0·34		
Central nerve system	1 (1·0)	0 (0·0)		0·47		
Soft Tissue	2 (2·0)	2 (1·8)		1·00		
Others	0 (0·0)	1 (0·9)		1·00		
Duration of PICU dependency — median days (IQR)	7 (3·75-15·75)	5 (3·9)	1·71 (127-2·30)	0·0066	1·59 (1·17-2·16)	0·0031
Duration of mechanical ventilatory support — median days (IQR)	5 (3·13)	3 (2·6)	1·69 (1·26-2·27)	0·0021	1·60 (1·18-2·18)	0·0027
Highest plasma level of urea – median mg/dl (IQR)	43 (32-56·75)	33 (20·25-43)	-15·7 (-22·3;-9·10)	<0·0001	-13·2 (-19·5;-6·9)	<0·0001
Duration of hospital stay — median days (IQR)	18 (9-32·3)	14 (9-29)	1·47 (1·09-1·99)	0·43	1·33 (0·98-1·82)	0·068
Direct healthcare costs (€) – mean (SD)~	62 260 (110 820)	36 380 (39 100)	-25 880 (-48 110;-3 640)	0·030	-22 560 (-45 390;260)	0·053
<i>Safety endpoints</i>						
Death during first week – no. (%)	6 (6·1)	2 (1·8)	0·28 (0·06-1·43)	0·15	0·81 (0·08-7·85)	0·86
90-day mortality – no. (%)#	15 (15·3)	6 (5·4)	0·32 (0·12-0·85)	0·018	0·40 (0·12-1·28)	0·12
Hypoglycaemia (blood glucose <40 mg/dl (<2·2 mmol/l)) during first week – no. (%)	14 (14·3)	26 (23·4)	1·84 (0·90-3·76)	0·11	3·32 (1·36-8·08)	0·0082

[^]Proportions: Chi square test (Fisher's exact test if necessary), means: independent t-test, medians: Mann-Whitney U test

*Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, **and age**; OR and HR are shown for Late-PN versus Early-PN;

~Only of Dutch and Belgian patients (Early PN n=98, Late PN n=110); # all non-surviving patients died in PICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality.

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU=Paediatric Intensive Care Unit.

Supplementary Table S6. Episodes of hypoglycaemia

	Early PN (n=35)	Late PN (n=48)	Univariable P-value
Lowest level of blood glucose – median mg/dl (IQR)	37 (33-38)	34·5 (29-37)	0·032
Time-to-recovery from hypoglycaemia* – median minutes (IQR)	58 (45-88)	58·5 (48-76)	0·27
Level of blood glucose at recovery– median mg/dl (IQR)	73 (54-94)	58·5 (48-76)	0·065

PN=parenteral nutrition

*Only in Belgian neonates (n=60)

Supplementary Table S7-1A Multivariable linear regression analysis determining significant and independent associations between baseline risk factors and acquiring new infections in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.54 (0.27-1.08)	0.082
Centre Rotterdam vs Leuven	2.02 (0.50-8.16)	0.32
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	2.29 (0.66-7.96)	0.19
Diagnosis group Surgical other vs medical	2.19 (0.74-6.50)	0.16
PELOD score (per point added)	1.02 (0.97-1.08)	0.43
PIM2 score (per point added)	1.42 (1.10-1.84)	0.0073
Weight for age Z-score (per Z-score added)*	0.94 (0.68-1.29)	0.94

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-1B Multivariable linear regression analysis determining significant and independent associations between baseline risk factors including age and acquiring new infections in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late-PN vs Early-PN	0.55 (0.27-1.10)	0.092
Age (per day added)	0.99 (0.93-1.05)	0.68
Centre Rotterdam vs Leuven	1.91 (0.46-7.97)	0.38
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	2.23 (0.63-7.85)	0.21
Diagnosis group Surgical other vs medical	1.95 (0.58-6.57)	0.28
PELOD score (per point added)	1.02 (0.97-1.08)	0.48
PIM2 score (per point added)	1.41 (1.08-1.83)	0.012
Weight for age Z-score (per Z-score added)*	0.92 (0.66-1.29)	0.63

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-2A Multivariable linear regression analysis determining significant and independent associations between baseline risk factors and **time-to-live discharge from the PICU in the **<4wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·61 (1·19-2·20)	0·0021
Centre Rotterdam vs Leuven	0·83 (0·45-1·54)	0·56
Centre Edmonton vs Leuven	1·43 (0·19-10·55)	0·73
Diagnosis group Surgery cardiac vs medical	1·29 (0·77-2·16)	0·34
Diagnosis group Surgical other vs medical	1·02 (0·67-1·56)	0·93
PELOD score (per point added)	0·99 (0·96-1·01)	0·24
PIM2 score (per point added)	0·74 (0·65-0·84)	<0·0001
Weight for age Z-score (per Z-score added)*	1·06 (0·93-1·22)	0·39

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-2B Multivariable linear regression analysis determining significant and independent associations between baseline risk factors including age and **time-to-live discharge from the PICU in the **<4wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·59 (1·17-2·16)	0·0031
Age (per day added)	1·01 (0·99-1·04)	0·30
Centre Rotterdam vs Leuven	0·90 (0·48-1·69)	0·74
Centre Edmonton vs Leuven	1·41 (0·19-10·41)	0·74
Diagnosis group Surgery cardiac vs medical	1·36 (0·80-2·30)	0·26
Diagnosis group Surgical other vs medical	1·17 (0·71-1·94)	0·53
PELOD score (per point added)	0·99 (0·96-1·01)	0·31
PIM2 score (per point added)	0·75 (0·65-0·85)	<0·0001
Weight for age Z-score (per Z-score added)*	1·08 (0·94-1·25)	0·28

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-3A Multivariable linear regression analysis determining significant and independent associations between risk factors and **time-to-life weaning from ventilatory support in the **<4wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·62 (1·19-2·21)	0·0020
Centre Rotterdam vs Leuven	0·77 (0·41-1·46)	0·42
Centre Edmonton vs Leuven	0·87 (0·12-6·45)	0·89
Diagnosis group Surgery cardiac vs medical	1·17 (0·70-2·00)	0·55
Diagnosis group Surgical other vs medical	1·18 (0·79-1·78)	0·42
PELOD score (per point added)	0·99 (1·00-1·02)	0·60
PIM2 score (per point added)	0·68 (0·59-0·78)	<0·0001
Weight for age Z-score (per Z-score added)*	1·06 (0·93-1·22)	0·39

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-3B Multivariable linear regression analysis determining significant and independent associations between risk factors **including age and **time-to-life weaning from ventilatory support** in the **<4wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·60 (1·18-2·18)	0·0027
Age (per day added)	1·01 (0·98-1·03)	0·71
Centre Rotterdam vs Leuven	0·80 (0·42-1·53)	0·49
Centre Edmonton vs Leuven	0·88 (0·12-6·47)	0·90
Diagnosis group Surgery cardiac vs medical	1·18 (0·70-1·98)	0·54
Diagnosis group Surgical other vs medical	1·22 (0·75-1·98)	0·42
PELOD score (per point added)	0·99 (0·97-1·02)	0·63
PIM2 score (per point added)	0·68 (0·59-0·78)	<0·0001
Weight for age Z-score (per Z-score added)*	1·06 (0·93-1·22)	0·39

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-4A Multivariable linear regression analysis determining significant and independent associations between risk factors and death during the first week in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.71 (0.09-5.61)	0.74
Centre Rotterdam vs Leuven	1.03 (0.05-20.67)	0.99
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	1.51 (0.08-29.14)	0.78
Diagnosis group Surgical other vs medical	1.29 (0.06-29.42)	0.87
PELOD score (per point added)	1.05 (0.94-1.16)	0.42
PIM2 score (per point added)	3.55 (1.59-7.94)	0.0020
Weight for age Z-score (per Z-score added)*	1.82 (0.67-4.93)	0.24

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-4B Multivariable linear regression analysis determining significant and independent associations between risk factors including age and death during the first week in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.81 (0.08-7.85)	0.86
Age (per day added)	0.97 (0.78-1.21)	0.77
Centre Rotterdam vs Leuven	0.72 (0.02-34.75)	0.87
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	1.19 (0.04-34.74)	0.92
Diagnosis group Surgical other vs medical	1.26 (0.06-28.64)	0.89
PELOD score (per point added)	1.05 (0.94-1.17)	0.41
PIM2 score (per point added)	3.57 (1.56-8.15)	0.0025
Weight for age Z-score (per Z-score added)*	1.71 (0.58-5.05)	0.33

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-5A Multivariable linear regression analysis determining significant and independent associations between risk factors and 90 day mortality in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.41 (0.13-1.30)	0.13
Centre Rotterdam vs Leuven	0.83 (0.10-7.08)	0.86
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.59 (0.09-4.01)	0.59
Diagnosis group Surgical other vs medical	0.56 (0.08-3.86)	0.55
PELOD score (per point added)	1.05 (0.98-1.14)	0.17
PIM2 score (per point added)	1.92 (1.33-2.78)	0.00052
Weight for age Z-score (per Z-score added)*	1.03 (0.60-1.78)	0.91

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-5B Multivariable linear regression analysis determining significant and independent associations between risk factors including age and 90 day mortality in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.40 (0.12-1.28)	0.12
Age (per day added)	1.01 (0.92-1.11)	0.78
Centre Rotterdam vs Leuven	0.91 (0.10-8.53)	0.94
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.64 (0.09-4.59)	0.66
Diagnosis group Surgical other vs medical	0.60 (0.08-4.54)	0.62
PELOD score (per point added)	1.05 (0.98-1.14)	0.17
PIM2 score (per point added)	1.95 (1.33-2.86)	0.00064
Weight for age Z-score (per Z-score added)*	1.06 (0.60-1.86)	0.85

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-6A Multivariable linear regression analysis determining significant and independent associations between risk factors and hypoglycaemia in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.05 (1.27-7.35)	0.013
Centre Rotterdam vs Leuven	0.12 (0.03-0.59)	0.0087
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.69 (0.17-2.88)	0.61
Diagnosis group Surgical other vs medical	0.96 (0.24-3.87)	0.95
PELOD score (per point added)	1.03 (0.96-1.09)	0.42
PIM2 score (per point added)	1.25 (0.94-1.67)	0.13
Weight for age Z-score (per Z-score added)*	0.88 (0.60-1.29)	0.51

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-6B Multivariable linear regression analysis determining significant and independent associations between risk factors including age and hypoglycaemia in the <4wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.32 (1.36-8.08)	0.0082
Age (per day added)	0.94 (0.88-1.01)	0.081
Centre Rotterdam vs Leuven	0.09 (0.02-0.46)	0.0042
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.52 (0.11-2.36)	0.39
Diagnosis group Surgical other vs medical	0.54 (0.12-2.52)	0.44
PELOD score (per point added)	1.02 (0.96-1.09)	0.47
PIM2 score (per point added)	1.15 (0.85-1.55)	0.37
Weight for age Z-score (per Z-score added)*	0.77 (0.51-1.17)	0.22

*neonates <1 week: birthweight-for-gestational age Z-score², neonates ≥1 week: weight-for-age Z-score³

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-7 Multivariable linear regression analysis determining significant and independent associations between risk factors and **acquiring new infections in the **<1wk-neonates****

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0·36 (0·15-0·83)	0·017
Centre Rotterdam vs Leuven	1·77 (0·19-16·42)	0·61
Diagnosis group Surgery cardiac vs medical	1·65 (0·21-12·7)	0·63
Diagnosis group Surgical other vs medical	1·70 (0·41-7·06)	0·47
PELOD score (per point added)	1·03 (0·96-1·10)	0·41
PIM2 score (per point added)	1·21 (0·89-1·64)	0·22
Weight for age Z-score (per Z-score added)*	0·98 (0·66-1·46)	0·92

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-8 Multivariable linear regression analysis determining significant and independent associations between risk factors and **time-to-life discharge from PICU in the **<1wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·69 (1·16-2·46)	0·0063
Centre Rotterdam vs Leuven	0·57 (0·18-1·79)	0·33
Diagnosis group Surgery cardiac vs medical	0·98 (0·38-2·56)	0·97
Diagnosis group Surgical other vs medical	1·00 (0·54-1·88)	0·99
PELOD score (per point added)	0·97 (0·93-1·01)	0·97
PIM2 score (per point added)	0·78 (0·66-0·91)	0·0018
Weight for age Z-score (per Z-score added)*	1·07 (0·90-1·27)	0·44

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-9 Multivariable linear regression analysis determining significant and independent associations between risk factors and **time-to-life weaning from ventilatory support in the **<1wk-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·61 (1·10-2·35)	0·014
Centre Rotterdam vs Leuven	0·48 (0·15-1·57)	0·23
Diagnosis group Surgery cardiac vs medical	0·77 (0·30-2·01)	0·60
Diagnosis group Surgical other vs medical	0·97 (0·52-1·81)	0·92
PELOD score (per point added)	0·98 (0·94-1·02)	0·28
PIM2 score (per point added)	0·69 (0·58-0·82)	<0·0001
Weight for age Z-score (per Z-score added)*	1·07 (0·91-1·27)	0·41

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-11 Multivariable linear regression analysis determining significant and independent associations between risk factors and 90 day mortality in the <1wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.31 (0.07-1.44)	0.13
Centre Rotterdam vs Leuven	5.01 (0.20-123.47)	0.32
Diagnosis group Surgery cardiac vs medical	2.58 (0.14-48.32)	0.53
Diagnosis group Surgical other vs medical	0.74 (0.08-6.79)	0.79
PELOD score (per point added)	1.09 (0.99-1.20)	0.077
PIM2 score (per point added)	1.92 (1.22-3.02)	0.0050
Weight for age Z-score (per Z-score added)*	0.93 (0.44-1.97)	0.86

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-12 Multivariable linear regression analysis determining significant and independent associations between risk factors and hypoglycaemia in the <1wk-neonates

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.57 (1.23-10.45)	0.019
Centre Rotterdam vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.00 (0.00-.)	1.00
Diagnosis group Surgical other vs medical	0.35 (0.06-2.10)	0.25
PELOD score (per point added)	0.98 (0.89-1.07)	0.57
PIM2 score (per point added)	1.28 (0.88-1.86)	0.20
Weight for age Z-score (per Z-score added)*	0.83 (0.50-1.36)	0.45

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-13 Multivariable linear regression analysis determining significant and independent associations between risk factors and **acquiring new infections in the **<1day-neonates****

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0·10 (0·01-0·64)	0·015
Centre Rotterdam vs Leuven	0·00 (0·00-·)	1·00
Diagnosis group Surgery cardiac vs medical	2·96 (0·10-92·62)	0·54
Diagnosis group Surgical other vs medical	0·57 (0·07-4·98)	0·61
PELOD score (per point added)	1·00 (0·86-1·17)	0·98
PIM2 score (per point added)	1·06 (0·64-1·75)	0·83
Weight for age Z-score (per Z-score added)*	1·37 (0·66-2·84)	0·40

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-14 Multivariable linear regression analysis determining significant and independent associations between risk factors and **time-to-life discharge from PICU in the **<1day-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1·95 (0·93-4·12)	0·078
Centre Rotterdam vs Leuven	0·08 (0·003-2·07)	0·13
Diagnosis group Surgery cardiac vs medical	1·89 (0·34-10·47)	0·47
Diagnosis group Surgical other vs medical	2·38 (0·64-8·92)	0·20
PELOD score (per point added)	0·93 (0·82-1·05)	0·25
PIM2 score (per point added)	0·87 (0·66-1·14)	0·31
Weight for age Z-score (per Z-score added)*	1·06 (0·78-1·46)	0·70

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

Supplementary Table S7-15 Multivariable linear regression analysis determining significant and independent associations between risk factors and **time-to-life weaning from ventilatory support in the **<1day-neonates****

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	2·63 (1·23-5·63)	0·013
Centre Rotterdam vs Leuven	0·09 (0·003-2·16)	0·14
Diagnosis group Surgery cardiac vs medical	1·75 (0·32-9·55)	0·52
Diagnosis group Surgical other vs medical	2·47 (0·69-8·87)	0·17
PELOD score (per point added)	0·95 (0·84-1·08)	0·44
PIM2 score (per point added)	0·74 (0·54-1·01)	0·060
Weight for age Z-score (per Z-score added)*	1·02 (0·74-1·40)	0·91

* birthweight-for-gestational age Z-score²

PN=parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.

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