Synbiotics, Prebiotics, Glutamine, or Peptide in Early Enteral Nutrition: A Randomized Study in Trauma Patients

Alenka Spindler-Vesel, Stig Bengmark, Irena Vovk, Ognjen Cerovic and Lidija Kompan

JPEN J Parenter Enteral Nutr 2007; 31; 119
DOI: 10.1177/0148607107031002119

0148-6071/07/3102-0119$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 31, No. 2
Printed in U.S.A.

Original Communications

Synbiotics, Prebiotics, Glutamine, or Peptide in Early Enteral Nutrition: A Randomized Study in Trauma Patients

Alenka Spindler-Vesel, MD, MS*; Stig Bengmark, MD, PhD, FRACS, FRCPS†; Irena Vovk, PhD‡; Ognjen Cerovic, MD, MS*; and Lidija Kompan, MD, PhD*

*From the *University Medical Centre, Ljubljana, Slovenia; the †Departments of Hepatology and Surgery, University College London, London University, England; and the ‡National Institute of Chemistry, Ljubljana, Slovenia*

ABSTRACT. *Background:* Since the hepatosplanchnic region plays a central role in development of multiple-organ failure and infections in critically ill trauma patients, this study focuses on the influence of glutamine, peptide, and synbiotics on intestinal permeability and clinical outcome. *Methods:* One hundred thirteen multiple injured patients were prospectively randomized into 4 groups: group A, glutamine; B, fermentable fiber; C, peptide diet; and D, standard enteral formula with fibers combined with Synbiotic 2000 (Synbiotic 2000 Forte; Medifarm, Sweden), a formula containing live lactobacilli and specific bioactive fibers. Intestinal permeability was evaluated by measuring lactulose-mannitol excretion ratio on days 2, 4, and 7. *Results:* No differences in days of mechanical ventilation, intensive care unit stay, or multiple-organ failure scores were found between the patient groups. A total of 51 infections, including 38 pneumonia, were observed, with only 5 infections and 4 pneumonias in group D, which was significantly less than combined infections ($p = .003$) and pneumonias ($p = .03$) in groups A, B, and C. Intestinal permeability decreased only in group D, from 0.148 (0.056–0.240) on day 4 to 0.061 (0.040–0.099) on day 7; ($p < .05$). In group A, the lactulose-mannitol excretion ratio increased significantly ($p < .02$) from 0.050 (0.013–0.116) on day 2 to 0.159 (0.088–0.311) on day 7. The total gastric retention volume in 7 days was 1150 (785–2395) mL in group D, which was significantly more than the 410 (382–1062) mL in group A ($p < .02$), and 620 (337–1190) mL in group C ($p < .03$). *Conclusions:* Patients supplemented with synbiotics did better than the others, with lower intestinal permeability and fewer infections. (*Journal of Parenteral and Enteral Nutrition* **31:**119–126, 2007)

Most of the immune system is localized in the gut and in the vicinity of the gut, which offers a great potential to affect its function and enhance resistance to disease. Central to disease resistance is the acute phase response and inflammatory cascade, which is reported to be exaggerated and prolonged in those who later have complications such as multiple-organ failure (MOF) and various infections, especially chest infections.[1,2] The gut becomes a "cytokine-generating organ," which precedes the development of secondary morbidity.[3,4] In order to control and modulate the acute-phase response, several immune-enhancing diets have been developed and tried, but results thus far have been quite disappointing.[5–7] It has recently been concluded that commercial (so-called) immunonutrition cocktails "do more harm than good."[7,8] More than ever, there is a great need for specific substances with the ability to modulate the immune response and improve resistance to secondary morbidity. Among those substances suggested as possessing such abilities are various antioxidants, glutamine, fermentable plant fibers, and lactic acid bacteria.

Received for publication February 14, 2006.
Accepted for publication October 3, 2006.
Correspondence: Lidija Kompan, MD, PhD, Central Intensive Care Unit, University Medical Centre Ljubljana, Zaloska 2, Ljubljana, Slovenia 1000. Electronic mail may be sent to lidija.kompan@mf.uni-lj.si.

Low levels of glutamine, which have been observed in the critically ill, are associated with immune dysfunction and increased mortality.[9] In experimental animals, oral intake of glutamine has been shown to prevent depletion of the antioxidant glutathione in the lymphocytes in Peyer's patches. Oral glutamine has also been shown to reduce cytokine release, organ damage, and mortality in rats with induced endotoxemia.[10,11] Therapeutic effects were observed only with doses >0.2 g/kg/d. Although supply of these high doses of glutamine is more easily achieved parenterally, it has been suggested that the enteral supply of glutamine maintains gut barrier function more effectively than *via* the parenteral route.[12] Immunoenhancing effects have also been reported from the use of prebiotics (plant fibers) and probiotics, eg, lactic acid bacteria (LAB). Glucans are reported to reduce the morbidity and mortality rate in hospital infections in trauma patients.[13] A significant reduction in morbidity has also been reported with the supply of synbiotics (combination of prebiotic fibers and probiotic LAB) perioperatively, as well as in acute pancreatitis.[14–17]

The acute phase response is immediate; hence attempts to modulate it must be early. Enteral nutrition has proven more effective in modulating the subsequent inflammation if introduced early.[18] The normal lactic acid microbial flora disappears within hours in critically ill patients, most likely as a result of the stress of the disease and the medical treatment insti-

tuted.[19] We therefore attempted to institute enteral nutrition and supply the supplementary treatments as early as possible. No patient was admitted to the study with a history longer than 24 hours.

To date, no study has looked at the effects of synbiotics in acute trauma patients. The influence of glutamine and peptides is also far from fully explored in this category of patients. This study was undertaken to investigate the possibilities of these various treatments. The primary endpoint was to determine whether and to what extent these specific compounds affect intestinal permeability (IP), whereas the secondary endpoints were to assess the influence of the treatments on the infection rate, mortality, intensive care unit (ICU) stay, days of mechanical ventilation and the occurrence of MOF.

MATERIAL AND METHODS

The study was conducted in a 20-bed university surgical ICU. Multiple injured patients with an Injury Severity Score (ISS) of >18 and at least a 4-day ICU stay were eligible for the study.[20] Intragastric tube feeding was begun upon admission to the ICU—at the latest 24 hours after injury—at a rate of 30 mL/hour for 4 hours, after which the feeding was interrupted for 2 hours to assess gastric intolerance. The gastric content was aspirated, and if the volume was <200 mL, the feeding was reinstituted, with the rate being increased by 50% to 100%. The maximum volume was maintained at 160 mL/hour. Enteral nutrition was stopped during 6 night hours. At the sign of increased gastric residual, 10 mg metoclopramide was administered 3 times daily and a constant feeding volume maintained for a period of 4 hours. If increased gastric residual was observed twice on repeat gastric aspirations, or vomiting occurred, feeding was discontinued for 6 hours. The aim of the feeding was to achieve the target value of between 0.2 and 0.3 gN/kg body weight/d and an average of 25 nonprotein kcal/kg body weight/d at 72 hours after admission. No preventive antibiotic or H_2-blocker treatment was given. Parenteral solutions were used to complement the nutrition needs. Using closed envelopes, the patients were randomly allocated into 4 groups at the beginning of the study:

- Group A: Alitraq (Abbott-Ross, Abbott Park, IL) 5.25 g protein, 16.5 g carbohydrate, 1.55 g fat and 1.55 g glutamine, 446 mg arginine, 154 mg α-linolenic acid per 100 mL. Osmolarity 480 mOsml/L.
- Group B: Nova Source (Novartis Medical Nutrition, Basel, Switzerland) 4.1 g protein, 14.4 g carbohydrate, 3.5 g fat, 2.2 g fermentable fibers as fermentable guar gum per 100 mL. Osmolarity 228 mOsm/L.
- Group C: Nutricomp peptide (B. Braun, Melsungen, Germany) 4.5 g hydrolyzed protein, 16.8 g carbohydrate, 1.7 g fat per 100 mL. Osmolarity 400 mOsm/L.
- Group D: Nutricomp standard (B. Braun) 3.7 g protein, 13.7 g carbohydrate, 3.3 g fat per 100 mL. Osmolarity 240 mOsm/L. Patients in this group also received a supplement of a synbiotic consisting of 10^{10} *Pediococcus pentosaceus* 5–33:3, 10^{10} *Lactococcus raffinolactis* 32–77:1, 10^{10} *Lactobacillus paracasei* subsp *paracasei* 19, 10^{10} *Lactobacillus plantarum* 2362 and 2.5 g of each of the following 4 fibers: β glucan, inulin, pectin, and resistant starch per sachet (Synbiotic 2000; Medipharm Kågeröd, Sweden and Des Moines, IA).[21,22] The contents of the sachets were dissolved in 100 mL of lukewarm sterile water, mixed carefully, and then added separately, before feeding was started.

The Acute Physiologic Chronic Health Evaluation (APACHE) II score was calculated individually for each patient at the time of admission to ICU.[23] MOF scores were determined daily from admission to day 7, or until the day of discharge from ICU. Organ functions were assessed by estimation of serum aspartate, alanine-aminotransferase, total bilirubin, creatinine, leukocyte and platelet counts, and respiratory gases in arterial blood. MOF was rated on a 3-point MOF scale either as not present, 0; moderate, 1; or severe, 2.[24] On days 2, 4, and 7 after admission to the ICU, IP was evaluated by measuring lactulose-mannitol (L/M) excretion. For the purpose of the study, after 6 hours of fasting, the patients were instantly infused *via* a nasogastric tube with 5 g of M and 10 g of L mixed in 100 mL of water. Four mL of 20% chlorhexidine was added to the urine bag. Urine was collected over a period of 6 hours, and 5 mL was stored at −20°C until analysis. Urinary L and M were determined simultaneously by thin-layer chromatography.[25] Investigators were blinded to the study groups. Urinary excretion was calculated from the urinary concentrations (c) of L and M, using the following formulas:

$$\%\mathrm{L} = \mathrm{c} \times \mathrm{L} \times \text{urine volume per 6 h} / \text{amount of L given enterally}$$

$$\%\mathrm{M} = \mathrm{c} \times \mathrm{M} \times \text{urine volume per 6 h} / \text{amount of M given enterally}$$

$$\mathrm{L/M\ ratio} = \%\mathrm{L}/\%\mathrm{M}.$$

Microbiological specimens were collected and nosocomial infections were recorded as recommended by the Centers for Disease Control and Prevention and consensus conferences on ventilator-associated pneumonia.[26,27]

Procalcitonin (PCT) levels were measured daily using a specific 2-monoclonal antibody immunoluminometric assay (ILMA; Brahms Diagnostica GmbH, Berlin, Germany).[28]

The study protocol was approved by the Medical Ethics Committee of the Republic of Slovenia. Before the study, informed consent was obtained from all patients or their relatives.

Statistical Analysis

Descriptive statistics were calculated for the entire sample and for the individual study groups. Group differences were tested with the Mann-Whitney *U* test, χ^2 and Fisher's exact test for numeric and categorical variables, respectively. Pearson's correlation test was performed to determine the associations among variables. In all analyses, a p value $< .05$ was deemed statistically significant.

TABLE I
Patient data

113 Patients, 25 women	Average	SD
Age, y	41.0	18.9
ISS	30	11
APACHE II	13	7
Days receiving mechanical ventilation	13.0	11.3
Days of ICU treatment	17.1	14.2
Initiation of EN after trauma, h	15.9	8.3
Volume of EN during first 24 h, mL	344	325
Total volume of EN during first 4 days, mL	2931	1480
Gastric retention volume during first week, mL	1095	1003
Average MOF scores	3.1	1.3
L/M index day 2	0.1120	0.1633
L/M index day 4	0.2186	0.3707
L/M index day 7	0.2041	0.5068

APACHE, Acute Physiologic Chronic Health Evaluation; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple organ failure.

RESULTS

One hundred thirty-two patients were initially considered for the study. Eight patients died before the fourth day, 9 were discharged from the ICU during the first 48 hours after admission, whereas informed consent was not obtained for 2 patients. Therefore, 113 patients (88 men and 25 women) were included in the final analysis. The patients' characteristics are shown in Table I.

Seven patients died during their stay in ICU, 1 patient from group A and 2 from each of groups B, C, and D. The differences in mortality between the groups were not statistically significant. The patients who died were significantly older than the survivors: 71 (65–72.5), *vs* 36 (23–51) years ($p < .0004$); had higher admission APACHE II scores: 18 (17.5–19.6) *vs* 13 (8–18; $p < .015$); developed higher MOF scores: 4.1 (3.8–4.6) *vs* 3.1 (2.0–4.0; $p < .02$); received less feeding in comparison to survivors during the first 4 days: 1670 mL (550–2815) *vs* 2900 mL (2277–3720; $p < .04$); and showed higher volumes of gastric retention: 815 mL (400–1575) *vs* 360 mL (165–378; $p < .0004$).

The patients developed 51 infections during their ICU stay: 16 in group A, 17 in group B, 13 in group C, and 5 in group D. Thirty-eight patients were diagnosed with pneumonia: 11 in group A, 12 in group B, 11 in group C, and 4 in group D. One patient in group A had a urinary tract infection; 1 patient in group A and 1 in group B had intravascular catheter infections; 6 patients had wound infections (1 in group A, 2 in group B, 2 in group C, and 1 in group D); 3 had positive blood cultures (1 in group A and 2 in group B). The numbers of specific infections (urinary, vascular, wounds, positive hemocultures, and others) were, with the exception of pneumonia, low and there were no statistically significant differences between the groups or the rate of pneumonia (exact χ^2 $p = .138$). However, difference in pneumonia became significant (Fisher's exact test $p = .032$; Table II) when group D (16% overall rate of pneumonia) was compared with the combined groups A-C (40%). The reduction in the cumulative infection rate was statistically significant among groups A, B, C, and D (exact χ^2 $p = .021$) and between combined infections in groups A, B, and C *vs* group D (Fisher's exact test $p = .003$).

TABLE II
Infections

	Group A	Group B	Group C	Group D	Total
Pneumonia	11	12	11	4	38
Urinary tract	1	0	0	0	1
Vascular	1	1	0	0	2
Wound	1	2	2	1	6
Positive hemocultures	1	2	0	0	3
Others	1	0	0	0	1
All infections	16	17	13	5	51

Significant difference in the cumulative infection rate among groups A, B, C, and D (exact χ^2 $p = .021$) and between infections in groups A-C *vs* D group (Fisher's exact test $p = .003$). Nonsignificant difference in the pneumonia rate among groups A, B, C, D (exact χ^2 $p = .1377$) but significant in groups A-C *vs* D group (Fisher's exact test $p = .03249$).

The differences between patients fed with glutamine supplements (group A) and those fed with supplements of fermentable fibers (group B) are shown in Table III. Group A commenced EN 15.5 (13–20.3) hours after injury, which was significantly ($p < .04$) later than group B, 12.5 (9.6–15) hours after injury. Yet group B patients had a significantly ($p < .05$) higher average gastric retention volume 740 (530–1510) mL compared with group A patients, who had 410 (382–1062) mL.

The patients in group A also exhibited significantly lower ISS than those in group C ($p < .005$) and had a lower average PCT value ($p < .005$; Table IV).

Group D patients had higher ISS and APACHE II than group A ($p < .02$ and .03, respectively) and a significantly higher gastric retention volume of 1150 (785–2395) mL compared with 410 (382–1062) mL in group A ($p < .02$). However, group D exhibited a lower PCT value. The L/M index on day 7 in group D was 0.061 (0.040–0.099), which was significantly less than in group A's index, 0.159 (0.088–0.311; $p < .05$; Table V).

A comparison of patients who received Synbiotic 2000 (group D) and those who received 1 fermentable fiber supplement without lactobacilli (group B) revealed no differences, with the exception that patients in group B received more feeding during the first 24 hours compared with group D ($p < .03$; Table VI).

Patients in group C exhibited a significantly higher average PCT (1.25 [range, 1.00–2.32], $p < .0003$) than those in group D, 0.20 (0.10–0.72), even if they received more feeding during the first 24 hours ($p < .04$) and had less gastric retention ($p < .03$) than those in group D ($p < .04$; Table VII).

No differences were found between the patients in groups B and C, except that the latter had a significantly higher average PCT ($p < .024$; Table VIII).

There was an increase in IP until day 7 in all groups except in group D, in which a significant drop in the L/M index was found on day 7, being 0.1476 (0.0565–0.2400) on day 4 and 0.0606 (0.0404–0.0995) on day 7 ($p < .05$). In contrast, there was a significant rise in

TABLE III
Comparison between multiple injured patients fed with glutamine supplements (A) and those fed with soluble fiber supplements (B)

	A (32 patients), median (Q_1–Q_3)	B (29 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	31 (23–50)	36 (22–51)	.84
ISS	26 (22–33)	30 (24–35)	.16
APACHE II	11 (4.5–18)	14 (11–18)	.06
Days receiving mechanical ventilation	10 (6–16)	12 (8–15)	.91
Days of ICU treatment	14 (8.3–23)	16 (10–21)	.92
Initiation of EN after trauma (h)	15.5 (13–20.3)	12.5 (9.6–15)	**.04**
Volume of EN first 24 h (mL)	250 (157–562)	430 (100–600)	.44
Collective volume of EN first 4 days (mL)	2720 (2356–3700)	3250 (2400–3700)	.20
Average gastric retention volume first week (mL)	410 (382–1062)	740 (530–1510)	**.05**
Average CRP	120 (95–142)	135 (108–164)	.22
Average PCT	0.51 (0.41–1.58)	0.50 (0.10–1.80)	.62
Average MOF	2.5 (2.0–3.6)	3.5 (2.6–4.0)	.20
L/M index day 2	0.050 (0.013–0.116)	0.041 (0.022–0.154)	.57
L/M index day 4	0.102 (0.029–0.201)	0.075 (0.031–0.170)	.83
L/M index day 7	0.159 (0.088–0.311)	0.083 (0.052–0.124)	.83

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

group A, from 0.041 (0.022–0.154) on day 2 to 0.159 (0.088–0.311) on day 7 ($p < .02$; Figure 1).

There was no correlation between the average amount of glutamine supplied up to day 4 (13 ± 6 g per day) and the L/M index on day 4 ($r = -0.02$; 95% CI, 0.37–0.34; exact $p = .91$), nor between the amount of glutamine given up to day 7 (12 ± 6 g per day) and the L/M index on day 7 ($r = 0.41$; 95% CI, 0.29–0.83; exact $p = .24$). No correlation was observed between the amount of glutamine given and the average MOF score ($r = -0.11$; 95% CI, 0.22–0.42; exact $p = .52$).

DISCUSSION

Severe trauma is associated with a high incidence of septic complications and the multiple organ dysfunction syndrome, which markedly influence patient outcome. Nutrition plays an important role in the function of the immune system in these critically ill patients. In recent years, enteral nutrition has become the preferred method of feeding critically ill patients, and several substrates with presumably immunomodulatory effects have been added to enteral diets. Nevertheless, analyses of separate groups of critically ill patients have shown that the beneficial effects are not the same for each patient population and substance added.[29,30]

In this study, no differences were observed in mortality, ICU stay, and days of mechanical ventilation between the groups treated with the various immunomodulatory supplements. Yet patients supplemented with Synbiotic 2000 developed fewer infections and had consequently lower PCT levels than those receiving fiber or peptide diets, even if they had larger gastric retention volumes. The gastric retention volume, as measured by repeat gastric aspirations, was asymptomatic and did not seem to increase the risk of regurgitation or chest infections, as other authors have recently reported in the literature.[31] Instead, the presence of synbiotics in the stomach and intestinal tract might have contributed to the elimination of potentially pathogenic flora from the stomach and hereby contributed to the reduction in the incidence of pneu-

TABLE IV
Differences between multiple injured patients fed with glutamine supplements (A) and those fed a peptide diet (C)

	A (32 patients), median (Q_1–Q_3)	C (26 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	31 (23–50)	41 (26–54)	.55
ISS	26 (22–33)	35 (25–42)	**.005**
APACHE II	11 (4.5–18)	13.5 (10–18)	.11
Days receiving mechanical ventilation	10 (6–16)	8 (4–15)	.20
Days of ICU treatment	14 (8.3–23)	11.5 (6–20)	.28
Initiation of EN after trauma (h)	15.5 (13–20.3)	12.8 (10–18)	.12
Volume of EN first 24 h (mL)	250 (157–562)	387 (87–740)	.21
Collective volume of EN first 4 days (mL)	2720 (2356–3700)	2675 (1515–3908)	.93
Average gastric retention volume first week (mL)	410 (382–1062)	620 (337–1190)	.90
Average CRP	120 (95–142)	134 (63–182)	.45
Average PCT	0.51 (0.41–1.58)	1.25 (1.00–2.32)	**.005**
Average MOF	2.5 (2.0–3.6)	3.4 (2.8–4)	.16
L/M index day 2	0.050 (0.013–0.116)	0.076 (0.032–0.103)	.22
L/M index day 4	0.102 (0.029–0.201)	0.085 (0.043–0.160)	.64
L/M index day 7	0.159 (0.088–0.311)	0.103 (0.066–0.183)	.76

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

TABLE V
Differences between multiple injured patients fed with glutamine supplements (A) and those fed soluble fiber supplements and lactobacilli (D)

	A (32 patients), median (Q_1–Q_3)	D (26 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	31 (23–50)	48 (29.5–60)	.10
ISS	26 (22–33)	34 (26–39)	**.02**
APACHE II	11 (4.5–18)	13.5 (11.5–19)	**.03**
Days receiving mechanical ventilation	10 (6–16)	11 (7–18.3)	.93
Days of ICU treatment	14 (8.3–23)	12 (8.5–21.3)	.61
Initiation of EN after trauma (h)	15.5 (13–20.3)	13.3 (10–17.3)	.08
Volume of EN first 24 h (mL)	250 (157–562)	125 (40–407)	.15
Collective volume of EN first 4 days (mL)	2720 (2356–3700)	2655 (2135–3560)	.78
Average gastric retention volume first week (mL)	410 (382–1062)	1150 (785–2395)	**.02**
Average CRP	120 (95–142)	124 (107–166)	.48
Average PCT	0.51 (0.41–1.58)	0.20 (0.10–0.72)	**.04**
Average MOF	2.5 (2.0–3.6)	3.6 (2.9–4.2)	.32
L/M index day 2	0.050 (0.013–0.116)	0.085 (0.022–0.133)	.34
L/M index day 4	0.102 (0.029–0.201)	0.148 (0.056–0.240)	.54
L/M index day 7	0.159 (0.088–0.311)	0.061 (0.040–0.099)	**.05**

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

monia. It should also be observed that enteral nutrition in this study was achieved by gastric feeding, so the larger amounts of fibers administered into the stomach in group D might add to the increased volumes of gastric contents, as it is well known from the literature that dietary fibers increase gastroesophageal reflux but not gastric empting.[32] In this study, synbiotic supplementation with 4 fibers (group D) influenced gastric emptying, in contrast to the smaller dose of only 1 fermentable fiber (group B).

The increase in IP in critically ill patients, which has been observed in different groups of patients with shock, burns, and multiple injuries, is known to decrease with the introduction of enteral nutrition.[18,33] In our group of 113 multiple injured patients, IP showed uniform growth until day 4 in 3 of the 4 patient groups, despite enteral nutrition, with only the patient group supplemented with Synbiotic 2000 exhibiting a significant drop on day 7. It should be emphasized that the glutamine-supplemented group showed a significant rise in IP, even though glutamine has been described as a substance that maintains gut structure in experimental settings in animals fed either enterally or parenterally.[34,35] Glutamine should therefore be expected to decrease IP. In fact, most human studies suggest that the parenteral supply of glutamine is associated with a significant decrease in IP, whereas studies using the enteral route show variable results.[36–38] Novak and colleagues[12] suggested that intolerance problems are the main obstacle to higher glutamine supplementation during enteral nutrition and thus recommended its parenteral use. Hulsewé and coauthors,[39] however, were unable to document any improvements in gut morphology and barrier function after the parenteral application of a glutamine-enriched solution. Our glutamine-supplemented patients received a relatively low dose of 13 ± 6 g glutamine per day, which could possibly explain the ineffectiveness of the treatment. However, no correlation was observed between the amount of glutamine given and the severity of IP, or between the amounts of glutamine given and the average MOF scores. In addition, the commercial diet, which was used in combination with glutamine supplementation, also contained

TABLE VI
Differences between multiple injured patients fed with soluble fiber supplements (B) and those fed with soluble fiber supplements and lactobacilli (D)

	B (29 patients), median (Q_1–Q_3)	D (26 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	36 (22–51)	48 (29.5–60)	.21
ISS	30 (24–35)	34 (26–39)	.23
APACHE II	14 (11–18)	13.5 (11.5–19)	.88
Days receiving mechanical ventilation	12 (8–15)	11 (7–18.3)	.83
Days of ICU treatment	16 (10–21)	12 (8.5–21.3)	.44
Initiation of EN after trauma (h)	12.5 (9.6–15)	13.3 (10–17.3)	.65
Volume of EN first 24 h (mL)	430 (100–600)	125 (40–407)	**.03**
Collective volume of EN first 4 days (mL)	3250 (2400–3700)	2655 (2135–3560)	.47
Average gastric retention volume first week (mL)	740 (530–1510)	1150 (785–2395)	.19
Average CRP	135 (108–164)	124 (107–166)	.58
Average PCT	0.50 (0.10–1.80)	0.20 (0.10–0.72)	.39
Average MOF	3.5 (2.6–4.0)	3.6 (2.9–4.2)	.99
L/M index day 2	0.041 (0.022–0.154)	0.085 (0.022–0.133)	.83
L/M index day 4	0.075 (0.031–0.170)	0.148 (0.056–0.240)	.42
L/M index day 7	0.083 (0.052–0.124)	0.061 (0.040–0.099)	.41

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

TABLE VII
Differences between multiple injured patients fed with peptide diets (C) and those fed with soluble fiber supplements and lactobacilli (D)

	C (26 patients), median (Q_1–Q_3)	D (26 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	41 (26–54)	48 (29.5–60)	.24
ISS	35 (25–42)	34 (26–39)	.61
APACHE II	13.5 (10–18)	13.5 (11.5–19)	.88
Days receiving mechanical ventilation	8 (4–15)	11 (7–18.3)	.20
Days of ICU treatment	11.5 (6–20)	12 (8.5–21.3)	.56
Initiation of EN after trauma (h)	12.8 (10–18)	13.3 (10–17.3)	.83
Volume of EN first 24 h (mL)	387 (87–740)	125 (40–407)	**.04**
Collective volume of EN first 4 days (mL)	2675 (1515–3908)	2655 (2135–3560)	.65
Average gastric retention volume first week (mL)	620 (337–1190)	1150 (785–2395)	**.03**
Average CRP	134 (63–182)	124 (107–166)	.86
Average PCT	1.25 (1.00–2.32)	0.20 (0.10–0.72)	**.0003**
Average MOF	3.4 (2.8–4)	3.6 (2.9–4.2)	.84
L/M index day 2	0.076 (0.032–0.103)	0.085 (0.022–0.133)	.90
L/M index day 4	0.085 (0.043–0.160)	0.148 (0.056–0.240)	.21
L/M index day 7	0.103 (0066–0.183)	0.061 (0.040–0.099)	.17

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

arginine in a dose of 446 mg per 100 mL. The latter has been reported to be unsuitable for critically ill patients.[7] A recent study on 185 trauma patients was unable to prove any advantage of enteral supplementation of glutamine alone or in combination with arginine.[40]

A significant drop in IP was seen in the group supplemented with the synbiotic formula. We therefore conclude that early enteral administration of Synbiotic 2000 to patients after injury induces a significant drop in IP by the end of the first week. In our previous study of multiple injured patients who received early enteral feedings with Jevity (Abbott-Ross), which contains 14.4 g of fibers per L, we observed a decrease of IP on day 4. Unfortunately, no comparison can be made between Synbiotic 2000 and Jevity, as no measurements were made on day 7 in the previous study.[18]

The effects observed with the synbiotic treatment used in this study are most likely specific, as they have not been documented before with any synbiotic or fiber treatment.[17,41,42] However, a minimal influence of a commercial probiotic composition plus a small dose of fiber in critically ill patients has recently been reported.[43,44] It was found to favorably alter the microbial composition of the upper gastrointestinal tract but not to have any effect on IP, nor to be associated with any measurable clinical benefit.[43] In that study, EN was commenced considerably later than in our present one, and a mixture of yogurt bacteria and lactobacilli was used, which probably have a low survival in gastric juice and therefore less immunologic effect. Our treatment was started as soon as possible after admission in apparently stabilized patients, and never >24 hours after trauma, and was continued as long as the patients remained in the ICU. The LAB preparations in that study were supplied in a concentration of 10^9 in contrast to 10^{10} in the present study. Furthermore, a freeze-dried powder dissolved before use was used in our study as opposed to capsules—which might be disputable—in the other study.[42]

Another study did not find any beneficial effects of 5×10^7 strains of *Lactobacillus plantarum* 299v when supplied postoperatively to surgical patients; the most

TABLE VIII
Differences between multiple injured patients fed with peptide diets (C) and those fed with soluble fiber supplements (B)

	C (26 patients), median (Q_1–Q_3)	B (29 patients), median (Q_1–Q_3)	*p* values for *U* test
Age, y	41 (26–54)	36 (22–51)	.77
ISS	35 (25–42)	30 (24–35)	.08
APACHE II	13.5 (10–18)	14 (11–18)	.72
Days receiving mechanical ventilation	8 (4–15)	12 (8–15)	.24
Days of ICU treatment	11.5 (6–20)	16 (10–21)	.27
Initiation of EN after trauma (h)	12.8 (10–18)	12.5 (9.6–15)	.60
Volume of EN first 24 h (mL)	387 (87–740)	430 (100–600)	.71
Collective volume of EN first 4 days (mL)	2675 (1515–3908)	3250 (2400–3700)	.46
Average gastric retention volume first week (mL)	620 (337–1190)	740 (530–1510)	.13
Average CRP	134 (63–182)	135 (108–164)	.78
Average PCT	1.25 (1.00–2.32)	0.50 (0.10–1.80)	**.024**
Average MOF	3.4 (2.8–4)	3.5 (2.6–4.0)	.86
L/M index day 2	0.076 (0.032–0.103)	0.041 (0.022–0.154)	.52
L/M index day 4	0.085 (0.043–0.160)	0.075 (0.031–0.170)	.99
L/M index day 7	0.103 (0.066–0.183)	0.083 (0.052–0.124)	.90

Significant differences in bold.
APACHE, Acute Physiologic Chronic Health Evaluation; CRP, C-reactive protein; EN, enteral nutrition; ICU, intensive care unit; ISS, Injury Severity Score; L/M, lactulose-mannitol; MOF, multiple-organ failure; PCT, procalcitonin.

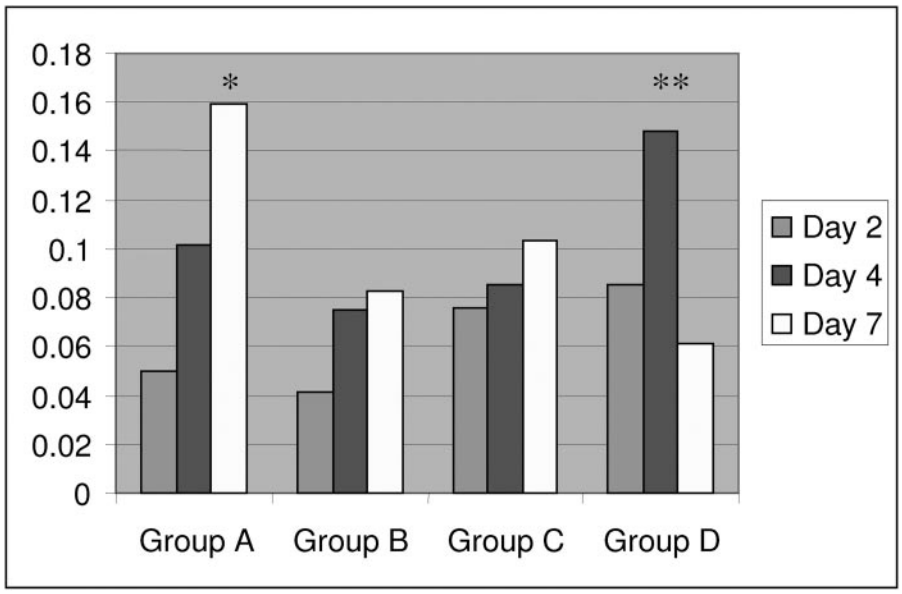

FIGURE 1. Dynamics of the lactulose-mannitol index in multiple injured patients fed with supplements of glutamine (A), soluble fibers (B), peptide diet (C), and the group fed with supplements of soluble fibers and lactobacilli (D). *Significant rise in group A from 0.050 (0.013–0.116) on day 2 to 0.159 (0.088–0.311) on day 7 ($p < .02$) and from 0.050 (0.013–0.116) on day 2 to 0.102 (0.029–0.201) on day 4 ($p < .057$). **Significant drop in group D, from 0.1476 (0.0565–0.2400 on day 4 to 0.0606 (0.0404–0.0995) on day 7 ($p < .05$).

obvious reason for failure is probably that the dose used was too small.[44]

As for the peptide diet, our main reason for choosing the group fed with this diet, which showed no difference in comparison to others, was that it did not contain glutamine or fibers, and hence its main purpose was to serve as a control. This diet has also been proposed to be more efficacious and better tolerated than whole-protein formulas in critically ill patients. However we were unable to find any advantage of this feeding, which is in line with other observations.[45]

It is difficult to deliver a sufficient amount of immunomodulatory substance to critically ill patients, as they often have intolerance problems, as discussed in the review of enteral immunonutrition.[12] Supplemented glutamine and fermentable fibers were diluted in a commercial diet. However, the Synbiotic was administered before feeding started in the morning; hence, some of its influence could be attributed to this administration protocol, which favors the full addition of immunonutrient. Our original intention was to deliver all the supplements in the same manner, but Synbiotic, which contains pectin, caused tube clogging when added to the formula, so the manufacturer's instructions were followed, with Synbiotic being administered before feeding.

Therefore, in order to avoid the influence of intolerance problems on the delivery of immunonutrients, it might be advisable to administer all immunomodulatory supplements separate from feedings.

ACKNOWLEDGMENTS

Financial support for the work was provided by the Ministry of Science of Republic of Slovenia, grant J3–3508.

REFERENCES

1. Biffl WL, Moore EE, Moore FA, Barnett CC Jr. Interleukin-6 delays neutrophil apoptosis via a mechanism involving platelet-activating factor. *J Trauma.* 1996;40:575–579.
2. Sautner T, Fugger R, Gotzinger P, et al. Tumour necrosis factor-alpha and interleukin-6: early indicators of bacterial infection after human orthotopic liver transplantation. *Eur J Surg.* 1995; 161:97–101.
3. Deitch EA. Role of the gut lymphatic system in multiple organ failure. *Curr Opin Crit Care.* 2001;7:92–98.
4. Dayal SD, Hasko G, Lu Q, et al. Trauma/hemorrhagic shock mesenteric lymph upregulates adhesion molecule expression and IL-6 production in human umbilical vein endothelial cells. *Shock.* 2002;17:491–495.
5. Galban C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med.* 2000;28:643–648.
6. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med.* 1995;23:436–449.
7. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med.* 2003;29:834–840.
8. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA.* 2001;286: 944–953.
9. Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med.* 2001;27: 84–90.
10. Manhart N, Vierlinger K, Spittler A, Bergmeister H, Sautner T, Roth E. Oral feeding with glutamine prevents lymphocyte and glutathione depletion of Peyer's patches in endotoxemic mice. *Ann Surg.* 2001;234:92–97.
11. Wischmeyer PE, Kahana M, Wolfson R, Ren H, Musch MM, Chang EB. Glutamine reduces cytokine release, organ damage, and mortality in a rat model of endotoxemia. *Shock.* 2001;16: 398–402.
12. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine

supplementation in serious illness: a systematic review of the evidence. *Crit Care Med.* 2002;30:2022–2029.
13. de Felippe Junior J, da Roche e Silva Junior M, Maciel FM, Soares Ade M, Mendes NF. Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1–3 polyglucose (glucan). *Surg Gynecol Obstet.* 1993;177:383–388.
14. Rayes N, Hansen S, Seehofer D, et al. Early enteral supply of fiber and Lactobacilli versus conventional nutrition: a controlled trial in patients with major abdominal surgery. *Nutrition.* 2002; 18:609–615.
15. Rayes N, Seehofer D, Hansen S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. *Transplantation.* 2002;74:123–127.
16. Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg.* 2002;89:1103–1107.
17. Bengmark S. Bio-ecological control of perioperative and ITU morbidity. *Langenbecks Arch Surg.* 2004;389:145–154.
18. Kompan L, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. *Intensive Care Med.* 1999;25:157–161.
19. Knight DJW, Ala'Aldeen D, Bengmark S, Girling KJ. The effect of synbiotics on gastrointestinal flora in the critically ill. *Br J Anaesth.* 2004;92:307–308.
20. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* 1974;14:187–196.
21. Kruszewska D, Lan J, Lorca G, Yanagisawa N, Marklinder I, Ljungh Å. Selection of lactic acid bacteria as probiotic strains by in vitro tests. *Microecol Ther.* 2002;29:37–51.
22. Ljungh Å, Lan JG, Yamagisawa N. Isolation, selection and characteristics of Lactobacillus paracasei ssp paracasei isolate F19. *Microbiol Ecol Health Disease.* 2002;suppl 3:4–6.
23. Seneff M, Knaus WA. APACHE: a prognostic scoring system. *Probl Crit Care.* 1989;3:563–578.
24. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrere JSF. Multiple organ failure. Generalised autodestructive inflammation? *Arch Surg.* 1985;120:1109–1115.
25. Vovk I, Simonovska B, Kompan L, Prošek M. TLC determination of mannitol and lactulose on amino HPTLC plates. *JPC J Planar Chromatogr Mod TLC.* 2003;16:372–374.
26. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. *Am J Infect Control.* 1988; 16:128–140.
27. Rello J, Paiva JA, Baraibar J, et al. International conference for the development of consensus on the diagnosis and treatment of ventilator-associated pneumonia. *Chest.* 2001;120:955–970.
28. Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. *Crit Care Med.* 2000;28:950–957.
29. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med.* 2001;29:2264–2270.
30. Montejo JC, Zarazaga A, Lopez-Martinez J, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. *Clin Nutr.* 2003;22:221–233.
31. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med.* 2005;33:324–330.
32. Bouin M, Savoye G, Hervé S, Hellot MF, Denis P, Ducrotté P. Does the supplementation of the formula with fibre increase the risk of gastro-oesophageal reflux during enteral nutrition? A human study. *Clin Nutr.* 2001;20:307–312.
33. Faries PL, Simon RJ, Martella AT, Lee MJ, Machiedo GW. Intestinal permeability correlates with severity of injury in trauma patients. *J Trauma.* 1998;44:1031–1035.
34. Khan J, Iiboshi Y, Cui L, et al. Alanyl-glutamine-supplemented parenteral nutrition increases luminal mucus gel and decreases permeability in the rat small intestine. *JPEN J Parenter Enteral Nutr.* 1999;23:24–31.
35. Kozar RA, Schultz SG, Bick RJ, Poindexter BJ, DeSoignie R, Moore FA. Enteral glutamine but not alanine maintains small bowel barrier function after ischemia/reperfusion injury in rats. *Shock.* 2004;21:433–437.
36. Conejero R, Bonet A, Grau T, et al. Effect of a glutamine-enriched enteral diet on intestinal permeability and infectious morbidity at 28 days in critically ill patients with systemic inflammatory response syndrome: a randomized, single-blind, prospective, multicenter study. *Nutrition.* 2002;18:716–721.
37. Velasco N, Hernandez G, Wainstein C, et al. Influence of polymeric enteral nutrition supplemented with different doses of glutamine on gut permeability in critically ill patients. *Nutrition.* 2001;17:907–911.
38. Peng X, Yan H, You Z, Wang P, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. *Burns.* 2004;30:135–139.
39. Hulsewe KW, van Acker BA, Hameeteman W, et al. Does glutamine-enriched parenteral nutrition really affect intestinal morphology and gut permeability? *Clin Nutr.* 2004;23:1217–1225.
40. Schulman AS, Willcutts KF, Claridge JA, et al. Does the addition of glutamine to enteral feeds affect patient mortality? *Crit Care Med.* 2005;33:2501–2506.
41. Bengmark S. Bioecological control of inflammation and infection in transplantation. *Transplant Rev.* 2004;18:38–45.
42. Bengmark S. Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients. *Clin Nutr.* 2004;23: 441–445.
43. Jain PK, McNaught CE, Anderson AD, MacFie J, Mitchell CJ. Influence of synbiotic containing Lactobacillus acidophilus La5, Bifidobacterium lactis Bb 12, Streptococcus thermophilus, Lactobacillus bulgaricus and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. *Clin Nutr.* 2004;23:467–475.
44. Woodcock NP, McNaught CE, Morgan DR, Gregg KL, MacFie J. An investigation into the effect of a probiotic on gut immune function in surgical patients. *Clin Nutr.* 2004;23:1069–1073.
45. Heimburger DC, Geels WJ, Thiesse KT, Bartolucci AA. Randomized trial of tolerance and efficacy of a small-peptide enteral feeding formula versus a whole-protein formula. *Nutrition.* 1995; 11:360–364.