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# Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: a randomized clinical trial

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**Abstract** *Objectives:* We compared early parenteral nutrition (PN) and early enteral immunonutrition (iEN) in critically ill patients, distinguishing those with and without severe sepsis or septic shock (SS) on admission to intensive care units (ICUs). *Design and setting:* Multicenter, randomized, unblinded clinical trial in 33 Italian general ICUs. *Patients and participants:* The study included 326 patients, 287 of whom did not have SS on ICU admission. Eligibility criteria excluded the two tails in the spectrum of critical conditions, i.e., patients either too well or too ill. Of the patients recruited 160 were randomized to iEN (142 without SS) and 166 to PN (145 without SS). *Interventions:* Patients were randomized to two arms: early iEN or early PN. *Measurements and results:* Primary endpoint was 28-day mortality for all patients and the occurrence of SS during ICU stay for patients admitted without such condition. While 28-day mortality did not differ between iEN and PN (15.6% vs. 15.1%), patients without SS who received iEN had fewer episodes of severe sepsis or septic shock (4.9% vs. 13.1%). ICU length of stay was 4 days shorter in patients given iEN. *Conclusions:* Compared to parenteral nutrition iEN appears to be beneficial in critical patients without severe sepsis or septic shock. Parenteral nutrition in these patients should be abandoned, at least when enteral nutrition can be administered, even at an initial low caloric content.

**Keywords** Critical illness · Enteral nutrition · Parenteral nutrition · Immunonutrition · Sepsis · Pneumonia

## Introduction

Early, adequate nutritional support is important for critically ill patients [1, 2]. Parenteral nutrition (PN) allows easy administration of the planned amount of calories, substrates, and micronutrients [3, 4, 5]. However, in addition to evidence of gut atrophy and bacterial translocation due to the absence of enteral foodstuff in animals [6], PN

causes more hyperglycemia and infections [7]. Therefore enteral nutrition (EN) may be best in critical illness [1, 2, 5, 7, 8, 9, 10, 11], although evidence rests mainly on studies of elective surgical or trauma patients [9, 10, 11, 12, 13]. The benefit of EN is reduced if the start of feeding is delayed by as little as 72 h after injury in animals [14] and by 4–6 days after surgery or onset of sepsis in humans [15]. Critically ill adults are consistently hypermetabolic and catabolic; they are often nonsurgical patients, and it is therefore difficult to establish the exact onset of the reaction to injury. Moreover, they are referred to ICUs with variable delays. In this patient population early nutrition is not always easy to arrange [1, 2, 9, 16], as reflected by the fact that PN is still widely used in ICU patients [9, 17]. Special enteral formulations designed to improve immune function have shown promising effects mainly in postsurgical and trauma patients [18, 19].

With the purpose of seeking which nutrition is best for critical patients, in 1999 we launched a multicenter, randomized, unblinded clinical trial comparing early PN (ensuring adequate nutritional support from the start) with early EN enriched with immune-modulating nutrients (iEN). The aim was to test whether iEN reduced (a) mortality and (b) severe sepsis or septic shock. The protocol therefore distinguished at study entry patients with or without severe sepsis or septic shock. The results for patients admitted with severe sepsis or septic shock have been reported elsewhere [20]. Here we present the overall result and concentrate on the findings on nonseverely septic patients.

## Materials and methods

The study was carried out by 33 adult ICUs affiliated with the Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GiViTI, Italian Group for the Evaluation of Interventions in Intensive Care Medicine). The ICUs had a mean of $8.3 \pm 3.4$ beds. Between November 1999 and December 2001 a total of 326 patients had been enrolled, 287 of whom did not have severe sepsis or septic shock. Recruitment in each ICU averaged 9.3 months (range 2–23). The mean number of patients randomized per ICU per month was $1.06 \pm 0.65$). Patients aged over 18 years judged by attending physicians to need artificial ventilation and nutrition for at least 4 days were eligible. Exclusion criteria were: contraindication to PN or EN, motor Glasgow Coma Scale less than 4, pure cerebral disease, spinal trauma, and referral from ICUs in which patients had spent more than 24 h. The protocol was approved by each hospitals' ethics committee. Patients' written consent was obtained when possible, and otherwise physicians enrolled patients according to the European Guidelines for Good Clinical Practice [21].

Baseline characteristics of patients were recorded at enrollment. The Simplified Acute Physiology Score II variables [22] were recorded at ICU admission. Length of stay (LOS) and vital status at discharge and 28 days after randomization were noted. For 14 days after enrollment the following data were recorded daily: nutritional regimen, presence/absence of septic conditions (according to the American College of Chest Physicians/Society of Critical Care Medicine) criteria [23], diagnosis of infections according to CDC criteria [24], Sequential Organ Failure Assessment (SOFA) score [25], and the Nine Equivalents of Nursing Manpower Score [26]. Infections were diagnosed by attending physicians; a suspected infection was not accepted as a diagnosis of infection (Electronic Supplementary Material, part B sets on CDC criteria).

Eligible patients were randomized into two arms. One was given PN (containing 59% carbohydrate, 23% fat, 18% protein, 1.2 kcal/ml), and the other was given iEN (Perative, 55% carbohydrate, 25% fat, 21% protein, 1.3 kcal/ml, containing per 100 ml: 0.8 g l-arginine, 0.15 g ω-3 fatty acids, 0.7 g ω-6 fatty acids, 2.9 mg vitamin E, 0.75 mg β-carotene, 2.2 mg zinc, and 7 μg selenium). PN and iEN were supplied by pumps 24 h a day. PN was delivered at 25–28 kcal/kg body weight per day, not supplemented with enteral feeding before day 6 after randomization. iEN started at 10 kcal/kg, rising to 25–28 kcal/kg by the fourth day. No adjuvant feeding solutions were allowed when at least 300 kcal were given on the first day, 600 kcal on the second, and 900 kcal from the third to the sixth days. From the sixth day a minimum of 25 kcal/kg was mandatory. Blood glucose was kept below 180 mg/dl according to standard practice at the time the study was done.

Block randomization (permuting blocks of four and six) was adopted, with stratification according to center and presence of severe sepsis or septic shock at baseline, as ascertained by attending physicians. Once patients were enrolled and baseline data collection was completed, the coordinating center communicated the computer generated randomization code by telephone to the participating ICU. The PN group had more men than the iEN group, more patients coming from wards and fewer from emergency rooms, and more with multiple organ failure. Other baseline characteristics were similar in the two arms (Table 1). No severe adverse events related to the experimental protocol were observed (e.g., fatal, life-threatening, or permanently disabling complications, or prolonged hospitalization). In 5.2% of the first 6 nutritional days recommended caloric intake was not reached in the iEN group, but in no patient did the iEN (delivered to the stomach in 94.4% of cases) have to be supplemented with parenteral solutions. Since the study compared two different nutritional approaches, the two arms were not isocaloric by design. Nevertheless, caloric differences between PN and iEN were not remarkable (Table 2).

Primary endpoint was 28-day mortality for all patients and the occurrence of severe sepsis or septic shock during

**Table 1** Baseline characteristics of nonseverely septic patients in the enteral immunonutrition (*iEN*) and parenteral nutrition (*PN*) groups (*IQR* Interquartile range, *SAPS II* Simplified Acute Physiology Score II, *NEMS* Nine Equivalent Manpower Score, *SOFA* Sepsis-Related Organ Failure Assessment)

| | iEN ($n = 142$) | PN ($n = 145$) |
|---|---|---|
| Sex: M/F | 101/41 | 112/33 |
| Age (years) | $51.5 \pm 22.9$ | $49.2 \pm 26.0$ |
| Age >60 years | 68 | 63 |
| Admission to ICU from | | |
| Emergency room | 94 | 84 |
| Operating room | 13 | 12 |
| Ward | 30 | 42 |
| Another ICU | 5 | 7 |
| Admission to ICU for | | |
| Respiratory failure | 68 | 69 |
| Cardiovascular failure | 5 | 3 |
| Neurological failure | 10 | 5 |
| Multiple organ failure | 59 | 68 |
| Admission | | |
| Nonsurgical patient | 105 | 106 |
| Emergency surgery | 30 | 30 |
| Malnutrition[a] | 5 | 5 |
| SAPS II, median (IQR) | 35.5 (27–45) | 37 (26–45) |
| Time to starting nutrition (h) | 30.1 (13.8) | 32.0 (12.2) |
| NEMS, median (IQR) | 32 (27–34) | 29.5 (27–34) |
| SOFA, median (IQR) | 6 (4–8) | 6 (4–8) |

[a] Body mass index $< 20$ in men, $< 19$ in women

**Table 2** Daily caloric intake (kcal/kg per day) in nonseverely septic patients in the enteral immunonutrition (*iEN*) and parenteral nutrition (*PN*) groups

| Day | iEN | PN |
|---|---|---|
| 1 | $11.3 \pm 4.7$ | $18.3 \pm 6.9$ |
| 2 | $16.7 \pm 5.6$ | $23.9 \pm 8.2$ |
| 3 | $21.2 \pm 5.8$ | $25.0 \pm 8.3$ |
| 4 | $24.3 \pm 6.9$ | $24.7 \pm 8.8$ |
| 5 | $24.3 \pm 8.5$ | $25.6 \pm 8.4$ |
| 6 | $24.5 \pm 8.2$ | $25.5 \pm 8.6$ |
| Mean | $20.0 \pm 8.3$ | $23.7 \pm 8.6$ |

ICU stay, regardless of the site of infection, for patients admitted without severe sepsis or septic shock. Sepsis was automatically defined according to adopted criteria [23]. Secondary endpoints for patients admitted without severe sepsis or septic shock were: length of stay (LOS), the occurrence of organ failure according to SOFA score, the number of days spent on a ventilator, all markers of the process of care quantifying clinical instability.

The study was sized to have 90% power to detect an improvement in 28-day mortality from the expected 35% with PN to 26% with iEN (25% relative improvement) or 80% power to detect an improvement from 35% to 28% (20% relative improvement), with a two-tailed 5% type I error. About 1,500 patients were needed. One interim analysis was considered after enrolling 750 patients, and the level of significance was planned to be 0.01, according to the Haybittle–Peto stopping rule [27].

Figure 1 shows the flow of participants. Three nonsurgical patients were erroneously randomized to the nonseptic stratum (two in the PN, one in the iEN), as they met septic criteria. The two patients assigned to the parenteral group were aged 66 and 71 years; their Simplified Acute Physiology Score II predicted 82% and 72% probability of dying [22], and their ICU LOS was 38 and 53 days. The first patient died in hospital 48 days after randomization. The patient randomized to the iEN arm was aged 74 years, with 35% expected probability of dying. He spent 28 days in the ICU and was discharged alive from hospital 35 days after randomization. These three patients were excluded from this analysis and included in that of septic patients where they actually belonged [20].

## Homogeneity and quality of the study

We organized a mandatory 3-day residential course on nutritional management in critical care for at least one physician and one nurse from each ICU before starting the trial. Each ICU also ran its own pilot phase during which it had to correctly perform and fully document the experimental protocol (6 days of early iEN) in three critical patients. During recruitment we provided each ICU with: (a) general and personalized progress reports focusing on problems experienced by investigators, (b) software for easy computation of the nutritional protocol, (c) four investigators' meetings centered on patient recruitment, and (d) site visits to ICUs with specific protocol problems.

## Premature stopping of the trial

When we became aware of the results of a meta-analysis on the same subject [28], we carried out an anticipated analysis. Since this interim analysis revealed excess mortality in the subgroup of severely septic patients randomized to iEN (data reported elsewhere [20]), we stopped randomizing them in April 2001. After that date the accrual rate of nonseverely septic patients, which was already lower than expected, further dwindled, so the trial was eventually stopped at the end of 2001.

## Statistics

Categorical variables were compared with the Mantel–Haenszel $\chi^2$ test or Fisher's exact test. Effect size was expressed in terms of absolute risk difference (ARD) with its 95% confidence interval (95%CI). Continuous variables were compared by the *t* test; results are expressed as mean and standard deviation (SD) or median and interquartile range (IQR). The cumulative incidences of severe sepsis or septic shock were computed with the Kaplan–Meier method and compared by the log-rank test.

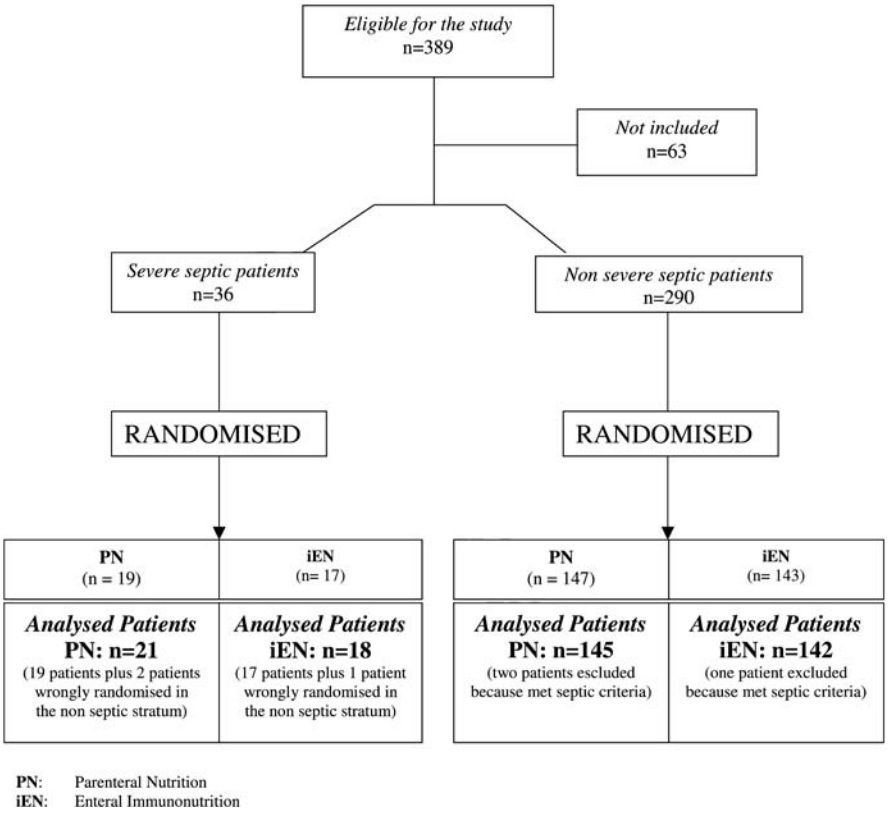


**Fig. 1** Flow of participants through each stage of the trial

Cumulative incidence can be taken as an analysis of time from randomization to the first occurrence of severe sepsis or septic shock for each patient. Patients who did not have such an event were right censored at the time of ICU discharge. Cox analysis was used to adjust for possible confounders. The confounders tested were: total calories per kg body weight received during the first 3 days, sex, source of ICU admission, and multiple organ failure on admission. The adjusted analysis was planned only for the first variable since the protocol considered different caloric intakes in the two arms for the first 3 days. Adjustment for the other variables was suggested by their relative imbalance at baseline. For each variable considered the proportional hazards assumption was checked with the graphic approach of comparing log–log survival curves and using time-dependent covariates in an extended Cox model. All analyses were by intention-to-treat and were carried out with SAS version 8.2.

## Results

Twenty-eight mortality did not differ between the two arms: 15.6% (25/160) with iEN and 15.1% (25/166) with PN ($p = 0.89$). The effect of iEN compared to PN on 28-day mortality differed in patients with and without severe sepsis or septic shock: the absolute risk difference was, respectively, 44.4% (8/18)–23.8% (5/21) = +20.6% in patients with severe sepsis or septic shock, and 12.0% (17/142)–13.8% (20/145) = –1.8% in patients without such condition. Nevertheless, the interaction test was not significant ($p = 0.136$), meaning that there is no evidence that the effects on 28-day mortality differed with or without severe sepsis or septic shock. In contrast, the effects did differ on ICU mortality at the interim analysis, as reported elsewhere [20]. This result was confirmed here (absolute risk difference: 30.2% and –5.9%, respectively; interaction test: $p = 0.01$, after applying Bonferroni's correction for multiple comparisons). We stopped recruiting severely septic patients and continued randomizing patients admitted without severe sepsis or septic shock. On account of this we concentrate below on the separate analysis of nonseverely septic patients. Table 3 summarizes results for each group and the estimated effect size. We found no real effect on mortality at 28 days, but a significant difference in the occurrence of severe sepsis or septic shock. The magnitude of this difference can be expressed as follows: the number of patients needing to be fed with iEN to prevent severe sepsis or septic shock in one patient in the ICU was 12.2 (95% CI: 6.8–62.5). PN patients had a longer ICU stay; other markers of process of care were similar in the two groups.

The site of the main infection in each patient is summarized in Table 4. The cumulative incidence of severe

**Table 3** Summary of results in nonseverely septic patients in the enteral immunonutrition (*iEN*) and parenteral nutrition (*PN*) groups (*ARD* absolute risk difference, *MH* Mantel–Haenszel $\chi^2$ test, *AMD* absolute mean difference, *LOS* length of stay, *NEMS* Nine Equivalents of Nursing Manpower Score, *SOFA* Sequential Organ Failure Assessment)

| | PN ($n=145$) | iEN ($n=142$) | ARD | AMD | 95% CI | Test | $p$ |
|---|---|---|---|---|---|---|---|
| Primary endpoint | | | | | | | |
| First major septic complication | 19 (13.1%) | 7 (4.9%) | 8.2 | – | 1.6 to 14.8 | Fisher | 0.022 |
| Secondary endpoints | | | | | | | |
| Multiple organ failure | 56 (38.6%) | 45 (31.7%) | 6.9 | – | −4.1 to 17.9 | MH | 0.220 |
| ICU LOS (days) | 21.6 (18.7%) | 17.6 (15.5%) | – | 4.0 | 0.04 to 8.01 | *t* for unequal variances | 0.047 |
| Hospital LOS (days) | 36.8 (28.5%) | 32.2 (29.1%) | – | 4.6 | −2.2 to 11.3 | *t* | 0.175 |
| SOFA, area under first 6-day curve | 27.6 (15.7%) | 25.6 (14.6%) | – | 2.0 | −1.5 to 5.5 | *t* | 0.265 |
| NEMS, area under first 6-day curve | 169.8 (47.0%) | 167.0 (45.1%) | – | 2.6 | −8.1 to 13.4 | *t* | 0.632 |
| Ventilator days/study days | 0.83 (0.23%) | 0.82 (0.21%) | – | 0.002 | −0.42 to 0.45 | *t* | 0.524 |

**Table 4** Site of the main infection per patient in the two arms (only the first infection per patient was considered) in the enteral immunonutrition (*iEN*) and parenteral nutrition (*PN*) groups

| Infection | iEN ($n=142$) | PN ($n=145$) |
|---|---|---|
| Pneumonia | 4 | 11 |
| Bacteremia | 1 | 2 |
| Abdominal | 1 | 2 |
| Lower respiratory tract | 1 | 1 |
| Bone | 0 | 1 |
| Urinary tract | 0 | 1 |
| Pneumonia and bacteremia | 0 | 1 |
| Total | 7 | 19 |

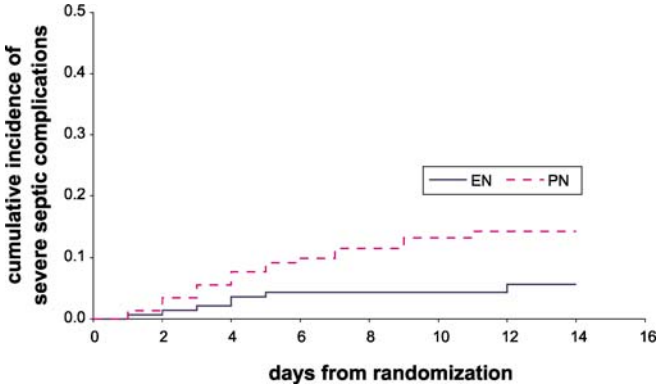


**Fig. 2** Cumulative incidence of severe sepsis or septic shock for enteral and parenteral nutrition (*iEN*, *PN*), in patients admitted without severe sepsis or septic shock. Log-rank test 5.44, $p=0.02$

sepsis or septic shock for both iEN and PN is plotted in Fig. 2. The distribution of the ICU LOS in censored patients (those who did not develop severe sepsis or septic shock) was similar to that in noncensored ones (median 14 days, IQR 9–24, vs. median 18.5, IQR 8–34). This reduces the likelihood of bias due to early censoring. The difference between the two curves proved to be significant (log-rank test 5.44, $p=0.020$). The Cox model gave a hazard ratio of 2.68 (95% CI: 1.13–6.38) for PN vs. iEN. None of the covariates tested (calories received in the first 3 days, sex, source of ICU admission, multiple organ failure on

**Table 5** Results of the Cox proportional hazards models on the occurrence of severe sepsis or septic shock (*HR* hazard ratio, *CI* confidence interval, *PN* parenteral nutrition, *iEN* enteral immunonutrition, *ER* emergency room)

| | HR | 95% CI | $p$ |
|---|---|---|---|
| Model 1 | | | |
| Treatment: PN vs. iEN | 2.68 | 1.13–6.38 | 0.026 |
| Model 2 | | | |
| Treatment: PN vs. iEN | 2.69 | 1.07–6.77 | 0.036 |
| kcal/kg in the first 3 days[a] | 1.00 | 0.98–1.02 | 0.813 |
| Model 3 | | | |
| Treatment: PN vs. iEN | 2.55 | 0.99–6.55 | 0.052 |
| kcal/kg in the first 3 days[b] | 1.00 | 0.98–1.02 | 0.734 |
| Sex: F vs. M | 0.80 | 0.31–2.06 | 0.646 |
| Source of ICU admission | | | |
| ER vs. operating room | 1.40 | 0.17–11.38 | 0.751 |
| Hospital ward vs. operating room | 4.81 | 0.61–38.23 | 0.137 |
| Another ICU vs. operating room | 4.31 | 0.38–49.22 | 0.239 |
| Multiple organ failure on admission | 1.00 | 0.45–2.26 | 0.993 |

[a] Continuous variable [b] Continuous administration

admission) confounded these estimates (Table 5). The average duration of severely septic conditions was similar for iEN and PN (4.6 and 3.6 days).

## Discussion

Apart from the fact that early nutrition seems favorably to influence morbidity and mortality [4, 5, 7, 8, 11, 12, 13, 18], there is still debate about the best nutritional approach for critically ill patients. We compared two strategies for providing early nutrition in critically ill patients: total early PN ensuring an adequate nutritional support from the start, and early iEN with a formula containing immune-modulating nutrients, thought to be beneficial in severely ill patients [2, 8, 12, 16, 19, 29, 30]. The macronutrient composition of the two diets was similar.

The data reported refer to patients admitted to ICUs without severe sepsis or septic shock. The protocol distinguished three different main analyses, with three different outcomes. (a) For the overall population the main outcome was 28-day mortality. (b) For patients entered with severe sepsis or septic shock the main outcome was ICU mortality. The rationale for this was that early iEN, irrespective of the final outcome, could help patients to overcome their septic condition. The assumption of accepting ICU mortality as a good endpoint in this case was that intensivists did not discharge patient to a ward if still septic. (c) For patients entered without severe sepsis or septic shock the main outcome was the occurrence of such a condition, during ICU stay. The rationale for this was that early iEN, irrespective of the final outcome, protected patients from developing sepsis.

Surprisingly, at interim analysis we found a significant, qualitative interaction between the presence of severe sepsis or septic shock and the treatment effect. At ICU discharge iEN was harmful in severely septic patients and beneficial in the other patients [20]. This result was confirmed in the present analysis. Therefore, although we had not defined in advance the threshold-for-stopping decision in case of futility, for ethical reasons we stopped recruiting severely septic patients and continued randomizing patients admitted without severe sepsis or septic shock. Sample size was not recalculated since it already gave 80% power for detecting the hyposthesized difference in the main outcomes in nonseverely septic patients (i.e., from 15% occurrence of severe sepsis or septic shock to 10%). Since randomization was from the outset stratified according to the presence or absence of severe sepsis or septic shock, the closing of one stratum did not affect the correctness of randomization. In this regard, although the analysis of patients admitted to ICU without severe sepsis or septic shock was originally planned as a subgroup analysis, the significant interaction test and the continuation in randomizing nonseverely septic patients, which provided about one-third more patients in this stratum, configures this study as other from the original one. Nevertheless, since this is a quite intriguing case, we provide the results on the original main outcomes (ICU and 28-day mortality) in all patients but concentrate on nonseverely septic ones.

Our nonseptic population consisted of critically ill patients, most with medical conditions (Table 1), excluding patients with either a very poor or a very good prognosis (i.e., those too ill: motor Glasgow Coma Scale lower than 4, pure cerebral disease, spinal trauma, unstable 48 h after admission; or those too well: expected ventilator dependency shorter than 4 days, in other words patients reasonably expected neither to die nor to become infected). This choice, recommended for clinical trials on septic patients [31], gave a homogeneous case-mix in terms of severity of illness, organ failure, LOS, nursing need, and invasive respiratory assistance. Recent recommendations about blood glucose control policies, which have been shown to reduce mortality (after our study was completed), were not implemented in the study design. A general recommendation existed at the time to keep blood glucose below 180 mg/dl. Unfortunately, stopping the trial prematurely because of a low recruitment rate meant that it was underpowered to evaluate the effect on mortality. Nevertheless, we could still see that iEN lowered the risk of developing severe sepsis or septic shock, compared to PN.

Our results in nonseptic patients raised many questions, but one is especially salient. Can the advantage of iEN over PN be attributed to the immune-modulating properties of the specific preparation used in this trial or to the route of administration itself? An answer might have been forthcoming if the trial had been carried out according to its original design, i.e., with a third arm receiving standard EN. However, the standard EN arm had to be dropped before the study began because of funding shortage. Therefore we can attempt to answer the question only by comparing our results with those from the literature. Our finding of a beneficial effect of iEN over PN in the incidence of severe sepsis or septic shock in nonseverely septic ventilated patients is consistent with results in various populations in which EN has proven better than PN [1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 16]. This suggests that the route of administration plays an important role in improving outcome. However, in our series the benefit of iEN (admittedly based on small numbers) seems due mainly to a difference in lung infections (Table 4), an effect that cannot strictly be explained by the route of administration, from a purely pathophysiological perspective. This finding is in fact at variance with the recently reported higher incidence of ventilator-associated pneumonia in EN vs. PN [32, 33] and in early vs. late bolus EN [34], despite a lower overall incidence of infections in EN than PN. Accordingly, we would have expected that properly administered early iEN, given by continuous pump infusion to minimize the risk of aspiration, would have been associated with a risk of pneumonia similar to that of patients given PN. Since we found

almost three times the lung infections in PN compared to iEN, it seems reasonable to assume some additional benefit of iEN over both EN and PN.

On the other hand, the incidence of blood-borne infections was very low, without any difference between groups. This is at odds with a previous study comparing standard and iEN in ICU patients with low- to medium-severity illness [35]. The low incidence of blood-borne infections may reflect good medical and nursing management of vascular lines, especially in the PN group. The same findings suggest that the route of administration itself may not explain our results. We also believe that the residential course which we offered participants at the beginning of the trial and the monitoring were useful in ensuring the quality of nutrition actually administered to patients. Our data are consistent with those from studies comparing EN with PN [1, 2, 3, 7, 8, 9, 10, 11, 12, 13] and immunonutrition with standard nutrition in elective surgical patients with low- to medium-severity illness [1, 2, 18, 19, 29, 30, 35]. Both the enteral route of administration and the so-called immunomodulating nutrients added to some EN formulae may have beneficial roles in nonseptic ICU patients, and these roles may be synergistic.

Caloric intake, which differed by design in the iEN and PN groups, does not explain the difference in severe sepsis or septic shock in the multivariate models. The fact that caloric intake did not influence the occurrence of severe sepsis or septic shock indirectly supports the notion that if feeding the patient is a primary goal of ICU physicians, it can be achieved, i.e., the desired amount of nutrients can be given to critically ill patients even by EN [36, 37, 38, 39, 40]. The advantage in terms of less severe sepsis or septic shock translates further into a lower burden of care, which is in turn reflected by a 4 days shorter ICU stay. Since the unblinded nature of the trial could have introduced an outcome detection bias, the consistency of these data is important in giving credibility to the results. Other parameters such as overall or highest SOFA scores, cumulative Nine Equivalents of Nursing Manpower Use Score scores and number of days on a ventilator were similar (Table 3). iEN does not, however, ensure better survival, as mortality rates at 28 days closely overlap.

In conclusion, (a) EN should be started as soon as possible by continuous pump infusion in all ICU patients, including those with medium- to high-severity illness; (b) PN should be abandoned in these patients, at least when EN can be administered, even at an initial low caloric intake; (c) iEN should be avoided in septic critically ill patients because of its proven excess risk, although it may be worth considering in nonseptic patients. Since the evidence supporting the use of immunonutrition in nonseptic patients is still provisional [41, 42], we suggest it be reserved for selected patients at high risk of infection. These patients should be at least enrolled in outcome research projects to gain conclusive evidence of any benefit of immunonutrition in this population.

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