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Original Investigation

Nitrogen Balance in Nutritional Monitoring of Critically Ill Adult Patients: A Prospective Observational Study

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Abstract

Objective: Nutritional monitoring is still controversial in critically ill patients. Although a high protein intake appears to be beneficial, protein nutritional adequacy can be optimized by appropriate monitoring. Nitrogen balance (NB) may be an important tool in this context. This study aimed to identify factors related to higher or lower NB values in critically ill patients, assess the impact of NB on outcomes (mortality), and evaluate whether the temporal evolution of NB impacts these outcomes.

Material and Methods: This prospective cohort evaluated patients with intensive care unit (ICU) stay ≥24 h in two hospitals. NB was evaluated on ICU days 1, 5, and 10.

Results: We evaluated 234 patients (63.7% men, 52.7 years old; 17.9% medical, 15.8% trauma, and 60.7% elective postoperative). Factors correlated with a more negative NB were mechanical ventilation, trauma or medical etiology, and chronic obstructive pulmonary disease, or cancer as comorbidities. There was no correlation between NB values and mortality. Among patients who were more severely ill [acute physiology and chronic health evaluation (APACHE) score >10] and had more negative 1st NB (greater catabolism), those who died revealed less negative NB over the course of days, whereas those who survived maintained stable NB (more negative).

Conclusion: In a heterogeneous ICU population, NB values did not correlate with mortality. However, in the more severely ill patients (lower APACHE) and in those who were more catabolic (more negative initial NB), evolution to less negative NB (lower catabolism) on days 5 and 10 correlated with higher mortality.

Keywords: Nutrition assessment, protein requirement, nitrogen, intensive care unit

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Informed Consent: Since this was an observational non-interventional study, by evaluating a stablished diagnostic method, informed consent was waived (by authorization of the Ethics Committee).

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Introduction

Nutrition in critically ill patients is still a subject of great discussion and controversy, mainly owing to the lack of data regarding the impact of each of its individual components, such as calorie intake, protein intake, micronutrients, and vitamins (1, 2). In recent years, data from large multicenter trials have helped clarify some of these issues in intensive care unit (ICU) patients (1, 3). However, several issues still remain unclear. The amount of protein supply (and its individualization) is still debatable (2, 4, 5).

Protein catabolism is an important accompaniment to critical illness, particularly when there is an intense inflammatory process (4, 6). This process (or its consequences) is more severe in elderly patients and patients with preexisting diseases [such as chronic obstructive pulmonary disease (COPD) and cancer]. However, protein catabolism is also highly accelerated in severe acute inflammatory processes, such as sepsis, burns, and multiple traumas (7-10). Owing to the varying heterogeneity between these groups and the intersection of factors (such as comorbidities, intensity of the inflammatory process, nutritional supply efficiency, abdominal losses, and dialysis), monitoring may be the key to individualize the critical nutritional protein intake. Nitrogen balance (NB) is a widely known tool, which has been used since many years in both acute and chronic patients. However, its contribution to helping unravel the diversity of factors that contribute to protein malnutrition (and eventual inability to replenish nutrition) still remains unclear (1).

Thus, this study aimed to evaluate the utility of NB in nutritional monitoring of adult patients hospitalized in the ICU, seeking to identify risk factors related to the status of protein metabolism (catabolism or anabolism). This study also assessed the NB evolution in critically ill patients at various stages of ICU admission and evaluated whether NB values (positive or negative) correlate with ICU outcomes (length of stay, clinical complications, and mortality).

Material and Methods

Prospective Cohort Study

Patients who were admitted to the adult ICUs of two institutions in southern Brazil were evaluated. The first hospital had a general ICU (medical, surgical, and trauma) and had nine beds during that time; the ICU of the other institution had eight beds and almost exclusively served oncological patients.

Inclusion Criteria

All patients admitted to the ICU for ≥24 h during the study period were included.

Exclusion Criteria

Patients with anuria were excluded from the analysis owing to the difficulty in evaluating excreted urea nitrogen.

Nitrogen balance was calculated using the difference between excreted nitrogen (urinary and nonmeasurable losses) and ingested nitrogen. Urinary nitrogen was obtained by assessing 24-hour urine and its transformation into grams of nitrogen and 4 g representing nonmeasurable losses of nitrogen (fecal, tegumentary, and body fluid losses). The NB values were classified as anabolism (positive values), normal (0 to -5), mild hypercatabolism (-5 to -10), moderate hypercatabolism (-10 to -15), and severe hypercatabolism (>-15). NB was measured on ICU admission days 1, 5, and 10. If the patient was discharged alive from the ICU, NB was no longer performed (therefore, it was not performed outside the ICU).

Definitions

1. Acute renal failure (ARF): any serum creatinine level ≥1.50 mg/dL, excluding patients with known prior renal disease (11)

2. Sepsis: according to the American College of Chest Physicians/Society of Critical Care Medicine criteria (12), in force at the time of collection

3. Use of vasoactive drugs: any dose of noradrenaline, dopamine, or vasopressin

4. Previous diseases (e.g., COPD): clinically defined by the assistant team

5. Trauma: any type of injury caused by an external aggressor, including traffic accidents, falls, violence, and work accidents

Clinical management of patients (e.g., ventilatory management, weaning and sedation, choice of antibiotics, tracheostomy, glycemic control, and vasoactive drugs), as well as nutritional management itself, was defined by the assistant team (physician and clinical nutritionist) from each ICU.

The study was conducted in accordance with the recommendations in the Resolution 466/2012 of the Brazilian National Council of Health. The present study was approved by the Research Ethics Committee of the Universidade Estadual do Oeste do Paraná. Since this was an observational non-interventional study, by evaluating an established diagnostic method, informed consent was waived.

Statistical Analysis

Descriptive statistical analysis was performed. Percentages were expressed as frequency, mean, and standard deviation. Baseline and epidemiological data analysis and outcomes were conducted using the Student's t-test, analysis of variance, and Tukey's test. p-value<0.05 was considered statistically significant.

Multivariate analysis by logistic regression was performed to identify the variables related to higher mortality using the XLSTAT® version 19.03 software (NY, USA).

Results

Total 234 patients (63.7% men; mean age, 52.7 years; etiology: 17.9% medical, 15.8% trauma, 60.7% after elective surgery, and 5.6% after emergency surgery; mean Acute Physiology and Chronic Health Evaluation (APACHE) score II: 18.3) were evaluated. ICU length of stay was 9.0 days, and ICU mortality was 20.9%. The most common comorbidities included hypertension, COPD, and obesity. Table 1 shows the clinical and demographic data and outcomes compared with the corresponding NB data.

Certain factors correlated with a more negative NB, including the presence and time of invasive mechanical ventilation (MV), cause of trauma on clinical admission, and COPD or cancer comorbidities.

While evaluating the first NB (ICU day 1), there were no NB positive patients. Majority of the patients had protein loss between 0 and -5 g (41.0%) or between -5 and -10 g (23.1%); 17.5% had severe hypercatabolism. This scenario has not changed much while evaluating the 2^{nd} and 3^{rd} NB, although in the second evaluation, there was a slight tendency (not significant) for less values of severe hypercatabolism (Figure 1).

While evaluating the factors related to ICU and hospital mortality, APACHE II (indicating greater severity), presence and duration of invasive MV, presence of complications such as ARF, and etiology owing to medical causes were found to be positively correlated with a higher mortality. In multivariate analysis, only the duration of MV and ARF correlated with higher mortality.

Alternatively, no correlation was observed between NB values (at any time of hospitalization) and higher mortality (Table 2).

Contrarily, when patients are compared based on severity of the illness, a different behavior is observed in reference to the APACHE value. Among patients with less severe illness (with lower APACHE), the initial NB tended to be less negative among patients who died; in both groups (dead and alive), NB evolved to be less negative, matching the values on day 5 (Figure 2). Among the more severe patients (APACHE>10), those who died revealed slightly more negative values in the 1st NB. However, in the 2nd NB, the values were reversed, with patients who died presenting less negative values and those who survived presenting stable NB (Figure 2).

Table 1. Clinical and demographic data and outcomes

	Total n=234	1st NB n=234 Mean±SD	2nd NB n=55 Mean±SD	Variation 2a-1a Mean±SD	3rd NB n=18 Mean±SD
Total	234	-11.1±13.52	-13.1±24.35	+4.7±18.43	-8.4±6.79
Male	149 (63.7%)	-11.7±14.52	-8.8±8.50	+5.5±21.23	-6.4±5.05
Age, years	52.5±17.40	-	-	-	-
≤40	64 (27.4%)	-13.0±22.33	-8.3±4.31	-0.3±3.74	-11.2±7.95
41-59	80 (34.2%)	-10.7±9.69	-6.4±3.21	+8.7±16.53	-3.8±2.45
≥60	90 (38.4%)	-11.2±16.16	-8.2±11.7	+7.8±26.53	-5.1±2.10
Initial APACHE	18.3±8.03	-	-	-	-
≤5	5 (2.1%)	-19.5±22.26	-	-	-
6-9	21 (9.0%)	-10.0±11.41	-4.1±2.52	+10.0±19.16	-2.0
10-19	125 (53.4%)	-11.3±16.76	-7.6±3.53	+2.9±7.85	-6.5±5.42
≥20	83 (35.5%)	-11.5±16.57	-8.7±9.89	+4.6±22.28	-10.3±7.51
Admission causes	-	-	-	-	-
Trauma	37 (15.8%)	-15.0±26.29*	-9.8±10.6	+0.9±16.34	-12.9±9.72
Elective surgery	142 (60.7%)	-9.7±10.89	-1.3±6.26*	+12.3±14.96	-5.0
Urgency surgery	13 (5.6%)	-10.5±3.69	-7.8±4.64	+2.8±2.12	-8.5±1.66
Medical	42 (17.9%)	-15.1±21.53*	-9.1±3.79	+5.1±23.65	-5.7±3.78
Comorbidities	-	-	-	-	-
No	60 (25.6%)	-14.0±22.66	-9.3±9.66	+1.2±14.63	-11.0±8.49
COPD	12 (5.1%)	-24.8±33.21*	-9.4±2.28	+21.4±46.39	-5.3±1.59
Cancer	125 (53.4%)	-9.4±10.37*	-1.1±6.6*	+13.4±15.42	-5.0
MV LOS, days	-	-	-	-	-
0 (no)	32 (13.7%)	-8.1±9.93*	-3.7±0.86*	+1.7±3.12	-
1-2	100 (42.7%)	-9.3±9.17	-2.3±6.97	+16.3±17.76	-
3-5	25 (10.7%)	-17.1±32.34	-5.2±7.79	+3.5±6.67	-
6-9	24 (10.3%)	-17.8±18.41*	-12.8±16.7*	+3.5±27.87	-2.8±1.15
≥10	53 (22.6%)	-12.3±17.17	-8.8±3.7	+3.3±19.00	-9.1±6.90
ARF	42 (17.9%)	-12.6±25.15	-5.4±7.18	+5.8±13.67	-7.5±3.08
Mortality, ICU	49 (20.9%)	-13.1±24.35	-4.5±6.88#	+5.3±8.69	-4.8±4.80
Mortality, Hospital	56 (23.9%)	-12.0±22.95	-4.5±6.44*	+4.4±8.53	-4.8±4.29

NB: nitrogen balance; SD: standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation score; MV: mechanical ventilation; COPD: Chronic obstructive pulmonary disease; LOS: length of stay; ARF: acute renal failure; ICU: intensive care unit
#p=0.054 from "total" (same column)
*p<0.05 from "total" (same column)

Discussion

In this heterogeneous population of ICU patients, NB in the first 24 h (1st NB) varied but was characteristically negative. No patient showed anabolism (NB positive), and 17.5% presented severe hypercatabolism (Figure 1). Several studies found that NB is consistently negative in the first 24 h of ICU in patients with severe MV (13), acute neurological diseases (3), general surgery (14), and cardiac surgery (2).

The present study revealed no differences in NB between the groups, regarding sex or age. Similar findings have been found no gender differences (13). Despite the lower natural muscle mass in elderly patients and consequently greater vulnerability to protein catabolism (particularly in trauma) (15, 16), no significant differences have been observed in the NB of critically ill patients in relation to age (7).

Although APACHE is a traditional and efficient marker of severity in different populations of ICU patients, this score was not correlated with the NB values in our patients. In patients with trauma (17) and ARF with hemodialysis (18), APACHE II had a good correlation with NB, whereas the Injury Severity Score did not show a good correlation (19). The authors speculate whether this finding is caused by the characteristics of our population, with high severity and mortality risk: only 2.1% had APACHE II of admission <5. Conversely, on the 2nd NB (ICU day 5), patients with high APACHE had a trend toward more negative NB. The more severe the disease, the greater the energy expended (and possibly hypercatabolism) persistently. It has been found that patients with increased APACHE II score exhibit higher metabolic rates that were demonstrated in indirect calorimetry after a few days of ICU stay (20).

The type of patient and the cause of ICU admission strongly correlated with NB in the present study. Trauma and medical patients had more negative NB values (greater hypercatabolism), whereas patients in postoperative elective surgery had a less negative NB value (more normal and close to anabolism) in the second collection (Table 1). The incidence of protein hypercatabolism has been separately described in multiple acute etiologies, such as traumas (21), severe burns (22), and acute neurological diseases (3). Essentially, independent of etiology, a clear correlation exists between acute disease severity and inflammatory process intensity (14). However, it has been found that in postoperative patients with abdominal surgeries, the traditional calculation of NB ignores the loss of protein by the abdominal fluids, underestimating the loss of nitrogen and overestimating the appropriate dose of protein. In these patients, NB may be more negative than the traditional measurement, as observed in the current study (14). Because surgical patients had less negative NB, this phenomenon may partially justify the findings of the present study.

Conversely, the presence of comorbidities and previous diseases was weakly correlated with NB status, except for COPD, which showed a higher catabolism value in the 1st NB (but not in the 2nd). Several studies with small n have demonstrated negative NB and protein hypercatabolism in different ICU diseases, such as acquired immune deficiency syndrome, Crohn's disease, and solid cancer, but only in a descriptive way or when compared with non-ICU patients or healthy individuals (23). Thus, the actual role of each of these comorbidities (discounting the effect of acute inflammatory process and organ dysfunction) remains unclear in critical ICU patients. It is noted in our study that the presence of cancer did not present a higher impact on negative NB. However, it should be noted that several patients with cancer were in the ICU because of post-

Table 2. Factors related to ICU mortality

	n	Alive	Dead	p
Total	234	185 (79.1%)	49 (20.9%)	–
Male, n (%)	149	118 (63.8%)	31 (63.3%)	0.918
Age, years, mean±SD	–	52.7±17.40	51.8±17.50	0.729
≤40	64	50 (27.0%)	14 (28.6%)	
41–60	85	65 (35.1%)	20 (40.8%)	
>60	85	70 (37.9%)	15 (30.6%)	
APACHE, mean±SD	–	17.2±7.48	22.2±8.90	<0.001
<5	5	5 (2.7%)	0	
6–9	21	18 (9.7%)	3 (6.1%)	
10–19	125	103 (55.7%)	22 (44.9%)	
≥20	83	59 (31.9%)	24 (49.0%)	
Comorbidities, n (%)	–	–	–	0.978
No	60 (25.6%)	47 (25.4%)	13 (26.5%)	
COPD	12 (5.1%)	09 (4.9%)	03 (6.1%)	
CHF	11 (4.7%)	08 (4.3%)	03 (6.1%)	
Cancer	125 (53.4%)	103 (55.7%)	22 (44.9%)	
Obesity	14 (6.0%)	11 (5.9%)	03 (6.1%)	
MV LOS, days, mean±SD	–	6.0±16.94	10.3±16.38	<0.001
0	32	30 (16.2%)	2 (4.1%)	
1–2	100	90 (48.5%)	10 (20.4%)	
3–5	25	16 (8.6%)	9 (18.3%)	
6–9	24	16 (8.8%)	8 (16.4%)	
>10	53	33 (17.9%)	20 (40.8%)	
ARF, n (%)	42	27 (14.6%)	15 (30.6%)	<0.001
Etiology	–	–	–	0.085
Elective surgery	142	118 (63.8%)	24 (49.0%)	
Urgency surgery	13	10 (5.4%)	3 (6.1%)	
Trauma	37	29 (15.7%)	8 (16.3%)	
Medical	42	28 (15.1%)	14 (28.6%)	
1st NB, mean±SD	234	-11.11±13.52	-13.12±24.35	0.445
(2nd–1st) NB, mean±SD	55	+4.5±21.04	+5.3±8.69	0.805

SD: standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation score; COPD: Chronic obstructive pulmonary disease; CHF: congestive heart failure; MV: mechanical ventilation; LOS: length of stay; ARF: acute renal failure; NB: nitrogen balance; ICU: intensive care unit

operative elective surgeries (with less severity and less hypercatabolism, for example, postoperative craniotomies caused by central nervous system cancer).

The presence of ARF had no correlation with the NB value in the present study. Because the incidence of dialysis was small, its impact could not be assessed. According to literature, patients with ARF on hemodialysis are among the main risk factors for hypercatabolism and negative NB, despite difficulties in their monitoring (7, 18). The use and duration of MV were strongly correlated with NB. Patients who were not submitted to MV had less negative NB, whereas patients with prolonged MV (>5 days)

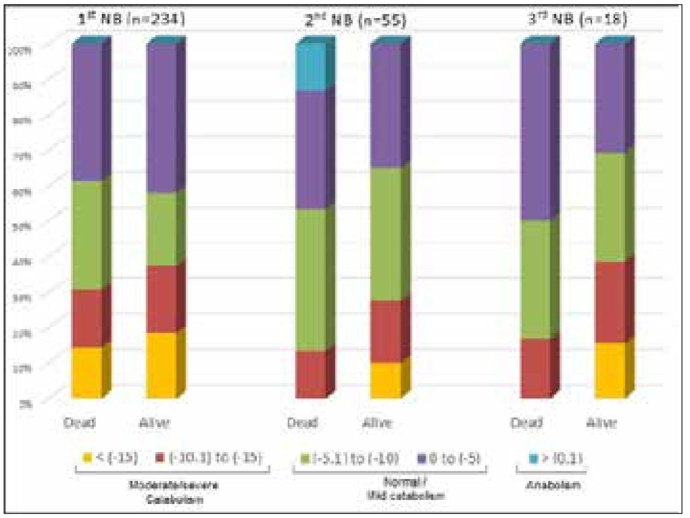

Figure 1. Value of NB (in g). More negative values indicate catabolism, and more positive values anabolism.
NB: nitrogen balance.

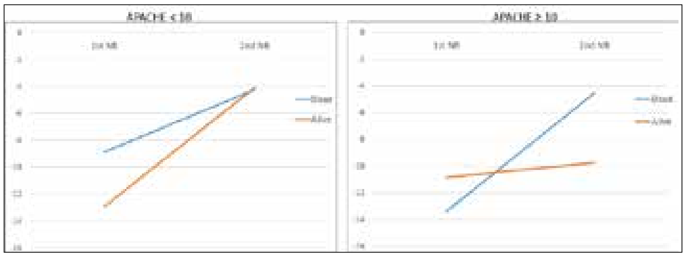

Figure 2. Variation between 1st and 2nd NB (in g) according to the initial APACHE.
NB: nitrogen balance; APACHE: Acute Physiology and Chronic Health Evaluation

had higher hypercatabolism. These findings probably correlate with the higher intrinsic severity and organ dysfunction of these patients.

While evaluating NB during hospitalization (ICU days 1, 5, and 10), it was verified that the evolution of NB values (level of catabolism) remains relatively constant (Figure 1), which is similar to the data found in literature (2, 3, 13). Nevertheless, when patients with a higher severity (higher APACHE) and/or lower initial catabolism (on ICU day 1) and those who performed the 2nd NB (i.e., at least 5 days in the ICU) were evaluated, a distinct distribution pattern was observed: in patients with higher APACHE (more severe) and initial hypercatabolism (supposedly more severe and with greater inflammation), the variation between the 1st and 2nd NB was clearly distinct from patients who were initially less hypercatabolic (Figure 2, 3); the attempt of NB positivity would only have been useful in less severe patients. The authors speculate that this difference could indicate that, in very hypercatabolic patients, an excess of ingested proteins (and therefore the attempt of less negative NB) could be as harmful as an excess of calories (previously demonstrated), or that this ingestion should not be maintained if the patient persists hypercatabolism after a few days. This behavior is also noticed when only patients who stayed in the ICU were analyzed for more than 10 days (n=18), and therefore, NB measurement was performed thrice (Figure 4).

In recent years, the increase in randomized multicenter studies has redefined the role of nutritional therapy in critically ill patients. The daily

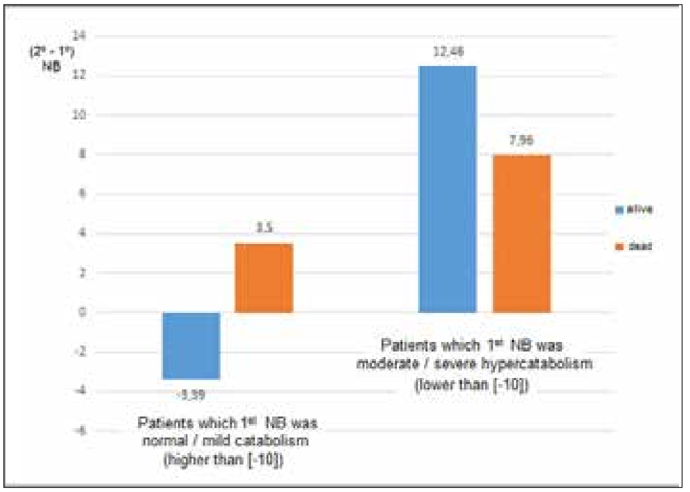

Figure 3. Variation between 1st and 2nd NB (in g) according to the 1st NB. Positive values indicate that the NB value was higher in the 2nd evaluation (day 5) than in the 1st evaluation (admission).
NB: nitrogen balance

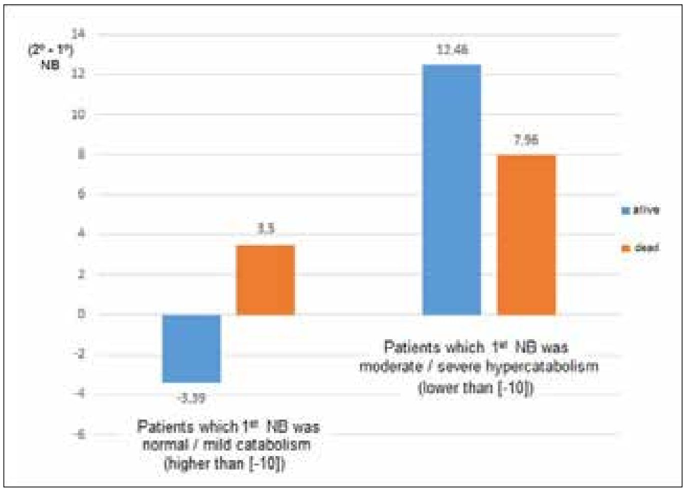

Figure 4. Variation among the 1st, 2nd, and 3rd NB, among patients that stayed in the ICU for ≥10 days (n=18).
NB: nitrogen balance; ICU: intensive care unit

calorie intake has clearly reported that lower values (caloric hyponutrition) in the initial days lead to less mortality in hypercatabolic critically ill patients (24). However, in relation to the protein requirements and the ideal value of protein intake in critically ill patients, there is still a lack of data that may lead to the best management in the ICU environment. Certain small-scale and/or observational studies have suggested that higher protein intake values (>1.5 or 2 g/kg/day in the ICU) during the first ICU days have a positive impact on ICU outcomes (2). Despite the physiological rationale behind this hypothesis (9, 25), multicenter randomized controlled trials are still needed to ratify this practice (25-27). The present study, on the contrary, suggests that at least in some groups of patients (perhaps the most severe ones), the persistence of more positive NB could be deleterious (accompanied by higher mortality). Thus, nutritional monitoring (even if imperfect, as in the case of NB) may be the key to find sub-groups that benefit from different nutritional strategies as well as different moments during the evolution of critical illness.

The present study has several limitations, some of which are inherent in nature. Because this is an observational study, it may not be possible to infer on the influence of therapeutic strategies, both clinical and nutritional (e.g., amount of proteins offered). As there are no pre-defined protocols; the great diversity among patient types makes it difficult to appropriately assess their population and outcome differences. Specifically, the amount of nitrogen (via proteins by diet) offered was not predetermined (because this was an observational cohort study), although the study followed local protocols of clinical nutrition teams.

In addition, factors such as prior nutritional status, type of nutrition, time to starting nutrition, and amount of lipid and carbohydrate were not predetermined or standardized. However, because this was a "real-life" study, the authors believe that these factors were distributed in a way that did not interfere with the main strength of the study-that is, in a "real-life" ICU, the impact and feasibility of systematic and serial NB monitoring.

The number of patients may not be large enough to answer questions about specific groups, such as patients with trauma or cancer. By a protocol decision, patients with anuric renal failure (and consequent need for dialysis) were excluded, thereby limiting the interpretation of these data to patients who have urinary excretion of urea nitrogen.

Conclusion

In a heterogeneous population of ICU patients, NB values were not correlated with mortality. However, in the more severely ill patients (with initial APACHE >10) and more catabolic values (with more negative initial NB), the evolution to less negative NB (less catabolism) on days 5 and 10 was correlated with higher mortality.

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