Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

High-Protein Enteral Nutrition Enriched With Immune-Modulating Nutrients vs Standard High-Protein Enteral Nutrition and Nosocomial Infections in the ICU
A Randomized Clinical Trial

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IMPORTANCE Enteral administration of immune-modulating nutrients (eg, glutamine, omega-3 fatty acids, selenium, and antioxidants) has been suggested to reduce infections and improve recovery from critical illness. However, controversy exists on the use of immune-modulating enteral nutrition, reflected by lack of consensus in guidelines.

OBJECTIVE To determine whether high-protein enteral nutrition enriched with immune-modulating nutrients (IMHP) reduces the incidence of infections compared with standard high-protein enteral nutrition (HP) in mechanically ventilated critically ill patients.

DESIGN, SETTING, AND PARTICIPANTS The MetaPlus study, a randomized, double-blind, multicenter trial, was conducted from February 2010 through April 2012 including a 6-month follow-up period in 14 intensive care units (ICUs) in the Netherlands, Germany, France, and Belgium. A total of 301 adult patients who were expected to be ventilated for more than 72 hours and to require enteral nutrition for more than 72 hours were randomized to the IMHP (n = 152) or HP (n = 149) group and included in an intention-to-treat analysis, performed for the total population as well as predefined medical, surgical, and trauma subpopulations.

INTERVENTIONS High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition, initiated within 48 hours of ICU admission and continued during the ICU stay for a maximum of 28 days.

MAIN OUTCOMES AND MEASURES The primary outcome measure was incidence of new infections according to the Centers for Disease Control and Prevention (CDC) definitions. Secondary end points included mortality, Sequential Organ Failure Assessment (SOFA) scores, mechanical ventilation duration, ICU and hospital lengths of stay, and subtypes of infections according CDC definitions.

RESULTS There were no statistically significant differences in incidence of new infections between the groups: 53% (95% CI, 44%-61%) in the IMHP group vs 52% (95% CI, 44%-61%) in the HP group (P = .96). No statistically significant differences were observed in other end points, except for a higher 6-month mortality rate in the medical subgroup: 54% (95% CI, 40%-67%) in the IMHP group vs 35% (95% CI, 22%-49%) in the HP group (P = .04), with a hazard ratio of 1.57 (95% CI, 1.03-2.39; P = .04) for 6-month mortality adjusted for age and Acute Physiology and Chronic Health Evaluation II score comparing the groups.

CONCLUSIONS AND RELEVANCE Among adult patients breathing with the aid of mechanical ventilation in the ICU, IMHP compared with HP did not improve infectious complications or other clinical end points and may be harmful as suggested by increased adjusted mortality at 6 months. These findings do not support the use of IMHP nutrients in these patients.

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Critically ill patients are at risk of serious nutritional deficits. Therefore, nutritional interventions are required for most ICU patients, with enteral nutrition preferred over parenteral nutrition.[1,2]

Immune-modulating nutrients, such as glutamine, arginine, nucleic acids, omega-3 fatty acids, selenium, and antioxidants, may modulate pathophysiological processes in critical illness, such as inflammatory and oxidative stress responses and impaired (cellular) immune function.[3,4]

Several meta-analyses have reported that use of immune-modulating nutrients in enteral nutrition is associated with reductions in infectious morbidity and improved recovery from critical illness compared with standard enteral nutrition.[5-7] The European Society for Clinical Nutrition and Metabolism guidelines conclude that there is no general indication for immune-modulating nutrients in enteral nutrition in patients with severe illness or sepsis and Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores of more than 15.[1] In contrast, guidelines of the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition indicate that immune-modulating nutrients in enteral nutrition should be used for appropriate patients including critically ill patients who breath with the aid of mechanical ventilation and with caution in patients with severe sepsis, with grade A recommendations for surgical and grade B recommendations for medical ICU patients.[2]

APACHE-II *Acute Physiology and Chronic Health Evaluation II*

DHA *docosahexaenoic acid*

EPA *eicosapentaenoic acid*

HP *standard high-protein enteral nutrition*

ICU *intensive care unit*

IMHP *high-protein enteral nutrition enriched with immune-modulating nutrients*

LCP *long-chain polyunsaturated fatty acids*

SOFA *Sequential Organ Failure Assessment*

Both guidelines recommend use of high-protein enteral nutrition to achieve target protein intake of 1.2 to 2.0 g/kg of body weight per day, supported by recent observational studies showing reduced mortality in ICU patients reaching higher protein targets.[8,9]

An enteral nutrition intervention study with appropriate power to detect effects on clinical outcome in heterogeneous mechanically ventilated critically ill patients comparing standard high-protein enteral nutrition (HP) with high-protein enteral nutrition enriched with the immune-modulating nutrients (IMHP) glutamine, omega-3 fatty acids, and anti-oxidants has not been performed. We aimed to evaluate whether a new IMHP enteral feed compared with an isocaloric enteral feed with similarly high-protein content reduced infectious morbidity in mechanically ventilated ICU patients and affected long-term morbidity and mortality.

Methods

Study Design

The MetaPlus trial was a randomized, multicenter, international, double-blind, parallel-group trial (protocol is available in Supplement 1). The study was performed in ICUs in 2 centers in the Netherlands, 4 in France, 6 in Germany, and 2 in Belgium (eMethod 1 in Supplement 2). The protocol and accompanying documents were approved by ethics committees and regulatory authorities (eMethod 2 in Supplement 2). Health care clinicians involved in the study at the participating ICUs provided both oral and translated written information according to local hospital policies and obtained written informed consent from patients or their legal representatives. The first patient was included on February 23, 2010, and the last patient completed the 28-day intervention period on November 14, 2011.

Participants

Adult mechanically ventilated ICU patients (age ≥18 years) admitted to 1 of the 14 participating ICUs who were expected to receive mechanical ventilation for more than 72 hours, to require enteral nutrition within 48 hours after ICU admission, to require enteral nutrition for more than 72 hours, and to need full enteral nutrition according to protocol recommendations were prescreened based on data from patient files. The main exclusion criterion was a Sequential Organ Failure Assessment (SOFA) score of more than 12 between ICU admission and 24 hours after ICU admission or randomization (if randomization occurred <24 hours after ICU admission). A complete list of inclusion and exclusion criteria is provided online (eMethod 3 in Supplement 2).

Randomization and Allocation

Patients were 1:1 randomized to receive IMHP or HP enteral nutrition, stratified per site and type of patient (medical, surgical nontrauma patients, trauma-surgical patients, and trauma-nonsurgical patients) using computer generated randomization lists. The ready-to-use IMHP and HP products had identical packaging with no differences in appearance, texture, or smell. Treatment assignments were made in blocks of 4 codes (2 codes per treatment). Investigators and clinicians were blinded to treatment allocation.

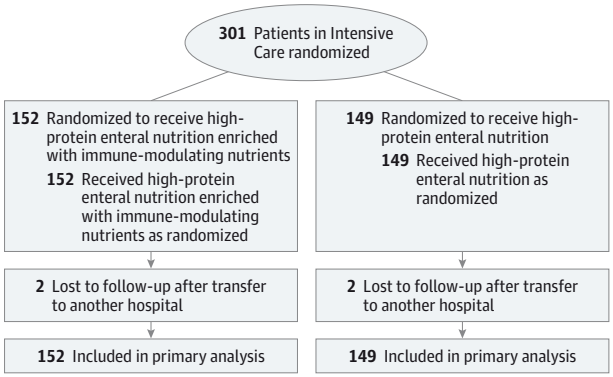
Intervention

Patients assigned to the IMHP group received a glutamine, omega-3 fatty acid, and antioxidant enriched tube feed (experimental product, NV Nutricia, Zoetermeer). Those assigned to the HP group received a high-protein tube feed (Nutrison Advanced Protison, NV Nutricia, Zoetermeer) (eTable 1 in Supplement 2). Patients were fed according to routine practice with recommendations toward early enhanced enteral feeding up to target energy requirement of 25 kcal/kg of body weight with a maximum of 2500 kcal/d. Patients received study formulations for a maximum of 28 days during their ICU stay. Before randomization, patients could be fed according to routine practice. Complementary feeding with enteral or parenteral nutrition was allowed with exceptions described (eMethod 5 in Supplement 2).

Screening and Baseline Measurements

At screening, age, sex, smoking behavior, alcohol consumption, weight, height, medical history, preexisting condi-

Figure. Study Flow of Patients in the MetaPlus Trial



The investigators and clinicians prescreened patients for potential eligibility based on medical records of patients. The informed consent procedure and subsequently the screening were only initiated if a patient seemed to be eligible. Data on the numbers of patients prescreened are not available.

tions, medication use, SOFA-score, and radiotherapy or chemotherapy over the last 3 months were recorded. At baseline, the APACHE-II score was determined.

Primary Efficacy Parameter

The primary end point was incidence of new infections. Infections were documented from the start of study product administration until ICU discharge or for a maximum of 28 ICU days and were classified according to the Centers for Disease Control and Prevention (CDC) definitions.[10]

Secondary Efficacy and Safety Parameters

The number of infections per patient per 100 ICU days and incidence per infection type were secondary end points. Other secondary end points included mortality (at ICU and hospital discharge, and at day-28 and 6 months), evolution of SOFA-scores (day 1-10), mechanical ventilation duration, and ICU and hospital lengths of stay. Blood glucose concentrations and daily insulin administration were recorded until day 7 to determine the time that glucose concentrations reached less than 144.1 mg/dL and less than 113.5 mg/dL (to convert glucose from mg/dL to mmol/L multiply by 0.0555), and incidence of hypoglycemia (plasma glucose concentration <79.2 mg/dL or <39.6 mg/dL). Blood samples were taken at baseline and at days 4 and 8 for plasma levels of glutamine, (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]):long-chain polyunsaturated fatty acids (LCP) ratio, selenium, vitamin C, vitamin E, and zinc. Severe adverse events were reported until day 28.

Safety and Statistics

The independent data monitoring committee (eMethod 4 in Supplement 2) advised that the study be continued without modification after every interim safety analysis based on severe adverse events and mortality data after every 6 deaths. After 105 patients, an interim analysis evaluated the incidence of infections (assumed ≥25%) for sample size calculation. The data monitoring committee recommended continuation without modification. Corrections for significance levels were not required.

To detect a 12.5% reduction in new infections (25% vs 12.5%) with a power of 80%, the sample size was calculated at 300 patients. A reduction of infections from 25% to 12.5% was estimated based on a systematic review that showed a reduction in incidence of abdominal abscesses (odds ratio [OR], 0.26; P = .005), nosocomial pneumonia (OR, 0.54; P = .007), and bacteremia (OR, 0.45; P = .0002) in ICU patients treated with pharmaconutrition.[7] All analyses were performed on an intention-to-treat basis within the total groups as well as prespecified medical, surgical, and trauma subgroups. In addition, a per-protocol analysis was performed for the primary end point based on those patients who received at least 50% of the recommended study product during the first 72 hours and subsequently during the ICU stay up to day 28 (eMethods 6 in Supplement 2).

Variables were summarized as frequencies and percentages, means and 95% confidence intervals or standard deviations, or medians and interquartile ranges (IQR), when appropriate. Data were compared using χ^2 tests, 2-sample t tests, Fisher exact tests, Wilcoxon rank-sum tests, and Poisson regression. In addition, a multivariable analysis was performed with 6-month survival as the end point using a Cox proportional hazard regression analysis, including as covariates: age, sex, body mass index, APACHE-II score, adjusted predicted mortality, baseline SOFA-score, baseline glutamine, and glucose, type of patient (medical, surgical nontrauma, surgical trauma, trauma nonsurgical), time between starting the study product and ICU admission, occurrence of preexisting infections, and antibiotic treatment at study initiation. The final model was constructed using univariate screening followed by a stepwise variable-selection procedure. The proportional-hazards assumption was tested at the .05 significance level using the Kolmogorov-type supremum test. Finally, time-to-event for 6-month mortality was visualized by Kaplan-Meier plots and compared using log-rank tests.

For all end points, 2-sided P values <.05 were considered statistical significant, without correction for multiple testing. Analyses were performed with SAS software, version 9.2 (SAS Institute Inc).

Results

Patients

A total of 301 patients were randomized and included in the intention-to-treat analysis (**Figure**). Baseline characteristics were comparable between study groups, both in the total study population and within subpopulations. No statistically significant differences were observed between study groups in mean duration of study product administration or total volume of study product administered (**Table 1**).

Table 1. Baseline Characteristics and Feeding Details[a]

	Total Group		Subgroups					
			Medical		Surgical		Trauma	
	IMHP (n = 152)	HP (n = 149)	IMHP (n = 54)	HP (n = 55)	IMHP (n = 81)	HP (n = 75)	IMHP (n = 55)	HP (n = 54)
Age, mean (SD), y	57 (19)	59 (18)	64 (15)	65 (14)	54 (21)	57 (19)	45 (20)	48 (20)
Men, No. (%)	100 (66)	102 (68)	35 (65)	32 (58)	54 (67)	52 (69)	41 (75)	46 (85)
Weight, mean (SD), kg	77.3 (14.1)	78.8 (15.9)	74.2 (13.6)	79.0 (14.5)	79.1 (13.7)	78.7 (17.2)	81.4 (13.4)	80.1 (17.8)
BMI, mean (SD)[b]	26.1 (4.5)	26.5 (4.8)	25.2 (4.6)	27.0 (4.7)	26.4 (4.1)	26.3 (5.0)	26.9 (4.9)	26.6 (5.1)
APACHE-II score, mean (SD)[c]	22.0 (8.5)	21.3 (7.7)	26.7 (8.0)	24.9 (7.8)	20.4 (7.6)	19.7 (6.8)	17.0 (7.4)	17.5 (6.4)
Adjusted predicted mortality, mean (SD), %	39.8 (27.3)	37.4 (12.9)	56.3 (25.2)	50.8 (26.2)	33.8 (24.0)	31.4 (23.0)	22.5 (21.9)	22.5 (16.8)
SOFA score, median (IQR)[d]								
Total	8 (7-10)	9 (7-10)	9 (7-10)	9 (7-10)	8 (7-11)	9 (7-10)	8 (7-10)	9 (7-10)
Respiratory	2 (1-3)	2 (1-3)	3 (2-3)	3 (2-4)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-2)
Coagulation	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)	1 (0-1)	0 (0-1)	1 (0-1)	0 (0-1)
Liver	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Cardiovascular	4 (3-4)	4 (3-4)	3 (3-4)	3 (1-4)	4 (3-4)	4 (3-4)	4 (3-4)	4 (4-4)
Central nervous system	2 (0-4)	2 (0-4)	2 (0-4)	1 (0-4)	2 (0-4)	2 (0-4)	2 (0-3)	3 (1-4)
Renal	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)
Primary admission diagnosis, No. (%)								
Sepsis	32 (21)	34 (23)	19 (35)	20 (36)	13 (16)	14 (19)	2 (4)	0
Pulmonary	19 (13)	23 (15)	12 (22)	17 (31)	7 (9)	4 (5)	0	2 (4)
Trauma	44 (29)	45 (30)	0	0	29 (36)	30 (40)	44 (80)	45 (83)
Neurologic	38 (25)	28 (19)	12 (22)	8 (15)	24 (30)	18 (24)	8 (15)	7 (13)
Cardiocirculatory	17 (11)	14 (9)	9 (17)	7 (13)	8 (10)	7 (9)	1 (2)	0
Abdominal	1 (1)	4 (3)	1 (2)	2 (4)	0	2 (3)	0	0
Other	1 (1)	1 (1)	1 (2)	1 (2)	0	0	0	0
Baseline blood plasma levels, mean (SD)								
Glutamine, mg/dL	365 (161)	356 (136)	393 (155)	406 (168)	355 (175)	324 (111)	306 (74)	306 (80)
Selenium, µg/L	0.94 (0.43)	1.03 (0.74)	0.84 (0.37)	1.08 (1.00)	0.98 (0.41)	1.00 (0.59)	1.02 (0.49)	0.90 (0.40)
(EPA+DHA):LCP ratio	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)	0.02 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
Glucose, mg/dL	7.9 (2.2)	7.6 (2.0)	7.8 (2.4)	7.7 (2.3)	8.0 (2.1)	7.7 (2.0)	7.5 (1.7)	7.4 (1.4)
Preexisting infections, No (%)	67 (44)	66 (44)	34 (63)	37 (67)	28 (35)	25 (33)	12 (22)	10 (19)
Baseline antibiotic treatment, No. (%)	111 (73)	111 (75)	49 (91)	47 (85)	53 (65)	51 (68)	34 (62)	37 (69)
Study product administration								
Time from ICU admission to study feeding start, median (IQR), h	31 (19-44)	30 (22-42)	26 (16-41)	31 (14-39)	36 (22-45)	27 (22-45)	40 (26-44)	38 (23-46)
Duration of administration, median (IQR), d	12 (8-21)	13 (8-25)	10 (5-15)	12 (6-23)	15 (10-21)	15 (8-28)	15 (10-26)	18 (11-28)
Total volume administered, median (IQR), mL	13 486 (7185-23 485)	13 880 (6770-28 770)	10 879 (4222-17 038)	13 370 (5390-25 249)	16 454 (8300-25 135)	13 412 (8900-30 530)	17 710 (8705-32 268)	23 228 (12 425-37 210)
Volume administered per ICU day, median (IQR), mL	899 (605-1179)	1027 (732-1243)	862 (560-1130)	1047 (787-1224)	968 (640-1259)	1012 (633-1299)	1026 (619-1336)	1132 (867-1414)
Energy administered per ICU day, median (IQR), kcal	1151 (774-1509)	1315 (937-1591)	1103 (717-1446)	1340 (1007-1567)	1239 (819-1612)	1294 (810-1663)	1313 (792-1710)	1449 (1110-1810)
Protein administered per ICU day, median (IQR), g	67 (45-88)	77 (55-93)	65 (42-85)	79 (59-92)	73 (48-94)	76 (47-97)	77 (46-100)	85 (65-106)
Patients with supplemental parenteral nutrition, No. (%)	23 (15)	20 (13)	5 (9)	3 (5)	15 (19)	12 (16)	10 (18)	11 (20)

Abbreviations: HP, high-protein enteral nutrition; ICU, intensive care unit; IMHP, high-protein enteral nutrition enriched with immune modulating nutrients; and SOFA, Sequential Organ Failure Assessment.

[a] In the IMHP and HP groups, we present surgical trauma patients both in the group of the surgical patients as well as in the group of trauma patients. The IMHP group (n = 152) is composed of 54 medical patients, 17 nonsurgical trauma patients, 38 surgical trauma patient, and 43 nontrauma surgical patients. The HP group (n = 149) is composed of 55 medical patients, 19 nonsurgical trauma patients, 35 surgical trauma patient, and 40 nontrauma surgical patients. The medical group comprised 54 IMHP and 55 HP patients; the surgical group, 81 IMHP and 75 HP patients; the trauma group, 55 IMHP and 54 HP patients.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] The APACHE-II score ranges from 0-71, with higher scores indicating more severe disease.

[d] The SOFA score ranges from 0 to 24, with higher scores indicating a greater number or severity of organ failure.

Table 2. Infections Diagnosed After Initiation of Study Products

	Mean [95% CI][a]		
	IMHP	HP	*P* Value
All patients	**n = 152**	**n = 149**	
Incidence of infections, No. of patients (%) [95% CI][b]	80 (53) [44-61]	78 (52) [44-61]	.96[c]
Total No. of infections	119	122	
No. of infections per patient	0.78 [0.64-0.93]	0.82 [0.67-0.97]	.73[d]
No. of infections per ICU day per patient	0.05 [0.03-0.06]	0.04 [0.03-0.05]	.97[d]
Duration of infections per patient, d[e]	8.3 [7.3-9.2]	8.5 [7.6-9.4]	.71[f]
Medical patients	**n = 54**	**n = 55**	
Incidence of infections, No. of patients (%) [95% CI][b]	21 (39) [26-53]	26 (47) [34-61]	.38[c]
Total No. of infections	32	40	
No. of infections per patient	0.59 [0.35-0.83]	0.73 [0.48-0.97]	.39[d]
No. of infections per ICU day per patient	0.05 [0.02-0.09]	0.04 [0.02-0.05]	.89[d]
Duration of infections per patient, d[e]	7.1 [5.2-9.0]	8.8 [7.5-10.2]	.12[f]
Surgical patients	**n = 81**	**n = 75**	
Incidence of infections, No. of patients (%) [95% CI][b]	50 (62) [50-72]	38 (51) [39-62]	.16[c]
Total No. of infections	75	58	
No. of infections per patient	0.93 [0.72-1.13]	0.77 [0.57-0.98]	.30[d]
No. of infections per ICU day per patient	0.05 [0.03-0.06]	0.04(0.03-0.05]	.33[d]
Duration of infections per patient, d[e]	8.3 [7.0-9.6]	7.9 [6.3-9.5]	.73[f]
Trauma patients	**n = 55**	**n = 54**	
Incidence of infections, No. of patients (%) [95% CI][b]	32 (58) [44-71]	36 (67) [53-79]	.36[c]
Total No. of infections	47	58	
No. of infections per patient	0.85 [0.62-1.08]	1.07 [0.81-1.33]	.24[d]
No. of infections per ICU day per patient	0.04 [0.03-0.05]	0.05 [0.04-0.06]	.36[d]
Duration of infections per patient, d[e]	9.7 [8.3-11.1]	9.8 [8.6-11.0]	.90[f]

Abbreviations: HP, high-protein feed (control); IMHP, immune-modulating nutrients enriched high protein feed (intervention).

[a] Results in surgical and trauma subgroups are correlated due to combined patients.

[b] Patients with at least 1 new infection after initiation of study product.

[c] χ^2 test.

[d] Poisson regression.

[e] Excluded observations with missing end dates.

[f] Two-sample *t* test.

Primary Outcome

There were no statistically significant differences in the incidence of new infections between groups. Overall, 53% of those in the IMHP group (95%CI; 44%-61%) vs 52% in the HP group (95% CI, 44%-61%; *P* = .96) had new infections. In the subgroups, 39% of medical patients in the IMHP group (95% CI, 26%-53%) vs 47% in the HP group (95% CI, 34%-61%; *P* = .38), 62% of surgical patients in the IMHP group (95% CI, 50%-72%) vs 51% in the HP group (95% CI, 39%-62%; *P* = .16), and 58% of trauma patients in the IMHP group (95% CI, 44%-71%) vs 67% in the HP group (95% CI, 53%-79%; *P* = .36) were observed to have new infections. The mean number of infections per patient, infections per patient per ICU-day, duration of infections, and incidence of specific types of infection were statistically nonsignificant between study groups (**Table 2** and **Table 3**). In a per-protocol analysis, there were no statistically significant differences in the incidence of new infections between groups in all patients: 62% in the IMHP group (95% CI, 51%-73%) vs 58% in the HP group (95% CI, 47%-69%; *P* = .59). The same held true for the subgroups with 53% in the medical IMHP group (95% CI, 34%-72%) vs 53% in the HP group (95% CI, 36%-69%; *P* = .95), 69% in the surgical IMHP group (95% CI, 53%-82%) vs 62% in the HP group (95% CI, 45%-77%; *P* = .48), 62% in the trauma IMHP group (95% CI, 41%-80%) vs 68% in the HP group (95% CI, 49%-83%; *P* = .62).

Secondary Outcomes

There were no statistically significant differences between IMHP and HP groups in any clinical outcome parameter, except the in the medical subgroup with 54% mortality in IMHP group (95% CI, 40%-67%) vs 35% mortality in the HP group (95% CI, 22%-49%; *P* = .04; **Table 4**). Kaplan-Meier 6-month survival curves and evolution of SOFA-scores are shown in eFigures 1 and 2 in Supplement 2. The Cox proportional hazard ratio for 6-month mortality adjusted for age and APACHE-II scores comparing IMHP with HP groups was 1.57 (95% CI, 1.03-2.39; *P* = .04; **Table 5**).

Baseline to day 4 mean plasma glutamine and selenium levels were statistically significantly larger in the IMHP group than in the HP group: glutamine levels increased by 1.1 mg/dL (95% CI, 0.67-1.53) in the IMHP group vs 0.42 mg/dL (95% CI, 0.1-0.7) in the HP group and selenium levels increased in the IMHP group by 11 µg/L (95% CI, 3.9-18.1) vs −2.3 µg/L (95% CI, −12.5-7.9) in the HP group (eTables 2 and 3 in Supplement 2). Between-group differences in increases in mean plasma for the (EPA + DHA):LCP ratio were 3.4% (95% CI, 3.0%- 3.8%) on day 4 and 5.1% (95% CI, 4.6%-5.5%)

Table 3. Infections Diagnosed After Initiation of Study Products by Patient Group and Infection Site[a]

	IMHP		HP		
Treatment Group	No. of Infections	No. (%) of Patients [95% CI]	No. of Infections	No. (%) of Patients [95% CI]	P Value
All Patients		n=152		n=149	
Total	119	80 (53) [44-61]	122	78 (52) [44-61]	>.99
Urinary tract	16	15 (10) [6-16]	17	15 (10) [6-16]	>.99
Surgical site	3	3 (2) [0-6]	6	6 (4) [1-9]	.33
Pneumonia	61	56 (37) [29-45]	66	59 (40) [32-48]	.64
Bloodstream	15	15 (10) [6-16]	12	12 (8) [4-14]	.69
Central nervous system	5	4 (3) [1-7]	1	1 (1) [0-4]	.37
Cardiovascular system	1	1 (1) [0-4]	2	2 (1) [0-5]	.62
Eye, ear, nose, throat, or mouth	2	2 (1) [0-5]	2	2 (1) [0-5]	>.99
Gastrointestinal system	5	5 (3) [1-8]	3	3 (2) [0-6]	.72
Lower respiratory other than pneumonia	11	11 (7) [4-13]	12	11 (7) [4-13]	>.99
Skin and soft tissue	3	3 (2) [0-6]	6	6 (4) [1-9]	.33
Systemic	0	0 [0-2]	1	1 (1) [0-4]	
Medical Patients		n=54		n=55	
Total	32	21 (39) [26-53]	40	26 (47) [34-61]	.44
Urinary tract	5	4 (7) [2-18]	4	4 (7) [2-18]	>.99
Surgical site	0	0 (0) [0-7]	0	0 [0-6]	
Pneumonia	14	12 (22) [12-36]	25	20 (36) [24-50]	.14
Bloodstream	6	6 (11) [4-23]	7	7 (13) [5-24]	>.99
Central nervous system	0	0 [0-7]	0	0 [0-6]	
Cardiovascular system	0	0 [0-7]	0	0 (0 (0-6)	
Eye, ear, nose, throat, or mouth	1	1 (2) [0-10]	1	1 [0-10]	>.99
Gastrointestinal system	1	1 (2) [0-10]	1	1 (2) [0-10]	>.99
Lower respiratory other than pneumonia	5	5 (9) [3-20]	2	2 (4) (0-13)	.27
Skin and soft tissue	0	0 [0-7]	0	0 [0-6]	
Systemic	0	0 [0-7]	0	0 [0-6]	
Surgical Patients		n=81		n=75	
Total	75	50 (62) [50-72]	58	38 (51) [39-62]	.20
Urinary tract	9	9 (11) [5-20]	6	6 (8) [3-17]	.59
Surgical site	3	3 (4) [1-10]	6	6 (8) [3-17]	.31
Pneumonia	38	35 (43) [32-55]	28	27 (36) [25-48]	.41
Bloodstream	9	9 (11) [5-20]	5	5 (7) [2-15]	.41
Central nervous system	5	4 (5) [1-12]	1	1 (1) [0-7]	.37
Cardiovascular system	1	1 (1) [0-7]	2	2 (3) [0-9]	.61
Eye, ear, nose, throat, or mouth	1	1 (1) [0-7]	1	1 (1) [0-7]	>.99
Gastrointestinal system	4	4 (5) [1-12]	2	2 (3) [0-9]	.68
Lower respiratory other than pneumonia	5	5 (6) [2-14]	6	5 (7) [2-15]	>.99
Skin and soft tissue	3	3 (4) [1-10]	6	6 (8) [3-17]	.31
Systemic	0	0 [0-4]	1	1 (1) [0-7]	
Trauma Patients		n=55		n=54	
Total	47	32 (58) [44-71]	58	36 (67) [53-79]	.43
Urinary tract	6	6 (11) [4-22]	12	10 (19) [9-31]	.29
Surgical site	2	2 (4) [0-13]	4	4 (7) [2-18]	.44
Pneumonia	26	26 (47) [34-61]	33	31 (57) [43-71]	.34
Bloodstream	4	4 (7) [2-18]	3	3 (6) [1-15]	>.99
Central nervous system	2	1 (2) [0-10]	0	0 [0-7]	
Cardiovascular system	0	0 [0-6]	0	0 [0-7]	
Eye, ear, nose, throat, or mouth	1	1 (2) [0-10]	0	0 [0-7]	
Gastrointestinal system	1	1 (2) [0-10]	1	1 (2) [0-10]	>.99
Lower respiratory other than pneumonia	5	5 (9) [3-20]	5	5 (9) [3-20]	>.99
Skin and soft tissue	2	2 (4) [0-13]	4	4 (7) [2-18]	.44
Systemic	0	0 [0-6]	0	0 [0-7]	

Abbreviations: HP, high-protein feed (control); IMHP, immune-modulating nutrients enriched high protein feed (intervention).

[a] *P* values were derived by the Fisher exact test. Results in surgical and trauma subgroups are correlated due to combined patients.

Table 4. Clinical Outcomes[a]

	IMHP (n = 152)	HP (n = 149)	*P* Value
Mortality, No. (%) [95% CI]			
ICU, all patients	30 (20) [14-27]	29 (20) [14-27]	.95[b]
Medical	17 (31) [20-46]	12 (22) [12-35]	.25[b]
Surgical	11 (14) [7-24]	16 (22) [13-33]	.20[b]
Trauma	5 (9) [3-20]	6 (11) [4-23]	.73[b]
Hospital, all patients	38 (25) [19-33]	33 (22) [16-30]	.56[b]
Medical	23 (43) [29-57]	16 (29) [18-43]	.14[b]
Surgical	13 (16) [9-26]	16 (22) [13-33]	.39[b]
Trauma	6 (11) [4-23]	6 (11) [4-23]	.97[b]
28 d, all patients	31 (20) [14-28]	25 (17) [11-24]	.42[b]
Medical	19 (35) [23-49]	13 (24) [13-37]	.19[b]
Surgical	11 (14) [7-23]	12 (16) [9-26]	.67[b]
Trauma	4 (7) [2-18]	2 (4) [0-13]	.68[d]
6 mo, all patients	53 (35) [28-44]	42 (29) [21-37]	.21[b]
Medical	29 (54) [40-67]	19 (35) [22-49]	.04[b]
Surgical	22 (28) [18-39]	21 (29) [19-41]	.90[b]
Trauma	8 (15) [7-27]	9 (17) [8-30]	.76[b]
Mechanical Ventilation, Median (IQR), d			
All patients	9 (5-15)	8 (5-15)	.84[c]
Medical	7 (4-11)	9 (5-14)	.19[c]
Surgical	11 (6-17)	7 (5-15)	.11[c]
Trauma	11 (5-17)	9 (6-15)	.71[c]
Length of Stay, Median (IQR), d			
ICU, all patients	18 (12-29)	18 (10-34)	.76[c]
Medical	14 (8-19)	15 (8-30)	.58[c]
Surgical	21 (14-30)	20 (11-39)	.87[c]
Trauma	25 (14-32)	23 (15-42)	.45[c]
Hospital, all patients	30 (21-44)	30 (20-49)	.99[c]
Medical	28 (19-34)	29 (16-46)	.98[c]
Surgical	31 (23-45)	31 (23-50)	.94[c]
Trauma	34 (24-63)	33 (24-53)	.62[c]

Abbreviations: HP, high-protein enteral nutrition; IMHP, high-protein enteral nutrition enriched with immune modulating nutrients; ICU, intensive care unit; IQR, Interquartile range; No, number of patients.

[a] For a breakdown of how patients were grouped, see the footnote in Table 1.

[b] χ^2 test.

[c] Wilcoxon rank-sum test.

[d] Fisher exact test.

on day 8 for the IMHP group vs −0.3% (95% CI, −0.4% to 0.2%) on day 4 and −0.5 (95% CI, −0.6 to 0.4%) on day 8 in the HP group; the mean increases for vitamin C levels were 0.15 mg/dL (95% CI; 0.11-0.20) on day 4 and 0.25 mg/dL (95% CI, 0.19-0.3) on day 8 for the IMHP group vs −0.05 mg/dL (95% CI, −0.10 to 0.01) on day 5 and −0.03 mg/dL (95% CI, −0.09 to 0.02) for day 8 in the HP group; and the mean increases for vitamin E levels were 8.8 ng/dL (95% CI, 7.8-9.90) on day 4 and 12.3 (95% CI, 11.0-13.6) on day 8 in the IMHP group vs 1.3 ng/dL (95% CI, 0.9-1.8) on day 4 and 2.8 ng/dL (95% CI, 2.2-3.5) on day 8 in HP group (eTables 4, 5, and 6 in Supplement 2). (To convert glutamine from mg/dL to µmol/L, multiply by 68.423; selenium from µg/L to µmol/L, multiply by 0.0127; vitamin C from mg/dL to µmol/L; multiply by 56.78; and vitamin E from ng/dL to µmol/L, multiply by 2.22.) There were no statistically significant differences in plasma levels of zinc (eTable 7 in Supplement 2).

There was no statistically significant difference in the daily amount of insulin administered (eFigure 3 in Supplement 2). The mean time to reaching a first glucose level of 144.1 mg/dL or less was 12.3 hours (95% CI, 8.9-15.6) in the IMHP group vs 20.2 hours (95% CI, 12.2-28.1; *P* = .07) in the HP group, and the mean time to reaching a glucose level of 113.5 mg/dL was 24.2 hours (95% CI, 19.1-29.3) in the IMHP group vs 35.1 hours (95% CI, 27.6-42.6; *P* = .02) in the HP group, with no statistically significant differences in the incidence of patients with at least 1 glucose level lower than 72.0 mg/dL: 23% (95% CI, 16%-30%) in the IMHP group vs 28% (95% CI, 21%-36%) in the HP group (*P* = .30) and with a glucose level of 39.6 mg/dL 7% (95%CI; 4%-13%) in the IMHP group vs 8% (95% CI; 4%-13%) in the HP group (*P* = .96).

Post hoc subgroup analyses of 6-month mortality according to glutamine, (EPA+DHA):LCP ratio, selenium levels, and APACHE-II quartiles, admission reason (head, brain, or neurological events; respiratory events; cardiac or circulatory events; sepsis; and multiple trauma), age (<50, 50-70, 70-80, >80 years) and type of patient (medical, surgical, trauma nonsurgical and trauma-surgical) showed no statistically significant differences in hazard ratios except in

Table 5. Cox Proportional Hazard Regression Analysis for 6-Month Mortality[a]

	Total No.	No. of Deaths	Degree of Freedom	Coefficient (SE)	Hazard Ratio (95% CI)	*P* Value
Treatment						
IMHP	152	53	1	0.45 (0.21)	1.57 (1.03-2.39)	.04
HP	149	42	0			
Age, y						
≤50	91	9	1	2.15 (0.43)	0.12 (0.05-0.27)	<.001
IMHP	49	5				
HP	42	4				
>50-≤70	116	31	1	1.42 (0.29)	0.24 (0.14-0.43)	<.001
IMHP	57	16				
HP	59	15				
>70-≤80	60	30	1	0.76 (0.28)	0.47 (0.27-0.81)	.006
IMHP	32	19				
HP	28	11				
>80	34	25	0			
IMHP	14	13				
HP	20	12				
APACHE II score[b]			1	0.05 (0.01)	1.05 (1.02-1.09)	<.001

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation II; HP, high-protein enteral nutrition; IMHP, high-protein enteral nutrition enriched with immune modulating nutrients.

[a] Analysis of time to mortality, based on the 6-month data set. The analysis was performed with the use of a Cox proportional hazards model and univariate screening followed by a stepwise variable-selection procedure. Two records were deleted from the analysis due to missing values for APACHE II scores and the analysis was based on the assumption of missing completely at random.

[b] Reference increment for APACHE II score: per 1 additional point. The score ranges from 0-71, with higher scores indicating more severe disease.

medical patients and age older than 80 years in favor of HP vs IMHP patients (eFigure 4 in Supplement 2).

Adverse Events

In total, 91 serious adverse events were reported among 43 IMHP patients and 48 HP patients (eTable 8 in Supplement 2). Only 1 in the IMHP group (diarrhea) and 1 in the HP group (clinical deterioration laparotomy) were possibly related to the study product. In total, 717 adverse events were recorded, 345 in 105 patients (69%) in the IMHP group and 372 in 105 patients (71%) in the HP group. In total, 95 adverse events were related to the study products (75 possibly, 18 probably, and 2 definitely related) with no statistically significant differences between groups.

Discussion

In this randomized double-blind multicenter trial comparing IMHP with HP nutrition in a heterogeneous ICU population of patients breathing with the aid of mechanical ventilation, we could not show any effect of the nutritional formulae on infectious complications. After adjustment for age and APACHE-II score, there was a higher 6-month mortality hazard ratio of 1.57 in IMHP patients compared with the HP patients. Because this study gave a signal for serious safety concerns of immune-modulating nutrients, statistical tests for mortality were also performed in predefined subgroups. Adjusting *P* values for multiple testing was not performed in order not to reduce the signal for safety concerns. Our results contrast published meta-analyses stating that immune-modulating enteral nutrition was associated with reductions in infectious morbidity and improved recovery in critically ill patients compared with standard high-protein enteral nutriton.[5-7]

Glutamine was selected in the IMHP feed based on results from meta-analyses evaluating glutamine supplementation and infectious complications and mortality.[11,12] However, a recent meta-analysis on parenteral glutamine, including the Scandinavian Glutamine Trial[13] and the Scottish Intensive Care Glutamine or Selenium Evaluative Trial (SIGNET),[14] and a meta-analysis on enteral glutamine supplementation showed no reductions in infectious complications or mortality rates.[15,16] Most recently, the Reducing Deaths Due to Oxidative Stress (REDOXS) trial reported increased mortality rates in patients receiving glutamine supplement without reductions in infections.[17] The magnitude of these findings is comparable with our study. In the REDOXS study, intravenous (Dipeptiven, Fresenius Kabi) and enteral alanyl-glutamine and glycine-glutamine dipeptides were used. Our experimental IMHP feed contained alanyl-glutamine dipeptide. In the REDOXS trial, a daily enteral glutamine intake of 30 g/d and intravenous glutamine intake of 0.35 g/kg ideal body weight per day was targeted, which is much higher than the recommended glutamine intake of 0.3 to 0.5 g/kg of body weight per day used in our study.[18] From day 3 through 14, the mean enteral nutrition intake in our study was 70% of target

energy intake (eFigure 5 in Supplement 2), resulting in an average glutamine intake of 0.28 g/kg of body weight per day.

The IMHP feed was enriched with omega-3 fatty acids EPA and DHA from fish-oils. Three randomized clinical studies evaluating an enteral formula with omega-3 fatty acids and antioxidants compared with a high fat formula[19-21] showed reduced length of ICU stay, improved SOFA-scores, and lower mortality in patients with acute lung injury or sepsis-induced respiratory failure. In addition, a meta-analysis showed reduced mortality with fish-oil enriched enteral nutrition.[16] In contrast, more recently, the EDEN-OMEGA-study, in which omega-3 fatty acids, EPA, DHA, and γ-linoleic acid and antioxidants were administered enterally in patients with acute lung injury, was prematurely terminated for not improving the primary end point of ventilator-free days and a higher 60-day in-hospital mortality that did not reach statistical significance (26.6% vs 16.3%; P = .054).[22] In this study, a twice-daily enteral bolus was administered with a daily intake of 16.2 g of EPA, DHA, and γ-linoleic acid, which is a similar intake of omega-3 fatty acids compared with previous studies.[19-21] Patients in the control group of the EDEN-OMEGA study received 16.2 g of protein more on a daily basis, which could also have contributed to the results of this trial. IMHP patients in our study had an EPA+DHA intake from day 3-14 of 0.07 g/kg of body weight per day (on average 5.6 g/d) and still experienced potential harm, despite continuous feeding and a control group with similar amounts of protein.

Levels of antioxidants, selenium, vitamin C, vitamin E, and zinc were increased in the IMHP experimental feed as suggested by the American Society for Parenteral and Enteral Nutrition and/Society of Critical Care Medicine guidelines and meta-analyses.[1,2,23,24] However, our results and those reported in the SIGNET[14] and REDOXS[17] trials did not show any benefit of selenium supplementation in intention-to-treat analyses. The Signet trial administered dosages of 500 µg/d intravenously, and the REDOXS trial administered 500 µg/d intravenously and 300 µg/d enterally. In our study, IMHP patients achieved a selenium intake from day 3 through14 of 2.66 µg/kg of body weight per day (on average 212 µg/d).

Concerning supplementation with glutamine, omega-3 fatty acids, and antioxidants in critically ill patients, older studies seem to show positive effects compared with more recent studies reporting no or negative effects. This declining incremental benefit over time was recently demonstrated for studies of parenteral glutamine supplementation.[25] Moreover, findings from single-center glutamine intervention studies seem to demonstrate positive effects, in contrast with multicenter studies, like ours, which have demonstrated negative effects of glutamine supplementation.[26] The strengths of the MetaPlus study include the prospective, randomized and blinded design, complying with current best practice in 14 ICUs in 4 European countries in a pragmatic way, the use of CDC definitions of infections and the intention-to-treat analysis, all augmenting external validity. Furthermore, the adequacy of delivery of feeding is clearly an additional strength. Within 3 days, on average 70% of target energy intake was reached in IMHP patients and 80% in HP patients, markedly higher than reported enteral intakes in previous studies (<55% of target).[17,27-29] Our feeding intervention can, therefore, be considered as successful. A limitation of the study is the lack of data on numbers of prescreened eligible patients for inclusion. This could have led to biased patient group selection, affecting the external validity of results. However, because baseline APACHE-II scores and the mean age of our ICU population are similar to recent large studies,[8,9,14,17,22] we believe the effects of bias are limited. In addition, the combined nutrient interventions in the experimental feed preclude firm conclusions on the effects of individual components. Moreover, the heterogeneous study groups may have reduced the power to detect beneficial effects in specific subgroups and should only be interpreted as exploratory, although we were not able to observe these effects within our prespecified subgroups. Furthermore, the lack of quantification of supplemental parenteral nutrition and intravenous glucose administration in the calculation of total energy intake is a limitation. However, the high-energy intake with enteral nutrition and the current practice in participating centers not to use supplemental parenteral nutrition when enteral nutrition intake is more than 60% to 80% of target, aiming for full enteral nutrition, minimizes the risk of a marked effect of supplemental parenteral nutrition and intravenous glucose and use of SPN was very low (13%-15% of patients).

The 6-month mortality rate in the HP group of 28% is low compared with the 6-month mortality rates reported in the REDOXS[17] (35%) and SIGNET[14] trials (43%). Protein intakes in these studies were much lower compared with the protein intake in our study (1.2 g/kg of body weight per day, day 3), in line with protein intakes of the high protein intake groups in 2 observational studies showing that higher protein intakes were associated with lower mortality.[8,9] Recently, a protein intake of 1.2 to 1.5 g/kg body weight per day for adult critically ill patients was suggested.[30] Our observed 28-day mortality rate in the HP group is comparable with mortality rates obtained in the observational studies that led to these recommendations. Therefore, we speculate that successful enteral feeding in mechanically ventilated critically ill patients with the HP control feed could have contributed to the low mortality rates. In previous nutritional intervention studies, high-protein tube feeds were not used, because, until recently, high-protein tube feeds were not commercially available. A balanced amino acid pattern in the HP enteral feed containing 9 g of glutamine as part of intact protein in 1500 mL of the formula may also have contributed to the low mortality rates in this group. Recently, it has been suggested that manipulation of the amino acid composition of enteral feeds leading to an unbalanced composition may have adverse clinical consequences.[31]

The MetaPlus trial results add to the possible harmful effects reported in at least 3 recent, large, multicenter trials

on immunonutrition: the REDOXS, EDEN-OMEGA, and SIGNET trials, showing no benefit or possibly harmful effects. However, in the MetaPlus study, lower dosages of the immune-modulating nutrients were used than in the other recent studies, and administered continuously and only by enteral feeding. Our results thus suggest that harmful effects may also be present using these lower dosages. We believe that these observations should lead to a critical appraisal of current guidelines on the use of immune-modulating nutrients in mechanically ventilated critically ill patients.

Conclusions

Among adult mechanically ventilated medical, surgical and trauma ICU patients, high-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition did not improve infectious complications or other clinical end points and may be harmful as suggested by increased adjusted mortality at 6 months. These findings do not support the use of high-protein enteral nutrition enriched with immune-modulating nutrients in these patients.

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