ORIGINAL ARTICLE

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

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ABSTRACT

BACKGROUND

Critically ill patients have considerable oxidative stress. Glutamine and antioxidant supplementation may offer therapeutic benefit, although current data are conflicting.

METHODS

In this blinded 2-by-2 factorial trial, we randomly assigned 1223 critically ill adults in 40 intensive care units (ICUs) in Canada, the United States, and Europe who had multiorgan failure and were receiving mechanical ventilation to receive supplements of glutamine, antioxidants, both, or placebo. Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally. The primary outcome was 28-day mortality. Because of the interim-analysis plan, a P value of less than 0.044 at the final analysis was considered to indicate statistical significance.

RESULTS

There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00 to 1.64; P=0.05). In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine than among those who did not. Glutamine had no effect on rates of organ failure or infectious complications. Antioxidants had no effect on 28-day mortality (30.8%, vs. 28.8% with no antioxidants; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P=0.48) or any other secondary end point. There were no differences among the groups with respect to serious adverse events (P=0.83).

CONCLUSIONS

Early provision of glutamine or antioxidants did not improve clinical outcomes, and glutamine was associated with an increase in mortality among critically ill patients with multiorgan failure. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT00133978.)

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Critically ill patients have oxidative stress. The most seriously ill patients in intensive care units (ICUs) have increased mediators of oxidant stress and a higher incidence of multiorgan failure than less seriously ill patients.[1-5] Meta-analyses of randomized trials suggest that glutamine and antioxidant supplementation in critically ill patients may be associated with improved survival.[6,7] However, recent large studies have not confirmed such an effect.[8,9] The objective of the present trial was to evaluate the effect of early glutamine and antioxidant supplementation in critically ill patients. Our a priori hypothesis was that supplementation with these nutrients would reduce 28-day mortality.

Methods

Study Participants

Consecutive adults who were receiving mechanical ventilation and who were admitted to participating ICUs were screened for eligibility. Patients were included if they had two or more organ failures related to their acute illness. A complete list of the eligibility criteria is included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design and Interventions

Using a factorial design, we randomly assigned patients to receive glutamine supplementation (0.35 g per kilogram of body weight per day intravenously according to ideal body weight, provided as 0.50 g of the dipeptide alanyl-glutamine [Dipeptiven, Fresenius Kabi] per kilogram per day given intravenously and 30 g of alanyl-glutamine and glycine-glutamine dipeptides per day given enterally) or matching placebo solutions. In addition, patients were randomly assigned to receive 500 μg of selenium intravenously (Selenase, Biosyn) plus the following vitamins and minerals enterally: 300 μg of selenium, 20 mg of zinc, 10 mg of beta carotene, 500 mg of vitamin E, and 1500 mg of vitamin C. The control group received placebo intravenously plus placebo enterally. Study-group assignments were concealed and stratified according to site with the use of permuted blocks of random size and a secure central Web-based system.

To maintain blinding, study supplements and placebos were prepared by an unblinded local study pharmacist and delivered as masked solutions to the ICU. The administration of all study solutions was initiated as soon as possible after randomization; the solutions were administered separately from standard nutrition, were provided continuously, and were administered for a maximum of 28 days, until discharge from the ICU or death. All patients were fed according to the Canadian Critical Care Nutrition practice guidelines, independently of the study supplements.[10] All other management decisions were at the discretion of the ICU team.

The primary outcome was 28-day mortality. Secondary outcomes and data collected in this trial are described in the Supplementary Appendix. In a sample of patients enrolled at seven sites in North America, blood was drawn at baseline, day 4, and day 7 for measurement of plasma glutamine and selenium levels according to standard techniques.

Study Oversight

This investigator-initiated trial was designed by the first author in consultation with the steering committee. The steering committee vouches for the data, the analysis, and the decision to submit the manuscript for publication. All sites listed in the acknowledgments in the Supplementary Appendix participated in the data collection. The last author was responsible for the analysis. The first author and the writing committee wrote the manuscript. The protocol was endorsed and conducted in collaboration with the Canadian Critical Care Trials Group.

The study was funded by the Canadian Institutes of Health Research. Fresenius Kabi provided the glutamine supplements and an unrestricted grant-in-aid. Biosyn provided the intravenous selenium to all participating European sites. None of these agencies had a decision-making role in the design or conduct of the study, analysis or interpretation of data, manuscript preparation, or decision to submit the manuscript for publication.

The study was conducted according to the protocol, which has been published previously[9,11,12] and is available at NEJM.org. This trial was conducted between April 2005 and December 2011 in 40 ICUs in participating countries after approval by local jurisdictional and institutional research ethics boards. Written informed consent was obtained from all patients or their legal representatives before enrollment.

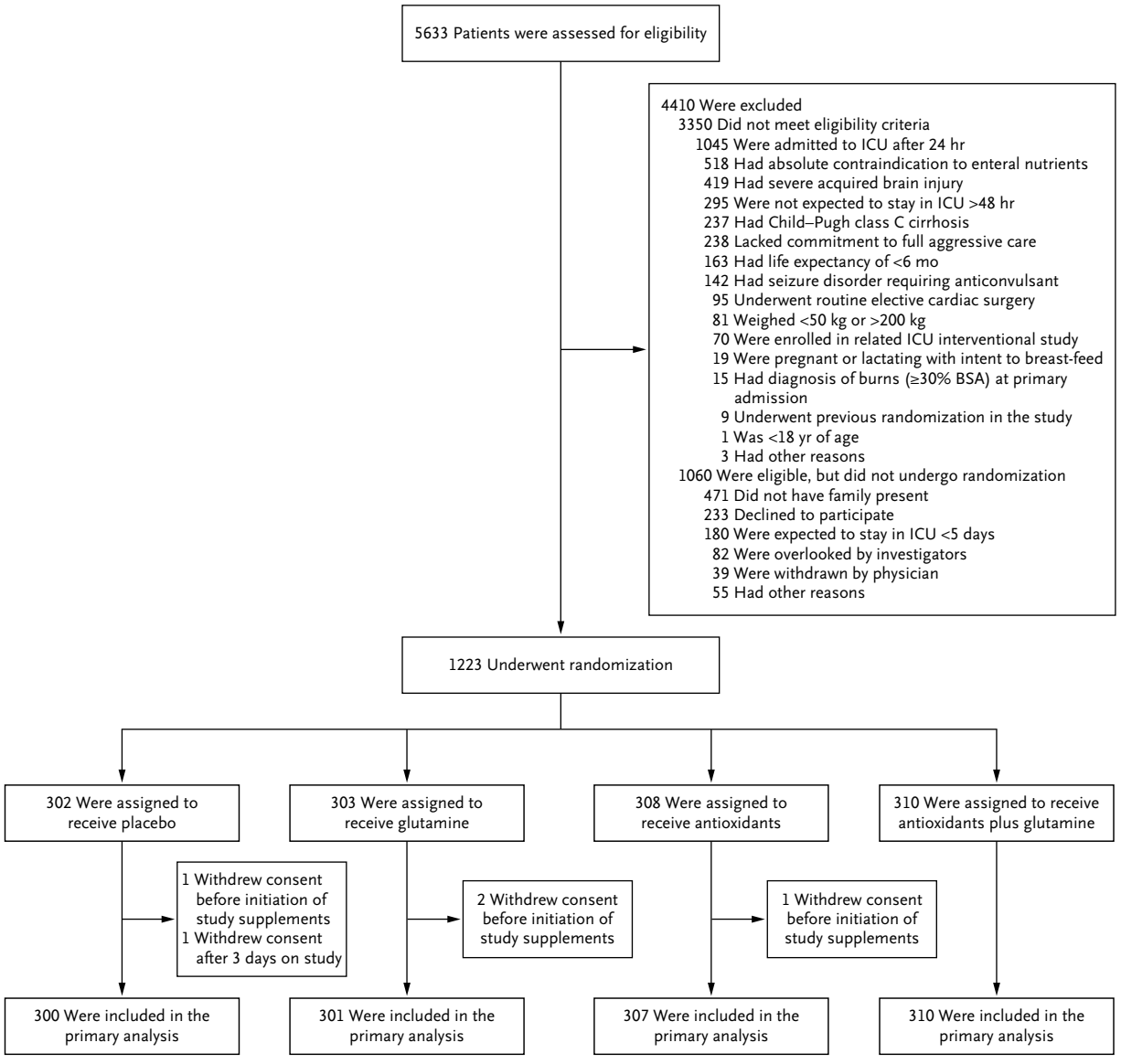

Figure 1. Study Enrollment and Randomization.
BSA denotes body-surface area, and ICU intensive care unit.

STATISTICAL ANALYSIS

Data were analyzed according to the protocol, which included details of the sample-size justification, the interim analyses, and the final analytic plan.[12] In brief, assuming a 28-day mortality of 30%, we planned to enroll 1200 patients who could be evaluated in order to provide 80% power if either intervention (or both interventions) resulted in a 25% relative risk reduction, to 22.5%. Because of two planned interim analyses, a P value of less than 0.044 at the final analysis was considered to indicate statistical significance.

In accordance with the intention-to-treat principle, all patients were included in the group to which they were randomly assigned. In addition, a prespecified efficacy analysis that included only patients who received a study agent for a minimum of 5 days was conducted. In the prespecified primary outcome assessment, we used logistic regression with terms for the pres-

ence or absence of cardiovascular dysfunction, both study agents, and their interaction. The interaction term was dropped when it was not significant. We included odds ratios and 95% confidence intervals in the comparison of 28-day mortality for each intervention, both overall and separately, in the presence and absence of the other intervention.[13] Finally, we conducted analyses involving prespecified subgroups, as described in the Supplementary Appendix.

For all analyses of secondary outcomes, we performed separate comparisons of the two groups that received glutamine with the two groups that did not receive glutamine and the two groups that

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Placebo (N=300)	Glutamine (N=301)	Antioxidants (N=307)	Antioxidants plus Glutamine (N=310)
Age — yr	62.8±13.7 (18.0–89.0)	62.5±15.0 (19.0–91.5)	63.6±14.3 (18.0–92.0)	64.3±14.0 (22.0–92.9)
Sex — no. (%)				
Female	122 (40.7)	110 (36.5)	130 (42.3)	130 (41.9)
Male	178 (59.3)	191 (63.5)	177 (57.7)	180 (58.1)
BMI — range†	29.9±8.3 (17.9–63.1)	29.9±8.9 (16.7–70.4)	29.2±7.9 (15.8–68.5)	30.1±8.6 (15.8–78.3)
APACHE II score — range‡	26.0±7.4 (6.0–49.0)	26.6±7.6 (8.0–48.0)	25.9±7.1 (9.0–51.0)	26.8±7.4 (10.0–49.0)
Charlson comorbidity index score — range§	1.7±1.8 (0.0–8.0)	1.5±1.6 (0.0–8.0)	1.8±1.8 (0.0–10.0)	1.8±1.8 (0.0–11.0)
Functional comorbidity index score — range¶	1.5±1.4 (0.0–6.0)	1.4±1.4 (0.0–7.0)	1.5±1.4 (0.0–6.0)	1.5±1.3 (0.0–7.0)
Admission category — no. (%)				
Medical	236 (78.7)	238 (79.1)	254 (82.7)	235 (75.8)
Surgical				
Elective	26 (8.7)	27 (9.0)	19 (6.2)	35 (11.3)
Emergency	38 (12.7)	36 (12.0)	34 (11.1)	40 (12.9)
Primary ICU diagnosis — no. (%)				
Cardiovascular or vascular disorder	70 (23.3)	54 (17.9)	53 (17.3)	60 (19.4)
Respiratory disorder	97 (32.3)	101 (33.6)	94 (30.6)	83 (26.8)
Gastrointestinal disorder	17 (5.7)	21 (7.0)	32 (10.4)	25 (8.1)
Neurologic disorder	2 (0.7)	4 (1.3)	5 (1.6)	2 (0.6)
Sepsis	86 (28.7)	88 (29.2)	98 (31.9)	106 (34.2)
Trauma	10 (3.3)	9 (3.0)	5 (1.6)	7 (2.3)
Metabolic disorder	6 (2.0)	8 (2.7)	9 (2.9)	5 (1.6)
Hematologic disorder	0	2 (0.7)	0	4 (1.3)
Renal disorder	0	2 (0.7)	0	5 (1.6)
Gynecologic disorder	1 (0.3)	0	0	0
Orthopedic disorder	0	1 (0.3)	2 (0.7)	3 (1.0)
Other disorder	11 (3.7)	11 (3.7)	9 (2.9)	10 (3.2)
Cause of shock — no. (%)				
Cardiogenic	72 (24.0)	54 (17.9)	57 (18.6)	57 (18.4)
Septic	191 (63.7)	206 (68.4)	218 (71.0)	211 (68.1)
Neurogenic	2 (0.7)	3 (1.0)	3 (1.0)	2 (0.6)
Anaphylactic	0	1 (0.3)	1 (0.3)	0
Hemorrhagic	13 (4.3)	10 (3.3)	9 (2.9)	16 (5.2)
Unknown	11 (3.7)	15 (5.0)	13 (4.2)	14 (4.5)
Other	2 (0.7)	3 (1.0)	2 (0.7)	5 (1.6)
Not in shock	9 (3.0)	9 (3.0)	4 (1.3)	5 (1.6)

Table 1. (Continued.)

Characteristic	Placebo (N=300)	Glutamine (N=301)	Antioxidants (N=307)	Antioxidants plus Glutamine (N=310)
Inclusion criteria — no. (%)				
PaO_2:FiO_2 ratio ≤300	282 (94.0)	285 (94.7)	287 (93.5)	285 (91.9)
Clinical evidence of hypoperfusion	277 (92.3)	278 (92.4)	286 (93.2)	293 (94.5)
Renal dysfunction	104 (34.7)	117 (38.9)	99 (32.2)	122 (39.4)
Platelet count ≤50×10^9/liter	16 (5.3)	21 (7.0)	12 (3.9)	18 (5.8)
Duration of ICU stay before randomization — hr				
Median	17.9	17.7	18.4	18.0
Interquartile range	13.4–21.5	12.7–21.1	12.3–21.5	13.3–21.6
No. of failed organs — no. (%)‖				
1	1 (0.3)	2 (0.7)	1 (0.3)	0
2	221 (73.7)	206 (68.4)	236 (76.9)	216 (69.7)
3	76 (25.3)	85 (28.2)	69 (22.5)	90 (29.0)
4	2 (0.7)	8 (2.7)	1 (0.3)	4 (1.3)
Time from first organ dysfunction — hr				
To initiation of enteral supplements				
Median	23.0	21.4	21.5	21.7
Interquartile range	17.0–27.3	15.9–26.4	16.8–26.0	17.0–27.0
To initiation of parenteral supplements				
Median	22.3	21.0	21.1	21.5
Interquartile range	16.5–26.5	14.8–25.0	16.0–25.5	16.3–26.0
To initiation of enteral nutrition				
Median	22.0	21.0	20.4	20.0
Interquartile range	12.5–36.8	11.1–35.0	12.0–34.8	11.8–36.2

* Plus–minus values are means ±SD. FiO_2 denotes fraction of inspired oxygen, ICU intensive care unit, and PaO_2 partial pressure of arterial oxygen.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ The Acute Physiology and Chronic Health Evaluation II (APACHE II) score ranges from 0 to 71, with higher scores indicating more severe disease.
§ The score on the Charlson comorbidity index reflects a weighted sum of 17 medical conditions; scores range from 0 to 37, with higher scores indicating a greater burden of illness.
¶ Scores on the functional comorbidity index range from 0 to 18, with higher scores indicating a greater burden of illness.
‖ Organ failures were defined according to the same criteria used for enrollment.

received antioxidants with the two groups that did not receive antioxidants. Counts and percentages are presented for categorical variables, medians and quartiles for skewed variables, and means, standard deviations, and ranges for other continuous variables. In particular, the quartiles for the duration of mechanical ventilation and of ICU and hospital stays were estimated with a Kaplan–Meier analysis in which data on patients who died before (or within 24 hours after) reaching these discharge or discontinuation events were censored after the end of follow-up (after all event times); death was thereby treated as an event that precluded the possibility of discharge or discontinuation of mechanical ventilation. We also reported length-of-stay variables with death treated as a discharge in patients who died before discharge. Survival rates up to 6 months are shown with the use of Kaplan–Meier curves and compared with the use of the Wald test from the Cox proportional-hazards model, with terms for each study-agent intervention and the presence or absence of cardiovascular dysfunction at baseline. Data on patients whose vital status was unknown at 6 months were censored on the date they were last known to be alive.

Table 2. Odds Ratio for Death According to Study Agent.*

Variable	Antioxidants		Glutamine-Specific Odds Ratio with Antioxidants (95%)	Overall Adjusted Odds Ratio with Antioxidants (95% CI)	P Value
	Yes	No			
Glutamine				1.09 (0.86–1.40)	0.48
Yes — no. of patients who died/total no. (%)	101/310 (32.6)	97/301 (32.2)	1.02 (0.72–1.43)		
No — no. of patients who died/total no. (%)	89/307 (29.0)	76/300 (25.3)	1.20 (0.84–1.72)		
Antioxidant-specific odds ratio with glutamine (95% CI)	1.18 (0.83–1.66)	1.40 (0.98–2.00)			
Overall adjusted odds ratio with glutamine (95% CI)		1.28 (1.00–1.64)			0.05†

* The overall adjusted odds ratios are the estimates of the pooled effect of each study agent, controlled for other study agents; this is the primary outcome. The specific odds ratios are estimates of the effect of each study agent separately with or without the other study agent. All odds ratios have been adjusted for the presence or absence of shock. An odds ratio of more than 1 indicates increased mortality associated with the study agent. P=0.49 for the test of interaction between antioxidants and glutamine.

† No adjustment was made to account for the two interim analyses or multiplicity of tests. Since the protocol specified a nominal significance level of 0.044 at the final analysis to account for the two interim analyses, the primary outcome did not reach formal significance for either intervention.

RESULTS

PATIENTS

We screened 5633 patients; 2283 were eligible, and 1223 were enrolled (Fig. 1). An additional 23 patients were enrolled to compensate for randomly assigned patients who did not receive study supplements because of early death, ICU discharge, or withdrawal from the trial. Five randomly assigned patients could not be evaluated because we could not ascertain their 28-day vital status; thus, there were 1218 patients in the final intention-to-treat analysis. There were no significant differences in baseline characteristics among the four groups (Table 1). Data on the timing and amount of study supplements and the amount of nutrition received are provided in Table 1 in the Supplementary Appendix. Overall, patients received 70.9% of enteral study supplements and 89.1% of parenteral study supplements prescribed.

PRIMARY OUTCOME

The overall 28-day mortality was 29.8% (95% confidence interval [CI], 27.2 to 32.5). At 28 days, there was a trend toward increased mortality among patients who received glutamine as compared with patients who did not receive glutamine (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% CI, 1.00 to 1.64; P=0.05) (Table 2). There was no significant difference in mortality between patients who received antioxidant supplementation and patients who did not receive antioxidants (30.8% and 28.8%, respectively; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P=0.48). There was no significant interaction between glutamine and antioxidants (P=0.49) (Table 2). In the efficacy analysis, the estimate of effects did not change significantly for glutamine versus no glutamine (odds ratio, 1.20; 95% CI, 0.89 to 1.62; P=0.23) or for antioxidants versus no antioxidants (odds ratio, 0.98; 95% CI, 0.73 to 1.32; P=0.90). There were no significant differences in 28-day mortality in any of our a priori subgroup analyses in the intention-to-treat analysis (Fig. 2) or the efficacy analysis comparing the effect of the different study supplements on 28-day mortality (data not shown), and no tests for between-subgroup heterogeneity showed significance (P>0.05 for interaction for all tests).

SECONDARY OUTCOMES

In-hospital mortality and mortality at 6 months were significantly higher among patients who received glutamine than among patients who did not receive glutamine (Table 3, and Fig. 1 in the Supplementary Appendix). There were also significant increases in the median time to discharge alive from the ICU and the median time to discharge alive from the hospital among patients who received glutamine as compared with those who did not (Table 3). For outcomes in the four individual study-agent groups, see Table 2 in the Supplementary Appendix. Glutamine supplementation as compared with no glutamine did not

have a significant effect on the outcomes of organ failure (Table 3 in the Supplementary Appendix) or infections (Table 4 in the Supplementary Appendix). Antioxidant supplementation as compared with no antioxidants did not have a significant effect on any secondary outcome (Table 3, and Tables 3 and 4 in the Supplementary Appendix).

ADVERSE EVENTS

A total of 52 serious adverse events were reported in 46 patients; 4 were considered to be potentially related to study supplements. There were no significant differences in rates of serious adverse events across groups (P=0.83) (Table 5 in the Supplementary Appendix). The frequency of high urea levels (>50 mmol per liter) was higher among patients who received glutamine than among those who did not (13.4% vs. 4.0%, P<0.001).

LABORATORY SUBSTUDY

Baseline median plasma glutamine and selenium levels were within normal limits in 66 substudy patients (Fig. 2 and Table 6 in the Supplementary Appendix). Glutamine supplementation as compared with no glutamine was associated with a significant increase in plasma glutamine levels on both day 4 and day 7 of the ICU stay (P<0.001 for both comparisons). Antioxidant supplementation as compared with no antioxidants was associated with a significant increase from baseline in plasma selenium levels on days 4 and 7 of the ICU stay (P<0.001 for both comparisons). However, median selenium levels remained within normal ranges in both groups at all time points.

DISCUSSION

In this international, randomized, blinded trial involving critically ill patients with multiorgan failure, a nonsignificant increase in 28-day mortality and significant increases in in-hospital and 6-month mortality were observed with the use of glutamine. No effect of glutamine was observed on any other outcome. Antioxidant supplementation was not associated with any effect on study outcomes. In our prespecified subgroup analyses, we did not identify any indication of benefit or harm in the various patient subgroups examined.

The mechanism whereby glutamine may cause harm is unknown. However, several factors may account for the discrepancy between the results of our study and previous findings. First, prior indications of benefit have emerged from the meta-analysis of smaller, less methodologically robust trials.[6] Second, in contrast to patients in previous studies in the ICU setting, patients in our trial received the highest dose of glutamine pre-

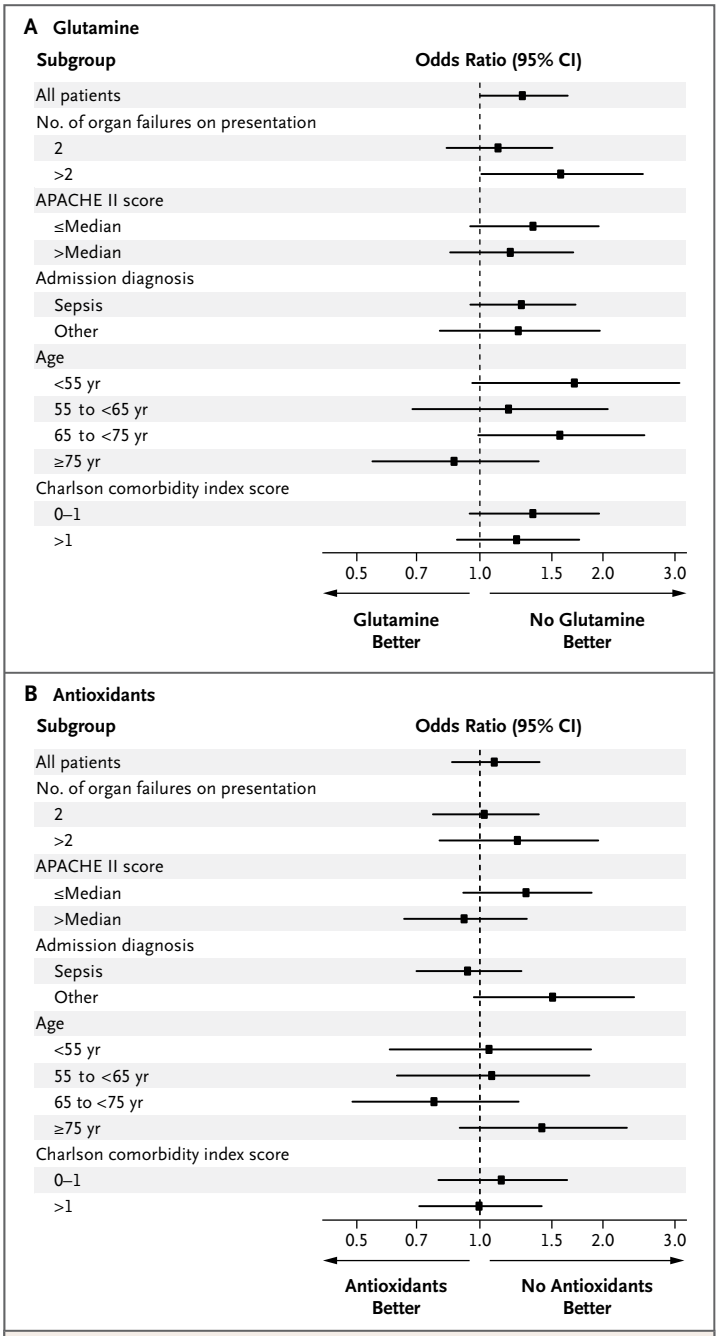

Figure 2. Prespecified Subgroup Analyses of Death at 28 Days, According to Study Group.

Odds ratios and 95% confidence intervals are shown for the primary outcome in each prespecified subgroup. Higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores indicate greater disease severity. CI denotes confidence interval.

Table 3. Clinical Outcomes in All 1218 Study Patients.

Variable	Glutamine	No Glutamine	P Value	Antioxidants	No Antioxidants	P Value
Death — no. of patients/total no. (%)						
At day 28	198/611 (32.4)	165/607 (27.2)	0.05*	190/617 (30.8)	173/601 (28.8)	0.48
At day 14	157/611 (25.7)	129/607 (21.3)	0.07	154/617 (25.0)	132/601 (22.0)	0.23
In hospital	227/611 (37.2)	188/607 (31.0)	0.02	216/617 (35.0)	199/601 (33.1)	0.51
At 6 mo†	259 (43.7)	218 (37.2)	0.02	242 (40.4)	235 (40.6)	0.87
Time from randomization to final discontinuation of mechanical ventilation and alive — days‡						
Median	11.0	8.7	0.03	9.1	10.5	0.67
Interquartile range	4.0–undefined	3.9–58.8		3.9–undefined	4.0–undefined	
Time from randomization to discharge alive from ICU — days‡						
Median	17.1	13.1	0.03	15.1	14.0	0.34
Interquartile range	7.3–undefined	7.1–undefined		7.2–undefined	7.2–undefined	
Time from randomization to discharge alive from hospital — days‡						
Median	51.0	40.1	0.04	43.8	42.7	0.39
Interquartile range	17.9–undefined	16.3–undefined		18.0–undefined	16.2–undefined	
Hospital length of stay — days§						
Median	16.0	17.1	0.15	16.9	16.6	0.97
Interquartile range	7.9–33.9	8.4–36.1		8.0–36.2	8.1–33.0	
ICU length of stay — days§						
Median	8.4	8.9	0.62	8.4	8.9	0.87
Interquartile range	4.4–16.0	5.1–15.3		4.6–15.3	5.1–15.8	
Time from randomization to final discontinuation of mechanical ventilation — days§						
Median	6.1	5.9	0.71	6.0	6.1	0.69
Interquartile range	2.8–12.8	2.9–11.9		2.8–11.8	2.9–12.7	

* A P value of less than 0.044 was considered to indicate statistical significance.
† The number of deaths at 6 months was estimated by means of the Kaplan–Meier method, and these numbers are slightly higher than the result of dividing the number of deaths by the number of randomly assigned patients because some patients were lost to follow-up (i.e., their data were censored) within 6 months after randomization.
‡ In this category, death was considered a competing risk for discharge, so that patients who died before (or within 24 hours after) discharge remained undischarged forever. Interquartile ranges are undefined because more than 25% of patients died before discharge.
§ In this category, death was considered as discharge for patients who died before discharge.

scribed for critically ill patients (i.e., 30 g per day more than the maximal dose used in other studies). Third, we provided both intravenous and enteral supplementation, whereas prior trials used either the intravenous or enteral route exclusively. Fourth, we targeted critically ill patients with multiorgan failure, the majority of whom were in shock, whereas previous studies typically excluded such patients. Fifth, we initiated treatment with the study supplements within 24 hours after admission to the ICU, whereas in other studies, supplements were administered later in the course of critical illness, when parenteral nutrition was required. Finally, most of our patients received enteral nutrition; in contrast, patients in prior trials received parenteral nutrition. The rationale for our study design reflected the view that glutamine is essential in critical illness because of rapid depletion of plasma glutamine levels; furthermore, lower plasma glutamine levels (<420 μmol per liter) have been associated with increased mortality.[14] As such, we hypothesized that critically ill patients with organ dysfunction would be most likely to have low plasma glutamine levels and poor clinical outcomes and would therefore benefit the most from supple-

mentation. However, we did not consistently find a deficiency of glutamine in the substudy involving 66 patients. Before our trial, we performed a dose-finding study[15] to evaluate the safety of this dosing strategy, but the design and small size of the earlier study made it insensitive to the possibly harmful effects that were identified in this larger trial.

With respect to antioxidant supplementation, our trial showed no effect overall or in any subgroup. This finding may reflect the true lack of usefulness of antioxidants; alternatively, it may be due to the characteristics of the study population or to the dose and method of administration in this trial. The laboratory substudy of North American patients did not reveal the selenium deficiency consistently observed in European and South American trials of selenium status in critically ill and healthy persons.[16,17] These differences may reflect the considerable depletion of selenium in soil observed in parts of Europe but not throughout North America.[18] We may have prescribed an insufficient dose of selenium or used an ineffective dosing schedule, since a higher-than-normal level of selenium in the blood may be associated with the best outcome[19] and an initial bolus of selenium might have been more effective than the continuous administration we used.[20]

The strengths of this study include the randomized and blinded design, rigorous determination and adjudication of infection, and intention-to-treat analysis, all of which augment the internal validity of the trial. The high rate of adherence to trial interventions, large number of patients, and enrollment in ICUs in North America and Europe bolster the external validity.

In conclusion, this trial showed that the early administration of glutamine in critically ill patients with multiorgan failure was harmful. The observation that the majority of these patients did not have glutamine deficiency early in the course of their critical illness challenges the prevailing concept that glutamine is an essential nutrient that is deficient in critically ill patients and requires immediate supplementation. We also conclude that antioxidant supplementation as provided in this trial conferred no therapeutic benefit.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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