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Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study

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Take-home message: In spite of experimental evidence, few clinical data exist for determining whether nutritional support should be started early, which feeding route should be used and how many calories should be provided in mechanically ventilated patients with shock. A marginal structural model study of a large, prospective database strongly suggests that mechanically ventilated patients with shock should be started on nutritional support within 48 h after mechanical ventilation initiation and that neither feeding route nor early calorie intake is associated with mortality.

On behalf of the OUTCOMEREA Study Group.

The members of the OUTCOMEREA Study Group are listed in the "Appendix".

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Abstract *Purpose:* Few data are available about optimal nutrition modalities in mechanically ventilated patients with shock. Our objective was to assess associations linking early nutrition (<48 h after intubation), feeding route and calorie intake to mortality and risk of ventilator-associated pneumonia (VAP) in patients with invasive mechanical ventilation (IMV) and shock. *Methods:* In the prospective OutcomeRea database, we identified adults with IMV >72 h and shock (arterial systolic pressure <90 mmHg) within 48 h after intubation. A marginal structural Cox model was used to create a pseudo-population in which treatment was unconfounded by subject-specific characteristics. *Results:* We included 3,032 patients. Early nutrition was associated with lower day-28 mortality [HR 0.89, 95 % confidence interval (CI) 0.81–0.98, $P = 0.01$] and day-7 mortality (HR 0.76, CI 0.66–0.87, $P < 0.001$) but not with lower day-7 to day-28 mortality (HR 1.00, CI 0.89–1.12, $P = 0.98$). Early nutrition increased VAP risk over the 28 days (HR 1.08, CI 1.00–1.17, $P = 0.046$) and until day 7 (HR 7.17, CI 6.27–8.19, $P < 0.001$) but decreased VAP risk from days 7 to 28 (HR 0.85, CI 0.78–0.92, $P < 0.001$). Compared to parenteral feeding, enteral feeding was associated with a slightly increased VAP risk (HR 1.11, CI 1.00–1.22, $P = 0.04$) but not with mortality. Neither mortality nor VAP risk differed between early calorie intakes of ≥20 and <20 kcal/kg/day. *Conclusion:* In mechanically ventilated patients with shock, early nutrition was associated with reduced mortality. Neither feeding route nor early calorie intake was associated with mortality. Early nutrition and enteral feeding were associated with increased VAP risk.

Keywords Critical illness · Mechanical ventilation · Parenteral · Enteral · Early nutrition

Introduction

Critical illnesses produce calorie and protein deficiencies due to increased catabolism and decreased oral nutrient intake. International guidelines recommend starting artificial nutrition within 24–48 h after intensive care unit (ICU) admission, preferably by the enteral route, with target intakes of 20–25 kcal/kg/day and 1.2–2 g protein/kg/day during the first week [1–4]. Adherence to these guidelines is poor [5, 6]. Early enteral nutrition (EN) raises major challenges, with 30–70 % of patients experiencing vomiting, which may increase their risk of ventilator-associated pneumonia (VAP) [7]. EN is often stopped during periods with vomiting and for planned diagnostic or therapeutic procedures, leading to lower calorie intakes [8, 9].

The increased morbidity and mortality of mechanically ventilated patients with shock is associated with major nutritional deficiencies [6, 10–15]. A severe inflammatory response, metabolic stress and no spontaneous food intake combine to cause nutritional deficiencies. Additional factors include gut dysfunction, EN intolerance, delayed absorption of nutrients, and gut ischemia with subsequent bacterial translocation and multi-organ failure [7, 13, 16]. Studies have investigated EN in patients treated for shock [6, 10, 12]. Whether EN exacerbates or alleviates gut ischemia in these patients is unknown [17–20]. Guidelines indicate that EN should be withheld or delayed in patients with haemodynamic instability or catecholamine therapy [2, 3]. A recent randomised controlled trial showed that early EN and early parenteral nutrition (PN) were associated with similar outcomes and infection rates [21]. However, the benefits from early EN may be greatest in those patients with the most severe critical illnesses [11]. No high-level evidence is available on whether early versus delayed feeding is associated with outcomes of patients with shock receiving invasive mechanical ventilation (IMV). Also controversial are the relative merits of EN versus PN and the optimal macronutrient intake [5, 6, 22, 23].

Here, our main purpose was to compare effects of both early versus late nutrition and EN versus PN on outcomes of patients with shock and IMV. We also assessed potential effects of the early calorie intake on patient outcomes. We used a large prospective database (OutcomeRea) and we built a marginal structural model to create a pseudo-randomised population, thereby reducing any influence of confounding factors.

Methods

Study design and setting

We performed a multicentre cohort study using the OutcomeRea prospective database [24]. Detailed demographic, clinical and outcome data of patients were entered prospectively into the OutcomeRea database by trained senior physicians or clinical research monitors in each participating ICU (details in the online supplement).

In accordance with French law, this observational study involving no changes in patient management and using an approved database did not require informed consent of the patients for study participation.

Participants

Eligible patients were consecutive adults (≥18 years) who were included in the OutcomeRea database between December 1996 and February 2013, received IMV for longer than 72 h and developed shock (arterial systolic pressure <90 mmHg) within 48 h after IMV initiation. Exclusion criteria were abdominal surgery within the past month and treatment-limitation decisions on admission.

Definitions

Patient groups

To study the effect of nutrition timing, we distinguished patients given nutrition within 48 h after intubation (early-nutrition group) vs. later (delayed-nutrition group). To assess the impact of the early feeding route, patients given early nutrition were separated into a PN group, given only PN, and an EN group, given EN with or without PN, during the first 3 days of nutritional support (Fig. 1).

Diagnosis of ventilator-associated pneumonia (VAP)

VAP episodes were recorded until day 2 after extubation. VAP was suspected in patients who had new and persistent or progressive infiltrates on the chest radiograph with at least two of the following criteria: peripheral leucocytosis (>10,000/mm^3), leucopenia (<4,000/mm^3), body temperature ≥38.5 or ≤35.5 °C, and purulent tracheal aspirates. In all study ICUs, the criterion for confirming VAP was a positive quantitative bacteriologic culture of respiratory tract material obtained by broncho-alveolar lavage [cut-off ≥10^4 colony-forming units (cfu)/mL], protected specimen brush (cut-off ≥10^3 cfu/mL) or tracheobronchial aspirate (cut-off ≥10^5 cfu/mL) [25].

Data collection

The following data were collected at ICU admission: age, sex, comorbidities, Simplified Acute Physiology Score II (SAPS II), height, weight, diagnostic category (medical, emergent surgery, scheduled surgery) and acute illness. Treatments (fluid load, vasoactive drugs, hypnotic drugs, opiates, neuromuscular blocking agents, antibiotics, proton pump inhibitor and insulin) and the Sequential Organ Failure Assessment (SOFA) score were collected at intubation. Feeding route was recorded daily. Daily calorie intake was recorded starting in 2005, in three categories: <20, 20–35 and >35 kcal/kg/day. Data were collected until death or day 28.

Statistical analysis

Patient characteristics were described as *n* (%) or median [interquartile range, IQR] for qualitative and quantitative variables, respectively. Chi square or Mann–Whitney tests were used to compare groups, as appropriate. The primary endpoint was day-28 mortality and the secondary endpoint was VAP risk as assessed by day-28 VAP-free survival. Risk factors for day-28 events were identified using univariate Cox models stratified by centre; we successively tested early nutrition, feeding route and calorie intake as risk factors for day-28 mortality and day-28 VAP-free survival. We developed a propensity score to predict the probability of risk-factor exposure (early nutrition, feeding route and calorie intake) in each patient. Because early nutrition was not randomised, we developed a propensity score that used the admission variables to predict the probability of early nutrition in a given patient. All variables associated with early nutrition were entered into the model (Table E1 in the online supplement). According to the marginal structural model approach, this propensity score was used to compute the inverse probability treatment weighted estimator (IPTW) for early nutrition. We thus obtained a pseudo-population in which all patients had the same probability of receiving early nutrition, as if they had been allocated to early nutrition at random [26]. Then, the effect of early nutrition on day-28 mortality and day-28 VAP-free survival was estimated using a Cox model, weighted by the IPTW for early nutrition, stratified by centre and adjusted for risk factors for the study events. The additional survival duration in the early-nutrition group was calculated using an accelerated failure time model.

In subgroup analyses, we compared early EN versus early PN and calorie intake <20 vs. ≥20 kcal/kg/day. The proportional risk assumption was tested using the Kolmogorov-type supremum test [27]. When it was not

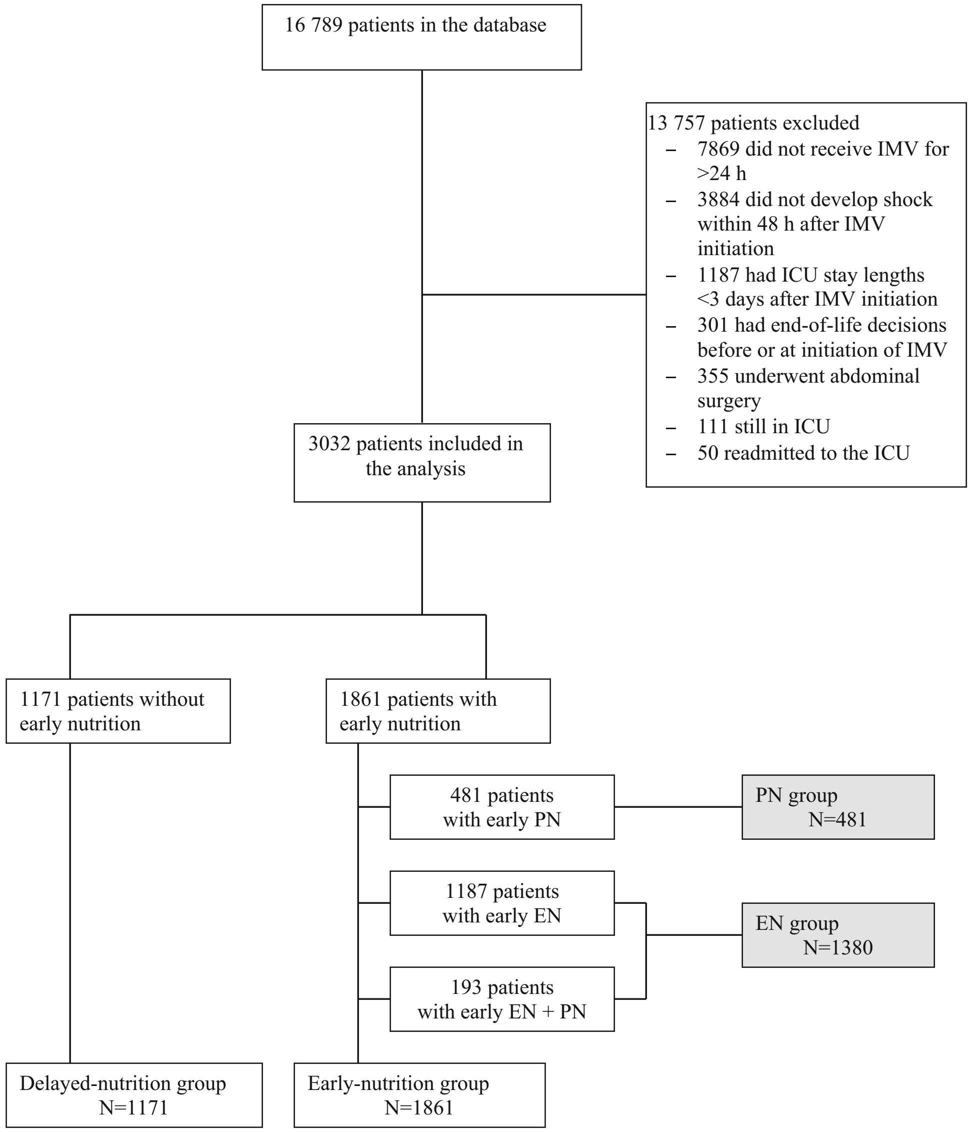

Fig. 1 Study flowchart. *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *PN* parenteral nutrition, *EN* enteral nutrition. In the PN group, patients received only PN; in the EN group, patients received EN with or without PN, during the first 3 days of nutritional support

satisfied, we separately analysed the risk of death using the best cut-off, as determined graphically. Truncation of extreme weights was used to validate the final models (Table E2) [26].

Last, subgroup analyses were performed for patients suffering from renal or liver failure. Patients with liver or renal values of the SOFA score >0 were considered as having a liver or a renal failure, respectively.

Results

Of the 16,789 patients recorded in the database, 3,032 met our eligibility criteria and were included in the analysis (Fig. 1). Table 1 reports their main characteristics and outcomes.

Early nutrition

Of the 3,032 study patients, 1,861 received early nutrition and 1,171 delayed nutrition. Table 2 lists the main characteristics of both groups. Median ICU stay length was 14 days [IQR 8–24 days] in the early-nutrition group and 9 days [6–17 days] in the delayed-nutrition group ($P < 0.001$). Crude day-28 mortality rates were 32.4 % with early nutrition and 29.2 % with delayed nutrition ($P = 0.06$). Table E1 lists the variables tested as factors potentially associated with early nutrition.

Effect of early nutrition on mortality

Table E2 reports the results of the univariate analysis. After adjustment for confounders, early nutrition was

Table 1 Main characteristics and outcomes of the study patients

	All patients ($n = 3{,}032$)
Variables at ICU admission	
Age (years), median [IQR]	66.3 [54.2; 76.3]
Gender (male/female), *n* (%)	1,919 (63.3)/1,113 (36.7)
Chronic disease at ICU admission, *n* (%)	
Renal failure requiring dialysis	144 (4.7)
Heart failure	395 (13)
Liver failure	230 (7.6)
Respiratory failure	547 (18)
Cancer or immune deficiency	489 (16.1)
Diabetes mellitus, *n* (%)	449 (14.8)
Chronic alcohol abuse, *n* (%)	536 (17.7)
Current smoker, *n* (%)	699 (23.1)
Weight (kg), median [IQR]	70 [60; 80]
BMI (kg/m^2), median [IQR]	24.3 [21.7; 27.7]
Obesity, *n* (%)	454 (15 %)
SAPS II, median [IQR]	51 [40; 64]
Diagnostic category at admission, *n* (%)	
Medical	2,265 (74.7)
Emergent surgery	437 (14.4)
Scheduled surgery	330 (10.9)
Acute illness at ICU admission, *n* (%)	
Shock or multi-organ failure	976 (32.2)
COPD exacerbation	119 (3.9)
Acute central nervous failure	535 (17.6)
Acute respiratory failure	951 (31.4)
Acute renal failure	67 (2.2)
Miscellaneous	357 (11.8)
Variables at intubation	
Time from admission to intubation (days), median [IQR]	0 [0; 0]
GCS score, median [IQR]	14 [7; 15]
SOFA, median [IQR]	8 [5; 10]
SOFA respiratory score, median [IQR]	2 [0; 3]
SOFA coagulation score, median [IQR]	0 [0; 1]
SOFA cardiovascular score, median [IQR]	3 [1; 4]
SOFA neurological score, median [IQR]	1 [0; 3]
SOFA hepatic score, median [IQR]	0 [0; 0]
SOFA renal score, median [IQR]	0 [0; 2]
Treatments, *n* (%)	
Fluid load	642 (21.2)
Vasoactive drugs	2,312 (76.3)
Hypnotic drugs	1,671 (55.1)
Opiates	1,548 (51.1)
NMB agents	535 (17.6)
Antibiotic therapy	2,275 (75)
Proton pump inhibitor	1,608 (53)
Prone position	27 (0.9)
Anticoagulant therapy	341 (11.2)
Outcome variables	
ICU stay length (days), median [IQR]	12 [7; 21]
ICU mortality, *n* (%)	846 (27.9)
ICU mortality predicted by SAPS II (%), median [IQR]	48.39 [24.7–75.3]
Hospital mortality, *n* (%)	1,209 (39.9)
Day-28 mortality, *n* (%)	945 (31.2)

Obesity was defined as BMI >30 kg/m^2, SAPS II values can range from 0 (lowest severity of critical illness) to 163 (greatest severity of critical illness, with 100 % predicted mortality). A score of 50 predicts 46.1 % mortality. The SAPS II was calculated 24 h after ICU admission. SOFA scores can range from 0 (no organ failure) to 24 (greatest severity of multi-organ failure). Main characteristics were recorded at study inclusion

ICU intensive care unit, *IQR* interquartile range, *BMI* body mass index, *SAPS II* Simplified Acute Physiologic Score version II, *COPD* chronic obstructive pulmonary disease, *GCS* Glasgow Coma Scale, *SOFA* Sequential Organ Failure Assessment, *NMB* neuromuscular blocking

Table 2 Main characteristics of patients in the groups with early (<48 h after intubation) versus delayed (≥48 h after intubation) nutrition

	Delayed nutrition (n = 1,171)	Early nutrition (n = 1,861)	P value
Variables at ICU admission			
Age (years), median [IQR]	64.9 [52.9; 76]	67.1 [55.1; 76.4]	0.02
Males, n (%)	740 (63.2)	1,179 (63.4)	0.93
Chronic disease at ICU admission, n (%)			
Renal failure requiring dialysis	53 (4.5)	91 (4.9)	0.65
Heart failure	135 (11.5)	260 (14)	0.05
Liver failure	125 (10.7)	105 (5.6)	<0.001
Respiratory failure	144 (12.3)	403 (21.7)	<0.001
Cancer or immune deficiency	183 (15.6)	306 (16.4)	0.55
Diabetes mellitus, n (%)	182 (15.5)	267 (14.3)	0.37
Chronic alcohol abuse, n (%)	209 (17.8)	327 (17.6)	0.85
Current smoker, n (%)	248 (21.2)	451 (24.2)	0.05
Weight (kg), median [IQR]	71 [63; 80]	70 [60; 80]	0.006
BMI (kg/m^2), median [IQR]	24.7 [22.5; 27.8]	24.3 [21.3; 27.4]	0.001
Obesity, n (%)	182 (15.5)	272 (14.6)	0.49
SAPS II, median [IQR]	53 [42; 66]	50 [38; 63]	<0.001
Diagnosis at admission, n (%)			
Medical	794 (67.8)	1471 (79)	
Emergent surgery	223 (19)	214 (11.5)	<0.001
Scheduled surgery	154 (13.2)	176 (9.5)	
Acute illness at ICU admission, n (%)			
Shock or multi-organ failure	413 (35.3)	563 (30.3)	0.004
COPD exacerbation	26 (2.2)	93 (5)	<0.001
Acute central nervous failure	236 (20.2)	299 (16.1)	0.004
Acute respiratory failure	269 (23)	682 (36.6)	<0.001
Acute renal failure	19 (1.6)	48 (2.6)	0.08
Miscellaneous	197 (16.8)	160 (8.6)	<0.001
Variables at intubation			
Time from admission to intubation (days), median [IQR]	0 [0; 0]	0 [0; 1]	<0.001
GCS score, median [IQR]	14 [6; 15]	14 [8; 15]	<0.001
SOFA, median [IQR]	8 [5; 10]	8 [5; 10]	0.98
SOFA respiratory score, median [IQR]	1 [0; 3]	2 [0; 3]	<0.001
SOFA coagulation score, median [IQR]	0 [0; 1]	0 [0; 1]	0.01
SOFA cardiovascular score, median [IQR]	3 [1; 4]	3 [1; 4]	0.006
SOFA neurological score, median [IQR]	1 [0; 3]	1 [0; 3]	<0.001
SOFA hepatic score, median [IQR]	0 [0; 0]	0 [0; 0]	0.045
SOFA renal score, median [IQR]	1 [0; 2]	0 [0; 2]	0.38
Treatments, n (%)			
Fluid load	225 (19.2)	417 (22.4)	0.04
Vasoactive drugs	884 (75.5)	1,428 (76.7)	0.43
Hypnotic drugs	650 (55.5)	1,021 (54.9)	0.73
Opiates	583 (49.8)	965 (51.9)	0.27
NMB agents	147 (12.6)	388 (20.8)	<0.001
Antibiotic therapy	818 (69.9)	1,457 (78.3)	<0.001
Proton pump inhibitor	680 (58.1)	928 (49.9)	<0.001
Prone position	9 (0.8)	18 (1)	0.57
Anticoagulant therapy	118 (10.1)	223 (12)	0.11

Obesity was defined as BMI >30 kg/m^2. SAPS II values can range from 0 (lowest severity of critical illness) to 163 (greatest severity of critical illness, with 100 % predicted mortality). A score of 50 predicts 46.1 % mortality. The SAPS II was calculated 24 h after ICU admission and 24 h after intubation. SOFA scores can range from 0 (no organ failure) to 24 (greatest severity of multi-organ failure). Main characteristics were recorded at study inclusion

ICU intensive care unit, *IQR* interquartile range, *BMI* body mass index, *SAPS II* Simplified Acute Physiologic Score version II, *COPD* chronic obstructive pulmonary disease, *GCS* Glasgow Coma Scale, *SOFA* Sequential Organ Failure Assessment, *NMB* neuromuscular blocking

associated with decreased day-28 mortality [hazards ratio (HR) 0.89, 95 % confidence interval (95 % CI) 0.81–0.98, $P = 0.01$] (Table 3). The Kolmogorov-type supremum test based on a sample of 1,000 simulated residual patterns showed that the effect on mortality varied over time ($P = 0.03$). In a multivariate Cox model, the early nutrition group had lower mortality within 7 days after intubation (HR 0.76, 95 % CI 0.66–0.87, $P < 0.001$) but not from day 7 to day 28 (HR 1.00, 95 % CI 0.89–1.12, $P = 0.98$) (Table 3). The additional survival duration of the early nutrition group was 3.3 days (95 % CI 0.8–6.2). Subgroup analyses showed that early

Table 3 Hazard ratios for effect of time of nutrition initiation, feeding route, and calorie intake on mortality and on risk of ventilator-associated pneumonia

	HR (95 % CI)	*P* value
Time of nutrition initiation: early nutrition vs. delayed nutrition[a]		
Day-28 mortality	0.89 (0.81–0.98)	0.01
Death within 7 days after IMV initiation	0.76 (0.66–0.87)	<0.001
Death 7–28 days after IMV initiation	1.00 (0.89–1.12)	0.98
Risk of VAP by day 28	1.08 (1.00–1.17)	0.046
Risk of VAP until day 7	7.17 (6.27–8.19)	<0.001
Risk of VAP from day 7 to day 28	0.85 (0.78–0.92)	<0.001
Feeding route: enteral vs. parenteral[b]		
Day-28 mortality	1.07 (0.95–1.20)	0.27
Risk of VAP by day 28	1.11 (1.00–1.22)	0.04
Calories delivered on days 2 and 3: ≥20 vs. <20 kcal/kg/day[c]		
Day-28 mortality	0.96 (0.83–1.12)	0.63
Risk of VAP by day 28	0.9 (0.8–1.01)	0.08

The analysis of factors associated with day-28 mortality was adjusted for age >66 years (median), admission diagnostic category, SOFA respiratory score >2, SOFA coagulation score >2, SOFA cardiovascular score >2, SOFA neurological score >2, SOFA hepatic score >2, SOFA renal score >2, cancer or immune deficiency, chronic disease, hypnotic drugs and anticoagulant therapy

HR hazard ratio, *95 % CI* 95 % confidence interval, *IMV* invasive mechanical ventilation, *VAP* ventilator-associated pneumonia

[a] HR <1 suggests a lower risk with early nutrition

[b] HR <1 suggests a lower risk with enteral nutrition

[c] HR <1 suggests a lower risk with ≥20 kcal/kg/day

nutrition was associated with decreased day-28 mortality in patients with renal failure (HR 0.87, 95 % CI 0.77–0.97, $P = 0.02$), but not in patients with liver failure (HR 0.99, 95 % CI 0.83–1.19, $P = 0.93$) (Tables E5, E6).

Effect of early nutrition on VAP risk

After adjustment for confounders, early nutrition was associated with an increase in VAP risk (HR 1.08, 95 % CI 1.00–1.17, $P = 0.046$) (Table 3). This effect varied significantly with time ($P < 0.001$). By multivariate analysis, the early nutrition group was at higher VAP risk within 7 days after intubation (HR 7.17, 95 % CI 6.27–8.19, $P < 0.001$) but at lower VAP risk 7–28 days after intubation (HR 0.85, 95 % CI 0.78–0.92, $P < 0.001$) (Table 3). Early nutrition was not associated with significant change in VAP risk in patients with renal failure (HR 1.04, 95 % CI 0.94–1.15, $P = 0.43$) or liver failure (HR 1.05, 95 % CI 0.90–1.22, $P = 0.58$) (Tables E5, E6).

Feeding route

Of the 1,861 patients given early nutrition, 481 received only PN and 1,380 received EN (only EN, $n = 1{,}187$; EN + PN, $n = 193$) (Table 4). Median duration of IMV was 9 days [5–10 days] in the PN group and 10 days [IQR 5–17 days] in the EN group ($P = 0.21$). Median ICU stay length was 14 days [8–25 days] in the PN group and 14 days [IQR 8–23 days] in the EN group ($P = 0.96$). Crude day-28 mortality rates were 31.8 % in the PN group and 32.6 % in the EN group ($P = 0.75$). Table E3 lists the variables tested as potentially associated with receiving EN.

Effect of feeding route on mortality

By multivariate analysis performed after checking that model assumptions were met, EN was not associated with lower mortality compared to PN (HR 1.07, 95 % CI 0.95–1.20, $P = 0.27$) (Table 3). When we confined the EN group to those patients who received no PN (i.e. to 1,187/1,380 patients given EN), we obtained similar results (HR 1.18, 95 % CI 0.98–1.44, $P = 0.08$).

EN was associated with increased day-28 mortality in patients with renal failure (HR 1.43, 95 % CI 1.23–1.67, $P < 0.001$) or with liver failure (HR 1.68, 95 % CI 1.34–2.10, $P < 0.001$). Feeding route had no impact on mortality in patients without renal failure or without liver failure (Tables E5, E6).

Effect of feeding route on VAP risk

Compared to PN, EN was associated with a higher risk of VAP (HR 1.11, 95 % CI 1.00–1.22, $P = 0.04$) (Table 3). When we compared the 1,187 patients who received only EN to the 481 patients who received only PN, we found a non-significant association between EN and VAP risk (HR 1.17, 95 % CI 1.00–1.38, $P = 0.06$).

EN was associated with VAP in patients with renal failure (HR 1.23, 95 % CI 1.08–1.41, $P = 0.002$) or liver failure (HR 1.25, 95 % CI 1.03–1.53, $P = 0.03$). Feeding

Table 4 Main characteristics of patients who received parenteral versus enteral feeding for early nutrition

	Parenteral nutrition ($n = 481$)	Enteral nutrition ($n = 1{,}380$)	*P* value
Variables at ICU admission			
Age (years), median [IQR]	66.9 [56.6; 76.7]	67.2 [54.3; 76.3]	0.38
Males, *n* (%)	315 (65.5)	864 (62.6)	0.26
Chronic disease at ICU admission, *n* (%)			
Renal failure requiring dialysis	26 (5.4)	65 (4.7)	0.54
Heart failure	64 (13.3)	196 (14.2)	0.63
Liver failure	39 (8.1)	66 (4.8)	0.007
Respiratory failure	66 (13.7)	337 (24.4)	<0.001
Cancer or immune deficiency	82 (17)	224 (16.2)	0.68
Diabetes mellitus, *n* (%)	60 (12.5)	207 (15)	0.17
Chronic alcohol abuse, *n* (%)	77 (16)	250 (18.1)	0.30
Current smoker, *n* (%)	102 (21.2)	349 (25.3)	0.07
Weight (kg), median [IQR]	70 [60; 80]	70 [60; 79]	0.30
BMI (kg/m^2), median [IQR]	24.3 [21.3; 27.7]	24.3 [21.3; 27.3]	0.97
Obesity, *n* (%)	59 (12.3)	213 (15.4)	0.09
SAPS II, median [IQR]	46 [35; 60]	51 [40; 64]	<0.001
Diagnostic category at admission, *n* (%)			
Medical	247 (51.4)	1,224 (88.7)	
Emergent surgery	129 (26.8)	85 (6.2)	<0.001
Scheduled surgery	105 (21.8)	71 (5.1)	
Acute illness at ICU admission, *n* (%)			
Shock or multi-organ failure	223 (46.4)	340 (24.6)	<0.001
COPD exacerbation	8 (1.7)	85 (6.2)	<0.001
Acute central nervous failure	21 (4.4)	278 (20.1)	<0.001
Acute respiratory failure	127 (26.4)	555 (40.2)	<0.001
Acute renal failure	14 (2.9)	34 (2.5)	0.60
Miscellaneous	81 (16.8)	79 (5.7)	<0.001
Variables at intubation			
Time from admission to intubation (days), median [IQR]	0 [0; 1]	0 [0; 1]	0.35
GCS score, median [IQR]	15 [12; 15]	14 [7; 15]	<0.001
SOFA, mean ± SD	8 [5; 10]	8 [5; 10]	0.98
SOFA respiratory score, median [IQR]	2 [0; 3]	2 [0; 3]	0.80
SOFA coagulation score, median [IQR]	0 [0; 1]	0 [0; 1]	<0.001
SOFA cardiovascular score, median [IQR]	3 [1; 4]	3 [1; 4]	0.008
SOFA neurological score, median [IQR]	0 [0; 2]	1 [0; 3]	<0.001
SOFA hepatic score, median [IQR]	0 [0; 1]	0 [0; 0]	0.003
SOFA renal score, median [IQR]	1 [0; 2]	0 [0; 2]	0.09
Treatments, *n* (%)			
Fluid load	106 (22)	311 (22.5)	0.82
Vasoactive drugs	400 (83.2)	1,028 (74.5)	<0.001
Hypnotic drugs	230 (47.8)	791 (57.3)	<0.001
Opiates	228 (47.4)	737 (53.4)	0.02
NMB agents	60 (12.5)	328 (23.8)	<0.001
Antibiotic therapy	380 (79)	1,077 (78)	0.66
Proton pump inhibitor	281 (58.4)	647 (46.9)	<0.001
Prone position	6 (1.2)	12 (0.9)	0.47
Anticoagulant therapy	44 (9.1)	179 (13)	0.03

Obesity was defined as BMI >30 kg/m^2. SAPS II was calculated 24 h after ICU admission. SAPS II values can range from 0 (lowest severity of critical illness) to 163 (greatest severity of critical illness, with 100 % predicted mortality). A score of 50 predicts 46.1 % mortality. SOFA scores can range from 0 (no organ failure) to 24 (greatest severity of multi-organ failure)

ICU intensive care unit, *IQR* interquartile range, *BMI* body mass index, *SAPS II* Simplified Acute Physiologic Score version II, *COPD* chronic obstructive pulmonary disease, *SOFA* Sequential Organ Failure Assessment, *NMB* neuromuscular blocking

route was not associated with VAP in patients without renal failure or without liver failure (Tables E5, E6).

Calorie intake

Among 2,276 patients fed within 3 days after intubation, 1,398 had their calorie intake recorded in the database. Their main data are shown in Table E4. Calorie intake was not associated with day-28 mortality (HR 0.96, 95 % CI 0.83–1.12, $P = 0.63$) or VAP risk (HR 0.9, 95 % CI 0.8–1.01, $P = 0.08$) (Table 3).

In patients with renal failure, calorie intake was not associated with day-28 mortality (HR 0.81, 95 % CI 0.64–1.02, $P = 0.07$), but calorie intake ≥20 kcal/kg/day was associated with decreased VAP risk (HR 0.68, 95 %

CI 0.57–0.83, $P < 0.001$) compared to calorie intake <20 kcal/kg/day. In patients with liver failure, calorie intake was associated with neither day-28 mortality (HR 1.06, 95 % CI 0.75–1.49, $P = 0.75$) nor VAP risk (HR 1.20, 95 % CI 0.88–1.63, $P = 0.26$) (Tables E5, E6).

Discussion

Our study based on a marginal structural Cox model and a large prospective high-quality database of patients with shock receiving IMV demonstrated that early nutrition, within 48 h after intubation, was associated with decreases in the risks of death and VAP. Neither the route of early nutrition nor delivery of less than 20 kcal/kg/day during the first few days of IMV was associated with mortality or risk of VAP.

A major finding from our study is that early nutrition was associated with decreased mortality in patients with shock and IMV, compared to delayed nutrition. This finding was entirely related to a decrease in mortality during the first 7 days of IMV. We are not aware of other studies investigating associations between early nutrition and outcomes of ICU patients, regardless of route of delivery. As EN is generally considered preferable over PN, previous studies, including meta-analyses, compared early EN to delayed EN. Guidelines recommend EN initiation as early as possible, and never later than 48 h after ICU admission [1–3]. However, data on outcomes associated with early EN are conflicting. In a retrospective multicentre study of over 4,000 patients receiving IMV, EN started within 48 h of MV onset was associated with a significantly decreased mortality, and this association was chiefly ascribable to the sickest patients [11]. Our study shows that the association between early nutrition and survival is robust even after adjusting for possible confounders. One meta-analysis suggested that early EN delivered within 36 h after hospital admission or surgery might decrease infections and hospital stay length but not mortality [28], whereas another showed significant decreases in mortality and pneumonia rates with early EN within 24 h of injury or ICU admission versus delayed EN [29]. However, the overall quality of the studies included in these meta-analyses was poor. More recently, an observational study suggested decreased mortality with EN started within 48 h of intubation versus delayed EN in patients receiving IMV and vasopressors [12]. However, the definition of early EN remains unclear and varies across studies and guidelines, depending on the landmark used (e.g. hospital admission, ICU admission, onset of illness, or intubation). Early EN was usually defined as EN initiation within 24–48 h after the landmark. In our study, we chose intubation as the landmark, as intubated patients are completely unable to eat. Our choice of a 48-h interval since intubation to define early EN is consistent with several recent studies on early EN in patients receiving MV [11, 12, 30, 31]. Two randomised trials focussing on the best time for starting supplemental PN in patients intolerant to EN yielded conflicting results [22, 32]. A recent randomised trial in patients with contraindications to EN demonstrated decreases in costs and IMV duration but no impact on mortality or ICU stay length with PN started within 24 h of ICU admission compared to standard care [33, 34]. However, in the standard-care group, 56.5 % of patients received PN within 3 days after admission and 29.2 % received EN despite contraindications to this route. Finally, a very recent randomised trial compared early EN to early PN (both initiated within 36 h after ICU admission) in unselected ICU patients and found no differences in outcomes [21]. Our study is thus the first to suggest a clear benefit from early nutrition, delivered enterally or parenterally, in patients with severe critical illnesses.

Another striking finding from our study is that the feeding route in patients with early shock and IMV was not associated with survival in the overall study population. This result is consistent with those from a study in unselected critically ill patients [21]. In our EN group, the risk of VAP was increased during the first 7 days but was decreased later on. Although EN is widely viewed as better than PN in ICU patients, this opinion does not rest on sound scientific evidence [35, 36]. According to several studies, EN may improve gut mucosal integrity, decrease nosocomial infections and organ failures, and improve outcomes, compared to PN. However, a meta-analysis comparing early EN to early PN in hospitalised patients showed fewer infections with EN but no effect on mortality [37]. In another meta-analysis, mortality was lower with PN than EN [38, 39]. In our study, results in patients with renal or liver failure suggest that early EN might be deleterious in the most severely ill patients with IMV and shock. Studies focussing specifically on shock showed that many patients received PN despite having no contraindications to EN [5, 6]. Guidelines indicate that EN should be withheld or delayed in patients with haemodynamic instability or catecholamine therapy, who make up over 50 % of all patients receiving IMV [2, 3]. Our results suggest that PN may be the best first-line route for early nutrition in patients with IMV and shock. Further work is needed to assess this possibility.

The mechanisms underlying the survival benefits associated with early nutrition in our study are unclear. Delaying nutrition allows more time for nutritional deficiencies to develop [40–42]. However, no accurate information exists on the calorie requirements of individual ICU patients, which may depend on the disease, pre-existing nutritional status and acute illness severity. In recent studies, lower calorie intakes than recommended in guidelines were associated with similar or improved outcomes [22, 23, 43]. In our work, patients given less than 20 kcal/kg/day during the first few days of IMV had similar outcomes to those with higher calorie intakes. Thus, complete (or nearly complete) absence of nutrient supply during the first few ICU days may have a greater adverse effect on outcomes of patients with shock and IMV than the amount of nutrients supplied. The optimal calorie and protein supply in early stage critical illnesses remains to be determined, and one possibility is that supplies exceeding a certain amount may be deleterious [22, 34]. Thus, during the early management of patients with shock and IMV, low-volume trophic feeding might deserve consideration not only for EN but also for PN. The main goal of nutritional support does not seem to be maintenance of gut mucosal integrity, but, instead, maintenance of immune function, tissue repair mechanisms and muscle mass.

Our study has several limitations. First, the database was not specifically designed for the study and contained no details on micronutrient supply, EN intolerance, glycaemia control, calorie and protein targets for individual patients, reasons for delayed nutrition, feeding formulae, exact nutritional and non-nutritional calorie intakes, actual nurse-to-patient ratio, feeding protocol of each ICU or treatment limitation decisions. Thus, we cannot exclude that between-group differences in these variables may have influenced our results. Second, the study was observational and the interventions were not randomised. Nutritional support modalities were not standardised but instead complied with the protocols of each ICU. Furthermore, substantial changes in ICU management have occurred over the 16-year inclusion period. The randomised controlled design remains the reference standard for demonstrating causal relationships between interventions and outcomes. Nevertheless, observational studies are more relevant to everyday practice. Moreover, by using propensity score analysis and minimising potential confounding, we produced comparable groups. However, we cannot rule out the existence of residual confounding factors. The major strengths of our study are the powerful design and large number of patients enrolled in numerous ICUs across France. We are confident that these strengths produced robust, reliable and widely applicable findings. Last, our study does not provide information on the physiological mechanisms underlying the survival benefits associated with early nutrition. This point deserves further investigation.

Conclusion

Our results obtained using a marginal structural model design strongly suggest that ICU patients with shock may benefit from starting nutritional support early after IMV initiation. Neither feeding route nor early calorie intake was associated with mortality. Despite our careful methodology involving a propensity score analysis to eliminate the potential impact of confounders, the results of our observational study require further evaluation using a randomised controlled design.

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