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Influence of an aggressive early enteral nutrition protocol on nitrogen balance in critically ill children

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Abstract

The objective was to determine stress related factors and nutritional indices affecting the nitrogen balance (NB) and the creatinine height index (CHI) in critically ill children on early enteral nutrition (EEN). Seventy-one consecutively enrolled critically ill children aged 2 to 204 months, requiring prolonged mechanical ventilation, were studied. All patients were on early intragastric nutrition (Nutrison Pediatric or Standard) from day 1 (energy intake equal to 1/2, 1, 5/4, 6/4 and 6/4 of the predicted basal metabolic rate on days 1–5, respectively). Nitrogen balance and CHI changes determined efficacy. Study patients had severe depletion of somatic protein status on stress day 1 (CHI $<60\%$) but they reached the normal range of somatic protein status at the end of the EEN, on post-stress day 5 (CHI $>80\%$, $p < .004$). On day 1, none of the patients had positive NB but after 5 days of EEN, 44 (62%) had positive NB and only 27 (38%) had negative NB ($p < .0001$). Multivariate stepwise regression analysis showed that only the difference of daily given—recommended dietary allowances protein and the total repleted energy were positively correlated ($r^2 = .47$, $p < .001$ and $r^2 = 34$, $p = .003$, respectively) and multiple organ system failure negatively correlated with the NB ($r^2 = -.24$, $p < .03$) on the 5th day of the EEN protocol. Our data suggest that achievement of positive protein and energy balance in relation to the basic metabolic rate using an aggressive EEN protocol improves NB during the acute phase of stress in 2/3 of critically ill children.

Keywords: Creatinine height index; Enteral nutrition; Myocardial contractility; Nitrogen balance; Severity of illness

1. Introduction

Critical illness initiates a cascade of events that lead to accelerated protein degradation, decreased rate of synthesis of selected proteins, and increased amino acid catabolism and nitrogen loss. Although catabolism of muscle protein may be useful to provide substrates for protein synthesis in the liver (acute phase protein synthesis) and immune cells (cell replication), severe depletion of lean body mass increases the morbidity and the mortality in the acute phase and delays the recovery from illness [2–3].

Until some years ago, critically ill children were poorly fed and nutrition was not a primary concern in the intensive care of these patients. With severe stress, both synthesis and degradation are elevated, degradation more so than synthesis [1]. Both situations result in a loss of body mass, predominantly lean tissue. The problem is exacerbated usually by the decline in food intake. Especially, enteral feeding is still too often neglected, and at high cost. Protein is broken down into amino acids, which provide glucose for inflammatory and wound tissue and the central nervous system. Healthy tissue is said to switch in part to deriving its energy needs from fat oxidation [16]. It is recognized that even specialized nutrition is often unable to reverse body protein loss during severe illnesses. Wasting can still occur during prolonged intensive care despite the provision of nutritional support, usually because of unresolved sources of continuing sepsis [4]. Nutritional support, however, may buy time necessary for the basic disease-related problems to improve, and give the patient an edge during convalescence. It has been shown that early enteral feeding in adult patients decreases fat oxidation and whole body protein catabolism while improving net nitrogen balance (NB) [5].

Although it generally is accepted that early enteral nutrition is of benefit to critically ill children, there is no evidence to support this assertion. We wanted to determine if early achievement of energy and protein balance improves NB and somatic protein status during post-stress catabolic illness in children.

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2. Methods and materials

2.1. Patients

Seventy-one mechanically ventilated critically ill children were enrolled in the study after Ethics Committee approval from the Institutional Review Board of our institution. Informed consent was obtained from the patients' parents. To be included in the study patients had to meet the following criteria: a) expected PICU-dependency of 5 days or more; b) mechanical ventilation (>24 hr); c) no chronic renal disease; d) no history of chronic gastrointestinal disease; e) enteral feedings starting within the first 12 hrs.

2.2. Protocol of enteral nutrition (EEN)

None of the patients received total parenteral nutrition (TPN). Nutrison Pediatric (<10 year-old) or Standard (>10 year-old), (N.V. Nutricia, Zoekermeer, Holland), was delivered through a nasogastric tube starting from the first 12 hrs of admission. Hourly amount was calculated according to the protocol, aiming at meeting patient's PBMR by the 2nd day of the critical illness, and exceeding that by 50% afterwards, (energy intake equal to ½, 1, 5/4, 6/4 and 6/4 of the PBMR on days 1–5, respectively). Protein Recommended Dietary Allowances (RDA) were met by day 2 and doubled that value thereafter (day 4).

2.3. Data collected

Data collected included demographics, clinical diagnoses, and vital signs. Patients were classified *a priori* into the following diagnostic categories: sepsis, brain injury, respiratory failure, neuromuscular disease and burns. Sepsis, septic shock, and systemic inflammatory response syndrome (SIRS) were defined using the criteria developed by the American College of Chest Physicians/Society of Critical Care Medicine consensus [15]. All patients with sepsis and septic shock were classified as the Sepsis group. The severity of illness was assessed by the Pediatric Risk of Mortality (PRISM) Score [17], the Therapeutic Intervention Scoring System (TISS) modified for children [18], and indices of organ failure. Multiple Organ System Failure (MOSF) was defined using the criteria by Wilkinson et al [9]. Blood samples were drawn on the days 1 and 5. Stress mediators measured were the acute-phase proteins CRP and fibrinogen. Also, among the biochemical indices of nutritional assessment, the visceral albumins pre-albumin and transferrin were quantitated. All patients had bedside two-dimensional echocardiograms (Ultramark 8 Ultrasound System, Advanced Technology Laboratory, Squibb, Washington) performed with standard views recommended by the American Society of Echocardiography. Echocardiographic measurements included ejection (EF) and shortening (SF) fractions. PBMR was calculated as previously described [6]. RDA for energy were estimated using the tables proposed by the Food and Nutrition Board National Research Council [19]. The recommended levels for protein intake were estimated using the tables proposed by the Food and Nutrition Board National Research Council and were compared with the actual protein given. Energy and protein intake (delivered), which did not differ significantly from the prescribed one, were calculated daily from each patient's chart. Survival was to the point of discharge from PICU.

2.4. Nitrogen balance (NB) studies

All patients had urinary catheters allowing accurate urine collection. Twenty-four hour urine collections were started on the first day of EEN, 12 hr after admission to the PICU. Especially, urine output was collected for 24 hr measurements of urinary urea nitrogen (N) and creatinine excretion, as determined by high-resolution liquid chromatography, and repeated at the end of the EEN period, on PICU day 5. In all patients, 2 g per day of nitrogen was added to the output to account for N lost through feces and skin [7]. NB was calculated by the difference between 24-hr nitrogen intake and total nitrogen output. Inclusion of non-feeding protein (blood products) in the calculated NB did not have any significant impact on the results of the study. Since its contribution was minimal and its data exhibited a non-normal curve of distribution (many patients not receiving any significant amount of human albumin), non-feeding protein was not included in our analysis.

2.5. Creatinine height index (CHI)

From the 24-hr urine creatinine excretion, the CHI was calculated as follows: (24-hr excretion of creatinine/creatinine excretion of normal individuals of same height and sex)*100; Thus the determined CHI was compared with predicted values based on height and sex and the somatic protein status was then calculated as follows: <80% = moderate depletion of somatic protein status, <60% = severe depletion of somatic protein status [8]. According to the protocol, and also to the severity of illness, all patients were exclusively tube-fed by a full-strength formula (which is by definition a meat free diet). They also had a normal renal function and were not exposed to steroids.

2.6. Statistical analysis

Normally distributed data are expressed as mean ± SEM, while non-normally distributed data are given as median and range. Statistical analysis was performed with a two-tailed t-test for normally distributed paired data after Levene's correction for equality of variances or by Mann-Whitney U − Wilcoxon rank sum W test for non-normally distributed data. Analysis of variance (ANOVA) was used when repeated measurements was performed. Two-way ANOVA was used for comparison of NB and CHI data. ANOVA was followed by Scheffe or Bonferroni post hoc

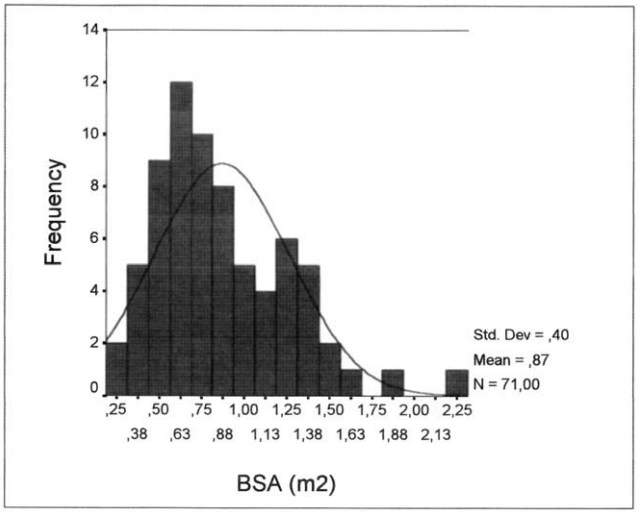

Fig. 1. Histogram of distribution of body surface area of the study population (SPSS frequency procedure).

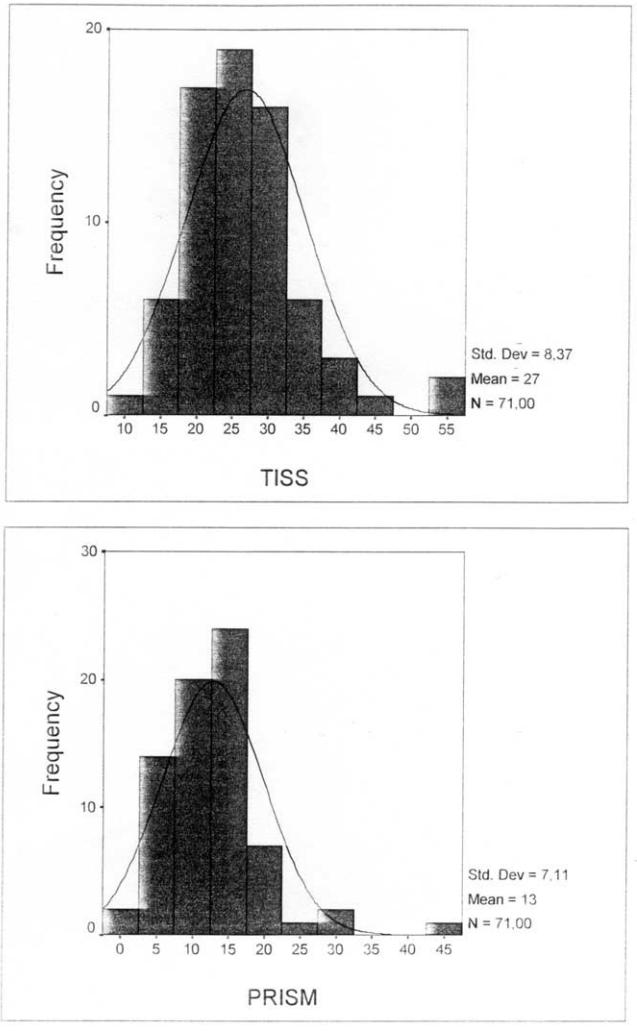

Fig. 2. Histogram of distribution of TISS *(top)* and PRISM *(bottom)* severity of illness scores of the study population (SPSS frequency procedure).

tests to detect differences within groups. Probability values of $<.05$ with two-tailed tests were considered significant. When a linear regression was calculated Pearson's correlation coefficient was employed. Fisher's exact test was used for the category data. Multivariate stepwise regression analysis was used to analyze the contribution of the various clinical factors, nutritional and stress indices, myocardial contractility, anthropometry, and severity of illness values to the variation in the NB. All analyses were done using the Statistical Package for the Social Sciences (SPSS) for Windows (release 8.0, SPSS, Chicago, IL) software package.

3. Results

3.1. Demographic characteristics

The patients aged between 2 and 204 months (mean 71.87, median 54 months). The 25th, 50th and 75th age percentiles were 24, 54 and 120 months. The responded mean—median differences regarding the weight and body surface area were not significantly different (24 vs. 20 kg, and .87 vs. .78 m^2, respectively), the population exhibiting a rather normal distribution (Fig. 1). Male to female sex ratio was 1.29:1.

3.2. Clinical characteristics

All 71 studied critically ill children had no contraindications to enteral feeding. There were 18 (25.4%) with sepsis (meningoccocal), 29 (40.8%) with brain injury (Glasgow score <8), 9 (12.7%) with respiratory failure (acute lung injury), 7 (9.9%) with acute neuromuscular disease, and 8 (11.3%) with burns. All patients had an acute onset of stress and both the PRISM and the TISS scores exhibited normal distributions of the studied population (Fig. 2). The duration of mechanical ventilation was 7 ± 0.9 days, (median 5 days, range 1 to 60 days), while the mean length of stay in PICU was 11.8 ± 1.3 days (median 8 days, range 5 to 70 days). Twenty patients developed MOSF (28%), 16 septic shock (23%), and 41 SIRS (58%). Four patients died (5.6%).

3.3. Nitrogen balance

One hundred forty two measurements were made in 71 patients. On day 1, none of the patients had positive NB. On day 5, 44 (62%) had positive NB and only 27 (38%) had negative NB. Overall, positive NB was increased by 70% after 5 days of EEN ($p < .0001$). More specifically, NB values ranged from -23 to -1 g/day on day 1, but NB turned to the right on day 5 (-6.6 to 11.5 g/day) (Fig. 3). When expressed per kg, NB at the beginning and the end of the EEN differed significantly ($p < .0001$).

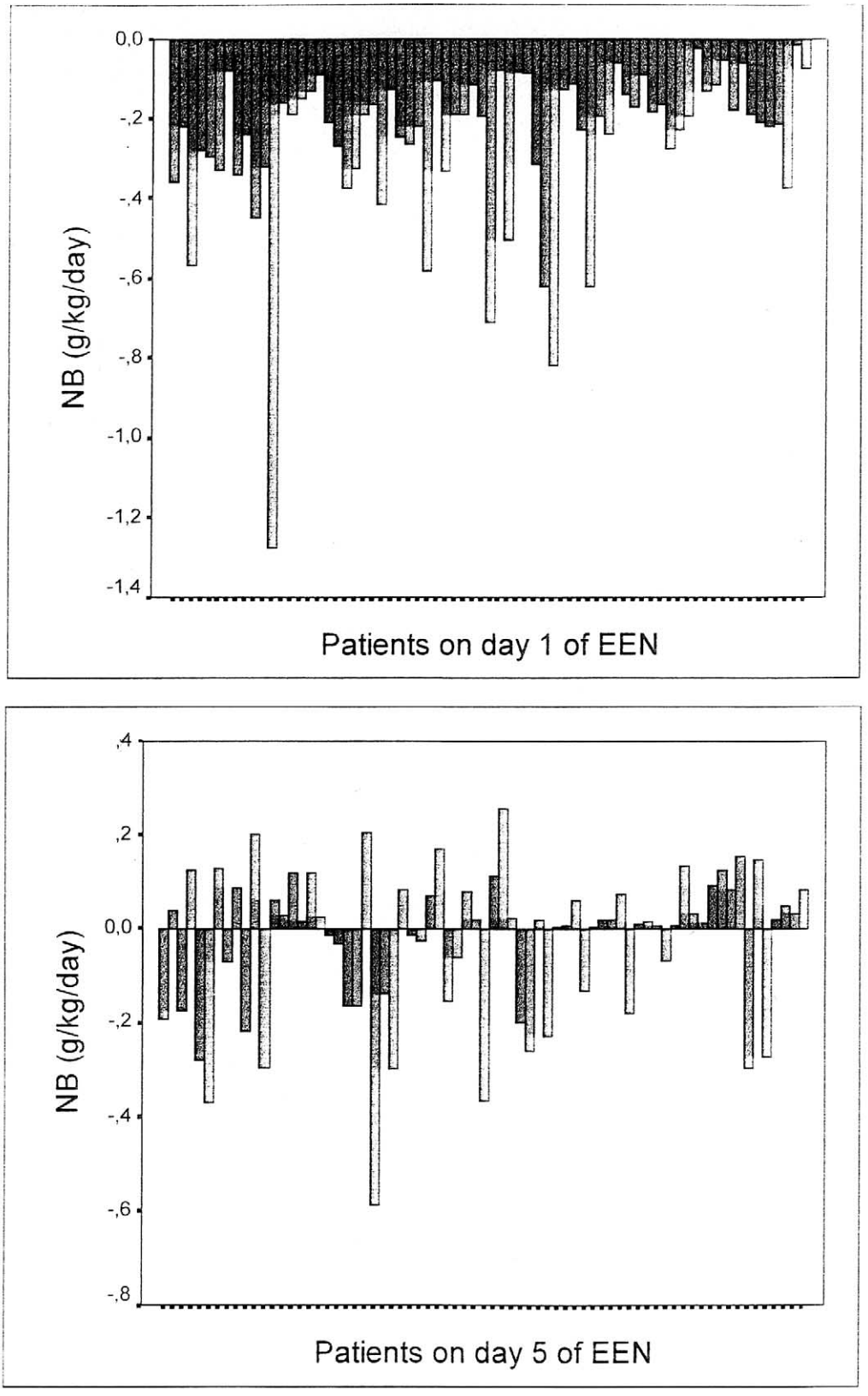

Fig. 3. Nitrogen balances (NB) on days 1 *(top)* and 5 *(bottom)* of a protocol of early enteral nutrition (EEN) in 71 critically ill children.

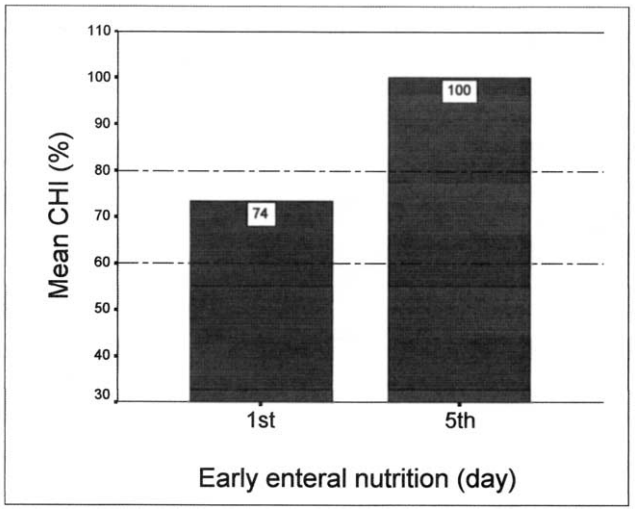

Fig. 4. Mean CHI, indicative of somatic protein status at the beginning and the end of a protocol of early enteral nutrition in critically ill children (CHI = Creatinine Height Index).

3.4. Creatinine height index

Most of the study patients had moderate or severe depletion of somatic protein status on stress day 1 (19.8% and 42.3%, respectively), but half of them reached the normal range of somatic protein status at the end of the EEN, on post-stress day 5 (63.4% with CHI >80%, $p < .004$) (Fig. 4). A normal CHI was not influenced by protein or energy intake and also, could not predict a positive final NB. However, there was a significant correlation between negative initial NB values and a moderate or severe somatic protein depletion (One-way ANOVA, F = 8, $p = .006$). Throughout the study, NB differed significantly between patients with or without severe depletion of somatic protein (mean differences −.14g/kg/day, $p < .03$, and −.12g/kg/day, $p < .02$, for days 1 and 5, respectively). Patients with SIRS had significantly higher percentage of depletion of somatic protein (44%) than patients without SIRS (27%, $p < .03$). CHI, however, did not differ significantly between patients with or without septic shock, or MOSF.

3.5. Nutrition and NB

Patients tolerated EEN well and 94.4% reached the targets of the protocol. Caloric intake approached PBMR the 2nd day (43 ± 1.7 vs. 43.2 ± 1.1 kcal/kg/day) and by the 5th day exceeded it significantly (66.2 ± 2.7 vs. 43.2 ± 1.1 kcal/kg/day, $p < .0001$). On day 1, protein intake was significantly less than the RDA (paired difference −1.9 ± .06 g/kg/day, $p < .0001$) whereas, it significantly surpassed RDA on day 5 (paired difference .6 ± .02 g/kg/day, $p < .0001$). Paired differences between the protein intake − RDA differences on days 1 and 5 differed significantly, favoring the repleted protein at the end of the EEN protocol (−1.3 ± .06 g/kg/day, $p < .0001$). Changes in CHI, NB, energy intake, protein intake, and differences of protein intake − RDA for protein on days 1 and 5 are shown in Table 1. Significant positive correlation was found between NB and the difference of given protein − RDA for daily protein on days 1 (r = .38, $p = .0001$) and 5 (r = .42, $p < .0001$). Patients with positive NB on day 5 had significantly better difference of given − RDA daily protein than those with a negative NB (.84 ± .06 vs. .5 ± .16 g/kg/day, respectively, $p < .05$).

Table 1
Paired samples tests and differences between CHI, NB, energy intake, protein intake, difference of protein intake—RDA for protein on post-stress day 1 and 5 by applying a protocol of early enteral nutrition (Mean ± SEM)

Nutritional indices	Paired Samples Tests (Mean ± SEM)		
	Day 1	Day 5	Paired Differences
CHI (%)	73 ± 4.4	100 ± 5.9	−27 ± 5.6*
NB (g/day)	−4.8 ± 39	.3 ± 37	−5.1 ± .6*
NB (g/kg/day)	−.26 ± .02	.03 ± .02	−.2 ± .02*
Energy intake (kcal/kg/day)	22 ± 1.1	66 ± 2.7	−44 ± 2.2*
Protein intake (g/kg/day)	.69 ± .03	1.9 ± .07	−1.3 ± .06*
PI-RDA (g/kg/day)	−.57 ± .05	.72 ± .07	−1.3 ± .06*

SEM, Standard Error of Mean; CHI, Creatinine Height Index; NB, Nitrogen Balance; PI, Protein Intake; RDA, Recommended Dietary Allowances.

* $p < .0001$

3.6. Relationships between NB, CHI, nutrition and stress and nutritional indices

Nutritional indices increased significantly by the 5th day of EEN (prealbumin 15.1 ± 2 vs. 21.9 ± 2.9 mg/dl, $p < .001$) and transferrin 187 ± 6.6 vs. 233 ± 7 mg/dl, $p < .001$), whereas none of the two stress mediators differed significantly between the 1st and the 5th day of the study (CRP 61.4 ± 10 vs. 55 ± 8 mg/dl and fibrinogen 293 ± 18 vs. 317 ± 18 mg/dl). Initial prealbumin levels were lower in patients with moderate or severe depletion of somatic protein, compared to patients with a normal range of somatic protein status (12.6 vs. 19.7 mg/dl) irrespective of the CRP levels, which did not differ between the two groups (62 vs. 61 mg/dl). By the end of EEN, the prealbumin levels of both groups improved (19 vs. 23 mg/dl), while the CRP levels still did not differ between the two groups (56 vs. 54 mg/dl). Similarly, the initial low prealbumin levels of the studied patients (all NB negative: 15.1 ± 2 mg/dl) improved by the end of the EEN, not only among these who turned to be positive (27 mg/dl), but also among those who remained in a negative NB (19 mg/dl), irrespective of the CRP levels, which did not differ significantly between the two groups (53 vs. 62 mg/dl). Only NB correlated significantly to CRP and fibrinogen on day 1 ($p < .01$), but not to prealbumin and transferrin. However, there were no significant correlations between NB, CHI and nutritional indices or stress mediators on day 5. Multivariate stepwise regression analysis, which was performed to determine which factors were indepen-

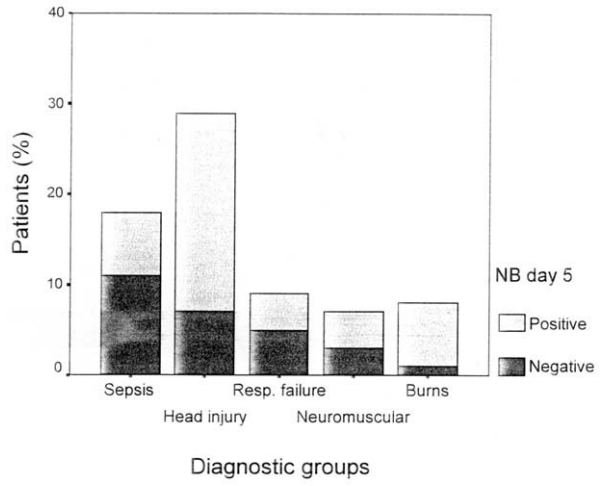

Fig. 5. Nitrogen balance (NB) in different diagnostic groups. There is a significant difference among some diagnostic groups (*$p < .01$, burns vs. sepsis).

dently contributed to the variation in nutritional indices on the 5th day of the EEN protocol, showed that: a) the differences of daily given—RDA protein and of repleted—PBMR energy intake were positively correlated to transferrin levels ($r^2 = .49$, $p < .02$ and $r^2 = .26$, $p < .02$, respectively) and b) differences of daily repleted-PBMR or of daily repleted-RDA energy intakes, were independently correlated to prealbumin levels ($r^2 = .41$, $p < .04$, $r^2 = .37$, $p < .04$, respectively).

3.7. Relationship between NB and clinical variables

3.7.1. Diagnostic groups

Only 39% of patients with sepsis, 44% with respiratory failure and 57% of those with a neuromuscular disease had had a positive NB by day 5. In contrast, 76% of patients with head injury and 87% of those with burns achieved a positive NB by day 5 (Fig. 5). However, although NB on day 5 differed significantly between diagnostic groups (Bonferroni multiple comparisons: burns vs. sepsis, $F = 3.7$, $p = .008$), this difference disappeared when groups corrected for the concurrent presence of somatic protein depletion ($F = .8$, $p < .6$). When stratified according to the sepsis classification, positive NB had 75% of the patients without sepsis, 56.3% with sepsis, and only 33.3% of those with septic shock ($p < .02$). However, the final paired differences of measured NB between days 1 and 5 did not differ between diagnostic groups, irrespective of the patient's classified sepsis status (General linear model, Bonferroni post hoc tests).

3.7.2. Drugs

On day 5, NB did not differ significantly between patients receiving or not opioids, neuromuscular blockade, sedative, or vasoactive agents. However, patients who were supported with vasoactive agents had had more negative NB upon enter the study ($-.21$ vs. $-.34$ g/kg/day, $p = .04$), and still tended to retain a more negative NB on day 5 ($-.067$ vs. $-.076$ g/kg/day, $p = .08$). Although patients who received neuromuscular blockade agents did not differ upon enter the study ($-.24$ vs. $-.26$ g/kg/day, $p = .8$), they also tended to have more negative NB on day 5 (.06 vs. $-.04$ g/kg/day, $p = .06$).

3.7.3. Severity of illness

By the end of the protocol, most patients with septic shock remained in negative NB (63%), in contrast to the patients without septic shock (31%, $p < .04$) Patients with septic shock had worst NB throughout the study ($-.4 \pm .07$ vs. $-.2 \pm .02$ g/kg/day, $p < .03$, on day 1, and $-.13 \pm .05$ vs. $-.004 \pm .02$ g/kg/day, $p < .03$, on day 5, for patients with or without septic shock, respectively). We found a very strong correlation between initial (first day in PICU) values of NB and EF ($r = .50$, $p < .0001$) or SF ($r = .42$, $p < .0001$) (Fig. 6, top). Initial NB was significantly negatively correlated with the probability of death based on PRISM ($r = -.45$, $p < .0001$) and the severity scoring system of TISS ($r = -.38$, $p < .001$). A significant correlation was also recorded between a negative NB on day 5 and a high PRISM score ($r = -.37$, $p = .002$) or a low EF ($r = .42$, $p < .0001$) or SF ($r = .38$, $p = .001$) (Fig. 6, bottom).

3.7.4. MOSF, SIRS

In regard to the NB, patients with SIRS were more negative on day 1 than patients without ($-.32 \pm .04$ vs. $-.16 \pm .01$ g/kg/day, respectively, mean difference $-.16 \pm .04$ g/kg/day, $p < .0001$), and this difference remained throughout the study ($.12 \pm .03$ g/kg/day, $p < .0001$), since only patients without SIRS achieved a positive NB by day 5 ($-.08 \pm .03$ vs. $.04 \pm .02$ g/kg/day, respectively). The incidence of positive NB among patients without SIRS (83.3%) or with SIRS (46%) differed significantly on day 5 ($p = .003$). MOSF developed 48% of the patients with negative NB in contrast to the 16% of patients with positive NB ($p < .01$). Overall, 37 patients out of 51 without MOSF (73%) achieved a positive nitrogen balance by the fifth post-stress day; 13 patients out of 20 with MOSF (65%) remained in negative NB throughout the study ($p = .006$) (Fig. 7). Accordingly, patients with MOSF had negative NB values on day 5 in contrast to patients without, who had positive NB ($-.14 \pm .04$ vs. $.01 \pm .02$ g/kg/day, respectively, $p < .003$). Patients with or without MOSF, however, did not differ regarding the difference of RDA − given protein during the 1st day of the EEN ($-.76 \pm .12$ vs. $-.5 \pm .04$ g/kg/day, with or without MOSF respectively, $p = .07$), whereas both groups had reached a positive protein balance by day 5 ($.39 \pm .2$ vs. $.85 \pm .06$ g/kg/day, with or without MOSF respectively, $p = .03$).

3.7.5. Outcome

There was a negative correlation between the somatic protein status and the length of PICU stay ($r = -.26$, $p <$

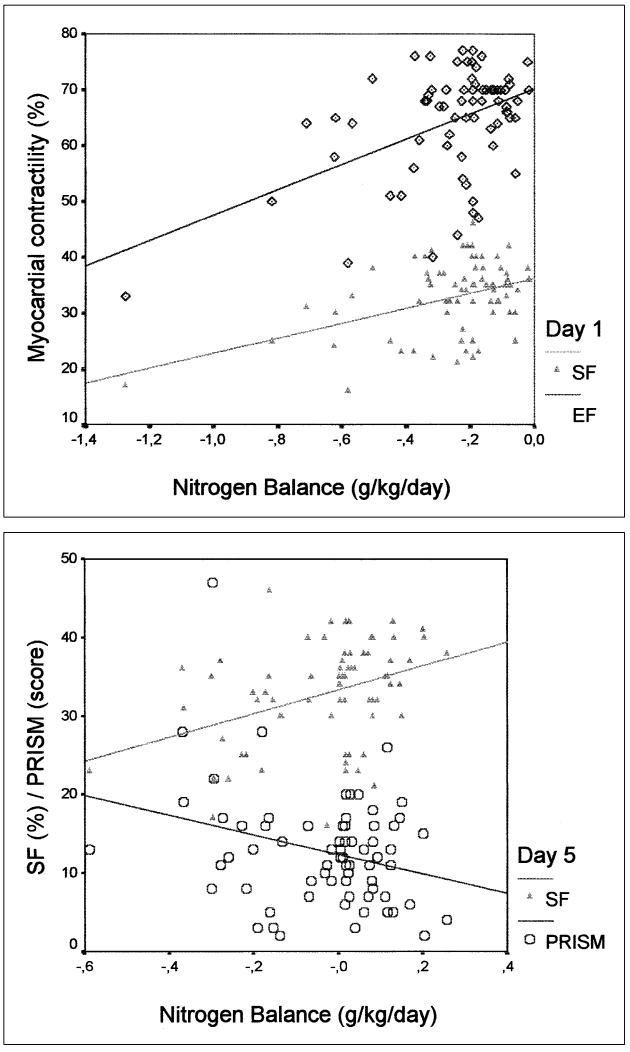

Fig. 6. Top: Correlation between initial values of nitrogen balance (NB) and the ejection (EF) and shortening fractions (EF) of myocardial contractility in stressed children; *bottom*: Correlation between values of NB and the Pediatric Risk of Mortality Score (PRISM) or SF at the end of an early enteral protocol on day 5.

.05) and mechanical ventilation (MV) duration ($r = -.27$, $p < .05$). Although they did not reach statistical significance, both, length of PICU stay (11 ± 1.3 vs. 13 ± 2.7 days) and days of MV (6.1 ± .8 vs. 8.4 ± 2.1 days) were less in the positive than in the negative NB group. The 4 patients who died had negative NB (100%), whereas among survivors, only 23 (34%) had a negative NB ($p < .02$). Non-survivors had significantly higher percentage of severe depletion of protein status compared to survivors (75% vs. 9%, $p = .001$). Nosocomial pneumonia developed 5 patients with negative NB (18.5%), but only 2 patients with a positive NB (4.5%, $p = .06$).

3.7.6. Regression analysis

Multivariate stepwise regression analysis showed that a high PRISM ($r^2 = -.30$, $p = .008$), a low EF ($r^2 = .29$, $p = .01$) or a high CHI ($r^2 = -.34$, $p = .001$) were independently contributed to the negative NB status of the study patients on stress day 1 (adjusted R square .35, $F = 14$, $p < .0001$). Repleted protein ($p = .9$) or energy ($p = .7$) on the same day did not contribute to the NB variation during the acute phase of stress. When multivariate stepwise regression analysis was performed to determine which factors were independently contributed to the variation in NB on the 5th day of the EEN protocol, only the difference of daily given − RDA protein and the total repleted energy were positively correlated ($r^2 = .47$, $p < .001$ and $r^2 = .34$, $p = .003$, respectively) and MOSF negatively correlated ($r^2 = -.24$, $p < .03$) with the NB on day 5 (adjusted R square .35, $F = 14$, $p < .0001$). Both, multivariate stepwise regression analysis and logistic regression analysis did not show any association between clinical disease groups and various risk factors such as negative NB or survival. Similarly, when applying regression analyses to different age subpopulations (classes less than 2, 4, 6, 10 years and more than 10, 12, 14 years), age never entered analyses as a risk factor for the variation in NB. However, when the NB variation was examined among the three main age groups (<6 years, 6–10 years, and >10 years old), significant differences were recorded after completing the early enteral protocol ($p < .0001$). The older the child the better the chances were to reach a positive NB (Fig. 8).

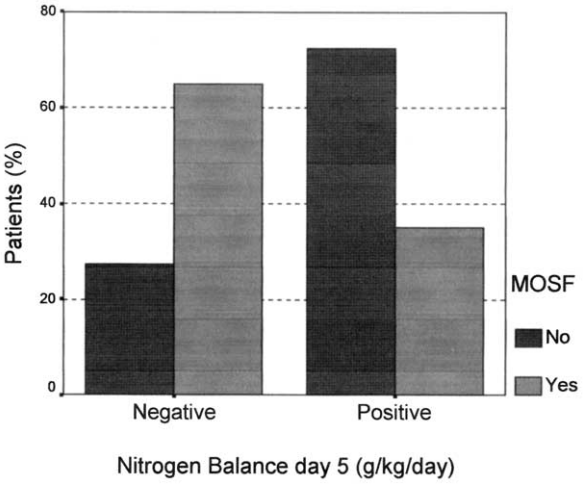

Fig. 7. Nitrogen balance in patients with or without multiple organ system failure (MOSF) on post-stress day 5 in PICU, after completion of an early enteral nutrition protocol. *$p < .01$.

4. Discussion

This study confirms that an anabolic state can be produced by providing higher than the RDA for protein along with the PBMR energy needs during the 2nd day of acute phase of critical illness, and approximating the predicted energy expenditure close to the convalescence period. Thus, restoration of somatic protein status and NB can be reached

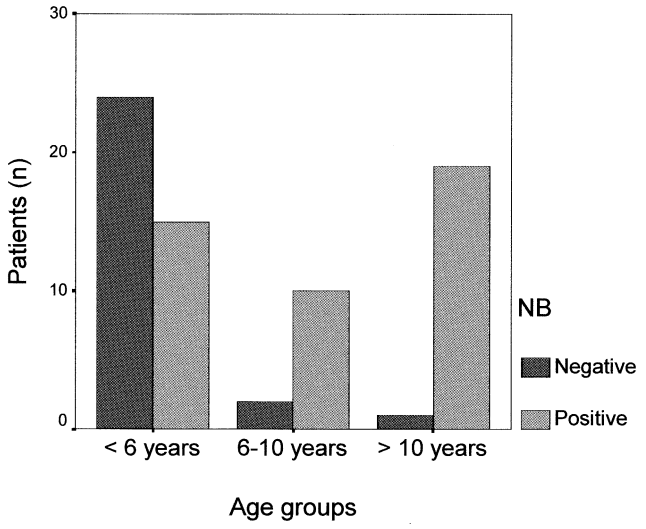

Fig. 8. Differences in nitrogen balance after 5 days of early enteral protocol among three age groups of critically ill children. *$p < .0001$.

within 5 days after starting tube feeding in 70% of the critically ill children. This is higher than it was thought previously [20]. Early administration of prolonged high calorie tube feeds in adult burned patients, restored NB within 10 days [10].

Previous studies have shown that reduced nitrogen or energy intake on one day cannot be compensated for by positive energy balance on the next day, because the nitrogen sparing effect of positive energy balances is limited in these patients [11]. Thus, despite adequate energy supply, more than half of our patients with severe depletion of somatic protein status upon admission were among those not achieving a positive NB. Similarly, in another study, despite the high caloric intake, the creatinine excretion remained high, a manifestation of increased dystrophy of muscle tissue [11]. This may be explained by the fact that in severe stress amino acids use for glucose and energy production is increased. Compared with normal subjects, the contribution of protein to energy production is enhanced and there is a reduction of the net protein synthesis [12]. Thus, tissue catabolism remains elevated even in patients receiving adequate energy and protein supply, indicating a state of nutritional resistance. Depressed protein synthesis may also contribute to the catabolic response [21]. It was shown, however, that reduced protein synthesis in skeletal muscle in early acute sepsis is not primarily associated with reduced muscle protein gene expression [22]. Additionally, despite the fact that both total muscle RNA and specific myofibrillar protein messenger RNA levels were reduced drastically in trauma and sepsis, studies using stable isotopes often have reported increased rates of whole body and muscle protein synthesis, in severely ill patients [23]. It may be hypothesized that increased availability of intracellular amino acids derived from proteolysis may stimulate directly protein synthesis, possibly with a posttranscriptional mechanism [24]. In this study, protein intake more than doubled RDA by day 5. The high protein intake early during the course of the stress state ($2.8 \pm .17$ g/kg/day), might explain the high percentage of positive NB achieved in critically ill children in this study. In adult patients with critical neurological disease, the NB was constantly negative at a lower protein supply of 1.5 g/kg/day [13]. The importance of high protein intake early during the course of critical illness is clearly depicted from the finding that patients with positive NB on day 5 had significantly better difference of given − RDA daily protein than those with a negative NB. Furthermore, only the difference of daily given − RDA protein and the CHI but not energy contributed independently positively to the variation in NB by the end of the EEN protocol. This is further supported by the finding that most of the patients with normal initial CHI achieved positive NB during the stress state, indicating that normal somatic protein status is a good predictor of adequate response to an aggressive enteral feeding regimen. It has been shown that early enteral feeding in adult patients decreases fat oxidation and whole body protein catabolism while improving net nitrogen balance [5]. This explains why critically ill children in this study who had severe depletion of somatic protein status during the acute stress phase, reached the normal range of somatic protein status by the end of the EEN protocol.

In metabolic response to stress, a combination of the counter regulatory hormones and the direct and indirect action of the various inflammatory mediators, prostaglandins and kallikreins [25], significantly modify priorities in liver synthesis. Preferential production of acute phase proteins rather than nutritional indices is followed by lean tissue catabolization to provide energy substrates for wound and inflammatory reactions. The increased levels of the inflammatory mediators, the depression of the nutritional indices, and the development of a negative NB verified the establishment of a situation of acute stress in our patients. While the increased levels of acute phase proteins in our patients revealed the continuation of a stress state throughout the study, however, the high protein intake of the EEN protocol was able not only to improve the NB, but also to raise these visceral proteins to normal ranges. Furthermore, results of this study showed that NB and somatic protein status were independently varied compared to the changes of the nutritional indices and were not strictly related to the continuation of a stress state.

It is at present unclear whether providing a caloric intake that is greater than the PBMR can prevent catabolism and result in an anabolic state, especially during the acute phase of any critical illness in children. Providing a caloric intake that is greater than the measured energy expenditure is known to induce lipogenesis and fatty deposition in the liver in critically ill adults [26]. Adult studies show that catabolism associated with critical illness is not affected by nutritional intake. Similarly, in this study, increased energy intake was not independently associated with reversal of severe catabolism. Instead, we showed that other clinical factors, such as severity of illness, presence of MOSF or

low myocardial contractility, independently contributed to the negative NB status during the acute phase of stress. Other studies have also shown that caloric intake alone is ineffective to prevent the massive loss of lean body mass that follows severe trauma and sepsis [27]. Especially, obligatory nitrogen losses due to paralysis in the spinal cord-injured patient prevents positive NB regardless of the calorie and protein intakes [28]. Looking at specific clinical indices of severity of illness, we found a very strong correlation between initial (first day in PICU) values of NB and EF or SF. This is the first time that such a correlation is described. Initial NB was also significantly negatively correlated to the probability of death based on PRISM and the severity scoring system of TISS. It is interesting to note that on day 5 of the stress state NB was still dependent on the initially estimated severity of illness based on PRISM, and the initial myocardial contractility as estimated by SF. Hence, it is probably unreasonable to anticipate great benefit in patients with acute overwhelming illness, especially when myocardial contractility has been severely depressed. Accordingly, half of the patients with septic shock or MOSF had difficulty in achieving a positive NB by the end of the aggressive enteral feeding. Severe sepsis and MOSF induce profound alterations in body composition that appear remarkably resistant to therapeutic interventions. In such an acute severe stress, as in ARDS or septic shock, net protein catabolism is accelerated and the anabolic response to feeding is impaired. Interestingly, it has been recently shown that protein utilization was significantly higher in patients with a negative NB [14]. Thus, only 50% of patients with sepsis or respiratory failure had had a positive NB by day 5, but 75% of patients with head injury and 100% of patients with neuromuscular disease and burns achieved a positive NB by day 5.

Critical illness nearly always is accompanied by a catabolic state that leads most obviously to skeletal muscle wasting but also to the malfunction of all organ systems including the immune, respiratory, and gastrointestinal systems. Although patients with or without MOSF did not differ regarding protein intake during the EEN, the majority of those with MOSF had negative NB values on day 5 in contrast to patients without, which had positive NB. Although there were difficulties in achieving a positive NB in patients with MOSF, however, we suggest these critically ill children should be also enterally fed early. Animal studies have shown that translocation of bacteria and endotoxin may initiate a SIRS and cause MOSF. As a cause of MOSF, however, simple splachnic ischemia and reperfusion may be sufficient with no absolute requirement for translocation. The strong correlation found between initial NB and SF values in this study, supports this hypothesis. Most of our patients were transferred to our unit from the wards or other hospitals in critical situation, having already developed MOSF. In this setting, enteral nutrition may preserve some splanchnic blood flow and prevent further mucosal breakdown. It is encouraging that patients with SIRS who were more negative on day 1 than patients without SIRS improved significantly after 5 days of EEN, not differing from their counterparts by the end of the study. Similarly, critically ill children with sepsis who responded to intensive treatment achieved a positive NB comparable to one of patients who did not respond.

The heterogeneous group of children is one of the shortcomings of this study. Regarding the wide range of age it is true that there has been an evidently heterogeneous population, although the difference between mean and median age was not so much different. In fact, the age variation in this study is representative of the population of a PICU setting; the weight and body surface area exhibited an approximately normal distribution. Additionally, age stratification of the data showed that younger children in stress had greater difficulty in achieving a positive NB compared to older patients. Similarly, despite the seemingly heterogeneous population regarding the disease groups, all patients were catabolic and had an acutely developed severe stress. Furthermore, the main clinical indices were those of severity of illness scores, which also exhibited a normal distribution. Finally, the inability of performing determination of protein flux using stable isotopic techniques or tissue biopsies of regional beds is another shortcoming. However, it was not technically or ethically possible to perform such interventions in a critically ill setting.

Emerging data from both animal and clinical studies suggest that improved clinical outcomes are possible with administration of specific growth factors, nutrients, and antioxidants in nutrition and metabolic support. The clinical utility, metabolic efficacy, and cost-effectiveness of these agents, given alone or in combination, will emerge over the next several years on the basis of randomized, blinded, and controlled trials. The specific formulae given to our patients were only high protein and omega-3 fatty acids enriched. Most of the survivors, in our study, had a positive NB just by completion of the EEN, whereas, only two patients with negative NB, who failed the EEN protocol, developed nosocomial pneumonia. The low incidence of nosocomial pneumonia in our critically ill patients (5.6%), which is lower than previously reported rates in adults (11.5%–54%) [29–30], may have been influenced by the early aggressive enteral nutrition employed in this study. It has been suggested that early post-stress enteral administration of nutrients is associated with decreased incidence of infections and bacterial translocation from the intestinal lumen [31]. Also, immediate postoperative enteral feeding in patients undergoing intestinal resection prevented an increase in gut mucosal permeability, and produced a positive NB [32]. Additionally, we found that there was a favorable influence of achieving early positive NB on the need for MV in patients of this study. Thus, although such a relation may have been affected by the severity of illness itself, it is also possible that by significantly improving protein metabolism, enteral feeding may decrease post-stress morbidity and mortality in critically ill children.

There is currently very little information about substrate utilization in critically ill children. The optimal composition that would be needed to produce an anabolic state in critically ill children is not known. Nutritional support in a critically ill child must first prevent the nitrogen loss associated with the catabolic state during a critical illness and then be able to produce an anabolic state during convalescence. This requires an understanding of not only the actual energy requirements but also the substrate utilization during a critical illness. In our study, only the daily given protein and somatic status were positively correlated to the NB. We showed that promotion of enteral feeding with specific high-protein content formulas, aiming at an early target volume of 150% of PBMR and doubling the RDA for daily protein intake, contributed to the restoration of the normal somatic protein status and of NB in 2/3 of the patients during the early post-stress phase of critical illness.

4.1. Conclusions

These results indicate that early aggressive NG nutrition with specific formulae is not only possible, but also efficacious for achieving increased protein intake and improved protein status in stressed children. Provision of protein intake higher than the RDA seems necessary during the acute phase of post-stress critical illness. Achievement of positive protein and energy balance in relation to the basic metabolic rate improves NB during the acute phase of stress in 2/3 of critically ill children.

References

[1] K.N. Frayn, Hormonal control of metabolism in trauma and sepsis, Clin Endocrinol 24 (1986) 577–599.

[2] B. Petersson, E. Vinnars, S.O. Waller, J. Wernerman, Long term changes in muscle amino acids after elective abdominal surgery, Br J Surg 79 (1992) 212–216.

[3] J.A. Windsor, G.L. Hill, Risk factors for postoperative pneumonia. The importance of protein depletion, Ann Surg 208 (1988) 209–214.

[4] C.J. Green, I.T. Campbell, P. McClelland, J.L. Hutton, M.M. Ahmed, T.R. Helliwell, R.G. Wilkes, A.A. Gilbertson, J.M. Bone, Energy and nitrogen balance and changes in midupper-arm circumference with multiple organ failure, Nutrition 11 (1995) 739–746.

[5] S.N. Hochwald, L.E. Harrison, M.J. Heslin, M.E. Burt, M.F. Brennan, Early postoperative enteral feeding improves whole body protein kinetics in upper gastrointestinal cancer patients, Am J Surg 174 (1997) 325–330.

[6] G. Briassoulis, S. Venkataraman, A. Thompson, Energy expenditure in critically ill children, Crit Care Med 28 (2000) 1166–1172.

[7] D.M. Hegsted, Balance studies, J Nutr 106 (1976) 307–311.

[8] F.E. Viteri, J. Alvarado, The creatinine height index: its use and the estimation of the degree of preterm depletion and repletion in protein calorie malnutrition, Pediatrics 46 (1970) 696–706.

[9] J.D. Wilkinson, M.M. Pollack, N.L. Glass, R.K. Kanter, R.W. Katz, C.M. Steihart, Mortality associated with multiple organ system failure and sepsis in pediatric intensive care unit, J Pediatr 111 (1987) 324–328.

[10] V.K. Sologub, T.L. Zaets, A.V. Tarasov, M.R. Mordkovitch, A. Yashin, Enteral hyperalimentation of burned patients: the possibility of correcting metabolic disorders by the early administration of prolonged high calorie evenly distributed tube feeds, Burns 18 (1992) 245–249.

[11] J. Takala, Nutrition and body composition in multiple organ failure, Nutrition 11 (1995) 769–770.

[12] R.N. Dickerson, P.A. Guenter, T.A. Gennarelli, D.T. Dempsey, J.L. Mullen, Increased contribution of protein oxidation to energy expenditure in head-injured patients, J Am Coll Nutr 9 (1990) 86–88.

[13] B. Young, L. Ott, R. Rapp, J. Norton, The patient with critical neurological disease, Crit Care Clin 3 (1987) 217–233.

[14] K.F. Joosten, J.J. Verhoeven, J.A. Hazelzet, Energy expenditure and substrate utilization in mechanically ventilated children, Nutrition 15 (1999) 444–448.

[15] Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee, American college of chest physicians/society of critical care medicine consensus conference, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, Crit Care Med 20 (1992) 864–874.

[16] H.B. Stoner, R.A. Little, K.N. Frayn, A.E. Elebute, J. Tresadern, E. Gross, The effect of sepsis on the oxidation of carbohydrate and fat, Br J Surg 70 (1983) 32–35.

[17] M.M. Pollack, U.E. Ruttimann, P.R. Getson, Pediatric risk of mortality (PRISM) score, Crit Care Med 16 (1988) 1110–1116.

[18] A.R. Keene, D.J. Cullen, Therapeutic intervention scoring system: update 1983, Crit Care Med 11 (1983) 1–3.

[19] Subcommittee on the Tenth Edition of the RDAs, Food and Nutritional Research Council: Recommended Dietary Allowances, 10th edn. Washington, DC: National Academy Press, 1989.

[20] D.K. Heyland, Nutritional support in the critically ill patients. A critical review of the evidence, Crit Care Clin 14 (1998) 423–440.

[21] M.B. Clague, M.J. Keir, P.D. Wright, I.D. Johnston, The effects of nutrition and trauma on whole-body protein metabolism in man, Clin Sci (Colch) 65 (1983) 165–175.

[22] D.C. Macallan, G.E. Griffin, Cardiac muscle protein gene expression in the endotoxin-treated rat, Clin Sci (Colch), 87 (1994) 539–546.

[23] Y.M. Fong, J.P. Minei, M.A. Marano, L.L. Moldawer, H. Wei, G.T. Shires III, G.T. Shires, S.F. Lowry, Skeletal muscle amino acid and myofibrillar protein mRNA response to thermal injury and infection, Am J Physiol 261 (1991) R536–R542.

[24] G. Biolo, S.P. Maggi, B.D. Williams, K.D. Tipton, R.R. Wolfe, Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans, Am J Physiol 268 (1995) E514–E520.

[25] A.E. Baue, Nutrition and metabolism in sepsis and multisystem organ failure, Surg Clin North Am 71 (1991) 549–565.

[26] G.P. Zaloga, P. Roberts, Permissive underfeeding, New Horiz 2 (1994) 257–263.

[27] G.F. Guarnieri, G. Toigo, R. Situlin, M.A. Del Bianco, L. Crapesi, A. Zanettovich, Direct biochemical analysis of human muscle tissue in hospital malnutrition, JPEN 11 (Suppl) (1987) S55–S63.

[28] D.J. Rodriguez, F.W. Clevenger, T.M. Osler, G.B. Demarest, D.E. Fry, Obligatory negative nitrogen balance following spinal cord injury, JPEN 15 (1991) 319–322.

[29] E.H. Ibrahim, S. Ward, G. Sherman, M.H. Kollef, A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting, Chest 117 (2000) 1434–1442.

[30] B. Veber, B. Souweine, B. Gachot, S. Chevret, J.P. Bedos, D. Decre, M.C. Dombret, B. Dureuil, M. Wolff, Comparison of direct examination of three types of bronchoscopy specimens used to diagnose nosocomial pneumonia, Crit Care Med 28 (2000) 962–968.

[31] J.C. Alverdy, E. Aoys, G.S. Moss, Total parenteral nutrition promotes bacterial translocation from the gut, Surgery 104 (1988) 185–190.

[32] C.S. Carr, K.D. Ling, P. Boulos, M. Singer, Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection, BMJ 312 (1996) 869–871.