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ORIGINAL ARTICLE

Serum selenium in critically ill patients: Profile and supplementation in a depleted region

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Background: General selenium supplementation to intensive care unit (ICU) patients in regions with selenium-rich soil does not improve outcomes. Still selenium supplementation may reduce morbidity and mortality in patients with low-serum selenium concentration (S-Se) in selenium-poor areas who respond to treatment. The primary aim of this observational study was to investigate S-Se in a selenium-deficient region at time of intensive care admission, and in addition to monitor S-Se during high-dose selenium supplementation for safety.

Methods: We measured S-Se in 100 consecutive patients admitted to a tertiary general ICU. After initial sampling, high-dose intravenous (iv) selenium supplementation was administered up to 20 days.

Results: At admission, in 95% of the cases, S-Se was below the saturation level for selenoenzymes, in 91%, below the Swedish reference level, and in 71%, below the level where selenoenzyme function may be impaired. At day 5 of substitution, all patients still remaining in the ICU (n = 26) were within the range for enzyme function, 12% were below reference, and 24% did not reach full enzymatic saturation. At day 10 and forward, all patients were within target for treatment. No patients were at risk for toxic S-Se concentration.

Conclusions: S-Se concentration was substantially lower compared to normal values at ICU admission in this cohort of unselected Swedish critical care patients. Selenium supplementation restituted S-Se to levels corresponding to enzymatic saturation and the Swedish reference interval for all subjects remaining in the ICU on day 5.

1 | INTRODUCTION

Selenium (Se) has been used in the prevention and treatment of patients with different diseases.[1,2] Several biological mechanisms have been proposed to explain the preventive effects: antioxidative, synthesis of selenoproteins, modulation of the immune system, etc. Chronic Se deficiency may lead to disabling disease or death.[3] Selenium is the cofactor in about 25 enzymes linked to the redox system, immune system, and thyroid hormone axis.[2,4] These enzymes are found in all tissues, circulation, the cytosol, and cellular and mitochondrial membranes. *Selenoprotein P* (SEPP1), a carrier protein of Se, is also suggested to protect the endothelium in severe insult, for example burns, trauma, and sepsis.[5,6] At onset of critical illness, both in adults and children, S-Se is low,[1,7-9] that may part be due to redistribution of Se from the circulation to immune cells.[10,11] After few days, S-Se often shows spontaneous increase, but in adult patients who do not recover, an association with a higher mortality rate has been seen.[9,12] In critically ill children, a spontaneous restitution of S-Se at

intensive care unit (ICU) day 5 correlated with improved organ function.[8] In burn trauma, S-Se reversely relates to the numbers of total infections.[13] Critically ill patients with a prolonged stay in the ICU have an increased risk of poor prognosis, often associated with the development of multiple organ failure (MOF).[14,15] The mechanisms for development of MOF are not clarified, but an increased production of reactive oxygen species (ROS) in parallel with an impaired antioxidative capacity due to glutathione and selenium depletion has been suggested.[16,17] An association between the number of organ failures and a high ratio of reduced glutathione (GSH/tGSH) is reported.[8] The higher the ratio, the more organ failures and prolonged ICU stay. The selenoenzyme glutathione peroxidase (GPX1) catalyses the conversion of peroxide to water. Thus, deficiency of S-Se may disrupt the enzyme leading to the accumulation of both GSH and peroxidase. Substitution of Se to adult critically ill patients increases the GPX1 activity,[6,18] and response to substitution is associated with reduced mortality in sepsis.[18] The main nutritional source for Se is via crops extracting Se from the soil.[19,20] Most studies have been conducted in areas adequate or rich in Se, that is central Europe and the United States, whereas Scandinavia is a depleted region.[20] People living in areas of low Se in soil, for example Tibet, may develop severe disability or death due to indwelling oxidative stress, as exemplified by Keshan, and Kashin-Beck disease.[3] Concerning nutritional intake, a large proportion of the Swedish population has a suboptimal intake,[21] reflected by low S-Se concentrations observed both in children and the elderly.[8,22] In both age groups, S-Se is below the necessary concentration for saturation of these enzymes (>80 μg/L, >1.01 μmol/L).[3,23,24] Concerning the elderly, subjects in the lower quartile (S-Se < 65 μg/L, <0.81 μmol/L) have a higher risk for all-cause and cardiovascular death, and substitution of Se proved to be cardioprotective and decrease mortality compared to controls.[24,25]

Selenium poisoning, *selenosis*, has been described after a median daily intake of 41 000 μg/d.[26] Features of selenosis range from diarrhea, garlic odor breath, red discoloration of nails and teeth, to MOF, circulatory collapse, and death.[26-28] Symptoms are reported from S-Se of 5-10 μmol/L.[27] A daily dose of >17 000 μg per os for at least 2 weeks was reported as safe in a Swedish clinical trial on carcinoma patients.[28]

The primary objective of the present study was to screen S-Se in a consecutive cohort of critically ill adult patients living in a Se-depleted geographical area at ICU admission and to determine the response of a high-dose iv (intravenous) selenium supplementation using a "modified Angstwurm protocol". We also sought to determine trajectory and fraction of the subjects who reached above reference values for selenoenzyme saturation (>1.01 μmol/L) and toxic concentrations.

Editorial Comment

Critically ill adult patients had a s-se concentration far below the normal reference levels for healthy Swedish subjects, concentrations which are below the lower limit thought to be required for adequate enzyme function. Substitution of high-dose iv selenium to this Swedish ICU cohort was shown to be feasible to restore s-selenium concentrations without reaching toxic concentrations.

2 | METHODS

A serum sample for measurement of selenium concentration was obtained at admission in 100 consecutive patients admitted to the general Intensive Care Unit at Karolinska University Hospital, Huddinge, Sweden, from August to October 2012. Inclusion criteria were ICU admission and age >18 years. Exclusion criteria were high-dose iv Se supplementation prior to admission, pregnancy, and a "do not resuscitate" (DNR) order at admission. High-dose iv Se supplementation was given until discharge from the ICU or a maximum of 20 days, whichever came first. Serum concentration was assessed at admission and S-Se and evaluated during substitution by sampling on days 5, 10, and 20 (if the patient still was in the ICU). In accordance with the routine protocol of the unit, selenium substitution was given to all patients with a bolus of 1000 μg of the inorganic compound sodium selenite (Na_2SeO_3, SelenaseT®, Biosyn, Arzneimittel GmbH), followed by a continuous infusion of 1000 μg/d day 0 to 10, and 500 μg/d day 11 to 20.

2.1 | Sample handling and analyses of selenium

For each sample, a tube was filled with 1 mL of blood and left for 2 hours to clot at room temperature. After spinning the clotted sample for 10 minutes at 2000 *g*, 300 μL serum was pipetted and transferred to an acid-washed plastic tube and stored at −80°C pending analyses. The analyses for S-Se were performed by Australian Laboratory Services (ALS) Scandinavia, Luleå, Sweden, using sector-field inductively coupled plasma mass spectrometry (ICP-MS).[29]

2.2 | Statistics

Normally distributed variables are presented as means and standard deviation (SD). Non-parametric data is presented as median and range or interquartile range (IQR) and compared using Kruskal-Wallis test, or Spearman's test. Normality was assessed using the Shapiro-Wilk test. A *P*-value less than .05 was considered as statistically significant. GraphPad Prism 6 was used for the statistical analyses (GraphPad Software, Inc), except the power analysis that was performed by Dell Statistica 13.2 (Dell Software, Inc).

2.3 | Ethics

The patient was asked for informed consent for the extra sampling. If communication was not possible, the next of kin was informed for

consent. Ethical approval was obtained from the Regional Ethical Review Board in Stockholm, Dnr: 2011/133-31/3.

3 | RESULTS

One hundred and forty-six consecutive critically ill patients were screened to participate in the current study from August to October 2012. Out of the eligible 129 patients, 29 did not participate due to causes depicted in Figure 1. The characteristics of the study cohort are shown in Table 1.

Serum selenium concentrations at admission to the ICU and during continuous selenium infusion are displayed in Figure 2. Median S-Se was 0.40 (0.32-0.51) μmol/L (range 0.13-1.76). Ninety-five percent of the patients had a S-Se below the saturation level for selenoenzymes (1.01 μmol/L), 91% below the normal range for Swedish population (0.80-1.56 μmol/L),[30] and 71% below 0.50 μmol/L were considered the level under which selenoenzyme function is severely impaired.[23,31] At day 5, all patients remaining in the ICU (n = 26) had reached the range of enzymatic function, although five patients had not targeted the lower limit for Se saturation; two of these were still below the normal range for Swedish population, see Table 2. All patients still on supplementation at day 10 and forward were within the range of enzyme saturation. No patients reached toxic serum concentrations (>5.0 μmol/L).

S-Se at admission was statistically associated with the SOFA score ($r = -.29$, $P < .003$) obtained the same day (Figure 3), but not with APACHE II ($r = -.19$, $P = .058$). Admission relationship data for S-Se and CRP showed a similar association as the SOFA score ($r = -.30$, $P < .002$) (Figure 4). Of the 26 patients still in the ICU day 5, CRP was available in 25 cases. Of these 25 patients, 14 patients had a lower CRP at day 5. Eleven patients had a higher CRP compared to admission of which four patients were in the subgroup with S-Se < 1 (range 0.59-0.97) μmol/L. Three of these 11 patients were still in the ICU day 10, all with a decrease in CRP.

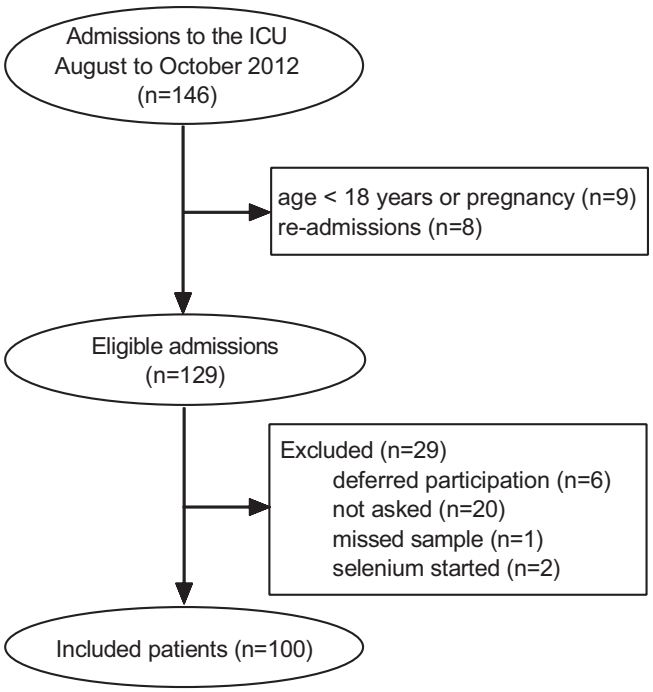

FIGURE 1 The inclusion/exclusion procedure for the feasibility study on high-dose selenium substitution

4 | DISCUSSION

The main finding of this prospective observational study was that critically ill adult patients had a S-Se far below the normal reference interval

TABLE 1 Demography and outcome data for patients supplemented with high-dose intravenous selenium

	Subject data
n	100
Age years mean (range)	57.0 (18-92)
Male gender (%)	60 (60)
BMI mean (range)	27.2 (17.0-60.4)
SOFA in mean (range)	6.5 (1-16)
APACHE II mean (range)	18.3 (0-39)
Surgical diagnosis n (%)	32 (32)
ICU mortality n (%)	9 (9)
30-d mortality n (%)	20 (20)
180-d mortality n (%)	27 (27)
LOS ICU days mean (range)	4.6 (0-36)
Mechanical ventilation n (%)	54 (54)

Abbreviations: APACHE II, 2nd revision Acute Physiology and Chronic Health Evaluation; BMI, Body mass index; ICU, Intensive care unit; LOS, Length of stay; SOFA, Sequential Organ Failure Assessment.

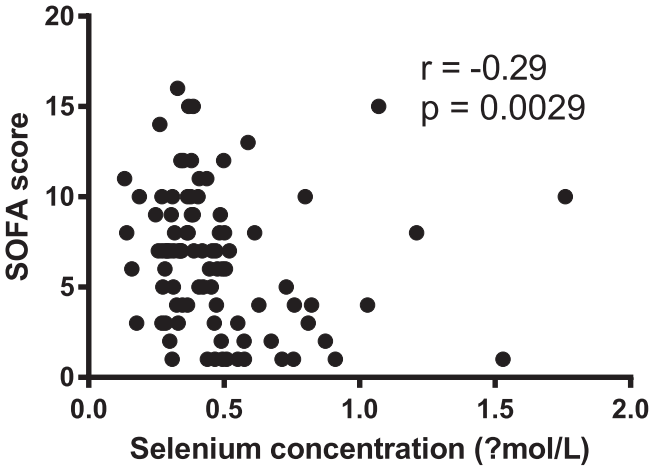

FIGURE 2 The cohort median selenium concentration (median, IQR) over the study time. The light grey shadow indicates values below the threshold for saturation of selenoenzymes (1.01 μmol/L).[3,23] Below 0.5 μmol/L (dark grey), selenoenzymes seize to function[32]

	Day 0 n = 100	Day 5 n = 26	Day 10 n = 11	Day 20 n = 4
Sample distribution				
Above Sat_{low} (1.01 μmol/L) n (%)	5 (5)	21 (76)	11 (100)	4 (100)
50%-99% of Sat_{low} n (%)	23 (23)	5 (24)		
<50% of Sat_{low} n (%)	72 (72)			
Within Swedish NR n (%)	9 (9)	23 (88)	11 (100)	4 (100)
Below NR n (%)	91 (91)	3 (12)		
Trajectory				
Delta Se (+) n (%)		25 (96)		
Delta Se (–) n (%)		1 (4)		

Abbreviations: NR, Normal range for selenium concentration; Sat_{low}, lower serum selenium concentration for saturation of selenoenzymes.

TABLE 2 Serum selenium concentrations (S-Se) at admission (day 0) and three consecutive sampling days after commencement of high-dose intravenous selenium substitution. Minimum S-Se regarded for the saturation of selenoenzymes is >1.01 μmol/L.[3,23] At S-Se <0.50 μmol/L, glutathione peroxidase seizes to function.[32] The normal range for a Swedish population is 0.80-1.5 μmol/L. Delta Se (+) indicates an increase in serum selenium concentration from admission (day 0) to day 5, and Se (–) indicates a decrease in selenium concentration

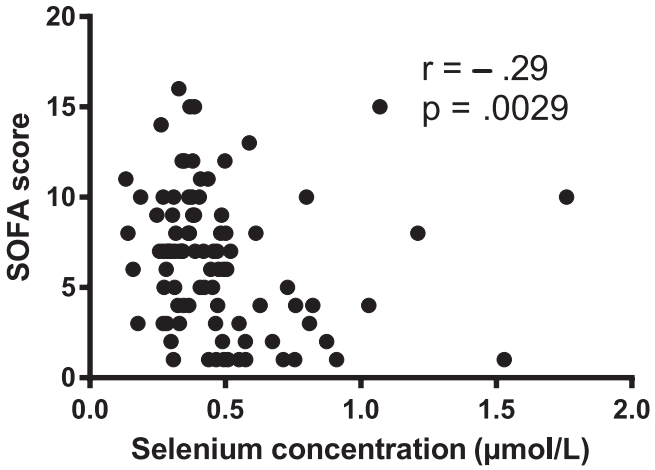

FIGURE 3 Admission data on the relationship between serum selenium concentration and SOFA (Sepsis Organ Failure Assessment) score in a mixed non-selected Swedish general intensive care population

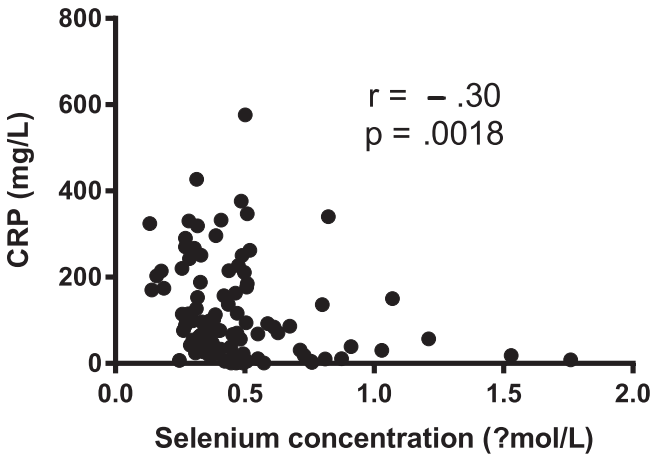

FIGURE 4 Relationship on admission between serum selenium concentration and C-reactive protein (CRP) in a mixed non-selected Swedish general intensive care population

for healthy Swedish subjects. Ninety-five percent of the patients had a S-Se of only 40% of the lower limit required for an adequate enzyme function. These results are comparable to recent data from critically ill Swedish neonatal and pediatric patients.[8] In addition, substitution of high-dose iv selenium to a Swedish ICU cohort proved to be feasible to restore S-Se without reaching toxic concentrations.

Assuming a slow flux between compartments and that low total body selenium is more common in Scandinavian populations as compared to comparable populations in central Europe may suggest a modified protocol for Se supplementation based on higher bolus dose and maybe higher and/or longer duration of treatment. Results from studies conducted in central Europe showed better outcome in patients who spontaneously restore S-Se back to normal within the first 3-5 days after admission, while sustained low S-Se was associated with a higher mortality rate.[9] The aim of any protocol would be to restitute S-Se within 3-5 days, which was accomplished in the present study. At the time of the study the routine protocol at the Karolinska Huddinge ICU was to provide Se supplementation in accord with the Angstwurm protocol.[18]

The major nutritional source for Se is via cereals and grain products. Thus, Se content in soil will be reflected in the Se status of the population. Scandinavia is meager in Se. Especially, elderly people with impaired nutritional status may be susceptible to low S-Se. This was shown in a non-critically ill Swedish population of >70 years of age. Alehagen et al[22,24] reported that the intake of Se was below the recommended daily allowance (RDA) of 50-60 μg,[32] and in the subgroup with S-Se <0.81 μmol/L, an increased risk for all-cause and cardiovascular mortality was found that persisted after adjustment for known risk factors.[22] These subjects were supplemented with 200 μg Se (Se-methionine) and coenzyme Q10 orally for 4 years and follow-up showed a 12% absolute risk reduction in mortality.[22] In a 12-year follow-up, this same group maintained a reduced cardiovascular mortality of 28% compared to controls with 39% (HR 0.59, 95% CI 0.42-0.81, P = .001).[25] Also, within normal range, there may be an association between S-Se and all-cause mortality. This was reported in

a review based on 13 887 individuals with different chronic disorders, such as, for example, cardiovascular, rheumatoid, endocrine, pancreatitis, and depression, followed for 12 years; an increase in S-Se up to 1.63 μmol/L was associated with a subsequent decrease in mortality.[33] The Swedish normal range for S-Se is 0.80-1.56 μmol/L,[30] compared to the United States, 0.89-1.90 μmol/L, which is rich in soil selenium.[31] Hurst and colleagues reported a requirement of at least 100 μg/d to saturate SEPP1.[34] This is 65%-100% more than RDA for Sweden.

Seventy percent of the patients in the current study was found to have a S-Se <0.50 μmol/L, considered the limit for loss of GPX1 activity,[31] and the study population was probably at the lower limit of body Se content. Septic patients from a selenium-rich region showed a S-Se in the same range at admission as in the current study,[6] and in a prior quality control study in our department. These Czech patients, however, exhibited a faster recovery of S-Se although substituted with only half the amount as compared to our patients. Since most patients recovered S-Se within few days,[6] this is likely to be explained by a redistribution from the body storages (biological inactive Se-methionine) to the blood stream. With saturated storages, the higher gradient for flux from storage to active compartments would be eased and recovery faster as compared to patients with a depleted selenium pool.

A recently published, randomized controlled multicentric trial showed no benefit for selenium supplementation, but rather a higher adjusted mortality in the supplemented group compared to controls, 33.3% vs 22.9%, respectively ($P < .03$), but without any information of response or no-response to the given substitution.[35] However, acute kidney injury was more common in the patients randomized for subsequent selenium supplementation ($P < .006$), and the 2 × 2 factorial study design assumed that procalcitonin and selenium did not interact is questioned.[35] Considering these biases, in a meta-analysis by Manzanares et al,[36] this study might have been given a too high weight. Most important, however, is that, this study includes patients in a geographic area high in selenium.[35] Furthermore, there was no analysis of whether selenium supplementation was beneficial for the cohort with the lowest S-Se at admission, which was the hypothesis suggested form the results of the earlier German study.[18]

Does low S-Se contribute to the severity of critical illness, development of organ failure and mortality, or is it a marker for severity of illness, or just marker for illness itself? Firstly, the level of severity of illness maybe assessed from the S-Se at admission as reported by investigations where Se level correlates to risk score models.[12] Secondly, the reduction in S-Se contributes to severity of illness, which is supported by several studies[6,8,18,37] and meta-analyses.[38-40] That does not mean that selenoenzymes in every compartment are desaturated. Knowledge about the redistribution between selenium storage and blood is largely lacking. Se replenishment by organic compounds (eg, Se-yeast and Se-methionine) is a slow process and targets albumin, erythrocytes, and storage.[41] Supplementation with the inorganic compound sodium selenite or selenate is rapid and redistribution into organic forms occurs within minutes. In chronically "Se-malnourished" patients, the Se pool is reduced and a situation of undersaturation of selenoenzymes may be expected. These patients have an increased urinary Se retention and organ distribution favors the most important Se-dependent functions.[41] To speculate, the transport of Se to tissue follows diffusion gradients influenced by transport proteins, mainly SEPP1, also considered to be the best biomarker for selenoenzyme expression and selenium status.[5,23] During supplementation in these patients, serum selenoproteins stabilize faster than the unstable S-Se indicating a flux to other tissues.[23] After a bolus of sodium selenite, Se is incorporated into selenoenzymes within minutes. In the critically ill offered high-dose supplementation, S-Se increases and stabilizes within days with a concomitant increase in GPX activity.[6,18,42] Effects on faster decrease, both of C-reactive protein and procalcitonin, have been described in supplemented patients compared to controls.[6] In contrast to most patients who spontaneously recover in S-Se within a few ICU days, a subgroup of 20%-25% may not recover and organ failures persist.[8] The septic patient with multiorgan failure is the one that seems to benefit the most from substitution. This finding is associated with low-serum GPX activity, which increases if Se is substituted.[18] To date, several studies have shown that Se supplementation in adults increases GPX activity,[6,18,42] and a study in children has shown that this is likely be coupled to selenium-dependent downregulation of GPX.[8] Thus, the patient subgroup, low in S-Se on admission with still persistent organ failures after a few dyas is probably the patients to target and who benefit the most from Se substitution.

The heterogeneity of ICU patients makes it necessary to include S-Se levels in the inclusion criteria and thereafter confine supplementation to those with infra-normal values and to dose the supplementation accordingly. Furthermore, such a randomized controlled trial should include geographical areas with both low and high selenium background. Finally, results should be evaluated in relation to success of supplementation.

A strength of this study was the inclusion of consecutive patients admitted to the ICU and the clinical characterization of the patients. Limitations were the small group, the single-center design, and the study design not including systematic observations of possible symptoms of selenium toxicity and post-ICU concentrations. In addition, the relatively small group that stayed in the ICU >5 days makes the results for secondary aim to monitor S-Se during supplementation over time less solid. The S-Se in the much larger German multicenter study, though, shows similar results.[35]

5 | CONCLUSIONS

In this critically ill study cohort from a Se-deficient area, S-Se was low at admission to the ICU. The prevailing serum concentrations were in most patients below the critical level for several selenoenzymes to function. After start of high-dose iv selenium substitution, all patients recovered S-Se within 5-10 days to levels corresponding to enzymatic saturation with no signs of serum concentrations outside the safe interval. To elucidate if high-dose selenium supplementation also provides morbidity and mortality benefits in critically ill, for example sepsis in regions meagre in selenium such as Scandinavia, is outside the scope of the present study. This calls for

randomized controlled clinical trials recruiting patients from geographical regions low and high in selenium and the evaluation of response to supplementation.

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CONFLICT OF INTEREST

LMB is a member of the Medical Advisory Board of Eurosets Srl., Mirandola, Italy; Medical Advisory Board of Xenios AG, Heilbronn, Germany; the EuroELSO Scientific Committee, and the EuroELSO Workgroup of Innovation and Technologies in ECLS, Newcastle upon-Tyne, UK; the ELSO Registry Committee, Ann Arbor, MI, USA; and the European ECMO Advisory Board, Pavia, Italy. LMB has received honoraries as a speaker for Evolan Pharma AB, Danderyd, Sweden, and Maquet/Getinge group, Solna, Sweden. IT is a Principal Investigator and is on the Advisory Board for the multicenter nutritional EuroPN study sponsored by Fresenius Kabi, Bad Homburg, Germany. No conflict of interest was reported for any of the other authors.

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