Supplementary Online Content

van Zanten ARH, Sztark F, Kaisers UX, et al. Effect of high-protein enteral nutrition enriched with immune-modulating nutrients versus standard high-protein enteral nutrition on risk of nosocomial infections in critically ill patients: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2014.7698

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Participating sites

Participating sites (number in brackets refers to number of patients enrolled at each site), principal investigators and sub-investigators (study coordinators (sc))

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12. Erasme University Hospital, Brussels, Belgium (5): J.L. Vincent, J.C. Preiser, D. Durand (sc), P. Leonard (sc)

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14. Hôpital Antoine-Béclère, Clamart, France (1): J.F. Zazzo

eMethods 2. Ethic Committees and authorities

Ethics committees and authorities that approved the study protocol and accompanying documents: Netherlands: METC Noord-Holland Alkmaar, CCMO;

Germany: Sächsische Landesärztekammer, Dresden, Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig, Leipzig, Ethik-Kommission der Bayerischen Landesärztekammer, München, Ethik-Kommission Westfalen -Lippe, Münster; Ethik-Kommission der Charité´Universitätsmedizin Berlin.

France: CPP Ile de France VII – Bicêtre, AFSSAPS;

Belgium: Ethisch Comité UZ Gent, Gent, Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège, Liège; Le Comite d'Ethique Erasme-ULB, Brussels

eMethods 3. Eligibility Criteria

Inclusion criteria.

1) Age ≥ 18 years.
2) Mechanically ventilated and expected to remain mechanically ventilated for more than 72 hours after start of administration of study product.
3) Start of study product administration within 48 hours after ICU admission.
4) Expected to require EN for at least 72 hours, aiming for full EN according to protocol recommendations
5) Written informed consent of patient or legal representative.

Exclusion criteria:

1) Requiring other specific EN for medical reason
2) Contra-indications to EN, such as severe or refractory shock.
3) Presence of partial or complete mechanical bowel obstruction, intestinal ischemia or infarction, pregnancy
4) BMI >40.0 kg/m^2.
5) Receiving supplements containing glutamine, vitamin C, vitamin E, selenium, zinc, omega-3 fatty acids EPA, DHA and/or GLA during the last two weeks before start of study product on doctors' prescription.
6) History of allergy or intolerance to study product components (test or control product).
7) SOFA-score >12 between ICU admission and 24 hours after admission or randomization (if randomized less than 24 hours after admission
8) Current or planned treatment with selective decontamination of the digestive tract (SDD) or selective oral decontamination (SOD)
9) Gastro-intestinal tract/short bowel syndrome (length of small bowel totaling 122 centimeters or less)
10) Participating in another intervention clinical trial concomitantly.

eMethods 4. Data Monitoring Committee (DMC)

Prof Jan Wernerman, PhD, MD, Karolinska Institutet, Stockholm, Sweden

Dr. Hans. Kieft, MD, PhD, Isala Klinieken, Zwolle, The Netherlands

Prof Renger. Witkamp, PhD, Division of Human Nutrition, Wageningen University & Research Centre, Wageningen, The Netherlands

Prof Richard D. Gill, Statistician, Mathematical Institute, Leiden University, Leiden, The Netherlands

eMethods 5. Allowed complementary feeding

Complementary feeding with EN or PN was allowed except for supplementation of glutamine, EPA, DHA and/or GLA.

The anti-oxidants, vitamin C, vitamin E, selenium, and zinc, were allowed only in cases of inadequate intake of study product to a maximum daily dose of anti-oxidants similar to 1500 mL of control product by calculating maximum amounts allowed to be supplemented minus the intake of supplemented anti-oxidants with study product assuming the administered product was the control product. Supplementation up to maximum allowed dosages of anti-oxidants could be used between ICU admission and start of study product.

eMethods 6. Per protocol analysis criteria: primary endpoint

Per protocol analysis was performed for the primary efficacy parameter of new infections excluding those patients with the following per protocol deviation criteria:

1) In- and/or exclusion criteria violations,

2) Subjects that were randomized to treatment X, but received treatment Y erroneously,

3) Received less than 50% of the by protocol-recommended intake of study product over the first 72 hours after first intake of study product,

4) Received less than 50% of the by protocol-recommended intake of study product from Day 4 until discharge from the ICU,

5) Use of forbidden nutritional supplements or forbidden concomitant medications and

6) Visit window violations.

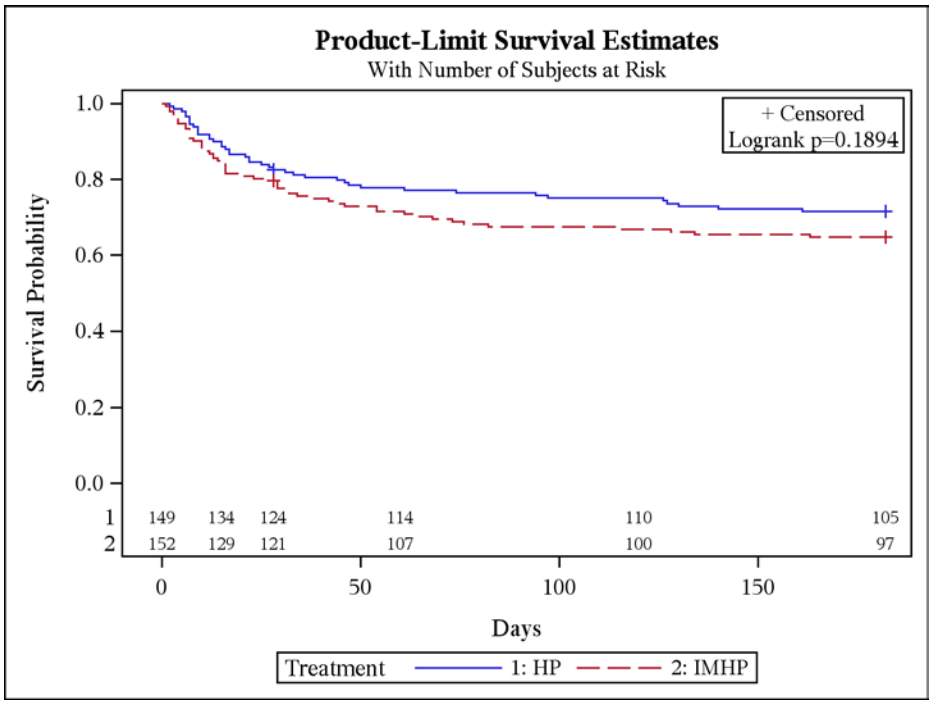
eTable 1. Nutritional composition of IMHP and HP enteral nutrition (per 1500 ml)

Nutrients	IMHP	HP
Energy (kcal)	1,920	1,920
Protein (g)	112.5	112.5
Casein (% of total protein)	41	100
Wheat hydrolysate (% of total protein)	39	0
Ala-Gln dipeptide (% of total protein)	20	0
Total glutamine (g)	30	9
Carbohydrates (g)	141.0	231.0
Fat (g)	96.0	55.5
MCT (g)	19.5	0
EPA + DHA (g)	7.5	0
Anti-oxidants		
vitamin C (mg)	690	195
vitamin E (mg alpha tocopherol)	266	23
Selenium (mcg)	285	113
Zinc (mg)	30	23
Other vitamins, minerals and trace elements	Normal Enteral Nutrition Values	Normal Enteral Nutrition Values
Fiber (g)	22.5	22.5

Abbreviations: IMHP, high-protein enteral nutrition enriched with immune modulating nutrients (Experimental product, NV Nutricia, Zoetermeer, The Netherlands) ; HP, high-protein enteral nutrition (Nutrison Advanced Protison, NV Nutricia, Zoetermeer, The Netherlands); Ala-Gln dipeptide, alanine glutamine dipeptide; MCT, medium chain triglycerides; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

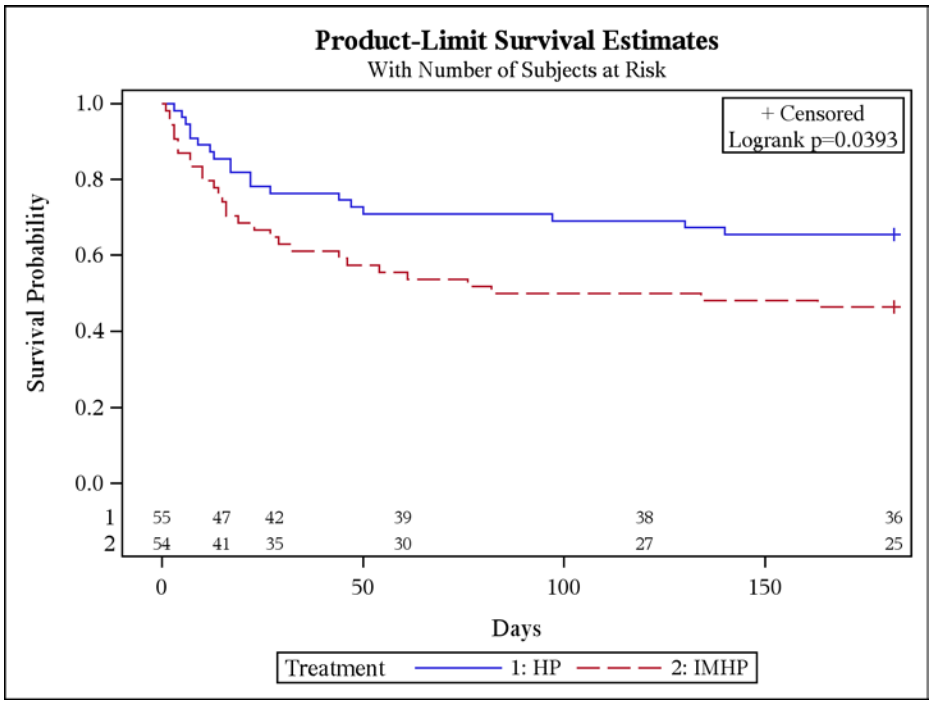
eFigure 1. Probability of 6 month survival

Panel A. Probability of 6 month survival in all patients (n=301)



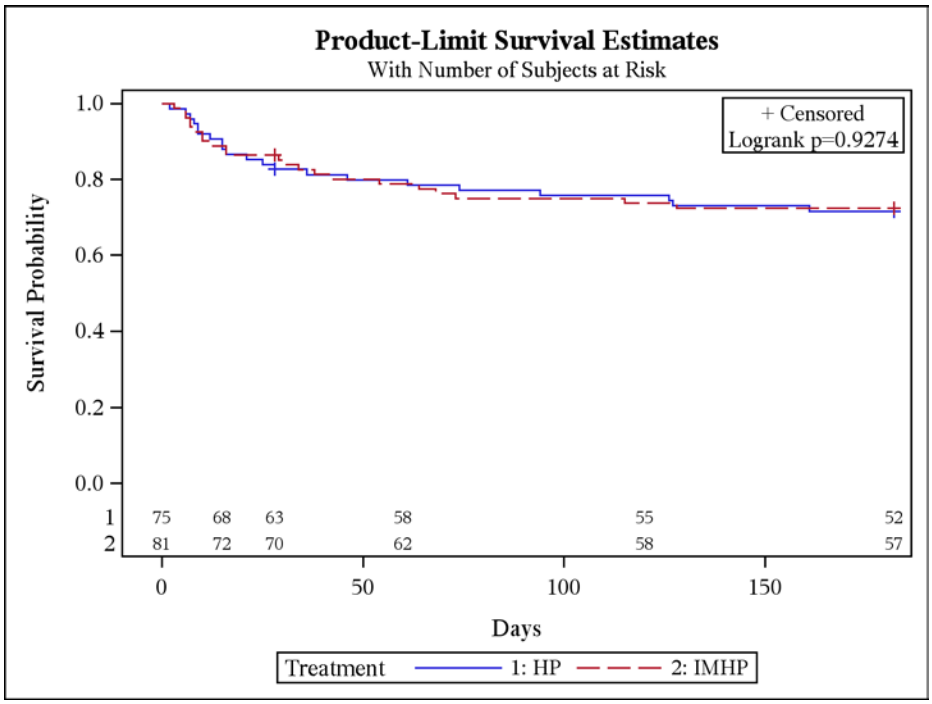
eFigure 1. Probability of 6 month survival

Panel B. Probability of 6 month survival in medical patients (n=109)



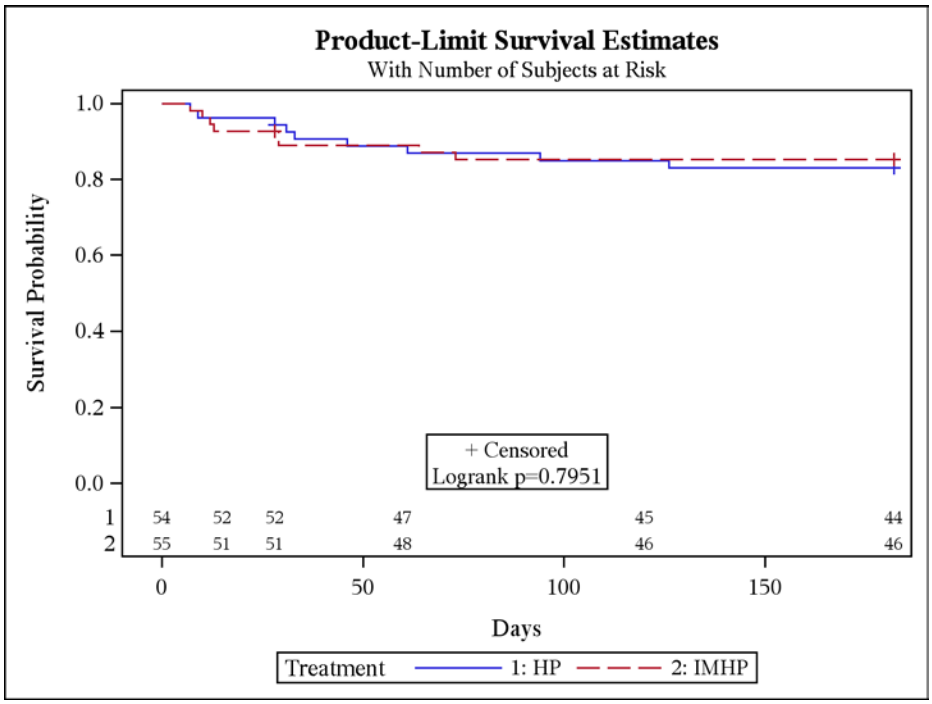
eFigure 1. Probability of 6 month survival

Panel C. Probability of 6 month survival in surgical Patients (n=156)



eFigure 1. Probability of 6 month survival

Panel D. Probability of 6 month survival in trauma patients (n=99)



Kaplan Meier Survival Probability Curve depicting the probability of survival for 180 days after randomization to IMHP (intervention) or HP (control) enteral feeding during ICU stay up to a maximum intervention duration of 28 days.

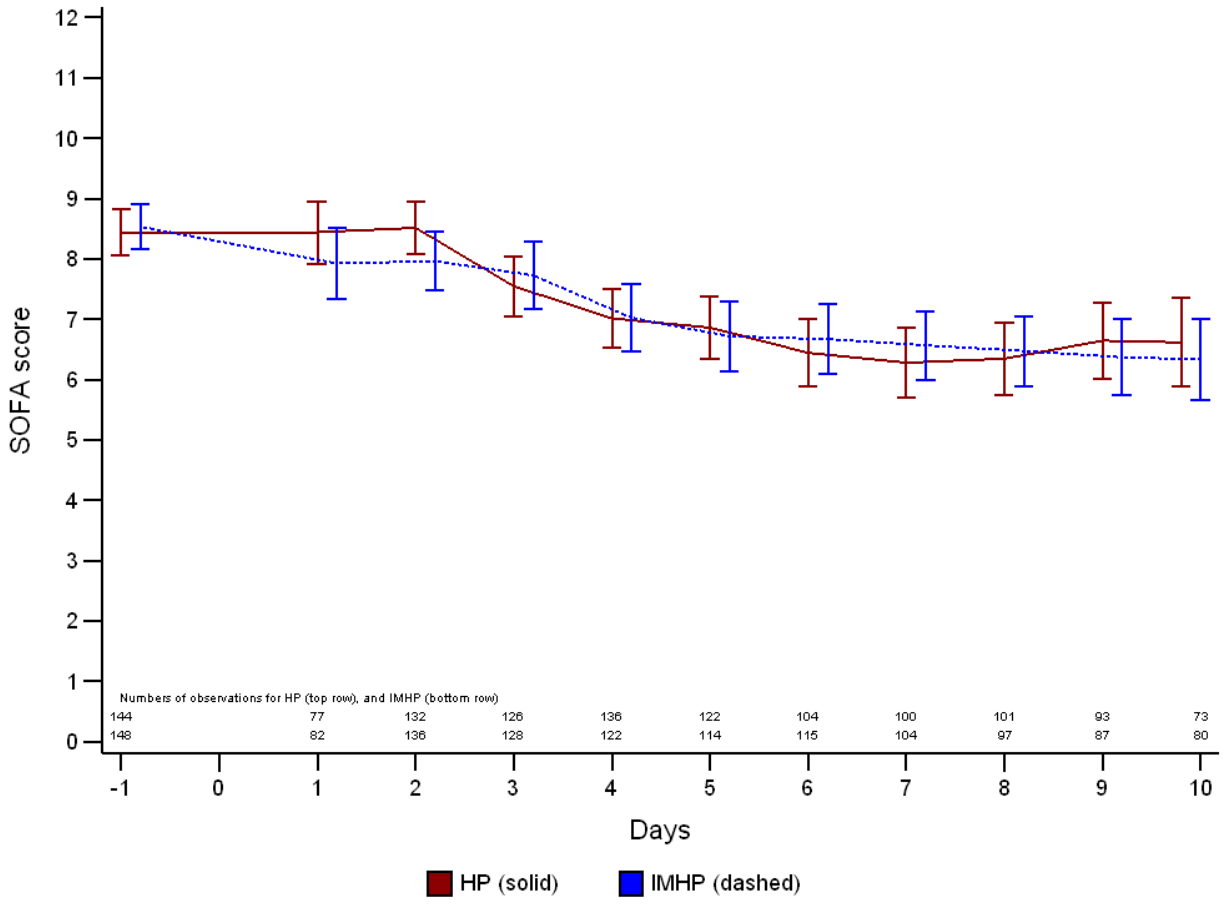
The continuous blue line shows survival among IMHP treated patients and the dashed red line survival among HP treated patients.

The top line of numbers on each graph shows the HP patients at risk and the lower line, the IMHP patients at risk at study start, and at days 15, 28, 60, 120, and 182.

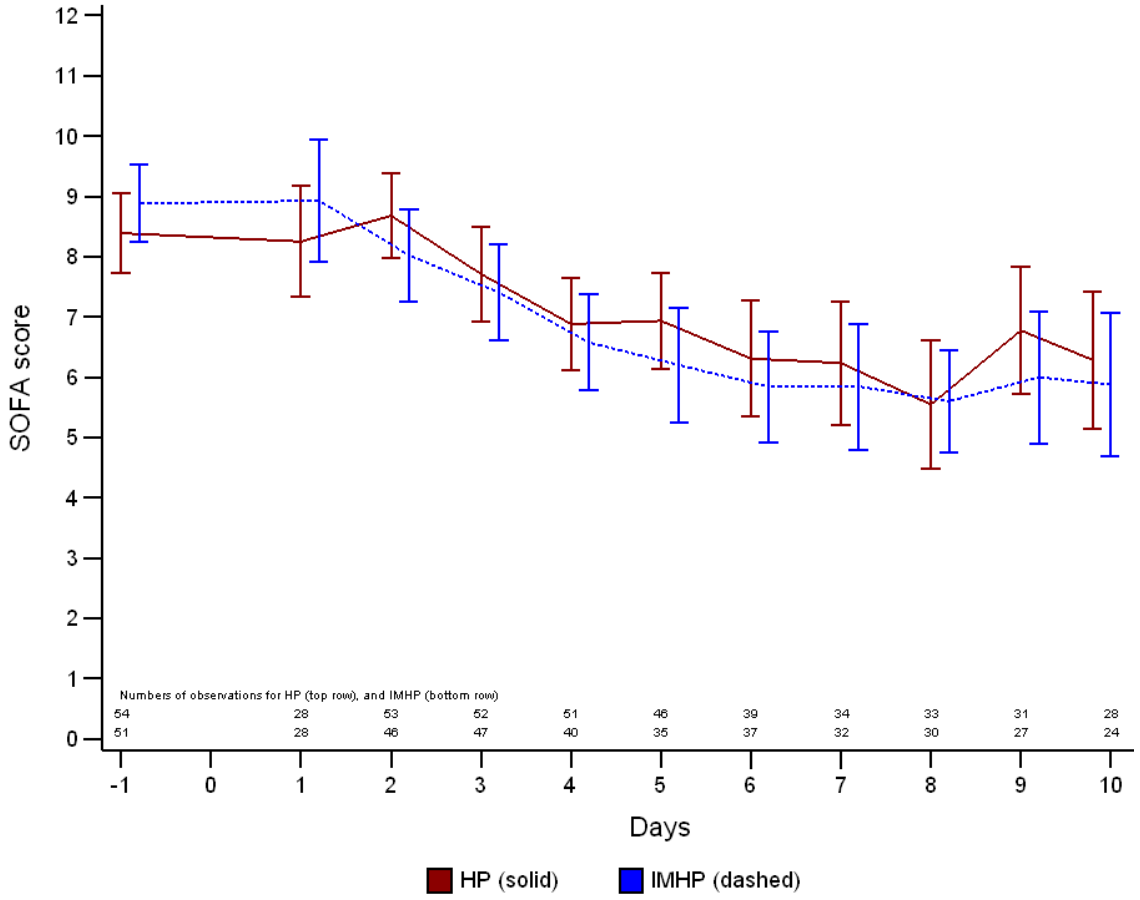
In the IMHP and HP groups we present surgical trauma patients both in the group of the surgical patients as well as in the group of trauma patients. The IMHP group (n=152) is comprised of 54 medical, 17 non-surgical trauma patients, 38 surgical trauma patient, and 43 non-trauma surgical patients. The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

eFigure 2. Baseline and daily SOFA-scores during the first 10 days of ICU stay in the two groups

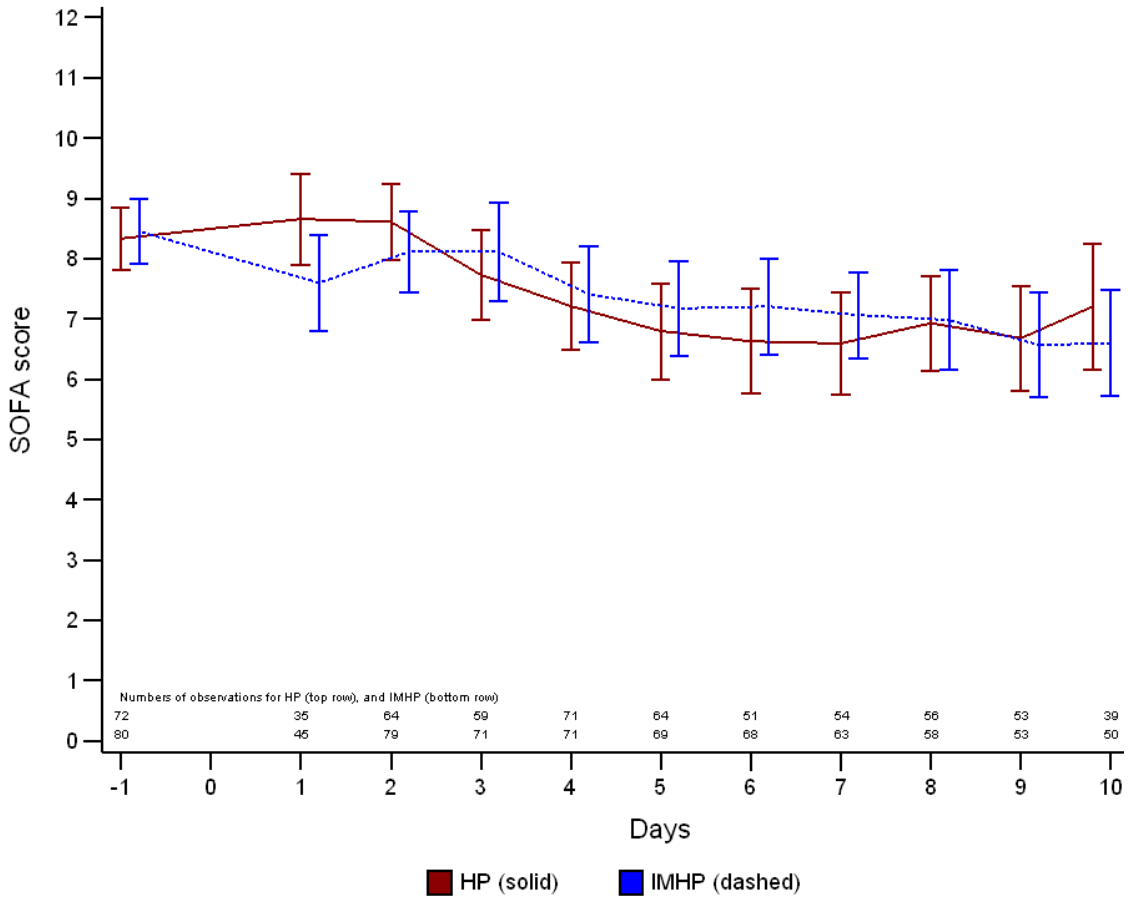
Panel A. Baseline and daily SOFA-scores during the first 10 days of ICU stay in all patients



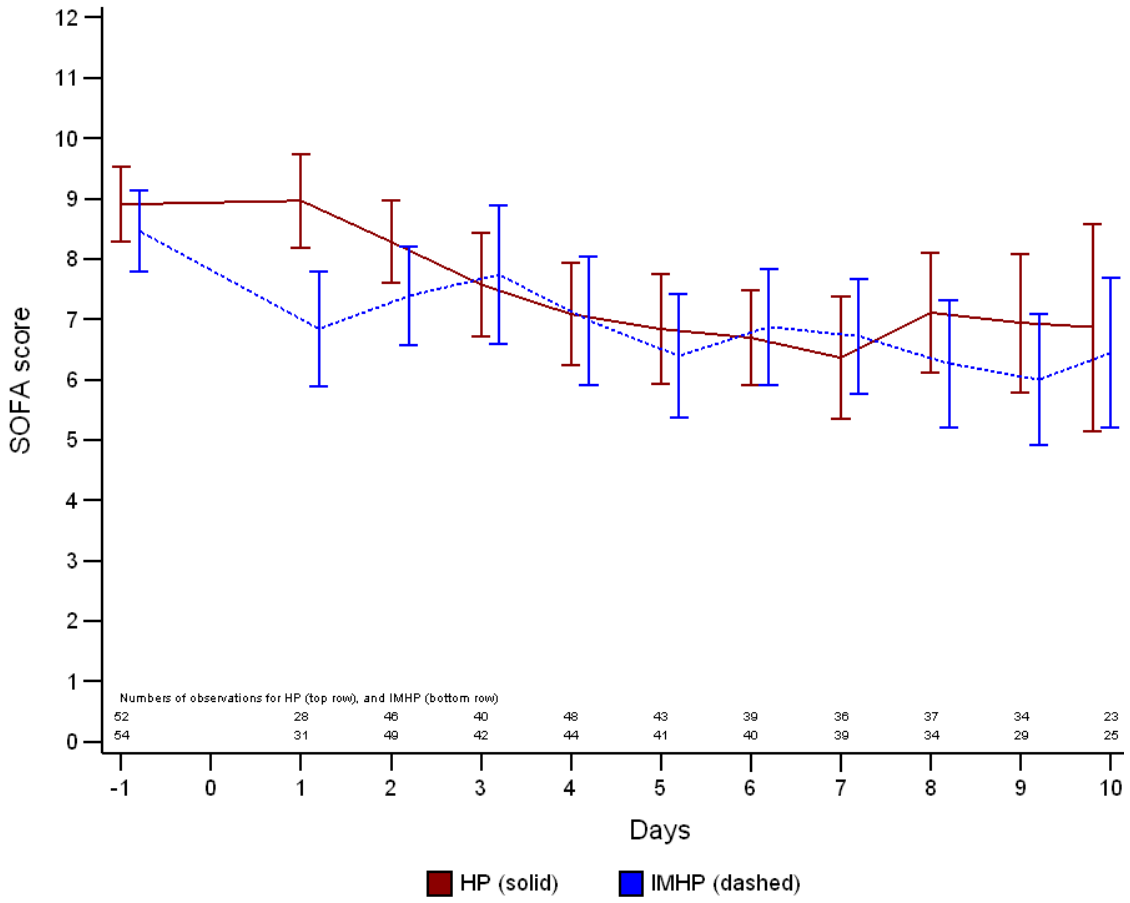
Panel B. Baseline and daily SOFA-scores during the first 10 days of ICU stay in medical patients



Panel C. Baseline and daily SOFA-scores during the first 10 days of ICU stay in surgical patients



Panel D. Baseline and daily SOFA-scores during the first 10 days of ICU stay in trauma patients



Sequential Organ Failure Assessment (SOFA) scores depicted are the highest daily mean SOFA-scores at baseline and on days 1-10 after randomization. Data are shown as mean values and 95% CI.
All patients (n=301) were included based on an intention-to-treat analysis. 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 comprised of 54 medical, 17 non-surgical trauma patients, 38 surgical trauma patient, and 43 non-trauma surgical patients. The HP group (n=149) is comprised of 55 medical, 19 non-surgical trauma patients, 35 surgical trauma patient, and 40 non-trauma surgical patients. The medical group comprises 54 IMHP and 55 HP patients. The surgical group comprises 81 IMHP and 75 HP patients. The trauma group comprises 55 IMHP and 54 HP patients.

Lower baseline numbers than patients randomized are due to missing values. There were no significant differences between groups in organ failures over time. -1 = baseline

eTable 2. Baseline, days 4 and 8 plasma levels of glutamine (µmol/L) and differences between baseline and day 4 and 8 levels in the two groups

		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	365, 339-391 (150)	356, 334-378 (149)	.60 [1]
	Median (Min-Max)	342 (31 – 1574)	322 (49 – 1023)	.55[2]
Day 4	**Mean, 95% CI (n)**	437, 406-468 (140)	387, 363-411 (144)	.01[1]
	Median (Min-Max)	410 (2 – 998)	374 (44 – 759)	.01[2]
Day 8	**Mean, 95% CI (n)**	386, 357-415 (121)	369, 345-393 (120)	.38[1]
	Median (Min-Max)	378 (1 – 918)	370 (46 – 733)	.35[2]
Day 4 - BL	**Mean, 95% CI (n)**	76, 46-105 (139)	29, 8-50 (144)	.01[1]
	Median (Min-Max)	70 (-1153 – 531)	20 (-366 – 372)	.002[2]
Day 8 - BL	**Mean, 95% CI (n)**	34, 1-67 (120)	23, -3-50 (120)	.61[1]
	Median (Min-Max)	34 (-1193 – 540)	31 (-761 – 507)	.40[2]

At baseline, low mean plasma glutamine levels were observed without differences between groups. On day 4 a significant increase in plasma glutamine was noted in the IMHP group.

BL: Baseline, CI: confidence interval, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

1: Two sample t-Test; 2: Wilcoxon Rank Sum Test

eTable 3. Baseline, day 4 and 8 plasma levels of selenium (µmol/L) and differences between baseline and day 4 and 8 levels in the two groups

		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	0.94, 0.87-1.01 (147)	1.03, 0.91-1.15 (145)	.22[1]
	Median (Min-Max)	0.82 (0.14 – 3.27)	0.87 (0.22 – 5.81)	.43[2]
Day 4	**Mean, 95% CI (n)**	1.08, 0.99-1.17 (141)	1.01, 0.94-1.07 (139)	.18[1]
	Median (Min-Max)	0.98 (0.33 – 4.13)	0.94 (0.12 – 2.34)	.47[2]
Day 8	**Mean, 95% CI (n)**	1.13, 1.04-1.23 (120)	1.13, 1.06-1.21 (116)	.99[1]
	Median (Min-Max)	1.07 (0.29 – 4.43)	1.05 (0.48 – 2.99)	.98[2]
Day 4 - BL	**Mean, 95% CI (n)**	0.14, 0.05-0.23 (139)	- 0.03, -0.16-0.10 (139)	.03[1]
	Median (Min-Max)	0.11 (-1.76 – 2.90)	0.06 (-4.89 – 1.60)	.11[2]
Day 8 - BL	**Mean, 95% CI (n)**	0.18, 0.06-0.30 (118)	0.08, -0.08-0.25 (116)	.34[1]
	Median (Min-Max)	0.16 (-2.37 – 3.65)	0.13 (-4.85 – 2.63)	.65[2]

At baseline, normal mean plasma selenium levels were observed without differences between groups. On day 4, a significant increase in plasma selenium was noted in the IMHP group.

BL: Baseline, CI: confidence interval, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

1: Two sample t-test; 2 : Wilcoxon Rank Sum Test

eTable 4. Baseline, day 4 and 8 (EPA+DHA)/LCP ratio in plasma and differences between baseline and day 4 and 8 levels in the two groups

		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	2.5, 2.4-2,7 (151)	2.6, 2.5-2.8 (148)	.34[1]
	Median (Min-Max)	2.3 (0.7 – 6.6)	2.6 (0.9 – 6.2)	.13[2]
Day 4	**Mean, 95% CI (n)**	6.0, 5.6-6.3 (142)	2.3, 2.2-2.5 (144)	‹ .001[1]
	Median (Min-Max)	5.8 (1.5 – 13.9)	2.3 (1.0 – 5.0)	‹ .001[2]
Day 8	**Mean, 95% CI (n)**	7.5, 7.0-8.0 (122)	2.1, 2.0-2.2 (120)	‹ .001[1]
	Median (Min-Max)	7.4 (1.5 – 14.1)	2.1 (0.9 – 4.2)	‹ .001[2]
Day 4 - BL	**Mean, 95% CI (n)**	3.4, 3.0-3.8 (141)	-0.3, -0.4—0.2 (143)	‹ .001[1]
	Median (Min-Max)	3.3 (-2.1 – 11.7)	-0.3 (-1.6 – 1.4)	‹ .001[2]
Day 8 - BL	**Mean, 95% CI (n)**	5.1, 4.6-5.5 (121)	-0.5, -0.6—0.4 (119)	‹ .001[1]
	Median (Min-Max)	5.1 (-1.6 – 10.7)	- 0.5 (-2.9 – 1.8)	‹ .001[2]

At baseline, low EPA+DHA)/LCP-ratios were observed without differences between groups. On days 4 and 8 significant increases in plasma EPA+DHA)/LCP-ratios were noted in the IMHP group.

BL: Baseline, CI: confidence interval, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

EPA+DHA)/LCP-ratio: Eicosapentaenoic acid + Docosahexaenoic acid) / Long Chain Polyunsaturated fatty acids-ratio.

1: Two sample t-Test; 2 : Wilcoxon Rank Sum Test

eTable 5. Baseline, day 4 and 8 plasma levels of vitamin C (µmol/L) and differences between baseline and day 4 and 8 levels in the two groups

		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	10.2, 8.4-12.0 (135)	11.9, 9.3-14.4 (131)	.28[1]
	Median (Min-Max)	7.5 (0.0 – 72.0)	8.4 (0.0 – 140.0)	.25[2]
Day 4	**Mean, 95% CI (n)**	18.8, 15.8-21.7 (131)	9.3, 7.8-10.8 (124)	‹ .001[1]
	Median (Min-Max)	14.0 (0.0 – 70.6)	6.8 (0.0 - 38.0)	‹ .001[2]
Day 8	**Mean, 95% CI (n)**	23.0, 19.7-26.3 (114)	9.7, 8.0-11.3 (104)	‹ .001[1]
	Median (Min-Max)	18.1 (0.0 – 77.2)	8.3 (0.0 -34.3)	‹ .001[2]
Day 4 - BL	**Mean, 95% CI (n)**	9.0, 6.4-11.7 (125)	-2.9, -5.4-0.4 (120)	‹ .001[1]
	Median (Min-Max)	6.3 (-38.8 – 64.0)	-1.0 (-132.0 – 16.2)	‹ .001[2]
Day 8 - BL	**Mean, 95% CI (n)**	14.0, 10.9-17.1 (109)	- 1.8, -5.1-1.4 (101)	‹ .001[1]
	Median (Min-Max)	11.8 (-21.1 – 62.0)	- 0.1 (-137.6 – 25.5)	‹ .001[2]

At baseline, low plasma vitamin C levels were observed without differences between groups. On day 4 and 8 significant increases in plasma vitamin C levels were noted in the IMHP group.

BL: Baseline, CI: confidence interval, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

1: Two sample t-test; 2 : Wilcoxon Rank Sum Test

eTable 6. Baseline, day 4 and 8 plasma levels of vitamin E (µmol/L) and differences between baseline and day 4 and 8 levels in the two groups

		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	19.8, 18.7-20.9 (150)	21.1, 19.8-22.3 (149)	.15[1]
	Median (Min-Max)	19.1 (7.4 – 45.5)	19.8 ± (3.0 - 54.2)	.14[2]
Day 4	**Mean, 95% CI (n)**	39.8, 37.3-42.3 (140)	24.0, 22.9-25.2 (144)	‹ .001[1]
	Median (Min-Max)	40.6 (4.3 – 84.2)	22.5 (8.5 – 50.2)	‹ .001[2]
Day 8	**Mean, 95% CI (n)**	47.7, 44.7-50.6 (121)	27.4, 26.0-28.8 (120)	‹ .001[1]
	Median (Min-Max)	47.3 (2.5 – 124.2)	26.9 (7.4 – 45.7)	‹ .001[2]
Day 4 - BL	**Mean, 95% CI (n)**	19.6, 17.3-22.0 (139)	3.0, 2.0-4.0 (144)	‹ .001[1]
	Median (Min-Max)	19.0 (-10.2 – 64.2)	2.8 (-12.5 – 19.8)	‹ .001[2]
Day 8 - BL	**Mean, 95% CI (n)**	27.4, 24.6-30.3 (120)	6.3, 4.9-7.8 (120)	‹ .001[1]
	Median (Min-Max)	27.1 (-12.0 – 86.0)	6.1 (-15.9 – 29.2)	‹ .001[2]

At baseline, low plasma vitamin E levels were observed without differences between groups. On days 4 and 8 significant increases in plasma vitamin E levels were noted in the IMHP group.

BL: Baseline, CI: confidence interval, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

1: Two sample t-Test; 2 : Wilcoxon Rank Sum Test

eTable 7. Baseline, day 4 and 8 plasma levels of zinc (µmol/L) and differences between baseline and day 4 and 8 levels in the two groups

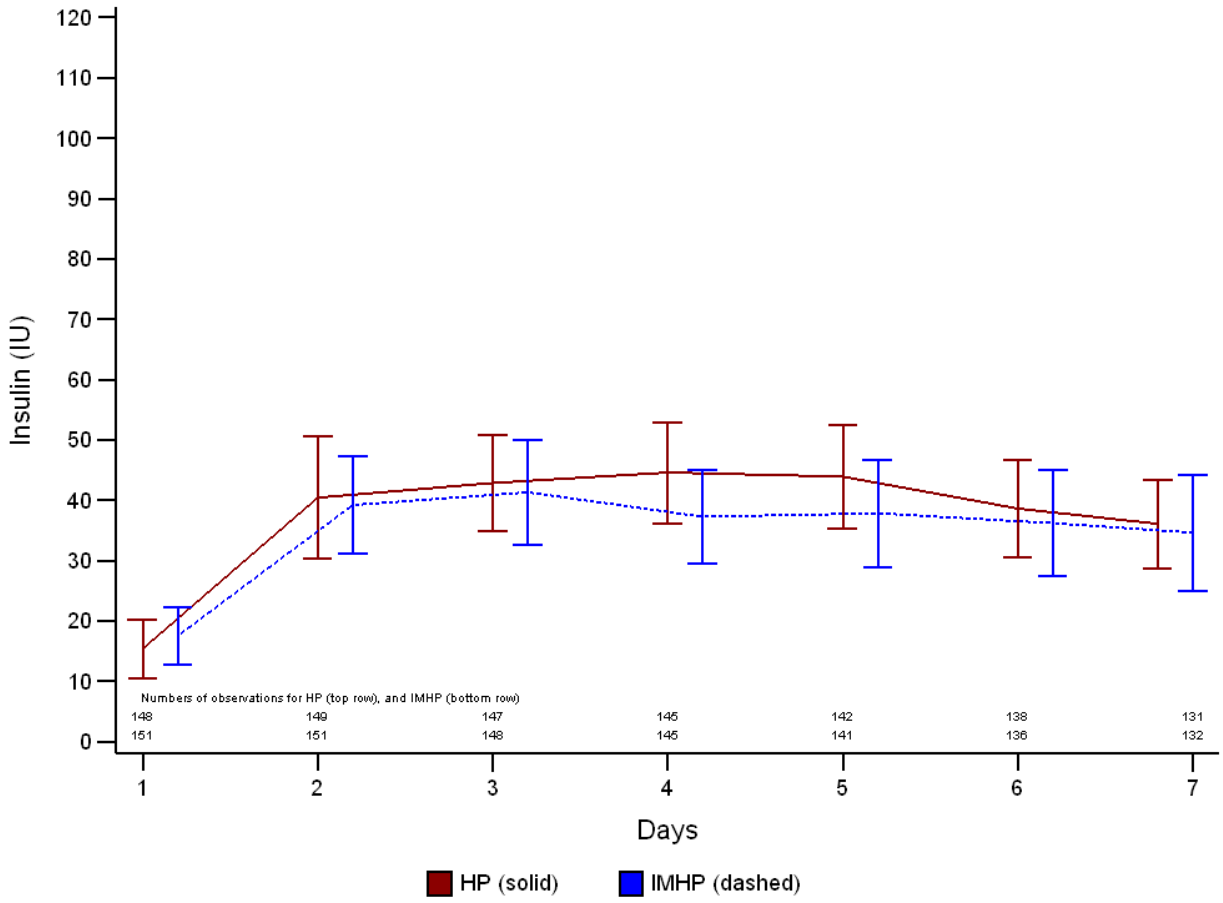
		Total population (n=301)		
Visit	**Statistics**	**IMHP (n=152)**	**HP (n=149)**	***P* value**
Baseline (BL)	**Mean, 95% CI (n)**	6.8, 6.1-7.6 (147)	6.5, 5.9-7.2 (145)	.54[1]
	Median (Min-Max)	6.3 (0.2 – 29.0)	5.9 (0.2-19.9)	.69[2]
Day 4	**Mean, 95% CI (n)**	7.8, 7.0-8.5 (140)	8.0, 7.3-8.7 (139)	.68[1]
	Median (Min-Max)	7.3 (0.2 – 28.6)	7.1 (0.2-25.4)	.70[2]
Day 8	**Mean, 95% CI (n)**	10.3, 9.3-11.2 (120)	10.4, 9.3-11.5 (116)	.85[1]
	Median (Min-Max)	9.4 (0.2 – 27.2)	9.5 (0.2 – 50.3)	.98[2]
Day 4 - BL	**Mean, 95% CI (n)**	1.1, 0.5-1.6 (138)	1.4, 0.8-2.1 (139)	.38[1]
	Median (Min-Max)	0.9 (-9.2 – 13.7)	1.3 (-13.4 – 13.0)	.32[2]
Day 8 - BL	**Mean, 95% CI (n)**	3.4, 2.6-4.2 (118)	3.5, 2.4-4.6 (116)	.91[1]
	Median (Min-Max)	3.1 (-7.4 – 20.1)	3.3 (-9.6 – 41.8)	.91[2]

At baseline, low plasma zinc levels were observed without differences between groups. On days 4 and 8, no significant increases in plasma zinc levels were noted in either group.

BL: Baseline, SD: Standard Deviation, n: number, IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

1: Two sample t-Test; 2 : Wilcoxon Rank Sum Test

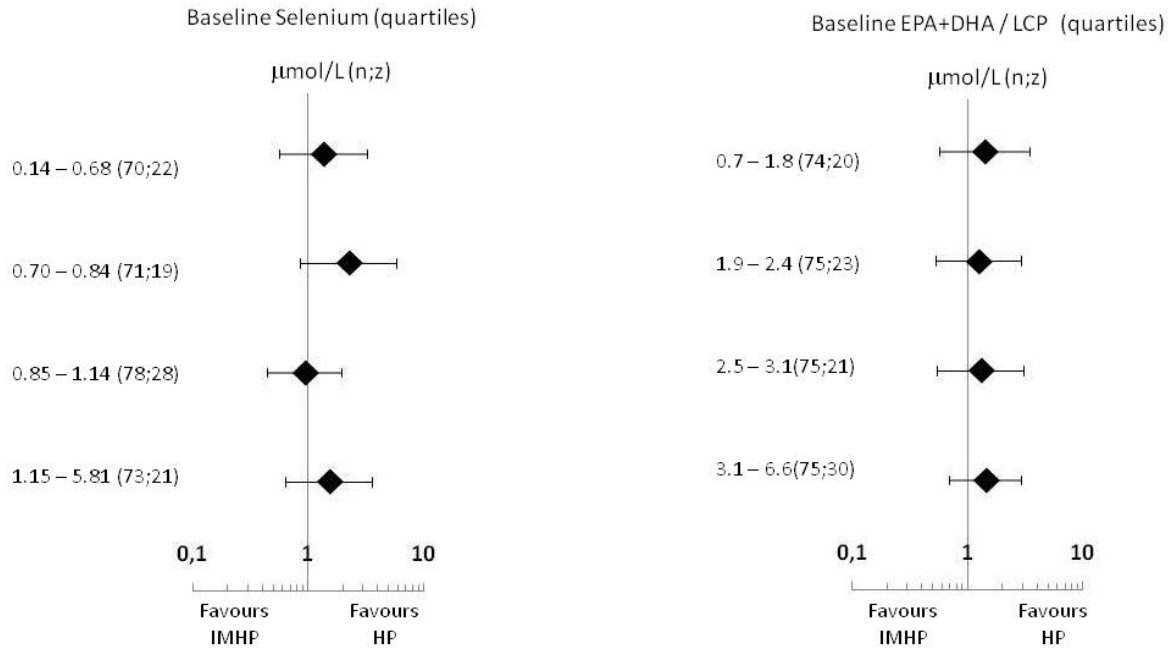
eFigure 3. Daily total insulin (IU) administration during the first 7 days of ICU stay after randomization to IMHP vs. HP enteral feeding

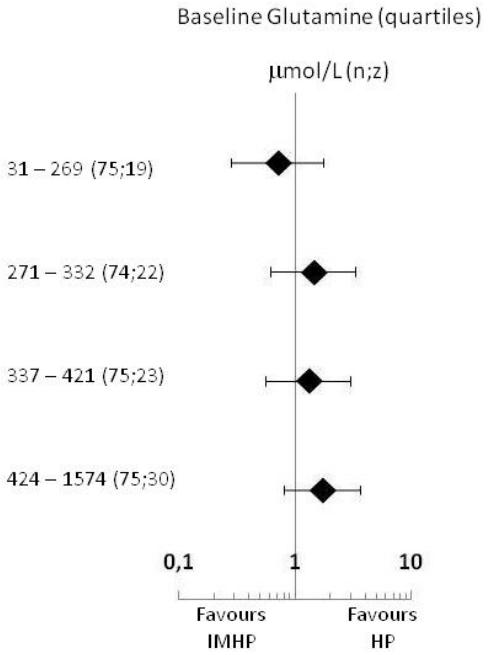


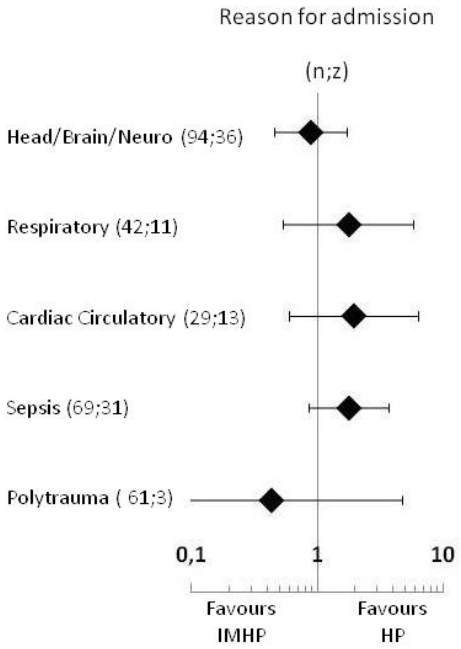
Insulin (IU) administered per day (mean (95% Confidence Interval)) on day 1-7 after randomization. All patients (n=301) are included based on an intention-to-treat analysis. There were no significant differences between groups in insulin administration over time.

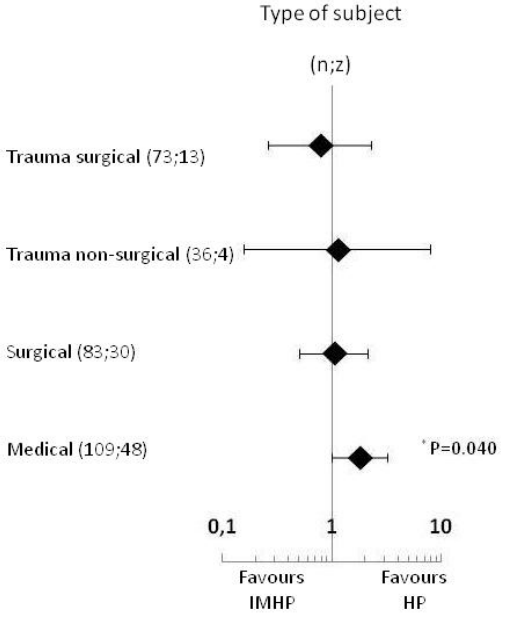
Data are shown as mean values with 95% confidence intervals.
IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

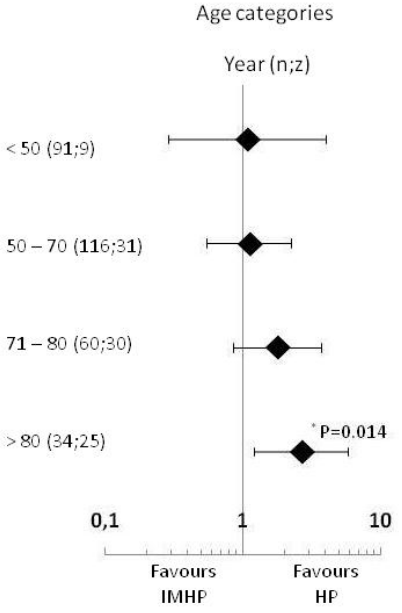
eFigure 4. Subgroup treatment effect analyses of 6-month mortality (post hoc analyses) related to IMHP vs. HP enteral feeding

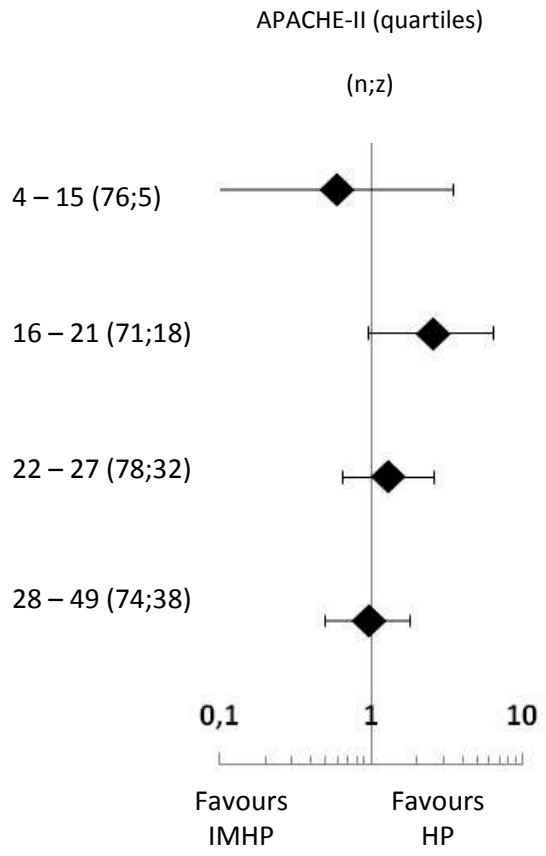



Baseline Glutamine (quartiles)
µmol/L (n;z)
31 – 269 (75;19)
271 – 332 (74;22)
337 – 421 (75;23)
424 – 1574 (75;30)
0,1
1
10
Favours IMHP
Favours HP


Reason for admission
(n;z)
Head/Brain/Neuro (94;36)
Respiratory (42;11)
Cardiac Circulatory (29;13)
Sepsis (69;31)
Polytrauma (61;3)
0,1
1
10
Favours IMHP
Favours HP


Type of subject
(n;z)
Trauma surgical (73;13)
Trauma non-surgical (36;4)
Surgical (83;30)
Medical (109;48)
*P=0.040
0,1
1
10
Favours IMHP
Favours HP


Age categories
Year (n;z)
< 50 (91;9)
50 – 70 (116;31)
71 – 80 (60;30)
> 80 (34;25)
*P=0.014
0,1
1
10
Favours IMHP
Favours HP



N: number of subjects; Z: number of patients who died.

Treatment effects are depicted as Hazard ratios and 95% confidence intervals comparing groups as quartiles (baseline selenium, EPA+DHA/LCP ratio, glutamine and APACHE-II scores) or categories (age) or qualitative groups (reason for admission, type of subject). Significantly lower mortality was observed in medical patients on HP (p=0.040) and in patients over 80 years of age on HP (p=0.014) compared to those in the same categories receiving IMHP. IMHP: immune-modulating nutrients enriched high protein feed (intervention), HP: high protein feed (control).

EPA+DHA)/LCP-ratio: Eicosapentaenoic acid + Docosahexaenoic acid) / Long Chain Polyunsaturated fatty acids-ratio.

eTable 8. Number and percentage of patients with at least one SAE and number of SAEs by body system organ class and preferred term.

	IMHP (n=152)		HP (n=149)		All (n=301)		
WHO SOC Preferred term	**Patients n (%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	***P* value ***
ALL AEs	39 (25.7)	43	38 (25.5)	48	77 (25.6)	91	.975[1]
Body as a whole - general disorders							
Any	4 (2.6)	4	6 (4.0)	6	10 (3.3)	10	.539
Multiple Organ Failure	3 (2.0)	3	5 (3.4)	5	8 (2.7)	8	.498
Edema			1 (0.7)	1	1 (0.3)	1	.495
Sudden Death	1 (0.7)	1			1 (0.3)	1	>.99
Cardiovascular disorders, general							
Any	8 (5.3)	8	2 (1.3)	2	10 (3.3)	10	.104
Failure	5 (3.3)	5	2 (1.3)	2	7 (2.3)	7	.448
Circulatory Failure	3 (2.0)	3			3 (1.0)	3	.248
Central & peripheral nervous system							
Any	3 (2.0)	3	5 (3.4)	6	8 (2.7)	9	.498
Brain Hypoxia	1 (0.7)	1			1 (0.3)	1	>.99
Brain Stem Disorder			1 (0.7)	1	1 (0.3)	1	.495
Cerebral Disorder			2 (1.3)	2	2 (0.7)	2	.244
Convulsions Grand Mal			2 (1.3)	2	2 (0.7)	2	.244
CSF Abnormal	1 (0.7)	1			1 (0.3)	1	>.99
Hypertension Intracranial	1 (0.7)	1	1 (0.7)	1	2 (0.7)	2	>.99
Gastro-intestinal system disorders							
Any	3 (2.0)	3	5 (3.4)	5	8 (2.7)	8	.498
Diarrhea	1 (0.7)	1			1 (0.3)	1	>.99
Gastroenteritis			1 (0.7)	1	1 (0.3)	1	.495
Gi Hemorrhage			1 (0.7)	1	1 (0.3)	1	.495
Intestinal Ischemia	1 (0.7)	1	1 (0.7)	1	2 (0.7)	2	>.99
Intestinal Perforation			1 (0.7)	1	1 (0.3)	1	.495
Peritonitis	1 (0.7)	1	1 (0.7)	1	2 (0.7)	2	>.99
Heart rate and rhythm disorders							

	IMHP (n=152)		HP (n=149)		All (n=301)		
WHO SOC Preferred term	**Patients n (%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	***P* value ***
Any	2 (1.3)	2	7 (4.7)	9	9 (3.0)	11	.10
Cardiac Arrest	1 (0.7)	1	6 (4.0)	7	7 (2.3)	8	.07
Fibrillation Ventricular			1 (0.7)	2	1 (0.3)	2	.50
Tachycardia	1 (0.7)	1			1 (0.3)	1	>.99
Liver and biliary system disorders							
Any	1 (0.7)	1			1 (0.3)	1	>.99
Hepatic Failure	1 (0.7)	1			1 (0.3)	1	>.99
Metabolic and nutritional disorders							
Any			1 (0.7)	1	1 (0.3)	1	.50
Acidosis Lactic			1 (0.7)	1	1 (0.3)	1	.50
Myo endo pericardial & valve							
Any	1 (0.7)	1	2 (1.3)	2	3 (1.0)	3	.62
Angina Pectoris			1 (0.7)	1	1 (0.3)	1	.50
Myocardial Infarction			1 (0.7)	1	1 (0.3)	1	.50
Myocardial Ischemia	1 (0.7)	1			1 (0.3)	1	>.99
Neoplasm							
Any			1 (0.7)	1	1 (0.3)	1	.50
Neuroblastoma			1 (0.7)	1	1 (0.3)	1	.50
Platelet, bleeding & clotting disorders							
Any	1 (0.7)	1	1 (0.7)	1	2 (0.7)	2	>.99
Embolism Pulmonary	1 (0.7)	1			1 (0.3)	1	>.99
Hemorrhage Nos			1 (0.7)	1	1 (0.3)	1	.50
Red blood cell disorders							
Any			1 (0.7)	1	1 (0.3)	1	.50
Aplasia Bone Marrow			1 (0.7)	1	1 (0.3)	1	.50
Resistance mechanism disorders							
Any	1 (0.7)	1	2 (1.3)	2	3 (1.0)	3	.62
Abscess	1 (0.7)	1			1 (0.3)	1	>.99
Sepsis			2 (1.3)	2	2 (0.7)	2	.24

	IMHP (n=152)		HP (n=149)		All (n=301)		
WHO SOC Preferred term	**Patients n (%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	**Patients n(%)**	**AEs (count)**	***P* value ***
Respiratory system disorders							
Any	10 (6.6)	11	7 (4.7)	7	17 (5.6)	18	.48[1]
Bronchial Obstruction	1 (0.7)	1			1 (0.3)	1	>.99
Pneumonia	1 (0.7)	1	1 (0.7)	1	2 (0.7)	2	>.99
Pneumothorax	1 (0.7)	1			1 (0.3)	1	>.99
Respiratory Distress Syndrome	1 (0.7)	1			1 (0.3)	1	>.99
Respiratory Insufficiency	7 (4.6)	7	6 (4.0)	6	13 (4.3)	13	.81[1]
Secondary terms							
Any	1 (0.7)	1	3 (2.0)	3	4 (1.3)	4	.37
Closed Head Injury	1 (0.7)	1			1 (0.3)	1	>.99
Surgical Intervention			3 (2.0)	3	3 (1.0)	3	.12
Urinary system disorders							
Any			1 (0.7)	1	1 (0.3)	1	.50
Renal Failure Acute			1 (0.7)	1	1 (0.3)	1	.50
Vascular (extracardiac) disorders							
Any	6 (3.9)	6	1 (0.7)	1	7 (2.3)	7	.12
Cerebral Hemorrhage	4 (2.6)	4			4 (1.3)	4	.12
Cerebral Infarction			1 (0.7)	1	1 (0.3)	1	.50
Cerebral Ischemia	2 (1.3)	2			2 (0.7)	2	.50
White cell and red cell disorders							
Any	1 (0.7)	1			1 (0.3)	1	>.99
Agranulocytosis	1 (0.7)	1			1 (0.3)	1	>.99

No differences in Serious Adverse Events or Adverse Events were observed between groups.

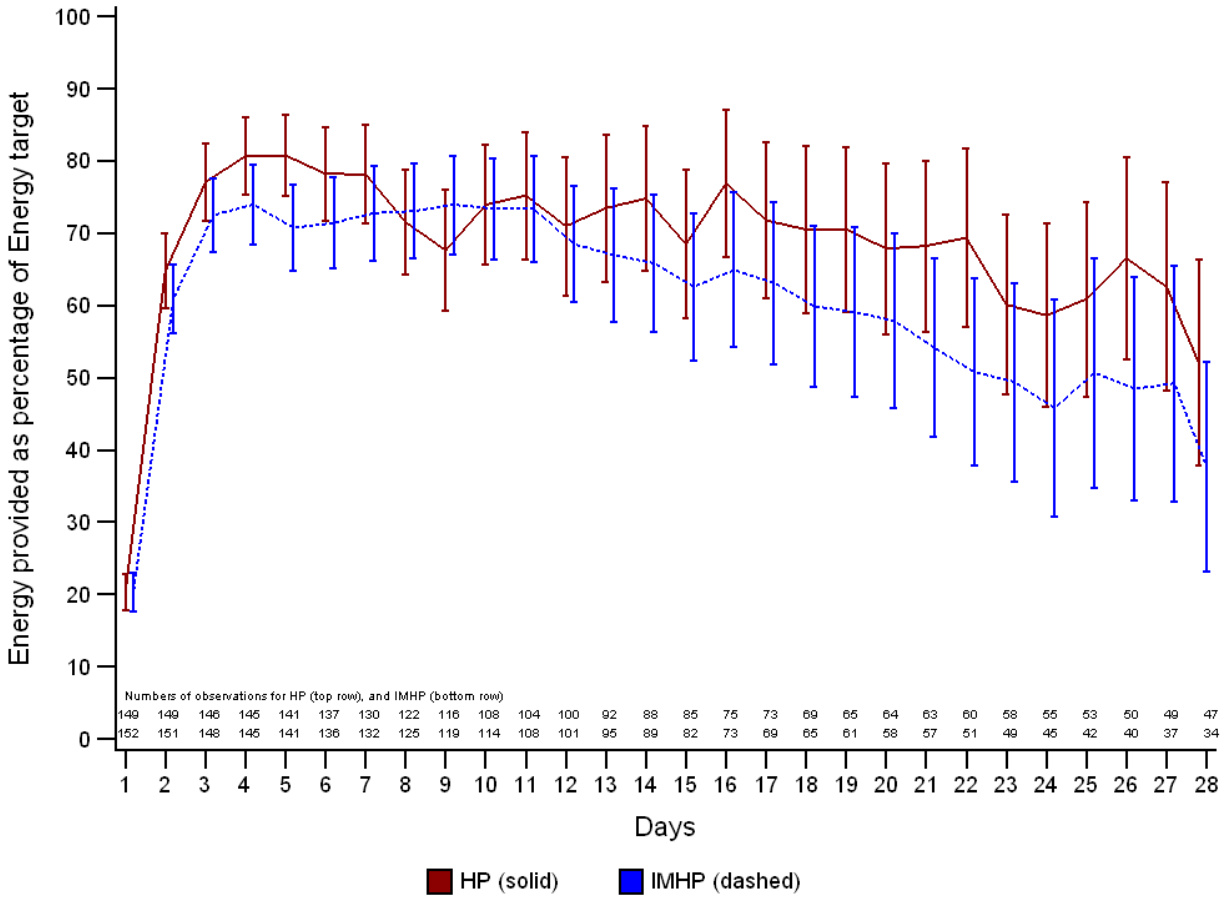
* P-values relate to number of patients (n), comparing IMHP versus HP.P-values were calculated using Fisher's Exact test;

'1' indicates Chi-square test was used.

n: Number of patients in the population or with at least one SAE

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

eFigure 5. Energy intake from study products as percentage of calculated energy target during ICU stay



Results are presented as Means (95% CI) from day 1 until day 28 (study intervention duration). All patients from the Intention to Treat analysis were included (n=301). Energy targets were calculated as follows: 25 kcal/kg body weight * day, with a maximum of 2500 kcal/day.

No statistically significant differences were observed between study groups in mean duration of study product administration or total volume of study products administered. At day 3, mean enteral feeding intake was >70% in both groups suggesting successful enteral feeding.