Monitoring nutrition in the ICU

Mette M Berger [1], Annika Reintam-Blaser [2,3]
Philip C. Calder [4], Michael Casaer [5], Michael J. Hiesmayr [6], Konstantin Mayer [7], Juan Carlos Montejo [8], Claude Pichard [9], Jean-Charles Preiser [10], Arthur R.H. van Zanten [11], Stephan C. Bischoff [12], Pierre Singer [13]

1. Service of Adult Intensive Care and Burns, Lausanne University hospital - CHUV, Lausanne, Switzerland
2. Department of Anaesthesiology and Intensive Care, University of tartu, Tartu, Estonia
3. Department of Intensive Care Medicine, Lucern Cantonal Hospital, Lucerne, Switzerland
4. Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, United Kingdom
5. Clinical Department and Laboratory of Intensive Care Medicine, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. michael.casaer@uzleuven.be
6. Division Cardiac-, Thoracic-, Vascular Anaesthesia and Intensive Care, Medical University Vienna, Waehringerguertel 18-20, A-1090 Vienna, Austria. michael.hiesmayr@meduniwien.ac.at
7. Universitätsklinikum Gießen Medizinische, Klinikstr. 33, 35392 Gießen, Germany. Konstantin.Mayer@innere.med.uni-giessen.de
8. Intensive Care Department. Universitary Hospital 12 de Octubre; Surgery Department, Facultad de Medicina, Universidad Complutense de Madrid; Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, España. jmontejohdoc@gmail.com
9. Clinical Nutrition, Geneva University Hospital, Geneva, Switzerland . Claude.Pichard@unige.ch
10. Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Belgium
11. Department of Intensive Care, Gelderse Vallei Hospital, Willy Brandtlaan 10,6716 RP Ede, the Netherlands. zantena@zgv.nl
12. Department of Nutritional Medicine/Prevention, University of Hohenheim, Fruwirthstrasse 12, 70593 Stuttgart, Germany bischoff.stephan@uni-hohenheim.de
13. Department of General intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Sackler School of Medicine, Tel Aviv University, Israel. pierre.singer@gmail.com

Corresponding author: Mette M Berger, Service of intensive care medicine and Burns
Lausanne University hospital (CHUV-BH08.612), Rue du Bugnon 46, 1011 Lausanne, Switzerland, Tel +41 21 31 42 095
Mail: Mette.Berger@chuv.ch

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Abstract:

Background and Aims: This position paper summarizes theoretical and practical aspects of the monitoring of artificial nutrition and metabolism in critically ill patients, thereby completing ESPEN guidelines on intensive care unit (ICU) nutrition.

Methods: Available literature and personal clinical experience on monitoring of nutrition and metabolism was systematically reviewed by the ESPEN group for ICU nutrition guidelines.

Results: We did not identify any studies comparing outcomes with monitoring versus not monitoring nutrition therapy. The potential for abnormal values to be associated with harm was clearly recognized. The necessity to create locally adapted standard operating procedures (SOPs) for follow up of enteral and parenteral nutrition is emphasised. Clinical observations, laboratory parameters (including blood glucose, electrolytes, triglycerides, liver tests), and monitoring of energy expenditure and body composition are addressed, focusing on prevention, and early detection of nutrition-related complications.

Conclusion: Understanding and defining risks and developing local SOPs are critical to reduce specific risks.

Key words: critical illness, energy balance, glucose, phosphate, standard operating procedures

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1. Introduction

Monitoring of the results of the medical interventions, and the achievement of the therapeutic goals that are needed to assess their success is required as follow up of most therapeutic interventions. No intensivist would imagine treating shock conditions with fluids and norepinephrine without measuring at least blood pressure to titrate therapy, and eventually using more advanced monitoring devices in the most complex patients. By analogy, in nutrition therapy, very simple tools are required for basic support during the first days, such as blood glucose and phosphate determinations, and more advanced tools and assessments will be needed in the complex long staying patients, such as indirect calorimetry and more advanced laboratory tests.

The metabolic response during nutrition therapy should be monitored for several reasons. The most important reason is that inappropriate nutrition therapy may harm patients, and alter physiologic equilibrium. An extreme example of a life-threatening complication related to the initiation of feeding is the refeeding syndrome (RS). Other less visible consequences are the metabolic, infectious, and muscular complications due to both under- or over-feeding, and to unbalanced nutrient supply such as insufficient provision of fat, electrolytes, or vitamins. Adequate nutrition largely depends on a structured approach involving protocols and standard operating procedures (SOPs) used for planning, initiation of nutritional therapy, and detection of complications. Further, as soon as therapeutic goals are defined, this implies the need for them to be monitored.

The main goals of monitoring of nutrition therapy in critical illness are:

- to assure that appropriate nutritional support is chosen and provided as planned and prescribed;
- to assure that estimated energy and protein requirements are met;
- to avoid or detect early any possible complication;
- to assess response to feeding;
- to detect specific electrolyte or micronutrient deficiencies in patients at risk due to special losses (e.g. drains, renal replacement therapy), or pathologies (e.g. major burns).

Reaching these goals in practice is complicated because of the lack of metabolic monitoring, and resulting limited availability of certitudes on macro-substrate needs. This issue becomes especially relevant in the new emerging category of "chronic critically ill patients" [1], requiring complex critical care therapy for more than two weeks, and up to several months. In these patients, the variable "time elapsed since the start of the acute disease" must be integrated into the monitoring process. The nutritional and metabolic data in chronic critically ill patients are sparse, challenging their clinical and metabolic follow up: the only certitude is that the body composition changes with a significant and rapid reduction of lean body mass, which in turn triggers modifications of energy expenditure and requirements. As it is nearly impossible to predict which patient is going to become a long stayer, these observations imply that clinicans should start being concerned already during the first days about the metabolic follow up as both over- and underfeeding contribute to complications. An expert group recently proposed priorities for research in clinical nutrition [2]. While nutritional monitoring has been addressed in a few reviews [3, 4], the issue of the metabolic response has not yet been addressed in guidelines. A recent study [3] addressed the question of the most frequently used indicators in the Australian and New Zealand specialists, and in the international community: the 8 most frequent indicators were by decreasing frequency: albumin, C-reactive protein, body weight (BW), organ functions core, nitrogen balance, serum creatinine and liver enzymes. The choices seemed to be guided by practical constraints, and low feasibility of more specific measures. The current position paper attempts to provide a better orientation about what is really useful and why, to complete the upcoming ESPEN-ICU guidelines and to assist future trials.

During the ESPEN-ICU guidelines expert group's meetings, it was decided that this topic needed to be addressed differently from the guidelines themselves. In the absence of data in the majority of the fields, a virtual round-table was chosen including all the members of the ICU guidelines group. The GRADE method [5] was not applicable, because there are no studies comparing the effect of a certain type or frequency of monitoring on outcome. Therefore, an adapted method was applied, including the search for literature in PubMed and the clinical skills and experise of the members of the group, that were requested to generate a text proposal, referenced whenever possible, that was then circulated within the group for approval.

2. Standard operating procedures (SOPs).

SOPs are a set of step-by-step instructions that aim to deliver care efficiently and reduce the risk of an undesirable event. SOPs may be assimilated to protocols, that assist professionals to carry out complex routine operations, while achieving efficiency and quality, and promote a common understanding, as every professional in the chain of care knows his/her role. SOPs are particularly important in the field of nutrition therapy, as several categories of healthcare professionals are involved. SOPs must be adapted to local possiblities, and should be established, followed, and audited in each department to avoid complications of nutrition. A simple example is a protocol describing the strict 30-45° elevated head-of-bed position procedure during enteral nutrition (EN) [6] to prevent aspiration of gastric contents. Table 1 summarises, for the most important nutrition oriented procedures including monitoring, the SOPs to be developed in each ICU with local adaptation.

In agreement with the 2017 recommendations by the ESICM [7], the general nutrition plan should propose that:

- if oral diet is not possible, patients should be considered for enteral nutrition (EN) within the first 48 hours
- EN should be initiated in the absence of contraindications [8]
- EN should be started slowly (10-20 ml/h) and progressed cautiously with monitoring of GI symptoms

Additionally, we suggest that:

- an initial maximum energy target in the acute phase (usually limited to 3 days after ICU admission) should not exceed 20 kcal/kg;
- a weight is defined for calculations. The reference weight is the “dry” predisease actual body weight for non-obese (BMI <30 kg/m^2), and adjusted body weight (aBW) for obese (BMI $\geq$ 30 kg/m^2) [9], where ideal body weight (IBW) is based on the Metropolitan Life Insurance (MetLife) tables.
- if EN progression does not succeed because of intestinal dysfunction, parenteral nutrition (PN), sole or combined to EN, should be initiated, at a timing proposed by the 2018 ESPEN ICU guidelines, i.e. 3 days of attempts.

3. Clinical monitoring

3.1 Gastro-intestinal symptoms

3.1.1. Abdominal examination: Daily assessment of GI symptoms, i.e. vomiting/regurgitation, abdominal pain, abdominal distension, absence/presence of stools, and aspect of GI contents [vomit, gastric residuals, stool] is essential for non-nutritional reasons [10], but also to detect intolerance to EN and trigger respective therapy (e.g. prokinetics, laxatives, postpyloric feeding). A systematic approach to management was summarized in 2012 [10].

3.1.2 Gastric residual volume (GRV) measurement has been widely used, but has become controversial since the randomised trial by Reignier et al [11] compared the provision of EN with and without measuring GRV: there was no difference in the incidence of ventilation-associated pneumonia [11]. However, before abandoning measurement of GRV, some aspects of this study suggest that generalising this strategy to all ICU-patients might not be safe. In the study, feeding had been initiated before study start, less than 10% of patients were surgical, all were mechanically ventilated, and vomiting occurred in 41.8% of patients with no GRV measurements versus in 26.5% in patients with (p=0.02). The ESPEN group's position is that events of vomiting should be minimized, particularly in spontaneously breathing patients with an unprotected airway (unless tracheotomised and canulized spontaneously breathing patients). Therefore, although frequent measurements of GRV in asymptomatic (regarding abdominal problems) patients with already installed full EN are obsolete, the strategy of not measuring GRV should not be generalized during initiation of EN and/or in patients presenting abdominal problems during EN. Importantly, in all patients, gastric overfilling should be avoided. An ultrasound evaluation of gastric filling may offer a good alternative to GRV measurements, but needs expertise and routine application. Spontaneously breathing patients with insufficient airway protection due either to neurologic dysfunction, muscle weakness, or dysphagia, need tight supervision: in these patients the prevention of vomiting and aspiration may be the difference between a good (or negative) ultimate outcome.

GRV volume measurement should be standardised. Two options are available:
- suctioning of the gastric tube with a syringe
- connecting a drainage bag positioned at the stomach level and observing for a period between 15 and 120 minutes.
The syringe method has the advantage that the interruption of the EN can be very short whereas this period may be quite long for the passive drainage method. Furthermore it is important that the period of drainage is standardised since the volume recorded may increase just due to the physiologic gastric secretion that is 100-200 ml/hour. Usually a short-term drainage (≅15 minutes) of 250 ml, or syringe volume > 300 ml is considered high, and triggers reducing or stopping EN until the scheduled control. Different centers, to avoid loss of enteral nutrients, recommend their nurses do reinject aspiration contents of 200 or 300 ml, then to discard the surplus. Considering the disagreable work it constitutes for the nurses, probably the lower value should be recommended, without evidence to support either value. Prolonged continuous drainage should be avoided because severe loss of chloride and alkalosis might be induced.

We suggest using X-ray to assure correct positioning of the nasogastric tube before initiating EN, as all alternative methods are subject to errors: Chest X-ray remains the gold standard [12]. Additional methods, such as a daily gas insufflation test, or the use of pH indicators, are required as the tube may be subject to secondary displacement.

3.1.3. Intra-abdominal pressure (IAP): Increased IAP is associated with occurrence of GI symptoms [13], but unlike clinical symptoms, it is a numeric variable facilitating interpretation of its evolution over time. In patients with pathologies at risk, a 6 hourly determination usually enables the detection of an incipient hypertension [14]. Increased IAP should not lead to the automatic discontinuation of EN, unless it is evolving into a clear abdominal compartment syndrome. However, great attention to the dynamics of IAP should be paid when increasing the volume of EN. Values reaching 20 mmHg should be considered as a limitation to EN start/progression [8]. In the future, the impact of different IAP protocols, and of IAP thresholds, on nutritional efficacy and prevention of complications of intra-abdominal hypertension (IAH) should be evaluated.

3.1.4. Dysphagia

Dysphagia is often present even after short periods of intubation (<48 hours)[15], and is a major risk factor for aspiration and ICU acquired pneumonia. Major risk factors are prolonged or repeated trans-esophageal echocardiography [16], muscle weakness, and neurological disorders. Diagnosis is frequently based on uncertain accuracy as shown by a large 2012 survey[17]. Dysphagia is diagnosed in two steps. First a scoring system from observation during water swallowing is used. Several scores exist: the simplest is a 4 point scale, ranging from 0 = no dysphagia, to 4 = no passage, and unable to swallow anything [18]. In a second step a functional analysis is performed by an otorhinolaryngologist or logopedic services [19]. This includes direct visualisation of swallowing of fluid with different textures by video-endoscopy. In patients with dysphagia, logopedic training and reassessment every 3 - 5 days is necessary. The presence of a gastric feeding tube reduces the efficacy of the swallowing training, due to the disturbed sensory feedback [20], a period of PN may be considered to allow optimal training to swallow without nasogastric tube may be considered.

In summary, we recommend that the clinical follow up of EN integrates:

- *assessment of clinical symptoms of GI dysfunction at least twice daily*
- *monitoring of gastric filling on a regular basis with clinical investigation, completed by ultrasound or measuring of gastric residual volumes*
- *measuring of intra-abdominal pressure (IAP) in case of clinical signs of abdominal distension and of massive fluid resuscitation [14].*
- *Detection of dysphagia after extubation*

3.2. Delivery of nutrients: volumes, energy and proteins

Monitoring of the delivery of energy and substrates may be best performed with a computerized system [21], taking into account different routes as well as non-nutritional calories [22]. Such a system facilitates an adequate and complete overview of nutritional therapy for ICU physicians who are often focusing on physiological parameters and less on nutritional management [23]. It also helps

assessing the amount of calories that are provided by sedatives (lipids) and drug dilution fluids (glucose) [24, 25].

Underfeeding: It has repeatedly been shown that there is a gap between the prescribed quantities and those really delivered to the patients, particularly with oral diets or EN [26]. Therefore, daily assessment of the provided volume of feeds enables the calculation of energy (kcal) and protein delivery, and should be a standard procedure [26, 27]. Underfeeding may be even more a concern after ICU discharge, warranting continuity in nutritional management and monitoring beyond the ICU [28, 29].

Overfeeding: This is defined as delivery of more than 110% of requirements, ideally of measured energy expenditure (EE) [30, 31]. Due to the ease of administration of PN, the risk of overfeeding is highest with this technique, especially if used in combination with EN or oral diet [31]. Overfeeding occurs independently of previous energy deficit: “Catch-up feeding”, i.e. attempting to compensate for a deficit that has build up over several days, should not be attempted as it is rapidly associated with alterations of liver function tests and hyperglycemia. On the other hand increasing feed delivery for short periods (hours) to compensate for interruptions (e.g. procedure-related) can be done [32].

The combination of hyperglycemia, high insulin dose for glucose control, high minute ventilation and hypercapnia should always trigger checking for the adequation of level of energy intake. The heart and the lungs are key organs in patients who have been underfed for a variable period: the nutrients given may exceed the transport capacity of the heart and the CO_2 elimination capacity of the lungs. Symptoms of heart failure or ventilatory insufficiency may indicate that the progression to full nutrition is too fast or that estimated energy goals are too high. In patients with early hypophosphatemia a more careful stepwise increase in the amount of nutrients, called “restricted caloric intake” was associated with a survival benefit [33].

Protein: There is uncertainty regarding optimal protein requirements in critically ill patients [34]. Measuring serum levels of proteins is unreliable because protein levels in blood are affected by acute illness [35] and inflammation [35]: most visceral proteins decrease under these conditions. Measurement of amino acid levels is not a

routine practice: currently available data do not allow recommendations for their use for clinical prescription. Protein loss estimation can be used as a rough guide for adjustment of protein supply.

Protein monitoring tools are limited to a rather imprecise appraisal of daily nitrogen balance based on urinary urea determination. This method gives only an estimate because loss as ammonia is not considered and loss from stool and skin is difficult to estimate. Urine collection over 24 hours can be difficult and is time consuming. The typical nitrogen loss is 100-150 mg/kg/day from urine. Multipled by 6.25 the corresponding protein amount can be calculated. If protein intake is stable, the maximum loss is observed during the first week, and losses decrease thereafter [36].

Depending on the composition of the available feeding solutions which have a fixed composition, protein delivery may be far below the recommended 1.2 - 1.3 g/kg that is considered appropriate in the majority of ICU patients [37]. Recently, based on the rationale that protein catabolism exceeds synthesis in the critically ill[38], the use of higher protein amounts up to 2.5 g/kg has been proposed [39], while other authors have hypothesized that caloric and protein overload in the acute phase of illness suppresses autophagy and may therefore contribute to development of critical illness myopathy [40]. Hence, the therapeutic window is narrow and requires monitoring. The last years have seen positive results from observational studies [41]. One trial was focused on early amino acid administration in patients at risk for renal failure [42], while a second trial combined early enhanced protein and energy (EAT-ICU) [43]. When the focus is put on calorie progression, special attention should be paid to the achievement of appropiate protein delivery.

An excessive supply of amino acids or protein will increase urea and ammonia production. Elevated urea and ammonia concentration may have several causes such as impaired kidney or liver function: the differential diagnosis should include the possibility of an excessive nitrogen supply, and significant tissue catabolism should be considered. Ammonium measurement should be done when increased nutrition is associated with deteriorating level of consciousness. It may also enable the detection of rare but life-threatening inherited errors of metabolism [44].

4. Monitoring laboratory variables

Studies comparing clinical outcomes in measuring versus not measuring laboratory parameters are not available. The variables addressed below have been associated with clinical complications and poor outcome, and should be considered as part of nutritional monitoring. Table 2 summarises the bundle of recommended variables to monitor and their relative cost reported to an ICU day's cost.

4.1. Blood glucose and insulin requirements

The last two decades have seen many studies showing that the management of blood glucose control is a cornerstone in the care of critically ill patients: hypo- and hyperglycemia are both associated with poor outcomes and mortality, fitting a U-shaped curve [45]. But the reporting and assessment of blood glucose lack standardization [46], as different methods of blood glucose concentration determination, different goals and management schemes have been used, and different performance in management has been achieved [47]. This disparity complicates the interpretation and comparison of clinical trials and achieving recommendations for a detailed optimal management strategy.

The foremost goal remains the security of the patient. During the first 24 hours, blood glucose measurements should be carried out at least 4-hourly based on data from randomized controlled trials [33, 48, 49]. Samplings that are even more frequent might be required in unstable patients, whereas frequency may be decreased after stabilization, usually after 48 hours. Blood glucose needs a tighter monitoring when nutrition is interrupted either for interventions, or on a regular basis.

However the target used for blood glucose control in most critical care patients is a concentration of 6 - 8 mmol/l (110 - 145 mg/dL), knowing that some societies recommend to simply keep blood blucose <10 mmol/L. The choice of the goal depends on the available measuring techniques, nurse staffing and expertise and nutritional regime [34, 50, 51]. Spontaneous hypoglycemia (occurring in the absence of insulin therapy) is an alarming clinical sign often reflecting liver failure, acute sepsis, or sometimes adrenal insufficiency.

Although high insulin needs most often reflect disease severity and insulin resistance [52], monitoring insulin needs may reveal accidental overfeeding reflected by an increasing cumulative 24 hour dose.

4.2. Phosphate

Phosphate is the major intracellular anion necessary for many biological processes especially for ATP regeneration from ADP but also for glycolysis, intracellular buffering and building of cell membranes. Hypophosphatemia is clinically associated with decreased cardiac function and arrhythmias as well as ventilatory insufficiency. Low and high phosphate values are both associated with excess mortality following a U-shaped curve form [45] (Figure 1a). Hyperphosphatemia mainly occurs with renal failure and may lead to hypocalcemia causing hypotension. Hypophosphatemia may be induced or aggravated by administration of insulin to achieve tight glucose control, and may be an indicator of a refeeding syndrome caused by entry of phosphate from the extra- to the intracellular compartment. Hypophosphatemia is also frequently caused by continuous renal replacement therapy (CRRT). Hypophosphatemia typically has two peaks in ICU patients. The first peak of frequency is during the first 12 hours after ICU admission even in the absence of any nutrition and the second 3-5 days after the start of artificial nutrition [33, 53]. While levels <0.3 mmol/l are considered a concern outside of the ICU, values <0.6 mmol/l should be of concern in the ICU as shown by Figure 1a.

Sampling routines should include the risk profile (starvation, use of diuretics, alcohol abuse): we suggest an early measurement 6 - 12 hours after admission, and thereafter daily for the first week. Daily measurement can be decreased to twice weekly if patients are stabilised, the nutrition target is stable and no CRRT is in use [33, 53]. For details, please see the upcoming ESPEN guidelines about refeeding.

Overlooking the rapid development of severe hypophosphatemia may lead to death after initiation of feeding, as patients admitted to the ICU are often malnourished either before or during admission to the hospital. Missed dyselectrolytemia might explain the dramatic increase in early mortality associated with intensive feeding in the INTACT trial including patients with acute lung injury and not fed for 6-8 days prior to the intervention [54, 55]. Even when meticulously monitoring and providing electrolytes, full early feeding may increase mortality in patients with an early phosphate decrease upon initiation of feeding [33]. Two

publications suggest that the harm by full early feeding in such patients goes beyond dyselectrolytemia [56, 57].

4.3. Other electrolytes: potassium, sodium, chloride and magnesium

Fluid and electrolyte balance is often poorly understood, and given limited attention, while inappropriate prescribing can cause increased morbidity and mortality [58]. All these electrolyte abnormalities are important to be detected, corrected and further monitored as they are associated with subsequent organ failure [59].

Potassium: Potassium is the most abundant monovalent intracellular cation and is the main contributor to the electro-chemical gradient across the cell membrane. A potassium < 3 mmol/l is considered to be severely low in adults. The most severe features are cardiac arrhythmias, but many other systems are also affected. Gastrointestinal symptoms include ileus and constipation, the kidney has impaired concentration capacity, compensation of metabolic alkalosis is delayed, neuro-muscular function is impaired but also endocrine function is affected with impaired glucose tolerance. While both hyper- and hypokalemia can be life-threatening because of cardiac arrhythmias, only hypokalemia is nowadays related to a severe nutritional complication, namely the refeeding syndrome, whereas hyperkalemia is frequently associated with acute and chronic renal failure (Figure 1.B). Potassium should be part of standard monitoring in all critically ill patients.

Hypokalemia may be induced or aggravated by administration of insulin to achieve tight glucose control (particularly dangerous if blood glucose levels are guided by point of care glucometers not measuring potassium simultaneously, rather than blood gas analyzers) [60]. Increased potassium losses through the GI tract may lead to severe hypokalemia; this may occur in a state of paralytic ileus, not only with diarrhoea.

Sodium: Sodium is the major extracellular cation, is associated with volume regulation and is one of the most tightly regulated electrolytes in humans. Both hypo- and hypernatremia occur in the ICU and are associated with poor outcome

(Fig.1.C). Hyponatremia occurs in the context of fluid overload [61], while hypernatremia has multiple etiologies [59] including being of nutritional origin.

Chloride: Chloride is the major extracellular anion, and is associated with sodium and acid-base disturbances. Patients with large drainage of gastric fluid may loose chloride and develop hypochloremic alkalosis. Accumulation of unmeasured anions such as ketones, citrate or acetate should be suspected in patients with an increased anion gap.

Magnesium: Hypomagnesemia may occur along with the refeeding syndrome, and may trigger or aggravate arrhythmias. Hypermagnesemia may occur in with the context of renal failure.

Normal values of K and Mg help preserve bowel motility, whereas low values may contribute to development of paralytic ileus.

4.4. Liver function tests (AST, ALT):

There are multiple reasons for alterations of liver function tests in critically ill patients, mainly sepsis and shock, but this may also reflect incipient overfeeding. Grau et al. showed that administration of energy exceeding 26-28 kcal/kg/day by any route was associated with liver dysfunction (defined as cholestasis or more than 10% increase in liver enzymes, bilirubin or INR from previously normal values) [62]. These data support the regular monitoring of liver function, but particularly cytolysis tests, to assist in early detection of possible overfeeding [62]. Recently, alpha-glutathione S-transferase (alpha-GST) has been suggested to be an even more sensitive marker of liver function and should possibly be included in the monitoring in the future [63, 64]. In children with long-term PN increases in liver enzymes and cholestasis where found to be reversible when LCT based fat solutions were substituted by fat solutions providing omega-3 fatty acids [65].

4.5. Triglycerides

Hypertriglyceridemia in the ICU is associated with sepsis, administration of propofol, lipid solutions, and overfeeding [66]. Therefore, rising triglyceride levels should trigger immediate re-evaluation of substrate delivery searching for a

454 selective lipid overfeeding especially when propofol [25] and lipid emulsions are
455 administered concomitantly. Importantly, not only lipids, but also overfeeding with
456 excess carbohydrates will lead to fatty liver due to stimulation of *de novo*
457 lipogenesis. Concentrations of triglycerides exceeding 500 mg/l (5.6 mmol/L),
458 levels that are considered very high in non-critically ill subjects, should trigger
459 prompt investigation [66].

460 Of note, the regular determination of blood cholesterol (total or HDL) has never
461 been shown to be of relevance during critical illness [67].

462

463 **4.6. Urea**

464 Dickerson et al. showed that older obese patients may develop higher blood urea
465 levels with similar nitrogen balance when compared to younger adults [68]. In
466 patients with renal failure with conservative management (decision against renal
467 replacement therapy), reduction of protein intake might be considered if blood urea
468 increases beyond 30 mmol/l (85 mg/dl), with a starting concern >20 mmol/l (55
469 mg/dl) without hard evidence. However, this approach is probably justified only if
470 uremia is caused by (protein) overfeeding (i.e. >1.5 g/kg): nitrogen balance studies
471 have shown that increasing intakes would increase plasma urea [69]. Otherwise the
472 negative effects of underfeeding may outweigh the negative effects of uremia.
473 Moreover, differential diagnosis of elevated uremia includes a search for a prerenal
474 mechanism of renal dysfunction. The EAT-ICU trial applied an advanced protein
475 titration protocol based on correcting nitrogen balances, yet reducing protein
476 administration when blood urea increased [32]. Nevertheless, early protein/energy
477 administration dramatically increased blood urea levels. Similar patterns of
478 increased ureagenesis have been found with additional amino acids in the
479 Nephroprotective trial [42]. Whether increased urea levels reflect an additional
480 metabolic burden, remains to be unravelled. Very recently, increased glucagon,
481 driving hepatic amino acid breakdown was identified as a possible explanation [70].

482

483 **4.7. Albumin**

484 Low albumin was for a long time erroneously considered to be a marker of
485 malnutrition [35]. It is a marker of severity of disease, when observed upon

admission to the hospital. Albumin is a low turnover protein with a half-life of 15 days and a replacement of 3% per day that cannot explain a decrease by up to 30% within 1-2 days of critical illness. Low albumin in critically ill patients is mainly caused by redistribution to the extracellular space from the intravascular compartment or by losses due to major bleeding: hypoalbuminemia < 20 g/L is associated with a reduction of oncotic pressure: the correction of low oncotic pressure is the only indication to albumin infusion in the absence of liver failure with ascites [71].

4.8. Transthyretin (Prealbumin)

An isolated low plasma prealbumin does not enable the diagnosis of malnutrition as it is influenced by inflammation [72]. But it is helpful in the assessment of response to nutritional therapy [73]. Repeated measurement once weekly may provide information even with high inflammation, and requires the simulatenous determination of C-reactive protein.

4.9. Glutamine

Ordinary food and commercial artificial feeding solutions are not a sufficient supply of glutamine (GLN) for the patient with multiple organ failure in the ICU, as requirements are increased. A low plasma concentration of glutamine at ICU admission has repeatedly been shown to be an independent risk factor for post-ICU mortality [74]. On the other extreme, very high glutamine levels are also associated with poor outcome [74]: therefore blind administration of GLN should not be undertaken.

The majority of ICUs do not receive rapidly the results of blood GLN determinations, but a point-of-care instrument used in cell culture studies has recently been validated for bedside use in the ICU setting and compared with a standard HPLC technique to measure plasma GLN: the instrument may be useful in order to identify patients with low or high glutaminemia. The accuracy of this instrument was high enough for safe supplementation of GLN to patients with low plasma values [75].

Such blood GLN determination, i.e. monitoring, should probably be considered in patients on prolonged CRRT (more than 2 weeks), as GLN freely passes the

membranes in proportionnaly larger amounts than other amino acids [76]. An RCT evaluating this strategy in this specific population will be of very high clinical relevance.

4.10. Markers of intestinal function

Two biomarkers may assist detection of intestinal dysfunction, but their use in routine practice could not be advised at this stage.

Citrulline is an amino acid synthesized almost exlusively in the intestinal mucosa. The plasma citrulline concentration has been shown to be a marker of the functional small bowel enterocyte mass [77], and, in patients with short bowel, of the capacity to survive independently of PN. In a study including 20 critically ill patients, citrulline concentration was not predictive of intestinal absorption function for example of glucose [78].

I-FABP (fatty acid binding protein) was investigated in a cohort of 134 multiple trauma patients[79]: sensitivity and specificity to detect abdominal injury was 78% and 62%. Clearly, more studies are required.

4.11. Micronutrients

4.11.1. Continuous renal replacement therapy (CRRT)

Due to the losses with the effluents of small water soluble molecules, prolonged need for CRRT (i.e. more than 2 weeks) will cause the loss of significant amounts of essential micronutrients, resulting in severe acute depletion. Deficiencies will need to be replaced to prevent metabolic complications. These acute deficiencies go undetected if not systematically searched for, and may be responsible for life threatening complications.

Among vitamins, thiamine and ascorbic acid are also lost in large amounts in the effluents. Carnitine is also lost which may produce severe alterations of lipid and energy metabolism at the mitochondrial level [80]. While all trace elements are lost, copper losses are particularly elevated and important [81], and may lead to life-threatening cardiac, immune and wound healing complications [82]. The biochemical consequences of the losses start appearing after 2 weeks of CRRT, and analytical

549 invstigations should be considered in case of cardiac, pressure sore and wound
550 healing deterioration.

551

552 **4.11.2. Major burns**

553 Another condition exposing to acute micronutrient deficiencies is major burns (i.e.
554 those exceeding 20% body surface): these are associated with large exudative
555 losses that contain significant amounts of Cu, Se, and Zn. Early i.v. repletion has
556 become a recognized strategy as it results in reduction of infectious complications
557 and improved wound healing [83, 84]: repletion is recommended by American and
558 European societies [85]. In the absence of a systematic repletion strategy, a weekly
559 determination of these elements should occur at least in patients with burns
560 exceeding 40% of body surface. In major burns, it has been shown that such
561 investigations will enable the detection of pathologically low values [86].

562

563 **4.11.3: Prolonged EN**

564 Enteral feeding solutions ensure the provision of recommended daily intakes (RDI)
565 of micronutrients provided more than 1500 kcal are delivered per day. As to PN,
566 the multi-component trace element and vitamin solutions, produced in a “one size
567 fits all” form, usually cover the daily recommended intakes of adult subjects.
568 Specific conditions with additional needs are discussed below.

569 Several studies have shown that in patients needing EN lasting for 6 months and
570 more, trace element deficiencies may develop, in particular of Cu and Se, leading
571 to repeated infections. Measurement of blood levels might contribute to the
572 differential diagnosis of clinical deteriorarion.

573

574 **5. Monitoring energy expenditure and body compostion**

575 **5.1. Indirect calorimetry - Energy needs**

576 Energy expenditure (EE) may be highly variable and change during the course of
577 critical illness [87, 88], therefore requiring re-evaluation of prescribed energy targets,
578 with monitoring the patient’s evolution. As predicted (calculated) energy targets are
579 highly inaccurate, particularly in obese patients [89, 90]. Zijlstra et al. showed a large

variation in EE between patients, but no wide variations within individual patients over the course of a day [91]. On the other hand, Kreymann et al. showed that in patients with septic shock, the EE changes between the different phases of disease may be quite large [88].

Measurement of EE should be performed at least in patients requiring intensive care for more than a week. A single indirect calorimetry study is therefore not sufficient: calorimetry should be repeated in patients staying for longer periods due to the decrease in lean body mass such as is the case in chronic critically ill patients (>21 days in ICU) [6].

Some energy delivery deficit in the acute phase (first 72 hours) of critical illness is probably desirable to accommodate the endogenous energy production and avoid overfeeding from the sum of exogenous plus endogenous substrates [92, 93]. But the extrinsic deficit, i.e. from feeding as opposed to endogenous production, should remain moderate. In the course of illness, monitoring of the ratio of provided to prescribed calories and protein is important to trigger immediate measures optimizing provision and minimizing unnecessary interruptions in nutrition to avoid further continuing deficit. Three studies (2 observational studies [94, 95] and one randomized trial [92]) indicate that the cumulative extrinsic energy balance after ICU admission beyond which energy-deficit related complications start increasing, is around -4000 kcal (or -50 kcal/kg). In a large observational study, definining their high-risk ICU patients on the basis of the NUTRIC score which combines APACHEII and SOFA scores, reaching EN >80% of target was associated with lowest mortality, whereas no such correlation was found in the low-risk patients [96].

5.2. Body composition: Bioimpedance analysis (BIA) and phase angle

BIA enables the determination of fat, and fat-free components of the body, but fluid resuscitation complicates the analysis particularly of the fat free mass. Recently it was shown that the calculation of the phase-angle might be more useful than complete body composition [97], as it reflects fat-free mass and cellular integrity. Loss of the lean body mass was associated with worse prognosis in chronic diseases and in critical illness as shown by this recent multicentric trial including 931 patients. There is still no information as to how frequent such determination

should be, but it might also be useful to observe the evolution of the fat mass, especially in the chronic critically ill.

Muscle mass determination by ultrasound and CT-scanner at the 3rd lumbar level (L3) [98], although very useful for diagnosis of sarcopenia in cancer patients [99], has not yet been validated as a monitoring tool for nutrition in critical illness. This is also the case for dynamometry which requires alert patients [100].

6. Conclusion

Clinical nutrition is an important part of critical care. Artificial nutrition has evolved from a support tool into a therapy that requires close attention and monitoring. As with any therapeutic strategy, only appropriate monitoring allows achieving safety and desired effect, especially in the most vulnerable patients such as the old, frail and malnourished patients. As effects of nutritional interventions are often hidden or delayed, standardization of monitoring becomes even more important. The use of a defined monitoring strategy involving SOPs and relevant laboratory tests is a further step into individualisation of nutritional therapy, and improving the definition of research goals.Importantly, we are still missing tools to determine the magnitude of endogenous glucose production, particularly in the early phase of acute illness: a similar gap also exits for indicators of protein and lipid metabolism. Research is warranted in this area.

Legends to the figure

Figure 1: Association between minimum (blue) and maximum (red) serum electrolyte concentrations during the ICU stay and hospital mortality in 6323 patients after major cardiothoracic surgery (34% women, median age 66 years, length of ICU stay 4 days) treated in the cardiothoracic ICU of the Medical University Vienna between 1999 and 2015.

A: Serum phosphate

B: Serum potassium

C: Serum sodium

643 **Table 1:** Minimal set of nutrition oriented standard operating procedures (SOPs)
644 for any ICU
645

Procedure	**Aimed impact**
Screening for nutritional risk and malnutrition using Nutritional Risk score (NRS-2002) using a cutoff of 5 points [Less efficient: subjective global assessment (SGA) or mini-nutrition assessment short form (MNA-SF)]	Detect the patients who are in need of special metabolic and nutritional attention Detect patients at risk of refeeding syndrome to initiate a progressive feeding strategy and intensify P, K and Mg determinations [33, 101, 102]
Placement of nasogastric tubes	Assure correct position of the tube before initiating EN (gold standard is X-Ray [12])
Feeding protocol for enteral and parenteral nutrition	Standardized nutritional therapy
Energy target determination and reevaluation	Individualized adaptation of energy delivery
Protein target determination	Particular attention to protein needs to cover 1.2 to 1.3 g/kg/day (NB: kcal from proteins is included in total energy count)
Blood electrolyte protocol: phosphate and potassium sampling 2 times/day during first 48 hours of feeding and Na, Cl, Mg, once daily	Detect electrolyte abnormalities associated with poor outcome
Refeeding syndrome management	Achieve optimal management of electrolytes (phosphate and potassium) and vitamins when disturbances are detected. Consider slow build-up of caloric and protein provision
Prevention of aspiration:	
Bed head tilt up 30-45° [6]	Prevent bronchoaspiration during EN
Assessment of gastric filling by ultrasound [103], or measurement of GRV in patients during initiation of enteral feeding, particularly with unprotected airway	Prevent bronchoaspiration due to gastric overfilling
Enteral access protocol: Consideration of postpyloric feeding with persistent large GRV on gastric feeding Consideration of percutaneous access with prolonged feeding	Improve feeding efficiency
Bowel management protocol	Prevent both constipation and diarrhea
Blood glucose control and insulin infusion protocol	Prevent hypo- and hyper-glycemia
Daily assessment of feed volume delivery	Prevent underfeeding
Patient weighing	Follow-up of fluid mediated weight gain and weight loss

646 Abbreviation: GRV = gastric residual volume

Table 2: Recommended blood and urinary laboratory determinations, proposed frequency, cost, and relative cost: the latter enables comparison between countries and is based on the Swiss average ICU day cost (4000 CHF/day) *.

Variable	Frequency	Relative cost index
Glucose	First 24 hr of ICU admission /feeding : every 4-6 hrs Later: at least 2 times daily	0.6 ‰
Phosphate	Within first 6-12 hr of admission Later: once a day	0.8 ‰
Potassium	First 24 hr of ICU admission /feeding : every 6 hr with blood gases	0.7 ‰
Sodium, Chloride, Magnesium	Once daily	0.6 and 2.1 ‰
Liver tests: AST, ALT	Twice weekly	2 ‰
Triglycerides [66]	Twice weekly	0.7 ‰
Prealbumin	Once weekly	5 ‰
Glutamine	In selected cases (renal remplacement therapy, burns, PN without glutamine)	3 ‰
Trace elements: Cu, Se, Zn	In selected cases (such as e.g. burns, addressed in the text)	11, 26 and 17 ‰
Urea – blood	3 times weekly	0.6 ‰
Urea – urine	6-hr urine collection once weekly in absence of renal failure	0.7 ‰
Ammonium	In case of unexplained worsening of consciousness state [44]	10 ‰
Carnitine	Considering the limited availability and cost, to be done only in presence of unexplained rapid muscle catabolism and hyperlactatemia [80] with adequate protein supply	51 ‰

Based on Swiss prices [104] on 1.1.2018 (1 CHF = 0.85 €)
*: an approach comparable to the "Big Mac Index" which is an informal way of measuring the purchasing power parity between currencies, first introduced by the Economist (https://www.economist.com/content/big-mac-index)

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