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Enteral nutrition is associated with improved outcome in patients with severe sepsis

A secondary analysis of the VISEP trial

List of abbreviations	
<i>APACHE II</i>	Acute Physiology and Chronic Health Evaluation II
<i>ASPEN</i>	American Society of Parenteral and Enteral Nutrition
<i>BEE</i>	basal energy expenditure
<i>BMI</i>	body mass index
<i>CI</i>	confidence interval
<i>EN</i>	enteral nutrition
<i>EPaNIC</i>	Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients
<i>ESPEN</i>	European Society of Clinical Nutrition and Metabolism
<i>GI</i>	gastrointestinal
<i>HES</i>	hydroxyethyl starch
<i>HR</i>	hazard ratio
<i>ICU</i>	intensive care unit
<i>IQR</i>	interquartile range
<i>IU</i>	international units
<i>LOS</i>	length of stay
<i>PN</i>	parenteral nutrition
<i>SE</i>	standard error
<i>SepNet</i>	German Competence Network Sepsis
<i>SOFA</i>	Sequential Organ Failure Assessment
<i>SPN</i>	supplemental parenteral nutrition
<i>VISEP</i>	Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis

Background

Nutrition is considered as an important therapeutic strategy modulating the metabolic stress response and affecting the clinical outcome of critically ill patients. The use of early enteral nutrition (EN) should be preferred over parenteral nutrition (PN) because it is more physiologic and associated with improved outcome [14, 22]. EN is, however, frequently characterized by a low caloric intake predominantly in the early phase of underlying disease [12, 25]. In order to improve energy delivery, an early supplemental use of PN is proposed [16]. The advantage of the one nutrition type is thereby regarded as the disadvantage of the other, as both have inherent risks of under- or overfeeding. On the one hand, large energy deficits resulting from a low caloric intake during EN may lead to increased infectious complications and a longer intensive care unit (ICU) stay [10, 13, 35]. On the other hand, PN is associated with nutritional excess leading to hyperglycemia, increased metabolic stress, and infectious morbidity [9, 28].

The guidelines of the European Society of Clinical Nutrition and Metabolism

(ESPEN) and the American Society of Parenteral and Enteral Nutrition (ASPEN) promote an early enteral start for nutrition [23, 31]. In patients receiving less than their targeted enteral feeding after 2 days, ESPEN recommends to then initiate the use of supplemental PN to achieve the caloric goal. ASPEN recommends retaining supplemental PN until days 7–10, allowing for a reduced caloric intake with EN alone unless the patient was previously malnourished. These guidelines are mainly based on nutritional data available from studies in mixed patient populations, while only few data exist for severely septic patients alone. Hence, the current Surviving Sepsis Campaign guidelines do not include specific nutritional recommendations [8], whereas the German Sepsis Society recommends the preferential use of early EN and the use of a combination of EN and PN if caloric requirements cannot be sufficiently covered with a low-evidence grade E [5]. In a former prospective observational study of 415 patients with severe sepsis or septic shock, we found that the use of PN was associ-

G. Elke and E. Kuhnt contributed equally to this article.

ated with increased morbidity and mortality [11].

Based on these former results, our present objective was to compare the outcomes of three nutritional strategies (EN vs. PN vs. combined nutrition, i.e., EN+PN) in patients with severe sepsis or septic shock using the database of the “Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)” trial [4]. In this analysis we only included patients with a length of ICU stay of more than 7 days to avoid the effect that patients with a short ICU stay receive less nutrition and thus confound the effect on outcome [3, 6, 18].

Methods

Study design and setting

This study was conducted as a secondary analysis of the VISEP trial, which was carried out by the German Competence Network Sepsis (SepNet) as a national, multicenter, randomized study with a two-by-two factorial design comparing intensive insulin therapy with conventional insulin therapy and hydroxyethyl-starch with Ringer’s lactate for volume resuscitation. SepNet officially approved the use of the data from the VISEP trial. A detailed description of the original study design is outlined elsewhere [4]. Briefly, patients were recruited from April 2003 to June 2005 in multidisciplinary ICUs at 18 academic tertiary hospitals in Germany. The leading ethics committee of the Friedrich Schiller University of Jena and the responsible ethics committee at each participating institution approved the study. All patients enrolled in the study had to fulfill the inclusion criteria for the presence of infection, systemic inflammatory response syndrome, and organ dysfunction or septic shock based on the consensus criteria of the American College of Chest Physicians and Society of Critical Care Medicine [2]. Patients were deemed to be eligible if the onset of the syndrome was less than 24 h before or less than 12 h after admission to the ICU if the condition developed in the ICU, and they were followed up for 90 days to determine outcome measures. All investigators agreed to base their patients’ management on the

international guidelines for the diagnosis and treatment of severe sepsis [33]. With respect to nutrition therapy, the preferential use of enteral nutrition was recommended. In patients not tolerating EN despite the use of jejunal feeding or with contraindications to enteral nutrition, parenteral nutrition should be used.

For the present analysis we evaluated the nutrition data that were collected daily during the study period of up to 21 days or until death or discharge from the ICU.

Patients

The intention-to-treat population of the VISEP trial comprised 537 patients with severe sepsis or septic shock. We excluded patients with invalid data on nutrition from our analysis. As proposed by previous studies [3, 6, 18], we further excluded patients with a length of ICU stay of 7 days or less in order to avoid potential confounding of a short ICU stay on the amount of nutrition therapy and outcome.

Patients were divided into groups according to the types of nutrition used in the VISEP trial, which were identified as exclusively EN, exclusively PN, and combined nutrition therapy (EN+PN). The latter involved all patients nourished enterally and parenterally either on the same or different treatment days during the study period. Days without EN or PN were included and counted as 0 kcal. The patients’ characteristics including demographic data, Acute Physiology and Chronic Health Evaluation II score (APACHE II score), and comorbidities were documented at the time of study entry. In surgical patients, the type of surgery (i.e., abdominal or gastrointestinal surgery) suspected to influence the route of nutrition therapy was also identified at study entry. Data comprising the timing, route, and amount of nutrition, blood glucose, and insulin doses were collected daily during the VISEP study period. The Harris–Benedict equation without activity adjustment was used to calculate the basal energy expenditure (BEE). The mean daily caloric intake was then divided by the BEE in order to estimate the ratio of caloric intake and energy expenditure.

Per protocol, secondary infections were classified according to the onset (microbiologically proven or clinically suspected), origin (community acquired or nosocomial), and site of infection. This was determined by the investigator on site and required daily documentation throughout the study.

Outcome measures

Clinical outcome was measured by the Sequential Organ Failure Assessment (SOFA), the need for renal-replacement therapy, the duration of mechanical ventilation, the incidence of severe hypoglycemia (≤ 40 mg of glucose per deciliter; 2.2 mmol per liter), length of ICU stay, secondary infections, and mortality.

Statistical analysis

Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Categorical outcome data were reported as absolute or relative frequencies and tested with the Chi-square test or Fisher’s exact test, as appropriate. Continuous data were presented by mean and standard deviation or median and interquartile range and were compared using the t-test, ANOVA, Mann–Whitney U test, or Kruskal–Wallis H test.

The rate of secondary infections and the length of stay in the ICU as well as mortality at 28 and 90 days were investigated by the Kaplan–Meier method and tested by log rank test in an unadjusted fashion. Multiple Cox regression models were applied for adjusted analyses of time to event data. These analyses included variables relevant for nutrition therapy or prognostic factors for patients with severe sepsis. Predictive factors with a p value < 0.2 in the unadjusted model were included in the adjusted Cox regression model.

Two-sided p values were reported and the level of significance was 0.05. Statistical analyses followed the intention-to-treat principle.

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Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial**Abstract**

Introduction. The optimal nutritional strategy remains controversial, particularly in severely septic patients. Our aim was to analyze the effect of three nutritional strategies—enteral (EN), parenteral (PN), and combined nutrition (EN+PN)—on the outcome of patients with severe sepsis or septic shock.

Patients and methods. This secondary analysis of the prospective, randomized-controlled, multicenter “Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis (VISEP)” trial only included patients with a length of stay in the intensive care unit (ICU) of more than 7 days. Besides patient characteristics, data on nutrition therapy were collected daily for up to 21 days. Morbidity as measured by the mean Sequential Organ Failure Assessment (SOFA) score,

incidence of secondary infections, renal replacement therapy, ventilator-free days and severe hypoglycemia, length of ICU stay, and mortality at 90 days were compared between the three nutritional strategies.

Results. In all, 353 patients were included in the analysis with the majority (68.5%) receiving EN+PN, 24.4% receiving EN, and only 7.1% receiving PN. Median caloric intake was 918 kcal/day (EN), 1,210 kcal/day (PN), and 1,343 kcal/day (EN+PN; $p<0.001$). In the latter group, calories were predominantly administered via the parenteral route within the first week. The rate of death at 90 days was lower with EN than with EN+PN (26.7% vs. 41.3%, $p=0.048$), as was the rate of secondary infections, renal replacement therapy, and duration of mechanical ventilation. In the adjust-

ed Cox regression analysis, the effect on mortality [hazard ratio (HR) = 1.86, 95% confidence interval (CI): 1.16–2.98, $p=0.010$] and the rate of secondary infections (HR = 1.89, 95% CI: 1.27–2.81, $p=0.002$) remained different between EN and EN+PN.

Conclusion. In patients with severe sepsis or septic shock and prolonged ICU stay, EN alone was associated with improved clinical outcome compared to EN+PN. This hypothesis-generating result has to be confirmed by a randomized-controlled trial in this specific patient population.

Keywords

Sepsis · Severe sepsis · Enteral nutrition · Parenteral nutrition · Combined nutrition therapy

Enterale Ernährung ist mit einem besseren Verlauf bei Patienten mit schwerer Sepsis assoziiert. Eine Sekundäranalyse der VISEP-Studie**Zusammenfassung**

Hintergrund. Eine optimale Ernährungsstrategie für Patienten mit schwerer Sepsis ist nach wie vor nicht eindeutig geklärt. Wir untersuchten den Einfluss unterschiedlicher Ernährungsstrategien (enteral, EN; parenteral, PN; und kombinierte Ernährung, EN+PN) auf den klinischen Verlauf bei Patienten mit schwerer Sepsis und septischem Schock.

Patienten und Methoden. Die vorliegende Sekundäranalyse der prospektiven, randomisierten, kontrollierten, multizentrischen Studie „Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis (VISEP)” wurde auf Patienten mit einer Intensivliegedauer >7 Tage beschränkt. Neben den Patientencharakteristika wurden Daten zur täglichen Ernährungstherapie über einen Zeitraum von bis zu 21 Tagen gesammelt. Der Einfluss auf die Morbidität, gemessen an der Höhe des mittleren SOFA-Scores,

die Häufigkeit von Sekundärinfektionen, Nierenersatztherapie, beatmungsfreien Tagen und schweren Hypoglykämien, Länge des Aufenthalts auf der Intensivstation sowie die 90-Tage-Sterblichkeit wurden zwischen den angewendeten Ernährungsstrategien verglichen.

Ergebnisse. Von 353 in die Analyse einbezogenen Patienten erhielten 68,5% EN+PN, 24,4% EN und 7,1% PN. Die täglich zugeführte Kalorienmenge lag im Median bei 918 kcal (EN), 1210 kcal (PN) und 1343 kcal (EN+PN; $p<0,001$). Hierbei wurden die Kalorien innerhalb der ersten Woche den Patienten mit EN+PN überwiegend parenteral zugeführt. Die 90-Tage-Sterblichkeit war bei Patienten mit EN verglichen mit EN+PN niedriger (26,7 vs. 41,3%; $p=0,048$), ebenso die Rate infektiöser Komplikationen, die Notwendigkeit einer Nierenersatztherapie wie auch die Beatmungsdauer. In einer u. a. für die Krankheits-

schwere adjustierten Cox-Regressionsanalyse blieb der Unterschied im Sterblichkeitsrisiko (Hazard Ratio, HR: 1,86; 95%-Konfidenzintervall, 95%-KI: 1,16–2,98; $p=0,010$) und bei den infektiösen Komplikationen (HR: 1,89; 95%-KI: 1,27–2,81; $p=0,002$) zwischen den Patienten mit EN+PN und EN bestehen.

Schlussfolgerung. Bei Patienten mit schwerer Sepsis und prolongierter Intensivliegedauer war EN verglichen mit EN+PN mit einem besseren klinischen Verlauf assoziiert. Diese im Kontext der vorliegenden Sekundäranalyse generierte Hypothese sollte anhand einer randomisiert-kontrollierten Studie in dieser spezifischen Patientenpopulation überprüft werden.

Schlüsselwörter

Sepsis · Schwere Sepsis · Enterale Ernährung · Parenterale Ernährung · Kombinierte Ernährungstherapie

Results**Study population**

A detailed flowchart of the study is given in **Fig. 1**. This study included 353 patients with severe sepsis or septic shock

and length of ICU stay of more than 7 days with complete nutrition data collection.

Patient characteristics

Tab. 1 summarizes the patient characteristics by the different types of nutrition therapy. The majority of patients received

EN+PN ($n=242$; 68.5%), whereof 233 patients were fed via the enteral and parenteral route on the same day and only 9 patients on different days. Patients in the EN and EN+PN groups were significantly older and had a higher APACHE II score compared to the patients receiving exclusively PN. After exclusion of the age sub-

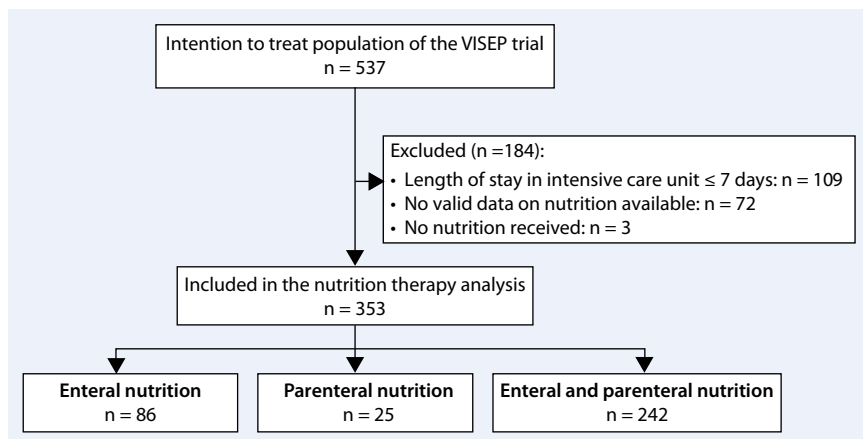


Fig. 1 ▲ Flowchart of study population

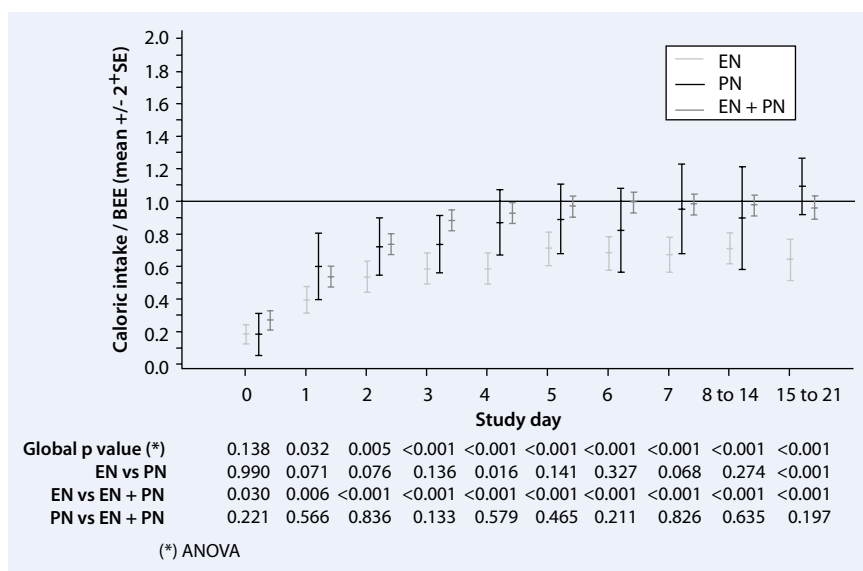


Fig. 2 ▲ Progression of daily caloric intake in relation to calculated basal energy expenditure (BEE). Mean ratios of daily caloric intake to BEE over the 21 study days in patients receiving enteral nutrition (EN, light gray bar), parenteral nutrition (PN, black bar), and combined enteral and parenteral nutrition (EN+PN, dark gray bar). Day 0 represents the time from randomization until the start of the next full 24-h study day; p values below the diagram indicate the significance of differences among the types of nutrition therapy per study day. The bars denote mean values ± 2 standard error (SE)

score, the median APACHE II score was 15 for EN and 16 for EN+PN vs. 13 for the PN group ($p=0.043$). Significant differences among the different types of nutrition were also found with respect to the proportion of preexisting diabetes and the type of surgery.

Nutrition therapy

Details on nutrition therapy and metabolism are outlined in **Tab. 2**. Median caloric intake and amount of protein were the highest for patients with EN+PN (1,343 kcal/day and 48.3 g/day, respectively) and the lowest in the EN group (medi-

an 918 kcal/day and 33.6 g/day, $p<0.001$). Accordingly, this resulted in a significantly higher ratio of mean daily caloric intake to calculated BEE by EN+PN (0.9; 0.7–1.1) than by EN (0.6; 0.4–0.9) or PN (0.8; 0.5–1.1, $p<0.001$). Median total duration of nutrition therapy in the ICU was 16 days and significantly longest with 18 days in patients receiving EN+PN compared to EN (14 days) and PN (8 days). Initiation of EN differed between EN (median day 1, IQR 0–1 days) and EN+PN (median day 3, IQR 1–5 days; $p<0.001$). No significant imbalances were found for the maximum and minimum blood glucose levels, while

a trend toward higher insulin doses was found for PN and EN+PN.

Fig. 2 shows the daily progression of caloric intake among the different nutrition strategies during the study course and **Fig. 3** the daily proportion of calories administered by the enteral and parenteral route explicitly for patients with EN+PN. In this group, calories were predominantly administered by PN within the first study week.

Outcomes

Tab. 3 summarizes the clinical outcomes. In patients with EN, the rate of renal-replacement therapy was significantly lowest (20.9%, $p=0.048$) and the number of ventilator-free days highest (median 4 days, $p<0.001$). These patients also had significantly fewer secondary infections on days 7 and 14 in the ICU (32.0 and 37.3%, $p<0.001$) and the lowest overall mortality on days 28 and 90 (12.8 and 26.7%, respectively, $p=0.048$).

Fig. 4 provides Kaplan–Meier analyses for overall survival (part a) and the proportion of patients without secondary infections (part b) according to the three groups of nutrition therapy.

In the adjusted Cox regression analysis, EN+PN was associated with a higher mortality [adjusted hazard ratio (HR)=1.86, 95% confidence interval (CI): 1.16–2.98, $p=0.010$] and a higher risk of secondary infections (HR=1.89 95% CI: 1.27–2.81, $p=0.002$) compared to EN (**Tab. 4**). Due to the observed colinearity of the route and amount of nutrition, we deliberately did not adjust for caloric or protein intake, respectively, in the Cox regression model.

Discussion

The present study evaluated nutrition therapy and clinical outcomes in a mixed medical and surgical population of 353 patients with severe sepsis or septic shock and a length of ICU stay of more than 7 days. In this high-risk subgroup of critically ill patients, we found that EN+PN was most frequently used with calories being administered early and predominantly via the parenteral route within the first 7 study days. In comparison to this strat-

Tab. 1 Patient characteristics					
Variable	Total	Enteral nutrition	Parenteral nutrition	Enteral + parenteral nutrition	p value ^a
	n=353 (100.0%)	n=86 (24.4%)	n=25 (7.1%)	n=242 (68.5%)	
Baseline characteristics					
Age, years, median; IQR	66; 56–74	69; 57–76	61; 50–64	66; 56–73	0.020
Gender, no. (%)					0.647
Male	219 (62.0)	56 (65.1)	17 (68.0)	146 (60.3)	
Female	134 (38.0)	30 (34.9)	8 (32.0)	96 (39.7)	
BMI, kg/m ²					0.333
Median; IQR	26; 23–30	25; 22–29	27; 23–28	26; 24–30	
APACHE II					0.002
Median; IQR	19; 16–24	20; 17–24	16; 12–18	20; 16–24	
Creatinine clearance					0.064
Median; IQR	52; 34–86	52; 36–88	74; 54–111	48; 33–79	
Diabetes, no. (%)					<0.001
Either type	97 (27.5)	36 (41.9)	2 (8.0)	59 (24.4)	
Type 1	41 (11.6)	14 (16.3)	1 (4.0)	26 (10.7)	0.005
Type 2	56 (15.9)	22 (25.6)	1 (4.0)	33 (3.6)	
Study intervention					
Fluid resuscitation, no. (%)					0.307
Ringer's lactate	177 (50.1)	47 (54.6)	15 (60.0)	115 (47.5)	
HES	176 (49.9)	39 (45.4)	10 (40.0)	127 (52.5)	
Insulin therapy, no. (%)					0.769
Conventional	180 (51.0)	45 (52.3)	11 (44.0)	124 (51.2)	
Intensive	173 (49.0)	41 (47.7)	14 (56.0)	118 (48.8)	
Admission category, no. (%)					0.780
Medical	165 (46.7)	43 (50.0)	12 (48.0)	110 (45.5)	
Surgical	187 (53.0)	43 (50.0)	13 (52.0)	131 (54.1)	
Missing	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Type of surgery, no. (%) ^b					<0.001
GI or abdominal	137 (38.8)	15 (17.4)	14 (56.0)	108 (44.6)	
Other	124 (35.1)	50 (58.1)	4 (16.0)	70 (28.9)	
None	91 (25.8)	21 (24.4)	6 (24.0)	64 (26.4)	
LOS ICU before study entry, no. (%)					0.215
0 days	101 (28.6)	19 (22.1)	7 (28.0)	75 (31.0)	
1 day	135 (38.2)	28 (32.6)	10 (40.0)	97 (40.1)	
2 days	27 (7.7)	8 (9.3)	2 (8.0)	17 (7.0)	
At least 3 days	90 (25.5)	31 (36.0)	6 (24.0)	53 (21.9)	

Sum of patient numbers within a variable may be lower than total column patient number due to missing data
BMI body mass index, *GI* gastrointestinal, *HES* hydroxyethyl starch, *IQR* interquartile range, *LOS ICU* length of stay in the intensive care unit^aKruskal–Wallis, chi-square, or Fisher's exact test for differences among types of nutrition therapy, as appropriate^bDuring last 30 days before study inclusion

egy, patients who received EN alone, albeit resulting in a low calorie and protein intake according to current recommendations [23, 31], had a lower mortality and lower morbidity as measured by the rate of infectious complications, renal-replacement therapy, and ventilator-free days.

The recent large randomized-controlled “Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients” (EPaNIC) trial compared early (within 48 h) vs. late initiation of PN (by day 8 after ICU admission) in combination with EN in a population

of 4,640 mixed ICU patients [7]. The total study population comprised more than 60% cardiac surgery patients (22% with sepsis upon ICU admission) with a short median ICU stay of 3–4 days and a 90-day mortality rate of only 11%. In the absence of a mortality effect, the late PN group had a shorter ICU and hospital stay, length of mechanical ventilation, and renal-replacement therapy and fewer infectious complications. Although the amount of calories administered was generally markedly lower in our study, both our EN+PN and their early initiation group were similar in terms of starting PN early (from day 1 on) and providing calories predominantly via this route in combination with EN within the first 7 days. Our results suggest that this approach is disadvantageous especially in the early disease phase of severely septic patients.

In contrast, previous observational studies suggested a better outcome with increased caloric and protein intake owing to the early supplemental or predominant use of PN in critically ill patients [1, 10, 13, 27, 32, 35]. In the majority of these studies, only a limited number of severely septic patients were included. In a recent randomized-controlled trial, Singer et al. [30] evaluated whether nutrition therapy guided by repeated energy expenditure measurements (study group) as compared to protocol-guided nutrition prescription (25 kcal/kg/day, control group) improved outcome. Their study comprised 130 critically ill patients (22% with severe sepsis) with a minimum ICU stay of 3 days. A combination of EN and supplemental PN was used from study day 1 to reach the energy target in both groups. A trend toward lower hospital mortality was found in the study group, whereas the duration of mechanical ventilation, the length of ICU stay, and the infection rate were significantly increased. Compared to the control group, patients in the study group received more energy and protein because of more frequent use and a relatively higher daily proportion of supplemental PN. The reported increase in ventilation and ICU stay may simply be a function of an increased survival of the patients receiving PN, as no adjustment was made for ventilator-free days or days in hospital but not in ICU. However, the

Tab. 2 Nutrition therapy and metabolism					
Variable	Total	Enteral nutrition	Parenteral nutrition	Enteral + parenteral nutrition	p value
	n=353 (100.0%)	n=86 (24.4%)	n=25 (7.1%)	n=242 (68.5%)	
Mean daily caloric intake					
kcal					<0.001
Median	1,199	918	1,210	1,343	
IQR	866–1,583	627–1,161	745–1,735	986–1,683	
kcal/kg					<0.001
Median	16.2	11.8	15.6	17.5	
IQR	11.1–21.3	8.1–17.6	10.6–21.4	12.9–22.7	
Mean protein intake, g/day					
Median	42.4	33.6	33.3	48.3	<0.001
IQR	26.1–61.3	23.0–42.5	17.9–65.1	29.3–66.8	
g/kg/day					
Median	0.57	0.43	0.55	0.65	<0.001
IQR	0.33–0.84	0.29–0.64	0.16–0.90	0.37–0.96	
Basal energy expenditure^b					
Kcal					0.071
Median	1,501	1,464	1,646	1,506	
IQR	1,330–1,711	1,295–1,662	1,399–1,793	1,333–1,701	
kcal/kg					0.302
Median	20	20	21	19	
IQR	18–21	19–21	18–22	18–21	
Caloric intake/BEE^c					
Median	0.8	0.6	0.8	0.9	<0.001
IQR	0.6–1.1	0.4–0.9	0.5–1.1	0.7–1.1	
Proportion of calories administered by enteral nutrition					
Median	0.4	1.0	0.0	0.3	–
IQR	0.1–1.0	1.0–1.0	0.0–0.0	0.1–0.6	
Parenteral nutrition					
Median	0.6	0.0	1.0	0.7	–
IQR	0.0–0.9	0.0–0.0	1.0–1.0	0.4–0.9	
Duration of nutrition					
Any type					<0.001
Median; IQR	16; 9–20	14; 6–18	8; 6–16	18; 11–21	
Enteral					
Median; IQR	10; 5–16	14; 6–18	0; 0–0	10; 6–15	
Parenteral					
Median; IQR	7; 1–15	0; 0–0	8; 6–16	10; 6–17	
First study day with nutrition					
Any type					0.710
Median; IQR	1; 0–1	1; 0–1	1; 0–1	0; 0–1	
Enteral nutrition					
Median; IQR	2; 0–5	1; 0–1	–	3; 1–5	–
Parenteral nutrition					
Median; IQR	1; 0–2	–	1; 0–1	1; 0–2	–
Enteral + parenteral nutrition					
Median; IQR	4; 2–7	–	–	4; 2–7	–
Mean insulin dose, IU/day^d					
Median	44.9	43.0	49.6	46.5	0.061
IQR	26.5–64.4	20.7–53.3	23.6–66.8	28.3–68.6	

Tab. 2 Nutrition therapy and metabolism (Continued)					
Variable	Total	Enteral nutrition	Parenteral nutrition	Enteral + parenteral nutrition	p value
	n=353 (100.0%)	n=86 (24.4%)	n=25 (7.1%)	n=242 (68.5%)	
Max blood glucose^amg/dl					0.400
Median	161.2	156.4	154.0	162.8	
IQR	142.9–196.5	141.8–189.2	141.7–186.0	144.3–197.5	
Min blood glucose^e					0.503
mg/dl					
Median	96.7	89.4	93.2	99.4	
IQR	77.6–123.7	78.5–114.4	77.1–125.4	59.7–164.3	

BEE basal energy expenditure, *IQR* interquartile range, *IU* international units, *max* maximum, *min* minimum^aKruskal–Wallis, chi-square, or Fisher's exact test for differences among types of nutrition therapy, as appropriate^bBEE was calculated by Harris–Benedict equation without activity factor^cCalculated as ratio of mean daily energy received and calculated BEE^dCalculated as mean of the daily dose for days with insulin therapy^eCalculated as the mean of the daily maximum or minimum glucose level, respectively

Tab. 3 Clinical outcome					
Variable	Total	Enteral nutrition	Parenteral nutrition	Enteral + parenteral nutrition	p value
	n=353 (100.0%)	n=86 (24.4%)	n=25 (7.1%)	n=242 (68.5%)	
Mean SOFA					0.124
Median	7	7	6	7	
IQR	5–10	5–9	5–8	5–10	
Hypoglycemia^a					0.802
No. of patients (%)	37 (10.5)	10 (11.6)	3 (12)	24 (9.9)	
Renal replacement					0.048
No. of patients (%)	105 (29.8)	18 (20.9)	5 (20)	82 (33.9)	
Ventilator-free days, median	2	4	3	1	<0.001
IQR	0–6	1–7	0–7	0–4	
Secondary infection^b, %					<0.001
At 7 days					
Estimate	39.5	32.0	32.9	42.8	
95% CI	34.6–44.9	23.2–43.1	18.0–55.3	36.8–49.4	
At 14 days					
Estimate	59.5	37.3	67.6	66.5	
95% CI	53.8–65.3	27.5–49.2	42.3–90.2	59.8–73.1	
LOS ICU^b, days					<0.001
Median	26	20	12	30	
IQR	14–48	13–28	10–45	16–54	
Overall mortality^b, %					0.048
At 28 days					
Estimate	21.0	12.8	16.0	24.4	
95% CI	17.1–25.6	7.3–21.9	6.3–37.2	19.5–30.3	
At 90 day					
Estimate	37.1	26.7	32.0	41.3	
95% CI	32.3–42.4	18.7–37.4	17.5–53.9	35.4–47.8	

IQR interquartile range, *LOS ICU* length of stay in the intensive care unit, *SOFA* Sequential Organ Failure Assessment^aHypoglycemia defined as blood glucose level ≤ 40 mg/dl (2.2 mmol/l)^bEstimated by the Kaplan–Meier method

authors attributed the increased morbidity of the study group in part to the higher metabolic load that actually exceeded the measured energy target within the first week. The most recent bicenter randomized-controlled trial by Heidegger et al. enrolled 305 critically ill patients with an ICU stay of 3 days or more and compared

EN supplemented by PN (SPN group) for coverage of energy target from day 4 to day 8 after ICU admission with EN alone [17]. Energy target was measured by indirect calorimetry in 65% of the patients or set to 25 (women) and 30 (men) kcal/kg ideal bodyweight, respectively. Patients in the SPN group received significantly

more energy between days 4 and 8 (mean 28 kcal/kg/day vs. 20 kcal/kg/day in the EN group). No mortality difference was found, but patients in the SPN group had fewer nosocomial infections, less number of antibiotic days, and a shorter duration of mechanical ventilation. The differences in outcome between the study by

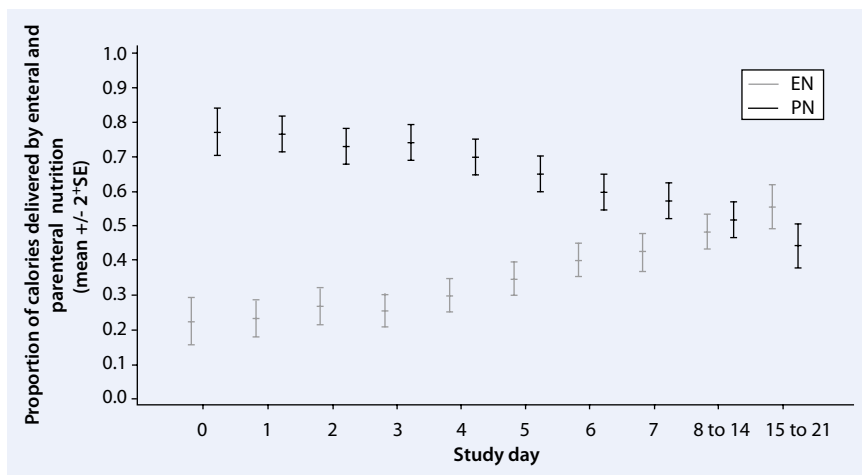


Fig. 3 ▲ Proportion of calories delivered by the enteral (EN, light gray bar) and parenteral route (PN, black bar) in the patients receiving combined nutrition therapy (EN+PN group). Day 0 represents the time from randomization until the start of the next full 24-h study day. The bars denote mean values ± 2 standard error (SE)

Heidegger et al. and our study might be mainly explained by the different patient population studied and the time point of starting PN in combination with EN. We only included patients with severe sepsis and septic shock, which likely accounts for the generally higher mortality observed in our study (21% vs. 16% at 28 days). Unlike their SPN group where PN was delayed until day 4, patients in our EN+PN group received PN early in the course of sepsis from day 1 on.

The negative effects of PN given as primary or supplementary therapy have been mainly linked to metabolic stress resulting from hyperalimentation with consecutive hyperglycemia and increased infectious complications, particularly during the early phase of critical illness [36]. In the presence of glycemic control, potential overfeeding might be indicated by metabolic stress markers such as higher insulin requirements, as suggested by previous studies [3, 11]. In our study, a trend toward higher insulin doses was observed with EN+PN or PN, whereby the randomized treatment arms (intensive and conventional insulin therapy) and the range of serum blood glucose (i.e., daily minimum and maximum values) were not significantly different, as was the rate of hypoglycemia.

Singer et al. [29] hypothesized that a transient metabolic shutdown is necessary for cell survival during severe sepsis similar to a state of hibernation [24].

According to this hypothesis it is likely that the energy requirements of our patients were markedly reduced since they were enrolled within the first 24 h after the onset of severe sepsis or septic shock. Kreyman et al. [19] showed that energy expenditure decreases with severity of illness resulting in prevailing hypometabolism in patients with severe sepsis and septic shock. One may speculate that a lower caloric intake by EN especially in the early phase of illness could be sufficient to maintain basal metabolism for survival and prevent metabolic stress.

The adverse outcome of the patients with EN+PN may also be explained by complications unrelated to hyperglycemia. In septic patients, the use of PN was associated with an increased risk of liver dysfunction [15] while low-dose enteral nutrition maintained the gastric mucosal balance and improved systemic and hepatosplanchnic blood flow [26]. PN may exhibit considerable hazard when given to patients with a functioning gastrointestinal tract, and this may have applied to 55.3% of the surgical patients with EN+PN who had no history of abdominal surgery present at study entry. On the contrary, the remaining patients with EN+PN were admitted with a history of abdominal surgery, implying that the decision of combined feeding was based on the presence of gastrointestinal dysfunction. In such patients with gastrointestinal dysfunction, Kutsogiannis et al. re-

cently demonstrated that both early and late supplemental PN were still found to be associated with worsening outcomes in an observational study of 2,920 critically ill patients (9% with sepsis) [21].

In the absence of a standardized nutrition protocol, not only the caloric intake but also the median protein intake in our study population was generally low according to current recommendations for protein administration in critically ill patients [20, 31]. It remains uncertain to what extent this has affected our results. However, the optimal goal of protein administration and possible impact on the inflammatory response in patients with severe sepsis still remains unknown and has not been addressed by randomized-controlled trials so far. In a retrospective study of 295 patients (34% with sepsis) remaining in the ICU for more than 7 days, Tsai et al. did not find differences in clinical outcomes with respect to protein delivery [34]. Neither did the very large observational study by Kutsogiannis et al., despite an improved delivery of 80% of the prescribed protein intake with supplemental PN [21].

Limitations

The main limitation is the design of our study. We are unable to imply causality to the association found because residual confounding due to inhomogeneous patient characteristics among the nutrition groups may still exist despite the adjustment for various covariates. Only a randomized-controlled trial of severely septic patients designed to separate the effects of the different route and amount of nutrition may corroborate our hypothesis-generating results. Owing to the low number of patients receiving PN only, the analysis lacks in power for the comparison of EN vs. PN and EN+PN vs. PN. We therefore focused on the comparison of EN and EN+PN, but presented data on PN for the sake of completeness.

A further limitation is that no standardized nutrition protocol was specifically followed in the study but investigators agreed to base their patients' management on the international guidelines for the diagnosis and treatment of severe sepsis [33]. This included the preferential use

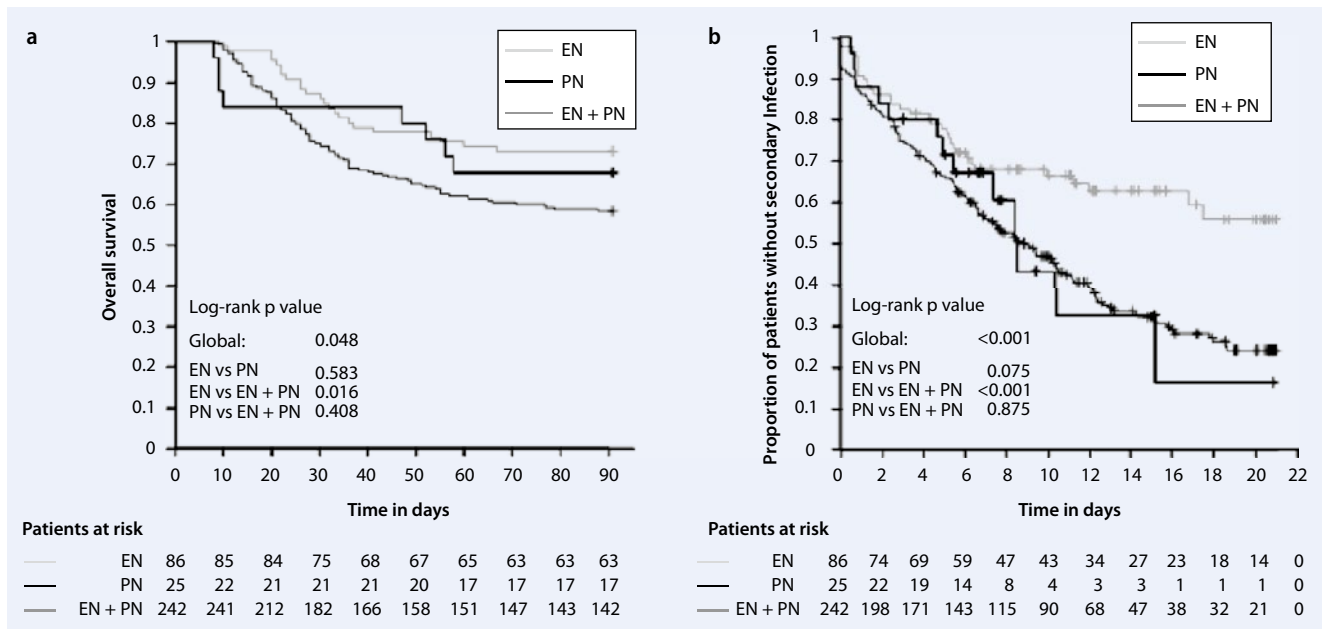


Fig. 4 ▲ Kaplan–Meier curves for overall survival and secondary infections. Overall survival (a) and the proportion of patients without secondary infections (b) among the patients receiving enteral (EN, light gray line), parenteral (PN, black line), or combined nutrition therapy (EN+PN, dark gray line). P values calculated by the log-rank test are displayed in each diagram

of EN as well as using PN for those patients intolerant to EN or with contraindications. Our study also lacks more detailed information on the specific formulations used including supplementary immunonutrition and administration of prokinetics in the different groups. Moreover, actual energy expenditure was not measured by indirect calorimetry but only calculated using the Harris–Benedict equation. This static approach only estimates the patient’s metabolic activity, and current guidelines [23, 31] recommend the routine use of indirect calorimetry albeit this technique is not commonly available in many ICUs. Initiation of EN differed between patients with EN and EN+PN, which might have influenced our results. However, Cahill et al. were able to show that even late EN alone (>48 h), as compared to either late (>48 h) or early (<48 h) supplemental PN, tended to decrease mortality in medical ICU patients with an ICU stay longer than 3 days [6]. Finally, the patients’ nutritional status before study entry was only characterized by the BMI at study entry that was in the range of 23–30 kg/m². We acknowledge that our results may not apply to severely septic patients with preexisting protein-energy malnutrition or obesity, who might profit from a daily increased energy and protein administration [1].

The strength of our study is the focus on a large study population of patients with severe sepsis or septic shock remaining at least 7 days in the ICU and that the data on nutrition therapy were prospectively collected for up to 21 ICU days.

Conclusion

- This secondary analysis of the VISEP trial revealed that the early and predominant use of parenteral nutrition combined with enteral nutrition resulted in a higher caloric intake in patients with severe sepsis and septic shock and prolonged ICU stay compared to early enteral nutrition alone.
- However, the use of enteral nutrition alone was associated with improved outcome in this specific subgroup of critically ill patients.
- These hypothesis-generating results have to be confirmed by a randomized-controlled trial in a homogeneous patient population of only severely septic patients.

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Conflict of interest. On behalf of all authors, the corresponding author states the following: G.E. received speaker’s honoraria from Abbott, B. Braun, and Fresenius Kabi. All other authors declare that they have no conflict of interest.

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Tab. 4 Cox model of overall mortality and secondary infections in patients with ICU LOS of more than 7 days

Predictive variable	Reference category	Unadjusted Cox model ^a			Adjusted Cox model ^b		
		HR	95% CI	p value	HR	95% CI	p value
Overall mortality							
Nutrition therapy, day 0 to 21					0.049		0.034
Parenteral	Enteral	1.27	0.57–2.84	0.558 ^h	2.00	0.86–4.64	0.105 ^h
Enteral + parenteral	Enteral	1.74	1.10–2.73	0.017 ^h	1.86	1.16–2.98	0.010 ^h
APACHE II^{c, d}		1.05	1.02–1.08	<0.001	1.04	1.01–1.07	0.020
Creatinine clearance at baseline^c		0.45	0.33–0.60	<0.001	0.47	0.34–0.64	<0.001
Type of surgery^e					0.965		
None	GI/abdominal	1.01	0.66–1.56	0.955 ^h			
Other	GI/abdominal	0.96	0.64–1.43	0.832 ^h			
Diabetes at baseline		1.29	0.89–1.86	0.181	1.11	0.75–1.65	0.600
Intensive insulin therapy^f		1.03	0.73–1.45	0.867			
HES^g		1.38	0.98–1.96	0.065	1.34	0.95–1.90	0.100
Secondary infection							
Nutrition therapy, day 0 to 21					0.001		0.007
Parenteral	Enteral	1.92	1.00–3.67	0.048 ^h	1.62	0.82–3.19	0.167 ^h
Enteral + parenteral	Enteral	2.04	1.40–2.99	<0.001 ^h	1.89	1.27–2.81	0.002 ^h
APACHE II^{c, d}		1.00	0.98–1.03	0.775			
Creatinine clearance at baseline^c		0.94	0.74–1.18	0.570			
Type of surgery^e					0.032		0.319
None	GI/abdominal	0.84	0.60–1.18	0.322 ^h	0.88	0.62–1.23	0.445 ^h
Other	GI/abdominal	0.64	0.46–0.89	0.009 ^h	0.77	0.54–1.09	0.134 ^h
Diabetes at baseline		0.85	0.62–1.16	0.302			
Intensive insulin therapy^f		0.89	0.68–1.18	0.426			
HES^g		1.09	0.83–1.44	0.530			

ICU LOS intensive care unit length of stay, APACHE Acute Physiology and Chronic Health Evaluation II, CI confidence interval, GI gastrointestinal, HR hazard ratio^aFor each predictive factor a separate cox regression model was estimated^bPredictive factors with a p value less than 0.2 in the unadjusted model were included in the adjusted Cox regression model^cHazard ratio per unit increase^dAPACHE II score at baseline without renal subscore^eDuring last 30 days before study inclusion^fStudy treatment of VISEP trial; reference category conventional insulin therapy^gStudy treatment of VISEP trial; reference category Ringer's lactate^hp value for the pairwise comparison of subcategories

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Fred Salomon (Hrsg.)
Praxisbuch Ethik in der Intensivmedizin
Konkrete Entscheidungshilfen in Grenzsituationen

Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft 2012, 2. Auflage, 392 S., 36 Abb., 31 Tab., (ISBN 978-3-941468-74-0), 49,00 EUR

Kaum eine andere Thematik wie die Ethik in der Intensivmedizin hat in den vergangenen Jahren eine solche zentrale Bedeutung erlangt.

Jede Ärztin, jeder Arzt, muss täglich multiple ethisch geprägte Entscheidungen nicht nur in der Intensivmedizin treffen, die zum Teil von erheblichem Gewicht sind und die Prognose von Patienten betreffen.

Es ist gut, dass sich die sehr hierarchisch und paternalistisch geprägte Medizin in den letzten Jahren zunehmend verändert, Patienten und ihre Angehörigen haben gerade in der Intensivmedizin ein enormes Gewicht bekommen, dabei spielt vor allen Dingen der Patientenwille, die Autonomie des Patienten, eine zentrale Rolle.

Sicherlich waren die lange geführten Diskussionen vor Verabschiedung der Novellierung des Betreuungsrechts vom 29. Juli 2009 ausschlaggebend, dass die Problematik zunehmend auch in das Bewusstsein einer breiten Öffentlichkeit getreten ist.

Fred Salomon als Herausgeber ist es gelungen, in einem kompakten aber sehr umfassenden Werk, mit verschiedenen hervorragenden und renommierten Autoren, ein aktuelles und fesselndes, sehr praktisch orientiertes „Lehrbuch“ zu Ethik in der Intensivmedizin zu verfassen.

Dieses Buch erscheint zu Recht nun schon in der 2. und aktualisierten Auflage – offensichtlich hat es eine große Leserschaft angesprochen- und beim erneuten Lesen der außerordentlich guten und exzellent geschriebenen Beiträge bestätigt sich der Eindruck, den der Leser schon bei der 1. Auflage gewonnen hat: Dieses Buch bietet zahllose relevante Informationen für den/die praktisch tätigen Intensivmediziner/in und sollte sicherlich auf jeder Intensivstation den dort tätigen Ärzten zur Verfügung gestellt werden.

Aber nicht nur für Ärzte ist dieses Buch lesenswert, auch für das gesamte Behandlungsteam sind die Beiträge außerordentlich wertvoll und können wichtige Impulse

leisten, um die tägliche, zum Teil sehr schwere Arbeit mit kritisch kranken Patientinnen und Patienten am Lebensende besser gestalten zu können.

Neben propädeutischen Beiträgen zur Menschenwürde auf der Intensivstation, bzw. dem Menschenbild als Entscheidungshintergrund intensivmedizinischen Handelns, finden sich konkrete Hilfen zur Umsetzung palliativmedizinischer Konzepte oder Begleitung Sterbender in der Intensivmedizin, aber auch in Bezug auf Angehörige und den alten Menschen.

Auch rechtliche Aspekte werden umfangreich thematisiert, so dass nach Lesen dieses Buches nur wenige Fragen übrig bleiben, die sicherlich in einer bald erscheinenden 3. Auflage ihre Vervollständigung erfahren werden. Also: sicherlich ein hervorragendes Werk, welches unbedingt nicht nur gelesen, sondern auch im klinischen Alltag umgesetzt gehört.

Eine wertvolle Hilfe im klinischen Alltag!

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