Intensive Care Med (2003) 29:834–840
DOI 10.1007/s00134-003-1711-5

BRIEF REPORT

Guido Bertolini
Gaetano Iapichino
Danilo Radrizzani
Rebecca Facchini
Bruno Simini
Paola Bruzzone
Giancarlo Zanforlin
Gianni Tognoni

Early enteral immunonutrition in patients with severe sepsis

Results of an interim analysis of a randomized multicentre clinical trial

Received: 24 May 2002
Accepted: 27 January 2003
Published online: 9 April 2003

An editorial regarding this article can be found in the same issue (http://dx.doi.org/10.1007/s00134-003-1710-6).

GiViTI stands for Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine). G. Bertolini, G. Iapichino, D. Radrizzani, and B. Simini are members of the GiViTI steering committee. The study was supported by Abbott Italia, Roma, Italy. A complete list of study participants appears in the appendix.

G. Bertolini (✉) · R. Facchini
GiViTI Coordinating Center,
Istituto di Ricerche Farmacologiche "Mario Negri",
Centro di Ricerche Cliniche per le Malattie Rare Aldo e Cele Daccò,
Ranica, Bergamo, Italy
e-mail: bertolini@marionegri.it
Tel.: +39-035-4535313
Fax: +39-035-4535371

G. Tognoni
Consorzio "Mario Negri Sud",
S. Maria Imbaro, Chieti, Italy

G. Iapichino · G. Zanforlin
Polo Universitario S. Paolo,
Istituto di Anestesia e Rianimazione dell'Università di Milano,
Milan, Italy

P. Bruzzone
Ospedale Maggiore IRCCS,
Polo Universitario S. Paolo,
Istituto di Anestesia e Rianimazione dell'Università di Milano,
Milan, Italy

D. Radrizzani
Servizio Anestesia e Rianimazione,
Azienda Ospedaliera Legnano,
Milan, Italy

Abstract *Objective:* To compare the mortality of critically ill patients given either enteral feeding with an immune-enhancing formula or parenteral nutrition (PN). We report the results of a planned interim analysis on patients with severe sepsis which was undertaken earlier than planned once a meta-analysis suggested excess mortality in patients with severe sepsis given enteral immunonutrition. *Design:* Randomised multicentre unblinded controlled clinical trial. *Setting* Thirty-three General Intensive Care Units in Italy. *Patients and participants:* Among the 237 recruited patients, 39 had severe sepsis or septic shock; 21 of them received PN. *Interventions:* Eligible patients received either total PN or enteral nutrition, the latter containing extra L-arginine, omega-3 fatty acids, vitamin E, beta carotene, zinc, and selenium. *Measurements and results:* The primary endpoint for the subgroup analysis on patients with severe sepsis was mortality on Intensive Care Unit (ICU). The ICU mortality of patients with severe sepsis given enteral nutrition (EN) was higher than for those given PN (44.4% vs 14.3%; p=0.039). More patients given EN than patients given PN still had severe sepsis when they died (38.9% vs 9.5%, p=0.055). Recruitment of patients with severe sepsis was subsequently stopped. *Conclusions:* Our results show that enteral immunonutrition, compared to PN, may be associated with excess mortality in patients with severe sepsis.

Keywords Critically ill patients · Enteral nutrition · Parenteral nutrition · Immunonutrition · Severe sepsis

Introduction

What type of nutrition and which route in critically ill patients is the object of debate. Parenteral and enteral nutrition are both championed [1]. Administration of parenteral nutrition (PN) is easier and more reliable [2]. However, its benefits are undermined by complications related to central venous access and bowel rest, with its attendant translocation of gut bacteria and infections [3, 4, 5]. Thus, many authors and medical societies [6, 7, 8, 9] emphasise that enteral nutrition (EN) may be best for the critically ill, although evidence supporting this statement derives mainly from small studies on elective surgery and trauma patients [10, 11].

Evidence exists in favour of special enteral diet formulations aimed at enhancing general and specific gastrointestinal immunity, which are dubbed immunonutrition [12, 13]. These studies suggested that immunonutrition could enhance resistance to infection, possibly by reducing the magnitude and duration of the inflammatory response, but, again, they were performed mainly in post-surgical patients so that their results are not directly applicable to the critically ill. We therefore launched a multicentre randomised unblinded trial comparing enteral immunonutrition with PN in critical illness. The hypothesis was that early enteral immunonutrition (i.e., started within 48 h of admission) would reduce mortality and the number of septic complications. For this reason, the protocol also considered two subgroup analyses distinguishing in one subgroup patients enrolled without severe sepsis or septic shock, and in the other subgroup, patients with severe sepsis or septic shock. The results of a meta-analysis suggesting an excess mortality associated with enteral immunonutrition in critical patients with sepsis published in April 2001 [14] prompted the anticipation of a planned interim analysis in the subgroup of patients enrolled with severe sepsis or septic shock.

Methods

The study was done in adult Intensive Care Units (ICUs) adhering to the Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva (GiViTI). For each enrolled patient we collected information on socio-demographic characteristics, acute diagnostic profile, SAPS II (Simplified Acute Physiology Score II) variables [15], length of stay (LOS), and vital status at ICU discharge and after 28 days from randomisation. Information about nutritional regimen, the classification of the septic condition according to the American College of Chest Physicians and Society of Critical Care Medicine criteria (ACCP/SCCM) [16], the SOFA (Sepsis-related Organ Failure Assessment) score of organ failure [17], and the NEMS (Nine Equivalents of nursing Manpower use Score) score of nursing workload [18], were daily recorded. A further two-level classification of the complexity of care provided was also obtained [19].

Eligible patients were those aged over 18 years, in a high level of care [19], who were judged to need artificial ventilation and nutrition for at least 4 days (both these criteria were implicitly defined by the attending physician). Exclusion criteria included motor Glasgow Coma Scale less than 4, pure cerebral disease, spinal trauma, and referral from ICUs in which patients stayed more than 24 h. A written consent from the patient was obtained whenever possible, otherwise clinical staff members were responsible for including patients in the study, according to the European guidelines for good clinical practice [20]. The protocol was approved by each hospital's ethics committee.

Eligible patients were randomised to receive either total PN (59% carbohydrate, 23% fat, 18% protein, 1.2 kcal/ml) or EN (55% carbohydrate, 25% fat, 21% protein, 1.3 kcal/ml). PN (25–28 total kcal/kg per day) was not integrated with EN before day 6 from randomisation. EN was started at 10 kcal/kg and progressed to 25–28 kcal/kg by the fourth day. EN used (Perative, Abbott) contained extra L-arginine (6.8 g/l), omega-3 fatty acids (1.5 g/l), vitamin E (29 mg/l), beta carotene (7.5 mg/l), zinc (22 mg/l), and selenium (70 μg/l). All patients started being fed within 48 h from ICU admission.

The randomisation code was generated by a computer programme at the co-ordinating centre and was revealed to investigators by telephone at the moment of randomisation, once baseline data collection was completed. Block randomisation (permuting blocks of 4 and 6) was adopted and stratified according to centre and presence of severe sepsis or septic shock. The septic condition at baseline and during their stay was ascertained by the attending physician, according to ACCP/SCCM criteria [16]. Such criteria were recorded daily as well, in order to appraise the correctness of group assignment. Any correction in group assignment was made before data analysis. The study was sized in order to have 80% power to detect an improvement in mortality from 35% to 28%, with a two-tailed 5% type I error. A total of 1,500 patients were needed. One interim analysis was planned, after enrolling 750 patients, at which point the Peto stopping rule would have been adopted [21].

The primary endpoint of the entire study was mortality at 28 days, but the protocol also considered two subgroup analyses, according to the septic condition. The primary endpoint for the subgroup of patients with severe sepsis or septic shock at randomisation was ICU mortality. Since this anticipated interim analysis showed a difference in ICU mortality, we also looked at 28-day mortality. Risk of death in the two arms was planned to be compared by the Mantel-Haenszel chi-squared test [22]. Given the small sample size in this interim analysis, we also used the more appropriate Fisher exact test. Effect size was expressed in terms of absolute risk difference with its 95% confidence interval (95% CI) [23]. Concerning ICU mortality (primary endpoint), a logistic regression model was used to analyse the difference in treatment effect according to presence or absence of severe sepsis (test of interaction), adjusting for possible confounders. Hence, all patients (with sepsis and without sepsis) were included in this model. Possible confounders tested were: total amount of calories per kg received in the first 3 days; age over 60 years; respiratory and cardiovascular failure on admission; and gender. The adjusted analysis was planned only for the first variable, since – according to the protocol – there were different caloric intakes in the two arms for the first 3 days. Adjustment for the other variables was suggested by their relative imbalance at baseline. Odds ratios (ORs) of ICU mortality with EN vs PN in patients with severe sepsis can be calculated by means of the formula: $OR = 1/\exp(ß_{treatment} + ß_{interaction})$ [24]. Although the analyst was not blinded to group assignment, all the analyses, except 28-day mortality, were planned. Analysis was by intention to treat.

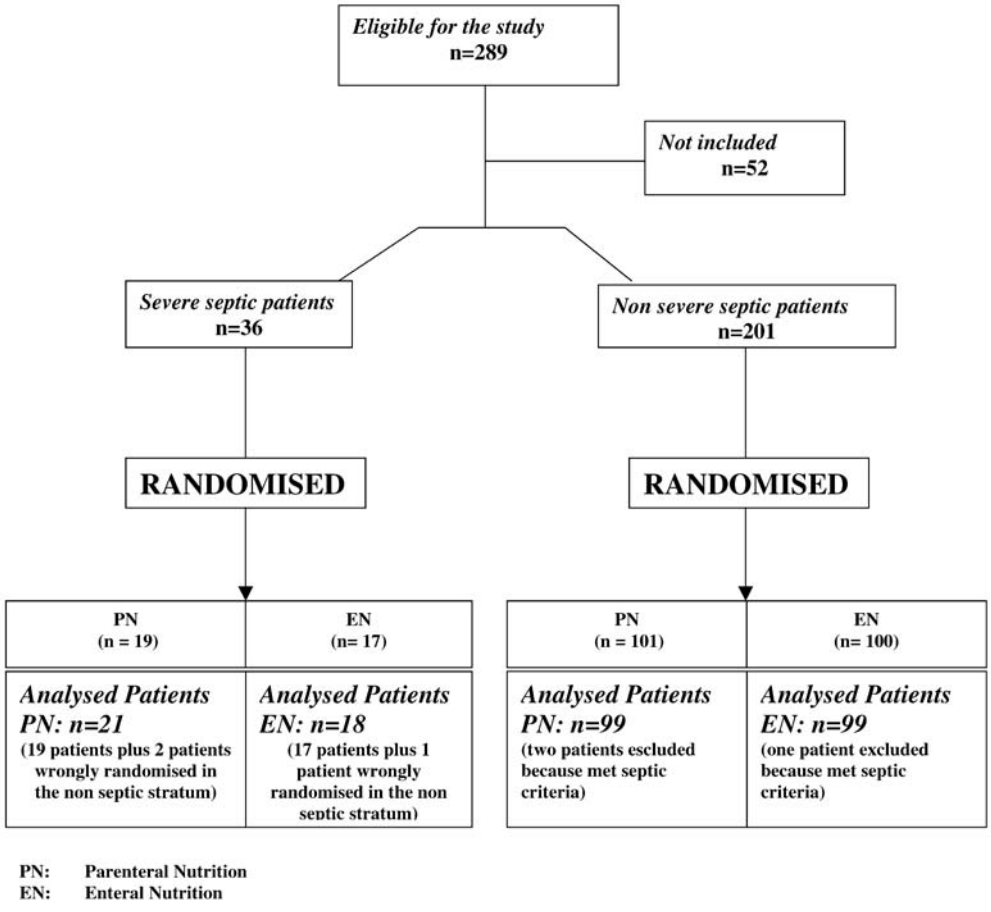

Fig. 1 Flow of participants through each stage of randomised trial

Results

Of the 237 patients randomised by 33 ICUs between November 1999 and April 2001, 39 had severe sepsis (Table 1). Each ICU recruited patients during an average of 6.9 months (range 2–14). Figure 1 shows the flow of participants. The coordinating centre noticed that three patients were erroneously randomised as being without sepsis (two of them received PN), whereas they met criteria for sepsis. They were subsequently analysed among patients with severe sepsis. More women, and more patients with unfavourable prognoses – age over 60 years and combined cardiovascular and respiratory failure – received PN. Patients were otherwise well balanced (Table 1). No severe adverse events (i.e., fatal, life-threatening, or permanently disabling complications or those prolonging hospitalisation) related to the experimental protocol were observed.

Patients given PN received more calories than patients given EN in the first 3 days because of the study design (Table 2). Length of ICU stay was similar in the two groups (median, inter-quartile range: 15, 11–29 in PN; 13.5, 9–26 in EN). Mortalities are shown in Table 3. We found a close to significant difference in ICU mortality: the number of patients needed to observe one more death due to harm caused by enteral immunonutrition was 3.3 (test based 95% CI: 1.7–66.7). Twenty-eight-day mortality did not differ significantly. Seven patients in the enteral arm and two in the parenteral arm still had severe sepsis when they died (38.9% and 9.5%, respectively; Fisher's exact test $P = 0.055$). Three logistic regression models testing the interaction between treatment effect and severe septic condition were performed: model 1 is the unadjusted analysis; model 2 is the planned adjusted analysis (for caloric intake); model 3 is the unplanned adjusted analysis (for caloric intake and unbalanced baseline characteristics; see Table 4). Among the variables tested in the latter model, gender and respiratory plus cardiovascular failure were excluded since they were not significant. In all the models the interaction was significantly or nearly significantly associated with outcome. All three models confirmed a worse outcome with EN in patients with severe sepsis: OR = 4.8 for model 1; OR = 2.4 for model 2; OR = 3.1 for model 3.

As a result of this interim analysis randomisation of patients with severe sepsis was stopped. Comparison of early parenteral and early enteral feeding in patients with non-severe sepsis continued.

Table 1 Baseline characteristics of patients in each group. (*EN* Enteral nutrition, *PN* Parenteral nutrition, *ER* Emergency room, *ICU* Intensive care unit, *IQR* Interquartile range, *SD* Standard deviation, *SAPS II* Simplified Acute Physiology Score II, *NEMS* Nine Equivalent Manpower Score, *SOFA* Sepsis-related Organ Failure Assessment)

	Patients with severe sepsis	
	EN (*n*=18)	PN (*n*=21)
Gender (*n*) male	11	10
Age mean (SD)	59.3 (17.6)	59.0 (21.4)
Age >60 years (*n*)	9	14
Admission to ICU from (*n*)		
ER	6	6
Operating room	1	2
Ward	10	11
Another ICU	1	2
Admission to ICU for (*n*)		
Respiratory failure	7	4
Respiratory and cardiovascular failure	11	17
Admission typology (*n*)		
Non-surgical patient	15	15
Emergency surgery	3	6
SAPS II median (IQR)	41 (39–46)	43 (35–51)
Time (hours) to starting nutrition mean (SD)	34.4 (10.4)	31.0 (11.2)
Principal infection (*n*)		
Pneumonia	14	13
Pneumonia plus cerebral abscess	0	1
Pneumonia plus peritonitis	1	1
Peritonitis	1	4
Mediastinal abscess	1	0
Pelvic abscess	0	1
Gynaecological sepsis	0	1
Cutaneous phlegmon	1	0
NEMS median (IQR)	39 (34–39)	39 (27–39)
SOFA median (IQR)	7 (5–8)	7 (6–8)

Table 2 Daily caloric intake (kcal/kg per day). (*SD* Standard deviation)

Day	Enteral nutrition Mean (SD)	Parenteral nutrition Mean (SD)
1	9.4 (1.8)	17.6 (6.4)
2	13.7 (4.5)	27.3 (4.9)
3	19.9 (3.0)	27.8 (4.5)
4	25.4 (2.0)	28.3 (4.3)
5	24.2 (7.3)	28.5 (4.3)
6	24.0 (7.3)	27.0 (5.6)
Mean (SD) for the first 6 days	19.1 (7.6)	25.9 (6.4)

Discussion

The role of nutritional support in influencing the outcome of critically ill patients is still not established. Available evidence has been obtained mainly from elective surgical patients or from non-surgical trauma patients with an overall good prognosis [10]. Hence, these results are not easily generalisable to all critical patients.

At the end of 1998 we designed a study to compare two opposite approaches in providing nutritional support to critical patient. The first approach (PN) gives the maximum priority to actually delivering the desired

Table 3 Summary of results. (*ARD* Absolute risk difference, *ICU* Intensive care unit, *EN* Enteral nutrition, *PN* Parenteral nutrition, *MH* Mantel-Haenszel chi-squared test)

	Mortality in patients with sever sepsis						
	EN (*n*=18)		PN (*n*=21)			*P* values	
	n (%)			ARD (95% CI)		MH	Fisher test
ICU mortality	8 (44.4%)		3 (14.3%)		30.1 (1.5-58.7)	0.039	0.072
28-day mortality	8 (44.4%)	5 (23.8%)		20.6 (-9.4-50.6)		0.179	0.196

Table 4 Results of logistic regression models. (*CI* Confidence interval)

	ß	Odds ratio (95% CI)	*P* value
Model 1			
Treatment	0.3113	1.365 (0.660–2.830)	0.4016
Septic condition	1.4231	4.150 (1.420–12.132)	0.0093
Interaction between treatment and septic condition	–1.8799	0.153 (0.028–0.835)	0.0301
Model 2			
Treatment	0.8297	2.293 (0.981–5.360)	0.0555
Septic condition	1.1986	3.315 (1.093–10.059)	0.0343
Interaction between treatment and septic condition	–1.7202	0.179 (0.031–1.024)	0.0532
kcal/kg in the first 3 days (treated as variable continuous)	–0.0237	0.977 (0.957–0.996)	0.0194
Model 3			
Treatment	0.9890	2.689 (1.072–6.744)	0.0350
Septic condition	1.2414	3.461 (0.977–12.254)	0.0543
Interaction between treatment and septic condition	–2.1216	0.120 (0.018–0.778)	0.0263
kcal/kg in the first 3 days (treated as variable continuous)	–0.0205	0.980 (0.959–1.001)	0.0661
Age >60 vs age <60	1.7510	5.760 (2.475–13.403)	<0.0001

amount of nutrition [25]. The second one recognised that early EN has an anabolic and protective effect on gut function and structure [26]. In addition, an immune-enhancing formula should improve the metabolic response to injury, by means of a drug-like effect [27]. For this reason such a formula has been recommended for the critically ill [7, 27]. Having chosen the latter approach, we expected the EN group to do better than the PN one, particularly in the acute phase of the critical condition and in severe sepsis.

The study was focused on ICU patients in the middle of the spectrum of severity, since we actually excluded patients with an expected ventilatory assistance shorter than 4 days (too healthy) as well as those not yet stable after 48 h from admission or with major clinical contraindication to the planned substrate supply (too ill). We further excluded patients whose negative prognosis was mainly determined by their principal diagnosis (motor Glasgow Coma Scale lower than 4, pure cerebral disease, spinal trauma). This choice has been recently recommended for clinical trials on patients with sepsis [28]. The conditions of our patients with severe sepsis, mainly pneumonia, were, in any case, remarkably critical and complex at ICU admission and during the stay, as expressed by admission and follow-up data (Table 1).

Because the accrual rate was much lower than expected and since the results of a meta-analysis hinted that enteral immunonutrition could do more harm than good in patients with sepsis [14], we were asked by the study advisory board to anticipate the planned interim analysis of patients with severe sepsis. The results showed that in these patients enteral diets supplemented with arginine and other immunomodulating additives may be associated with a worse outcome compared to patients receiving PN. ICU mortality and prevalence of sepsis at death were higher in patients given enteral immunonutrition. Why?

Our design does not allow us to distinguish between the route of feeding and the formula administered. Interestingly, though associated with a better outcome, caloric intake did not explain the whole difference in ICU mortality between the two arms in the multivariate models. In accordance with other observations [6, 7, 8, 9, 10, 11], we can exclude that the route of administration explains these results per se. Indeed, others have suggested that over-stimulation of the inflammatory response could be detrimental for the critically ill [29, 30]. Thus, the key mechanism behind our results may lie in the complex interaction between the immune-stimulating formula and the metabolic environment in severe sepsis [29, 30, 31].

Several nutrients (arginine, glutamine, ω-3 fatty acid, nucleotides, vitamins, and trace elements) are supposed to be responsible for the drug-like effect of a modified formula. Unfortunately, the EN immune-enhancing formula we used combines more than one of these nutrients, so that it is not easy to conjecture about each single element's role.

It is unclear why the advantage of PN dwindled after ICU discharge. The reason cannot be that patients given PN were discharged in pre-terminal conditions; those who died did so a median of 11.5 days after discharge. In any case, ICU mortality was adopted because it was considered better than 28-day mortality as an estimate of the capacity of intensive care in achieving the physiological goals required before patients are transferred to the ward.

The statistical significance of our results may seem quite thin, indeed just one more death in the group given PN would make the difference in ICU mortality non-significant. Furthermore, analysis with Fisher's exact test instead of Mantel-Haenszel chi-squared yields $P = 0.07$. Nonetheless, the relevance of our results is not so much that it implies that immunonutrition is worse than PN, but that – unlike the widely accepted belief by clinicians and that purported by various manufacturers of immune-

enhancing enteral diets – it is not better than PN in severe sepsis. Moreover, this finding corroborates the results of a subgroup analysis [14] of an independent meta-analysis [31], in which patients with sepsis given enteral immunonutrition had worse outcomes than patients given standard EN.

Both the strict consistency of our findings with those of the meta-analysis and the futility, if not the questionable ethics, of pursuing testing a treatment associated with a likely higher risk, urged us to stop randomising patients with severe sepsis. Joining our results with the already available evidence, we think that the use of diets supplemented with arginine and other immunomodulating additives is not desirable in patients with severe sepsis.

Appendix: Participating clinicians (with their hospitals in capitals) and advisory board members

Participating clinicians: ANCONA Pennacchioni S; AOSTA Vernero S; BENEVENTO Pezza B; BIELLA Giachello S; BOLOGNA BELLARIA Mingarelli M; BOLOGNA MAGGIORE Marri I; BORGOMANERO (NO) Musso T; BRESCIA Antonini B; CAGLIARI Murru S; CASTELLANA GROTTE (BA) Di Masi P; CITTADELLA (PD) Todesco L; DESIO (MI) Ostaldo M; DOLO (VE) Altafini L; FAENZA (RA) Casalini P; FERRARA Marchi M, Tonini P; FIRENZE Oggioni R; GENOVA Garavini L; LANCIANO (CH) Genovesi N, Carinci P; LANUSEI (NU) Lerede D; LECCO CIVILE Holzer G; LECCO MANZONI Tavola M; MACERATA Paternesi N, Brunori M; MANTOVA Sgarioto V; MILANO MAGGIORE Sicignano A; MILANO S. CARLO Raffaeli M, Cibin C; MILANO S. PAOLO Zanforlin G; MILANO S. RAFFAELE Colombo S; NAPOLI De Cristofaro M; OLBIA Messina M; PALERMO Tetamo R; PAVIA Negri G; PERUGIA Gorietti A; PESARO Breschi C; PESCIA (PT) Dal Poggetto L; PISA Malacarne P; RAVENNA Garelli A; ROMA Morrone L; TORINO S. G. BOSCO Livigni S; TORINO UMBERTO I Segala V; TORINO LE MOLINETTE Cavallo R; VICENZA S. BORTOLO Lieta E, Digito A, Marcante S

Advisory board members: M. Braga (Ospedale S. Raffaele, Milano), F.B. Pallavicini (Ospedale San Martino, Genova), M.G. Gentile (Ospedale Niguarda, Milano); M. Zanello (Ospedale Bellaria, Bologna)

References

1. Preiser JC, Berre J, Carpentier Y, Jolliet P, Pichard C, Van Gossum A, Vincent JL (1999) Management of nutrition in European intensive care units: results of a questionnaire. Working Group on Metabolism and Nutrition of the European Society of Intensive Care Medicine. Intensive Care Med 25:95–101
2. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition (A.S.P.E.N.) (1998) Safe practices for parenteral nutrition formulations. JPEN J Parenter Enteral Nutr 22:49–66
3. Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, Hollander D, Gornbein J, Kopple JD, Vijayaroghavan SR (1995) Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. JPEN J Parenter Enteral Nutr 19:453–460
4. Border JR, Hassett J, LaLuca J, Seibel R, Steinberg S, Mills B, Losi P, Border D (1987) The gut origin septic states in multiple trauma (TSS=40) in the ICU. Ann Surg 206:427–448
5. Deitch EA, Winterton J, Li M, Berg R (1987) The gut as a portal of for bacteremia: role of protein malnutrition. Ann Surg 205:681–690
6. Cerra FB, Benitez MR, Blackburn GL, Irwin RS, Jeejeebhoy K, Katz DP, Pingleton SK, Pomposelli J, Rombeau JL, Shronts E, Wolfe RR, Zaloga GP (1997) Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. Chest 111:769–778
7. Jolliet P, Pichard C, Biolo G (1998) Enteral nutrition in intensive care patients: a practical approach (ESICM statement). Intensive Care Med 24:848–859
8. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstain-Wagner TB, Kellum JM, Welling RE, Moore EE (1992) Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 216:172–183
9. Heyland DK, Cook DJ, Guyatt GH (1993) Enteral nutrition in the critically ill patient: a critical review of the evidence. Intensive Care Med 19:435–442
10. Heyland DK (2000) Enteral and parenteral nutrition in the seriously ill, hospitalized patient: a critical review of the evidence. J Nutr Health Aging 1:31–41
11. Lipman TO (1998) Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. JPEN J Parenter Enteral Nutr 22:167–182
12. Heys SD, Walker LG, Smith I, Remin O (1999) Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer. A meta-analysis of randomized controlled clinical trial. Ann Surg 229:467–477
13. Beale RJ, Bryg DJ, Bihari DJ (1999) Immunonutrition in the critically ill: a systematic review of clinical outcome. Crit Care Med 27:2799–2805
14. Heyland DK, Novak F (2001) Immunonutrition in the critically ill patients: more harm than good? JPEN J Parenter Enteral Nutr 25:51–55
15. Le Gall JR, Lemeshow S, Saulnier F (1993) A New Simplified Acute Physiology Score (SAPS II) Based on a European/North American Multicenter Study. JAMA 270:2957–2963
16. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644–1655

17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendoca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Medi 22:707–710
18. Miranda RD, Moreno R, Iapichino G (1997) Nine equivalents of nursing manpower use score (NEMS). Intensive Care Med 23:760–765
19. Iapichino G, Radrizzani D, Bertolini G, Ferla L, Pasetti G, Pezzi A, Porta F, Miranda DR (2001) Daily classification of the level of care. A method to describe clinical course of illness, use of resources and quality of intensive care assistance. Intensive Care Med 27:131–136
20. Human Medicines Evaluation Unit (1996) ICH topic E6: guideline for good clinical practice. European Agency for the Evaluation of Medical Products, London, pp 17–20
21. Pocock SJ, Hughes MD (1989) Practical problems in interim analyses, with particular regard to estimation. Control Clin Trials 10:209–221
22. Mantel N (1963) Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J Am Stat Assoc J 58:690–700
23. Kleinbaum DG, Kupper LL, Morgenstern H (1982) Epidemiologic research. Principles and quantitative methods. Van Nostrand Reinhold, New York, pp 296–297
24. Hosmer DW, Lemeshow S (1989) Applied logistic regression. Wiley, New York, pp 68–71
25. Iapichino G, Gattinoni L, Solca M, Radrizzani D, Zucchetti M, Langer M, Vesconi S (1982) Protein sparing and protein replacement in acutely injured patients during TPN with and without aminoacid supply. Intensive Care Med 8:25–31
26. Cerra FB, McPherson JP, Kostantinidis FN, Kostantinidis NN, Teasley KM (1988) Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. Surgery 104:727–733
27. Barton RG (1997) Immune-enhancing enteral formulas: are they beneficial in critically ill patients? Nutr Clin Pract 12:51–62
28. Cohen J, Guyatt G, Bernard GR, Calandra T, Cook D, Elbourne D, Marshall J, Nunn A, Opal S (2001) New strategies for clinical trials in patients with sepsis and septic shock. Crit Care Med 29:880–885
29. Moore FA (2001) Effects of immune-enhancing diets on infectious morbidity and multiple organ failure. JPEN J Parenter Enteral Nutr 25:36–43
30. Suchner U, Heyland DK, Peter K (2002) Immune-modulatory actions of arginine in the critically ill. Br J Nutr 87[Suppl 1]:121–132
31. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U (2001) Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 286:944–953