ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Children

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ABSTRACT

BACKGROUND

Recent trials have questioned the benefit of early parenteral nutrition in adults. The effect of early parenteral nutrition on clinical outcomes in critically ill children is unclear.

METHODS

We conducted a multicenter, randomized, controlled trial involving 1440 critically ill children to investigate whether withholding parenteral nutrition for 1 week (i.e., providing late parenteral nutrition) in the pediatric intensive care unit (ICU) is clinically superior to providing early parenteral nutrition. Fluid loading was similar in the two groups. The two primary end points were new infection acquired during the ICU stay and the adjusted duration of ICU dependency, as assessed by the number of days in the ICU and as time to discharge alive from ICU. For the 723 patients receiving early parenteral nutrition, parenteral nutrition was initiated within 24 hours after ICU admission, whereas for the 717 patients receiving late parenteral nutrition, parenteral nutrition was not provided until the morning of the 8th day in the ICU. In both groups, enteral nutrition was attempted early and intravenous micronutrients were provided.

RESULTS

Although mortality was similar in the two groups, the percentage of patients with a new infection was 10.7% in the group receiving late parenteral nutrition, as compared with 18.5% in the group receiving early parenteral nutrition (adjusted odds ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66). The mean (±SE) duration of ICU stay was 6.5±0.4 days in the group receiving late parenteral nutrition, as compared with 9.2±0.8 days in the group receiving early parenteral nutrition; there was also a higher likelihood of an earlier live discharge from the ICU at any time in the late-parenteral-nutrition group (adjusted hazard ratio, 1.23; 95% CI, 1.11 to 1.37). Late parenteral nutrition was associated with a shorter duration of mechanical ventilatory support than was early parenteral nutrition (P=0.001), as well as a smaller proportion of patients receiving renal-replacement therapy (P=0.04) and a shorter duration of hospital stay (P=0.001). Late parenteral nutrition was also associated with lower plasma levels of γ-glutamyltransferase and alkaline phosphatase than was early parenteral nutrition (P=0.001 and P=0.04, respectively), as well as higher levels of bilirubin (P=0.004) and C-reactive protein (P=0.006).

CONCLUSIONS

In critically ill children, withholding parenteral nutrition for 1 week in the ICU was clinically superior to providing early parenteral nutrition. (Funded by the Flemish Agency for Innovation through Science and Technology and others; ClinicalTrials.gov number, NCT01536275.)

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Critically ill children cannot normally be fed by mouth, and as a result a pronounced macronutrient deficit often develops after a few days. This macronutrient deficit has been associated with infections, weakness, prolonged mechanical ventilation, and delayed recovery.[1-3] In order to prevent or limit the development of this macronutrient deficit, current guidelines, which are based largely on small studies with surrogate end points and on expert opinion, advise care providers to initiate nutritional support soon after a child's admission to the pediatric intensive care unit (ICU).[4-6] The preferred route for the administration of nutritional support in the pediatric ICU is the nasogastric tube,[7] but enteral nutrition is often delayed or interrupted.[8,9] Since nutrition should equal basic metabolic needs and in children should allow for growth, children require relatively more macronutrients than adults. Hence, the current standard of pediatric intensive care is to meet these requirements early.[7,10] When enteral nutrition fails, parenteral nutrition is advised,[5,6] but current nutritional practices in pediatric ICUs vary owing to concerns about the overdosing of parenteral nutrition.[8,11]

There is a dearth of adequately powered, randomized, controlled trials that address the effects of parenteral nutrition on clinical outcomes in critically ill children.[12] With respect to critically ill adults, recent large, randomized, controlled trials have questioned the benefit of early parenteral nutrition.[13-15] Therefore, in this international, multicenter, randomized, controlled trial, we investigated whether a strategy of withholding parenteral nutrition up to day 8 (late parenteral nutrition) in the pediatric ICU is clinically superior to the current practice of early parenteral nutrition.

METHODS

DESIGN AND OVERSIGHT

The Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial was a multicenter, prospective, randomized, controlled, parallel-group superiority trial.[16] The institutional review board at each participating site approved the protocol (available with the full text of this article at NEJM.org).[16] The first and last authors vouch for the fidelity of the study to the protocol and for the accuracy and completeness of the reported data.

From June 18, 2012, through July 27, 2015, all children (from term newborns to children 17 years of age) who were admitted to one of the participating pediatric ICUs were eligible for inclusion if a stay of 24 hours or more in the ICU was expected, if they had a score on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) of 2 or more (with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk),[17] and if none of the criteria for exclusion were met (see Table S1 in the Supplementary Appendix, available at NEJM.org). Written informed consent was requested from parents or legal guardians before elective admission to the pediatric ICU. For emergency admissions, consent was requested within 24 hours after the child's admission to the pediatric ICU.

At each center, consecutive, eligible patients were randomly assigned to one of the two treatment groups in a 1:1 ratio. Concealment of group assignment was ensured by the use of a central computerized randomization system. The randomization was stratified in permuted blocks of 10 according to age (<1 year or ≥1 year) and diagnosis on admission (medical–neurologic, medical–other, surgical–cardiac, or surgical–other). The block size was unknown to the medical and research teams. Outcome assessors and investigators who were not directly involved in ICU patient care were unaware of the treatment assignments.

An independent data and safety monitoring board planned to perform two interim analyses of the safety end points, one after 480 patients had been enrolled and a second after 50% of all patients had been enrolled. The board advised that recruitment could be continued to completion.

PROCEDURES

All participating centers used early parenteral nutrition as the standard of care. Among patients assigned to receive early parenteral nutrition, parenteral nutrition was initiated within 24 hours after admission to the pediatric ICU. The dose and composition varied according to local guidelines (Table S2 in the Supplementary Appendix)[16]; parenteral nutrition was used to supplement any enteral nutrition that was provided, with a goal toward meeting local macronutrient and caloric targets (Table S3 in the Supplementary Appendix). Among patients assigned to the late-parenteral-

nutrition group, parenteral nutrition was withheld up to the morning of day 8 in the pediatric ICU. A mixture of intravenous dextrose (5%) and saline was administered to the late-parenteral-nutrition group to match the amount of intravenous fluid administered in the early-parenteral-nutrition group.[16] When blood glucose levels spontaneously dropped below 50 mg per deciliter (2.8 mmol per liter) in the late-parenteral-nutrition group, the standard 5% dextrose solution was replaced with a 10% dextrose solution until blood glucose levels exceeded 80 mg per deciliter (4.4 mmol per liter) and remained stable.[16]

In both study groups, enteral nutrition was initiated early and was increased in accordance with local guidelines. Both study groups also received intravenous micronutrients (trace elements, minerals, and vitamins) starting from day 2 and continuing until the enteral nutrition provided reached 80% of the caloric targets. Starting from the morning of day 8 in the pediatric ICU, supplementary parenteral nutrition was provided for patients in both groups who were not yet receiving 80% of the caloric target enterally. In Leuven, Belgium, an insulin infusion was started in both groups to target blood glucose levels of 50 to 80 mg per deciliter (2.8 to 4.4 mmol per liter) in infants (<1 year of age) and 70 mg per deciliter (3.9 mmol per liter) to 100 mg per deciliter (5.6 mmol per liter) in children (≥1 year of age). In Rotterdam, the Netherlands, all patients received an insulin infusion designed to target blood glucose levels of 72 to 145 mg per deciliter (4.0 to 8.0 mmol per liter), with the exception of patients with traumatic brain injury, for whom the target was 108 mg per deciliter (6.0 mmol per liter) to 145 mg per deciliter. In Edmonton, Canada, patients received an insulin infusion when blood glucose levels exceeded 180 mg per deciliter (10.0 mmol per liter). No specific lower boundary was set.

DATA COLLECTION

All patient data were stored in a logged database that was closed 90 days after enrollment of the last patient. Because the treatment assignment affected the blood glucose level during the first 24 hours after admission, as expected, the Pediatric Risk of Mortality score could not be used to account for the severity of illness at baseline, and the Pediatric Logistic Organ Dysfunction (PELOD) score (which ranges from 0 to 71, with higher scores indicating more severe illness) was used instead. The risk of malnutrition at admission was quantified with use of the STRONGkids score.[17] The determination of the presence of infection on admission to the pediatric ICU or infection acquired after randomization was based on the consensus opinion of two infectious disease specialists, who made their decision on the basis of guidelines in the study protocol (Table S4 in the Supplementary Appendix)[13]; both specialists were unaware of the study-group assignments. During the time patients were in the ICU, daily records were kept regarding all procedures, treatments, nutrition provided, and results of laboratory analyses. Information on vital status at 90 days was obtained from national death registries, hospital information systems, and regional networks of pediatricians and general practitioners.

END POINTS

The two primary end points were new infection acquired during the ICU stay and the duration of ICU dependency, which was adjusted for five prespecified baseline risk factors (diagnostic group, age group, severity of illness, risk of malnutrition, and treatment center).[16] Among patients with a new infection, the duration of antibiotic treatment was compared between the study groups. The duration of pediatric ICU dependency was quantified as the number of days in the pediatric ICU and as the time to discharge alive from the pediatric ICU, to account for death as a competing risk. Discharge from the pediatric ICU was defined a priori as the moment when a patient was ready for discharge from the pediatric ICU (i.e., no longer required or was no longer at risk for requiring vital organ support).[16] Secondary safety end points were death during the first 7 days in the pediatric ICU, during the total stay in the pediatric ICU, during the stay in the index hospital, and at 90 days after admission to the pediatric ICU and randomization; the number of patients with hypoglycemia (glucose level <40 mg per deciliter [2.2 mmol per liter]); and the number of readmissions to the pediatric ICU within 48 hours after discharge. Secondary efficacy outcomes were the time to final (live) weaning from mechanical ventilatory support, the duration of pharmacologic or mechanical hemodynamic support, the proportion of patients receiving renal-replacement therapy, markers of liver dysfunc-

tion and inflammation, and the time to (live) discharge from the hospital.

STATISTICAL ANALYSIS

We calculated that with a sample of 1440 patients (approximately 720 patients per group), the study would have at least 70% power to detect a 5-percentage-point lower rate of new infection in the late-parenteral-nutrition group than in the early-parenteral-nutrition group, assuming an estimated rate of 20% in the early-parenteral-nutrition group, with the use of a two-tailed test at an alpha error rate of 5%. All analyses were conducted on an intention-to-treat basis.

Variables were summarized as frequencies and percentages, medians and interquartile ranges, or means and standard errors. Univariable comparisons were performed with use of the chi-square test (Fisher's exact test) and the Wilcoxon rank-sum test. Kaplan–Meier plots were used to illustrate time-to-event effects with univariable significance that were analyzed by means of log-rank testing. The time-to-event effect size was estimated with use of Cox proportional-hazards analysis, with data censored at 90 days. To take into account death as a competing risk for outcomes related to duration of care, data for nonsurvivors were censored at 91 days (i.e., beyond the date for censoring of data for all survivors). These time-to-event outcomes were assessed univariably and with adjustment for baseline risk factors (diagnostic groups, age group, severity of illness, risk of malnutrition, and treatment center). The adjusted multivariable analysis of the effect of the intervention on dichotomized outcomes was performed with the use of logistic regression.

All P values were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. No corrections were made for multiple comparisons. Because efficacy end points were not assessed in the interim analyses, no adjustment of the P value threshold for significance was required.

To determine whether the effect of the intervention on the primary end points was influenced by baseline risk factors, P values for interaction were calculated with the use of multivariable logistic-regression analyses and multivariable Cox proportional-hazard analyses with a threshold for significance of interaction set at $P<0.10$. All analyses were performed with the use of JMP software, version 11.2.0 (SAS Institute).

RESULTS

PATIENTS

A total of 1440 patients underwent randomization and were included in the analysis (Fig. 1). At baseline, the characteristics of the patients were similar in the two groups (Table 1). Caloric and macronutrient intake per day up to day 16 in the pediatric ICU, which illustrates adherence to the protocol, is shown in Figure 2, as well as in Figures S1 and S2 in the Supplementary Appendix.

PRIMARY OUTCOMES

The rate of acquisition of a new infection was 7.8 percentage points lower (95% confidence interval [CI], 4.2 to 11.4) among children receiving late parenteral nutrition than among children receiving early parenteral nutrition (adjusted odds ratio, 0.48; 95% CI, 0.35 to 0.66) (Table 2). This result was attributable primarily to the fact that fewer patients in the late-parenteral-nutrition group acquired an airway or bloodstream infection (Table 2). Late parenteral nutrition was also associated with a shorter stay in the pediatric ICU by a mean of 2.7 days (95% CI, 1.3 to 4.3) (Table 2), with a higher likelihood of an earlier discharge alive from the pediatric ICU at any time (adjusted hazard ratio, 1.23; 95% CI, 1.11 to 1.37) (Table 2 and Fig. 3, and Fig. S3 and Table S5 in the Supplementary Appendix).

There were no significant interactions ($P<0.10$) between treatment assignment and any of the prespecified risk factors (Table S6 in the Supplementary Appendix). However, for the interaction between treatment assignment and risk of malnutrition, the P value was 0.11, with a lower odds of infections with late parenteral nutrition than with early parenteral nutrition among children at high risk of malnutrition (odds ratio, 0.28; 95% CI, 0.10 to 0.70) than among those at medium risk of malnutrition (odds ratio, 0.54; 95% CI, 0.38 to 0.76). There was also a higher likelihood of an earlier discharge alive from the pediatric ICU with late parenteral nutrition among the children at high risk of malnutrition (hazard ratio, 1.61; 95% CI, 1.12 to 2.31) than among the children at medium risk of malnutrition (hazard ratio, 1.19; 95% CI, 1.06 to 1.33) ($P=0.19$ for the interaction).

Similarly, there was no significant interaction between treatment assignment and age group. A post hoc subgroup analysis of the 209 term neo-

nates who were less than 4 weeks of age at the time of study inclusion revealed that the benefits of late parenteral nutrition were similar to or greater than those for children 4 weeks of age or older (odds ratio for new infections, 0.47 [95% CI, 0.22 to 0.95] among neonates and 0.48 [95% CI, 0.33 to 0.69] among older children; P=0.99 for interaction; hazard ratio for the likelihood of earlier live discharge from the pediatric ICU, 1.73 [95% CI, 1.27 to 2.35] among neonates vs. 1.17 [95% CI, 1.04 to 1.31] among older children; P=0.03 for the interaction). In addition, the effect of late parenteral nutrition on primary outcomes was unaltered after adjustment for the amount of enteral nutrition provided (Table S7 in the Supplementary Appendix).

SECONDARY OUTCOMES

Mortality was similar in the two groups at all prespecified time points (Table 2 and Fig. 3). The percentage of patients with an episode of hypoglycemia (glucose level <40 mg per deciliter) was higher in the group receiving late parenteral nutrition than in the group receiving early parenteral nutrition (Table 2). Adjustment for hypoglycemia did not alter the effect size of late parenteral nutrition on the primary outcomes (odds ratio for new infection, 0.45 [95% CI, 0.32 to 0.62] and adjusted hazard ratio for the likelihood of an earlier live discharge from the pediatric ICU, 1.26 [95% CI, 1.13 to 1.41]) (Table S7 in the Supplementary Appendix). Rates of readmission to the pediatric ICU within 48 hours after discharge and of the occurrence of serious adverse events were similar in the two study groups (Table 2).

The duration of mechanical ventilatory support was shorter and the likelihood of being weaned alive earlier from mechanical ventilation was higher among patients receiving late parenteral nutrition than among those receiving early parenteral nutrition (Table 2, and Table S5 in the Supplementary Appendix), whereas there was no significant between-group difference in the duration of hemodynamic support. After adjustment for prespecified risk factors, late parenteral nutrition was also associated with a lower need for renal-replacement therapy (Table 2, and Table S5 in the Supplementary Appendix). The peak plasma total bilirubin levels were higher in the late-parenteral-nutrition group than in the early-parenteral-nutrition group during the first 7 days in the pediatric ICU (Table 2) and during the duration of the pediatric ICU stay (Table S8 in the Supplementary Appendix), whereas the peak plasma γ-glutamyltransferase and alkaline phosphatase levels were higher with early parenteral nutrition (Table 2). There were no significant between-group differences in the results of other liver tests (Table 2). Although there were fewer new infections with late parenteral nutrition than with early parenteral nutrition, the peak plasma levels of C-reactive protein were

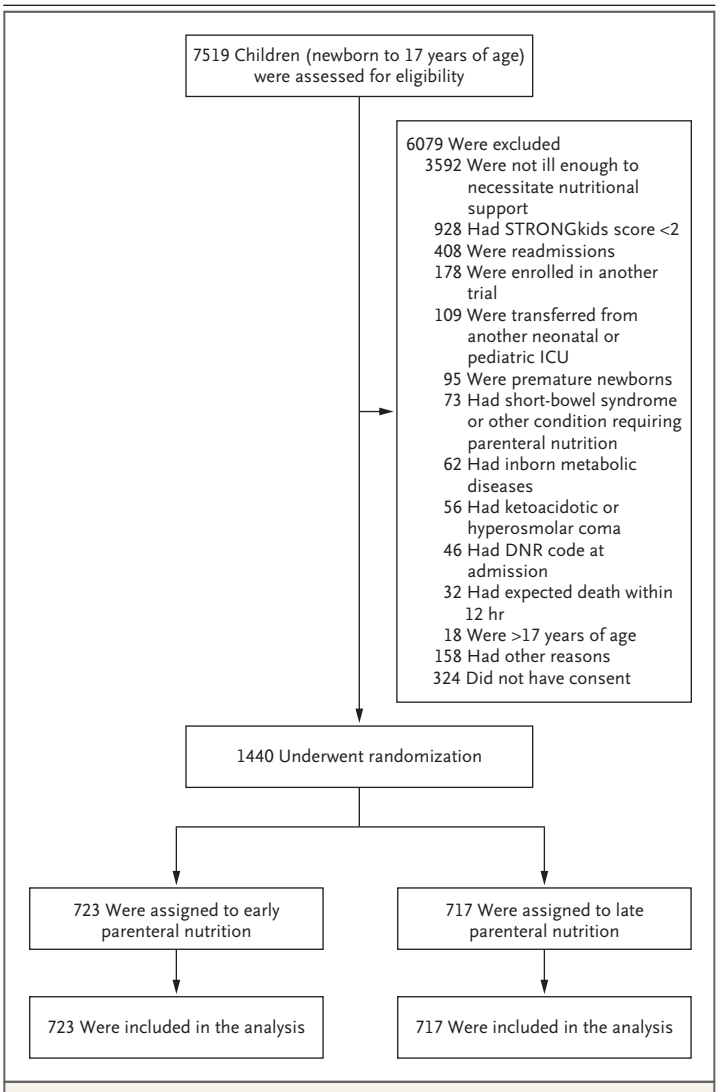

Figure 1. Screening and Randomization.

The scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[17] DNR denotes do not resuscitate, and ICU intensive care unit.

Table 1. Baseline Characteristics.*

Characteristic	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)
Median age (IQR) — yr	1.4 (0.3 to 6.1)	1.5 (0.2 to 7.2)
Age <1 yr — no. (%)	328 (45.4)	325 (45.3)
Male sex — no. (%)	415 (57.4)	415 (57.9)
Median weight (IQR) — kg	10.0 (4.8 to 20.0)	10.3 (4.5 to 21.5)
Median standard deviation score (IQR)†	−0.5 (−1.4 to 0.5)	−0.4 (−1.4 to 0.5)
Median height (IQR) — cm	80 (58 to 113)	80 (56 to 120)
Median standard deviation score (IQR)†	−0.3 (−1.5 to 0.8)	−0.3 (−1.4 to 0.8)
Median BMI (IQR)	15 (14–17)	15 (14–17)
Median standard deviation score (IQR)†	−0.5 (−1.5 to 0.5)	−0.5 (−1.6 to 0.6)
STRONGkids risk level — no. (%)‡		
Medium	644 (89.1)	644 (89.8)
High	79 (10.9)	73 (10.2)
Median PELOD score, first 24 hr in pediatric ICU (IQR)§	21 (11 to 31)	21 (11 to 31)
Emergency admission — no. (%)	383 (53.0)	400 (55.8)
Diagnostic group — no. (%)		
Surgical		
Abdominal	53 (7.3)	60 (8.4)
Burns	5 (0.7)	5 (0.7)
Cardiac	279 (38.6)	268 (37.3)
Neurosurgery–traumatic brain injury	63 (8.7)	53 (7.3)
Thoracic	34 (4.7)	27 (3.8)
Transplantation	7 (1.0)	17 (2.4)
Orthopedic surgery–trauma	28 (3.9)	26 (3.6)
Other	21 (2.9)	27 (3.8)
Medical		
Cardiac	30 (4.1)	31 (4.3)
Gastrointestinal–hepatic	2 (0.3)	4 (0.6)
Oncologic–hematologic	8 (1.1)	7 (1.0)
Neurologic	51 (7.1)	52 (7.3)
Renal	1 (0.1)	1 (0.1)
Respiratory	99 (13.7)	96 (13.4)
Other	42 (5.8)	43 (6.0)
Condition on admission — no. (%)		
Mechanical ventilation required	639 (88.4)	622 (86.8)
ECMO or other assist device required	19 (2.6)	25 (3.5)
Infection	287 (39.7)	271 (37.8)

* There were no significant differences in characteristics between treatment groups at baseline. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), ECMO extracorporeal membrane oxygenation, and ICU intensive care unit.

† Age- and gender-specific standard deviation scores were calculated with the use of reference data from the World Health Organization.[18]

‡ Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

§ Pediatric Logistic Organ Dysfunction (PELOD) scores range from 0 to 71, with higher scores indicating more severe illness.

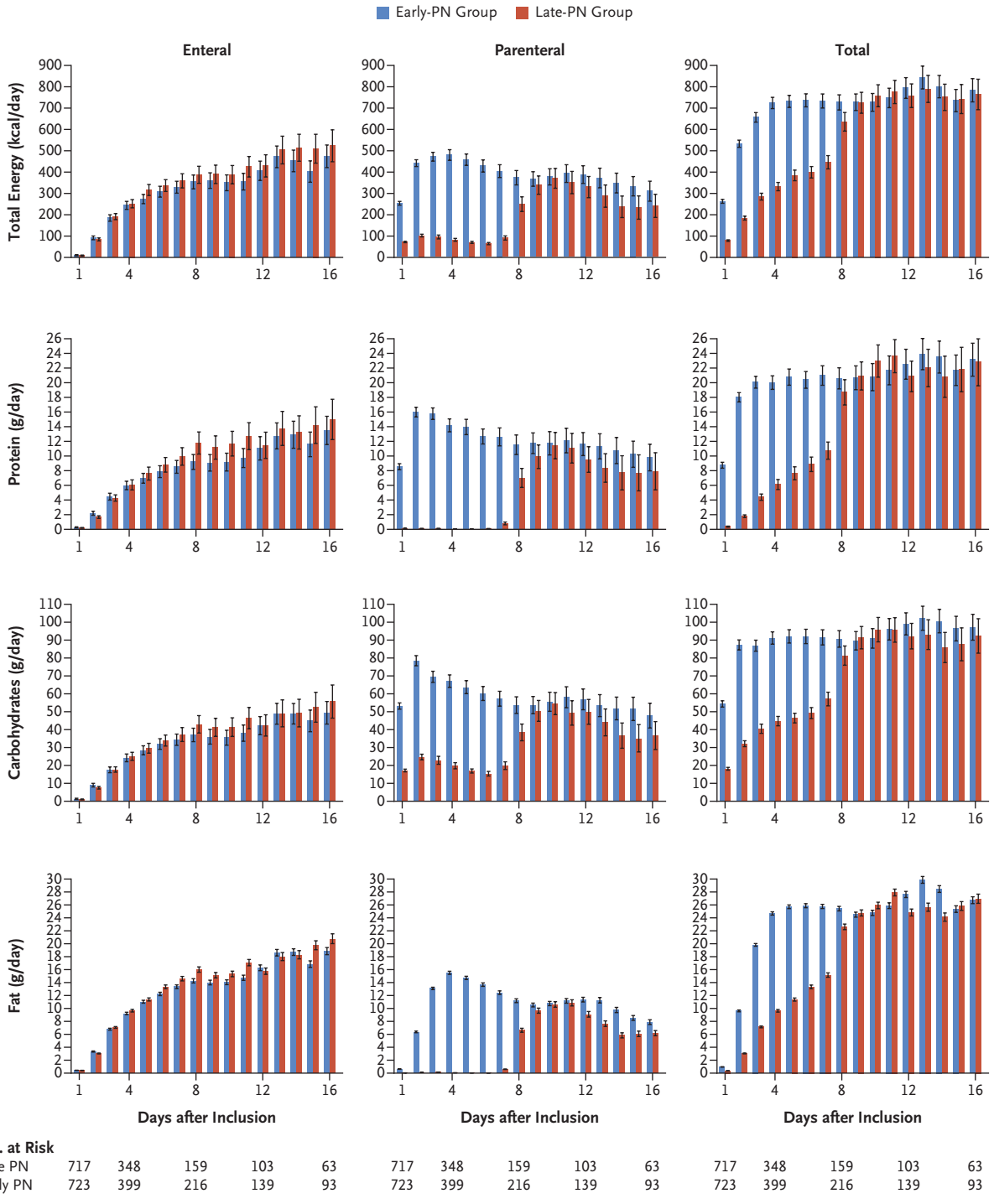

Figure 2. Daily Caloric and Macronutrient Intake.

The daily amount of energy (kilocalories per day) and substrate (grams per day) provided by the enteral route, the parenteral route, or both (total) are shown for participants' first 16 days in the pediatric intensive care unit (ICU). I bars indicate the standard error. PN denotes parenteral nutrition.

Table 2. Outcomes.*

Outcome	Early Parenteral Nutrition (N = 723)	Late Parenteral Nutrition (N = 717)	P Value	Adjusted Odds Ratio or Hazard Ratio (95% CI)†	P Value
Primary					
New infections — no. (%)	134 (18.5)	77 (10.7)	<0.001	0.48 (0.35–0.66)‡	<0.001
Airway	59 (8.2)	30 (4.2)	0.002		
Bloodstream	23 (3.2)	10 (1.4)	0.03		
Urinary tract	7 (1.0)	2 (0.3)	0.17		
Central nervous system	3 (0.4)	2 (0.3)	1.00		
Soft tissue	7 (1.0)	4 (0.6)	0.54		
Other focus	5 (0.7)	8 (1.1)	0.42		
No focus identified	30 (4.1)	21 (2.9)	0.25		
Total duration of antibiotic treatment for patients with new infection — days	21.3±3.1	17.4±1.9	0.77		
Total duration of stay in pediatric ICU — days§	9.2±0.8	6.5±0.4	0.002	1.23 (1.11–1.37)	<0.001
Patients requiring ≥8 days in pediatric ICU — no. (%)	216 (29.9)	159 (22.2)	<0.001		
Secondary					
Safety					
Death — no. (%)					
Within 8 days of admission to pediatric ICU	21 (2.9)	19 (2.6)	0.87	0.73 (0.34–1.51)‡	0.39
During stay in pediatric ICU	36 (5.0)	32 (4.5)	0.70	0.73 (0.42–1.28)‡	0.27
During hospital stay	44 (6.1)	37 (5.2)	0.49	0.72 (0.43–1.19)‡	0.20
Within 90 days after enrollment	49 (6.8)	38 (5.3)	0.26	0.64 (0.39–1.05)‡	0.08
Hypoglycemia: glucose <40 mg/dl during first 7 days in pediatric ICU — no. (%)	35 (4.8)	65 (9.1)	0.001		
Hypoglycemia refractory to treatment for ≥2 hr — no. (%)	0	1 (0.1)	1.00		
Readmission to pediatric ICU within 48 hr after discharge — no. (%)	9 (1.2)	13 (1.8)	0.39		
Efficacy					
Duration of mechanical ventilatory support — days	6.4±0.7	4.4±0.3	0.01	1.19 (1.07–1.32)	0.001
Duration of hemodynamic support — days	3.0±0.3	2.4±0.2	0.35		
Kidney failure with renal-replacement therapy — no. (%)	26 (3.6)	18 (2.5)	0.28	0.49 (0.24–0.96)‡	0.04
Liver dysfunction during first 7 days in pediatric ICU¶					
Highest plasma level of total bilirubin — mg/dl	1.5±0.1	1.7±0.1	0.003		
Highest plasma level of alkaline phosphatase — IU/liter	171±3	171±5	0.04		
Highest plasma level of γ-glutamyltransferase — IU/liter	58±6	45±3	0.001		

Highest plasma level of alanine aminotransferase — IU/liter	72±8	113±20	0.64		
Highest plasma level of aspartate aminotransferase — IU/liter	179±26	262±48	0.76		
Highest plasma level of C-reactive protein during first 7 days in pediatric ICU, as measure of inflammation — mg/liter	79±4	90±4	0.007		
Duration of hospital stay — days					
Index hospital	21.3±1.3	17.2±1.0	0.005	1.19 (1.07–1.33)	0.001
Index and transfer hospital	22.6±1.3	18.6±1.0	0.01	1.21 (1.08–1.34)	<0.001

* Plus–minus values are means ±SE. No censoring was applied for the unadjusted comparisons of outcomes regarding duration of care. Data for all adjusted outcomes for duration of care were censored at 90 days, and data for nonsurvivors were censored at 91 days. To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.
† Odds ratios and hazard ratios were adjusted for the following risk factors: treatment center, age group, diagnosis group, PELOD score within the first 24 hours after admission, and STRONGkids category.
‡ These values are adjusted odds ratios. All other values in this column are hazard ratios.
§ The duration of stay in the pediatric ICU was defined as the time from admission until the patient was ready for discharge. A patient was considered to be ready for discharge as soon as all clinical conditions for discharge were fulfilled (i.e., the patient no longer required or was no longer at risk for requiring vital-organ support).
¶ Total bilirubin levels were available for 1256 patients, alkaline phosphatase levels for 1234 patients, γ-glutamyltransferase levels for 1222 patients, alanine aminotransferase levels for 1265 patients, aspartate aminotransferase levels for 1264 patients, and C-reactive protein levels for 1301 patients.

higher with late parenteral nutrition during the first 7 days in the pediatric ICU (Table 2).

The mean duration of stay in the index hospital was 4.1 days shorter (95% CI, 1.4 to 6.6), and the likelihood of an earlier discharge alive from the hospital was higher (adjusted hazard ratio, 1.19; 95% CI, 1.07 to 1.33) in the late-parenteral-nutrition group than in the early-parenteral-nutrition group (Table 2 and Fig. 3, and Table S5 and Fig. S3 in the Supplementary Appendix). This effect of late parenteral nutrition remained significant when any eventual additional stay in a transfer hospital was taken into account (Table 2 and Fig. 3, and Table S5 and Fig. S3 in the Supplementary Appendix). Adjustments for hypoglycemia or for the amount of enterally administered nutrition did not alter the effect of late parenteral nutrition on any of the secondary outcomes (Table S7 in the Supplementary Appendix).

DISCUSSION

The results of our trial showed that withholding parenteral nutrition for 1 week in the pediatric ICU was clinically superior to providing early parenteral nutrition; late parenteral nutrition resulted in fewer new infections, a shorter duration of dependency on intensive care, and a shorter hospital stay. The clinical superiority of late parenteral nutrition was shown irrespective of diagnosis, severity of illness, risk of malnutrition, or age of the child. The observation that critically ill children at the highest risk of malnutrition benefited the most from the withholding of early parenteral nutrition was unexpected. However, this finding was reinforced by the apparently greater benefit of this strategy for critically ill term neonates than for older children. Indeed, immediate initiation of nutrition is currently advised for neonates because they are considered to have lower metabolic reserves.[7]

The benefits of late parenteral nutrition were evident irrespective of the variability in nutritional care and blood-glucose management across participating centers. Late parenteral nutrition resulted in more instances of hypoglycemia than were seen with early parenteral nutrition, but this higher rate did not affect the overall effect of the intervention on the outcome. In addition, in earlier studies, such brief episodes of hypoglycemia in critically ill children or in premature or

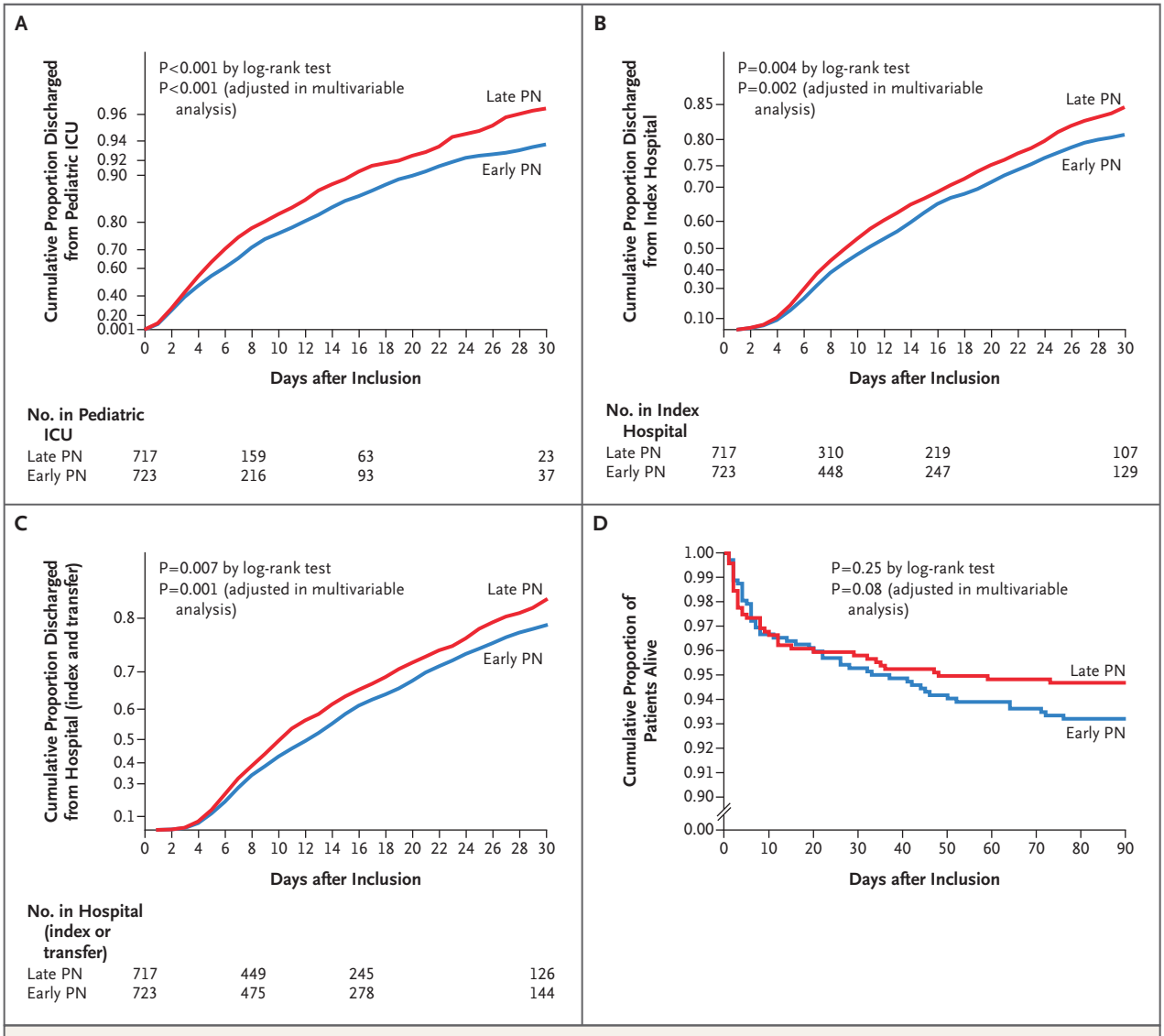

Figure 3. Kaplan–Meier Plots for the Time to Discharge and for Survival Up to 90 Days.

Panels A, B, and C show the cumulative proportions of patients discharged from the pediatric ICU, the index hospital, and all hospitals (index and transfer hospitals), respectively. Data for surviving patients were censored at 90 days, whereas data for nonsurvivors were censored at the time of death. For the sake of clarity, only the first 30 days are shown. Panel D shows the survival rate up to 90 days. P values were adjusted for diagnostic group, age group, severity of illness, risk of malnutrition, and treatment center.

mature newborns were not shown to have a negative effect on long-term neurocognitive outcomes.[19-21]

The finding that the rate of new infections was substantially lower with late parenteral nutrition than with early parenteral nutrition but that the rate of inflammation (as indicated by elevated plasma levels of C-reactive protein) was higher illustrates the limitation of surrogate end points in clinical trials.[22-26] As was seen in a previous study involving adults, plasma levels of γ-glutamyltransferase and alkaline phosphatase were lower in children who received late parenteral nutrition than in those who received early parenteral nutrition, a finding that was suggestive of less cholestasis in children in the late-parenteral-nutrition group.[13,27,28] However, late parenteral nutrition resulted in higher plasma bilirubin levels than did early parenteral nutrition in these critically ill children, as it has in

adult patients, which provides further support for the concept that increases in plasma bilirubin levels in response to critical illness may be partially adaptive.[29]

The underlying mechanisms of the clinical benefits observed when there is a substantial macronutrient deficit early in critical illness in children remain speculative. Preservation of autophagy may play a role, given its importance for innate immunity and for quality control in cells with a long half-life, such as myofibers.[30-32]

A limitation of this study is that the patients, their parents, and the staff providing intensive care were aware of the treatment assignments. However, outcome assessors and caregivers on the pediatric wards were unaware of the treatment assignments. The strength of the study is its external validity, given the multicenter study design. In conclusion, in critically ill children, withholding parenteral nutrition for 1 week while administering micronutrients intravenously was clinically superior to providing early parenteral nutrition to supplement insufficient enteral nutrition.

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REFERENCES

1. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. JPEN J Parenter Enteral Nutr 1985; 9:309-13.
2. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children — an international multicenter cohort study. Crit Care Med 2012;40: 2204-11.
3. de Betue CT, van Steenselen WN, Hulst JM, et al. Achieving energy goals at day 4 after admission in critically ill children; predictive for outcome? Clin Nutr 2015;34:115-22.
4. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev 2009;2: CD005144.
5. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. 1. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41:Suppl 2:S1-87.
6. Mehta NM, Compher C. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 2009;33:260-76.
7. Goday PS, Mehta NM. Pediatric critical care nutrition. New York: McGraw-Hill, 2015.
8. Kerklaan D, Fivez T, Mehta NM, et al. Worldwide survey of nutritional practices in PICUs. Pediatr Crit Care Med 2015;17: 10-8.
9. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2010;34:38-45.
10. Mehta NM, Jaksic T. The critically ill child. In: Duggan C, Watkins J, Walker WA, eds. Nutrition in pediatrics. 4th ed. Hamilton, ON, Canada: BC Decker, 2008: 663-73.
11. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009; 361:1088-97.
12. Fivez T, Kerklaan D, Mesotten D, Verbruggen SC, Joosten KF, Van den Berghe G. Evidence for the use of parenteral nutrition in the pediatric intensive care unit. Clin Nutr 2015 November 23 (Epub ahead of print).
13. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011; 365:506-17.
14. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013; 309:2130-8.
15. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled

clinical trial. Lancet 2013;381:385-93.
16. Fivez T, Kerklaan D, Verbruggen S, et al. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. Trials 2015;16:202.
17. Hulst JM, Zwart H, Hop WC, Joosten KF. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. Clin Nutr 2010;29:106-11.
18. WHO Multicentre Growth Reference Study Group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization, 2006 (http://www.who.int/growthref/en/).
19. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA 2012; 308:1641-50.
20. McKinlay CJ, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507-18.
21. Tin W, Brunskill G, Kelly T, Fritz S. 15-Year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012;130:e1497-503.
22. Chaloupecky V, Vislocky I, Pachl J, Sprongl L, Svomova V. The effect of early parenteral nutrition on amino acid and protein metabolism in infants following congenital heart disease surgery in extracorporeal circulation. Cor Vasa 1994;36: 26-34.
23. Chaloupecký V, Hucín B, Tláskal T, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. J Thorac Cardiovasc Surg 1997;114:1053-60.
24. Larsen BM, Goonewardene LA, Joffe AR, et al. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. Clin Nutr 2012; 31:322-9.
25. Larsen BM, Field CJ, Leong AY, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. JPEN J Parenter Enteral Nutr 2015;39:171-9.
26. Lekmanov AU, Erpuleva UV, Zolkina IV, Rossaus PA. Study of glutamine solution use efficiency in pediatric patients with heavy thermic burns and concomitant injuries in the intensive care unit. Anesteziol Reanimatol 2013;Jan-Feb(1): 49-51. (In Russian.)
27. Vanwijngaerden YM, Langouche L, Brunner R, et al. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. Hepatology 2014;60:202-10.
28. Vanwijngaerden YM, Wauters J, Langouche L, et al. Critical illness evokes elevated circulating bile acids related to altered hepatic transporter and nuclear receptor expression. Hepatology 2011;54: 1741-52.
29. Jenniskens M, Langouche L, Vanwijngaerden YM, Mesotten D, Van den Berghe G. Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med 2016;42:16-27.
30. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature 2011;469:323-35.
31. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. Cell Metab 2009;10:507-15.
32. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013; 1:621-9.