Feeding should be individualized in the critically ill patients

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Purpose of review
Any critical care therapy requires individual adaptation, despite standardization of the concepts supporting them. Among these therapies, nutrition care has been repeatedly shown to influence clinical outcome. Individualized feeding is the next needed step towards optimal global critical care.

Recent findings
Both underfeeding and overfeeding generate complications and should be prevented. The long forgotten endogenous energy production, maximal during the first 3 to 4 days, should be integrated in the nutrition plan, through a slow progression of feeding, as full feeding may result in early overfeeding. Accurate and repeated indirect calorimetry is becoming possible thanks to the recent development of a reliable, easy to use and affordable indirect calorimeter. The optimal timing of the prescription of the measured energy expenditure values as goal remains to be determined. Optimal protein prescription remains difficult as no clinically available tool has yet been identified reflecting the body needs.

Summary
Although energy expenditure can now be measured, we miss indicators of early endogenous energy production and of protein needs. A pragmatic ramping up of extrinsic energy provision by nutrition support reduces the risk of overfeeding-related adverse effects.

Keywords
clinical outcome, critical illness, energy balance, nutritional needs, protein marker

INTRODUCTION

As the simplest procedures have the largest chance of being applied successfully, it is tempting to imagine that all patients could be fed alike through the intensive care (ICU) stay, using fixed weight-based equations to calculate energy goals. But to hypothesize that all critically ill patients have similar requirements, or that their needs stay stable through the ICU course, equals considering that a teenager and a centennial can thrive on the same energy and substrate intake. This is obviously not the case. Hippocrates already new that the energy, macronutrients, and micronutrients needs differed over life periods. More detailed age and gender requirements have been established during the 20th century by international organisations [1].

The age of patients admitted to an adult ICU ranges from 16 years to over 100 years, a difference, which results in major metabolic differences, which have been verified by multiple metabolic studies using indirect calorimetry in healthy individuals [2] and in patients [3]. Further, the patients admitted to the ICU suffer a variety of disorders that affect their metabolic rate differently. A hemiplegic stroke patient with minimal muscle activity does not compare with an agitated young trauma patient, a patient with massive burns (Fig. 1), or a shivering febrile patient. The type of mechanical ventilation and the depth of sedation also modifies energy expenditure, the controlled modes reducing it by about 10% but in an uneven way [4]. Numerous studies have shown that both underfeeding and overfeeding are deleterious as they promote additional catabolism, or generate immune and metabolic impairments [5▪▪], respectively.

These observations lead to the conclusion that precise measurement of energy needs is required to tailor nutrition support with the aim of optimizing

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KEY POINTS

- Critically ill differs from healthy by several aspects including the fact that the endogenous energy production that occurs in healthy during fasting, is not suppressed by exogenous feeding in inflammatory critically ill patients: it is maximal during the first 3–4 days.
- Ramping up feeding during the first days after ICU admission enables a metabolic adaptation, and avoid the side effects related to immediate full feeding (early overfeeding, intestinal intolerance).
- Repeated indirect calorimetry studies enable assessment of the changing energy expenditure resulting from the combination of changes in metabolic status, loss of lean body mass and from physical activity.
- Optimal protein prescription remains difficult as no clinically available tool has yet been identified reflecting the body needs.
- Indicators of early endogenous energy production and of protein needs are still missing in clinical setting.

clinical outcome during the ICU stay. If this step is successful, it would pave the way to a better recovery after the acute episode.

The aim of the present review is to discuss the available options. The first part addresses the issue of the individual energy requirements, based on indirect calorimetry determinations. The second part focuses on the substrate needs, that is, protein carbohydrates and lipids to optimize the nutrition support.

ENERGY NEEDS

Determinants of resting energy expenditure

In 2003, Peter Rich calculated the cost of living, that is, of producing ATP [6]: depending on the intensity of physical activity and the related O_2 consumption, there was an irrepressible minimum of energy needed. On the basis of a standard adult male consumption of 380 l O_2/day, Rich calculated that ATP must be reformed at a rate of 9×10^{20} mol/s to ensure the mitochondrial transmembrane proton flux

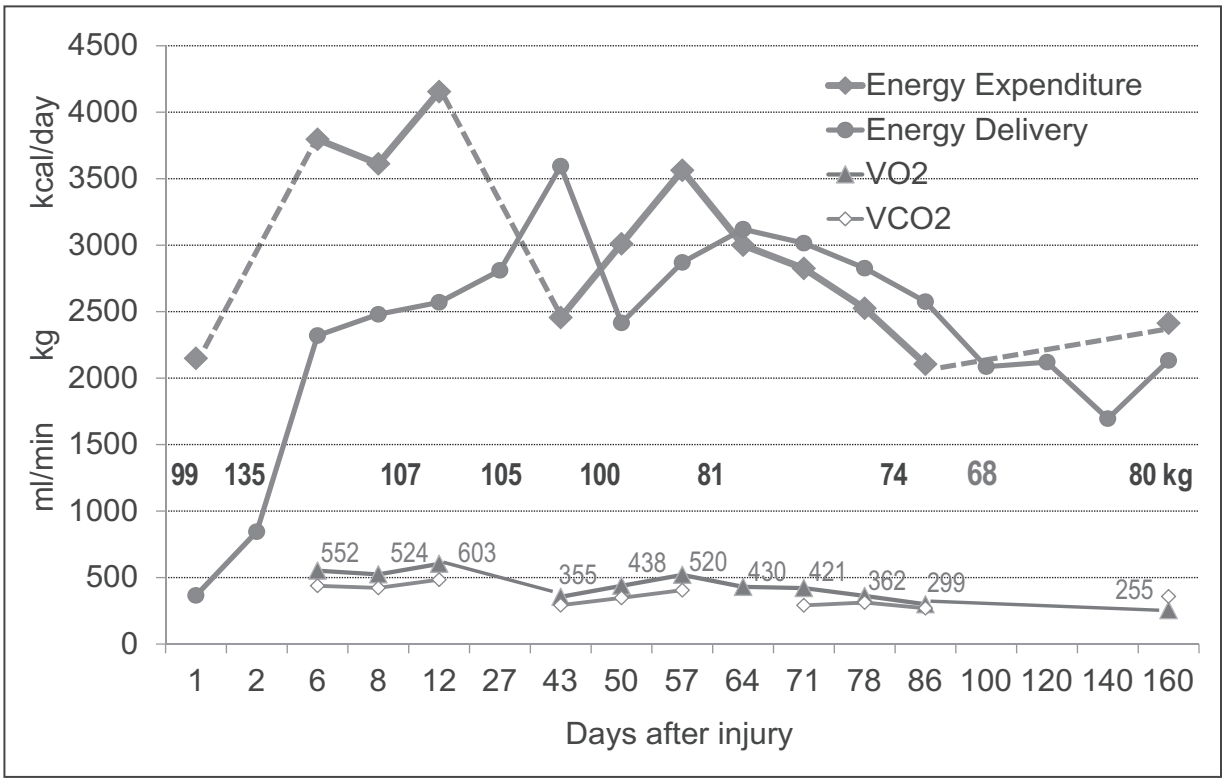


FIGURE 1. Evolution of measured energy expenditure, VO_2 and VCO_2 in a young man weighing 99 kg upon admission with major burns covering 85% body surface. The energy expenditure variations were important over time particularly during the early phase, and paralleled the loss of body weight, that is, of lean body mass. The energy expenditure value on day 1 corresponds to the Harris and Benedict prediction of basal energy expenditure. Also shown that despite availability of measured energy expenditure, the energy delivery was inferior to it for 2 weeks.

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Table 1. Relative organ weight and oxygen consumption (VO_2) in a 70 kg adult human: whereas the muscles have a low VO_2, their important mass makes them the predominant O_2 consumer

Organ	Mean weight (g or kg)	Blood flow (ml/min)	VO_2 (ml/min)	Percent of total VO_2
Brain	1300–1400	750	47	20
Liver	2000	1400	67	20
Intestine	3500			5
Heart	300	250	46	10 (may ↑ 4 times)
Kidneys	200–300	1100	16	10
Muscle	25–35 kg	1200	70	30 (may ↑ 20 times)
Skin	3.5–4 kg	500	5	2 (may ↑ 4 times)
Other	24 kg	600	12	4
Total	70	5800	234	100

Adapted from Bioénergétique. Leverve X, Péronnet F, Fontaine E. In Traité de nutrition Clinique 2016, p. 46.

(3×10^{21} protons/s), which equals an ATP production similar to the subject's body weight.

Oxygen consumption, that is, energy expenditure is mainly driven by the muscle mass, representing 30% of the body's oxygen consumption (Table 1). The skeletal muscle has a low VO_2 per gram of tissue compared with the brain, but its important mass results in the muscle being the largest O_2 consumer [7]. As expected, physical agitation and muscle activity will increase energy expenditure , whereas a muscle hypotonia/paralysis, or a declining muscle mass reduces energy expenditure. This was shown by the decrease of REE of over 21 days that paralleled the muscle mass decline measured by DEXA in New Zealand trauma patients [8]. The rapid reduction and massive of the muscle mass in ICU patients during the first 10 days of their stay measured by ultrasound of the thigh, has been confirmed by several studies [5▪▪]. It emphasizes the importance of repeated indirect calorimetry studies: Singer *et al.* showed the daily variability in the TICACOS study [9], a variability, which was confirmed by EAT-ICU study [10].

The impact of physical exercise is also observable in critical care patients. In 49 hemodynamically stable critically ill patients and 15 healthy volunteers, Hickman *et al.* [11] showed that physical exercise quantified in watt (W) impacts on REE. Critically ill patients do differ from healthy subjects. Exposing them to exercise is probably well tolerated, although the stage of the exercising introduction is not well defined. When ICU patients are compared with healthy volunteers, the VO_2 increase differs, and is absent in patients submitted to passive mobilization [11]. Until now, the patients have been submitted to limited challenges (around 6–10 W). But as the patients 'get walked' around the ICU, a new concept, this energy challenge becomes significant, and needs further studies to assess the magnitude of the associated energy expenditure changes. Sommers *et al.* [12▪] showed that it seems well tolerated to perform exercise testing in critically ill patients staying for 2 weeks: in 37 patients (half were on mechanical ventilation) submitted to an incremental ergometer test, only one episode of transient bradycardia was observed. Another group tested the feasibility of exercise testing in 52 patients with recent cardiac decompensation (left ventricular ejection fraction 31%) 4 days (1–10) after hospital discharge [13▪]. Aerobic exercise capacity was severely reduced with a peak oxygen consumption (pVO_2) of 14.1 (11.2–16.3) ml/kg/min [13▪].

Of note, abnormal body temperature of febrile or hypothermic patients also increase or reduce energy expenditure of ICU patients by about 10%/°C, respectively. Infections impact on EE: Kreymann *et al.* [14] showed a progressive decrease of energy expenditure during the progression of sepsis to severe sepsis. They observed the lowest energy expenditure during the phase of shock, increasing thereafter during recovery. Same pattern is observed in burns. Simple inflammation also impacts on energy expenditure: Hickman *et al.* observed that differences between Harris–Benedict prediction (which reflects basal metabolic rate) and indirect calorimetry were positively correlated with C-reactive protein (CRP) in patients with sepsis ($P = 0.003$).

Predictive equations remain largely used in daily practice as indirect calorimetry devices remains little available. As shown by the NutritionDay survey [15], energy deliveries are poorly adapted: the most frequently observed values of energy delivery are 500, 1000, and 1500 kcal/day.

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The equations have all been shown to be wrong in the majority of cases [16]: further they are static, providing 'permanent targets', leading to significant underfeeding or overfeeding.

Evaluations of the commercially available indirect calorimetry devices have shown significant differences in VO_2 and VCO_2 values between the different devices, as well as compared with aging gold standard the Deltatrac (Datex, Finland), raising the issue of the clinical relevance of their clinical use [17–19,20]. To address this problem, an international study group of investigators for Indirect Calorimetry (ICALIC) defined the characteristics of an ideal device [21▪]. Its analytic performances have been assessed against a mass spectrometer in ranges of gas volume and pressure mimicking the situations encountered in adult healthy volunteers, and patients breathing spontaneously or being on mechanical ventilation. The new calorimeter is currently under clinical testing within the frame of ICALIC initiative. A new device (Q-NRG, Cosmed, Italy) is expected to achieve ultimate accuracy for measuring VO_2, and derived calculated energy expenditure, while being easy to use, very reactive (results obtained within a few minutes) [22,23], and affordable. If proven, these unique characteristics should allow for routine and repeated determination of energy needs and optimal prescription of nutrition support.

Does measured energy expenditure reflect the needs?

The thermodynamic answer to the question is 'yes' as shown by multiple studies [24]. But this positive answer does not answer if it can be translated into nutrition needs through the acute disease course. Indirect calorimetry measures O_2 consumption and CO_2 production. It reflects the total substrate oxidation. But indirect calorimetry is unable to distinguish the respective contribution of exogenous (food) and endogenous substrates to the overall energy production, nor their relative proportions. Further, the needs change over time, and so does the body's response to stress.

The high endogenous energy production during the first days may cover more than half of the energy expenditure, as shown by a tracer study in young critically ill trauma patients after 3 days of starvation [25]: whereas the measured energy expenditure was 1824 kcal/day, their livers were producing 310 g glucose per day, the equivalent of 1230 kcal, by endogenous glucose production. This gluconeogenesis had a price though: the protein balance was −117 g/day. Covering the total measured energy expenditure with extrinsic energy (i.e. feeding), therefore, appears as nonsense during the first days, and results in early overfeeding, that is, metabolic stress. But the metabolic condition of the patients change over time with abating inflammation and decreasing lean body mass, and the capacity of the body to use extrinsic energy supply improves progressively [5▪▪,21▪]. A recent tracer study in critically ill 63-year-old patients showed a decline in endogenous glucose production between days 4 and 9 [5▪▪] from 180 to 111 g glucose per day. This decline in endogenous production after a peak between day 1 and day 4 is the metabolic justification for ramping up feeding whatever the feeding route.

How can clinicians and dieticians handle the patients facing the above described variability of energy expenditure until reliable indirect calorimetry devices get widely available? Considering the overall failure of equations, ESPEN proposes to use the simplest: 20 kcal/kg during the first week [26▪▪], to be achieved progressively, ramping up whatever the route during the first 3–4 days (preference to enteral over parenteral): although not individualized, this strategy prevents overfeeding in majority of patients. ESPEN then proposes to increase energy delivery empirically after the first week, to adapt to recovery associated to an increased energy expenditure mostly because of an increase of the muscular activity.

Studies with individually adapted energy goals

Only few studies have integrated measured energy expenditure of critically ill patients in their design for goal prescription, nor observed the dynamic evolution of energy expenditure. Some recent trials have shown a strong relationship between the measured energy expenditure, the level of feeding and the mortality [27▪]. Studies are summarized in Table 2: the trials that do not provide more calories than energy expenditure (i.e. that do not overfeed) in any study period are associated with clinical benefits mainly in the form of nosocomial infection reduction.

SUBSTRATE NEEDS

An unresolved question is if the doses and proportions of macrosubstrates are the same in healthy and in critically ill patients. The studies manipulating the proportions of the different macronutrients are few.

Carbohydrates: tracer studies have shown the maximal oxidation capacity of glucose (5 mg/kg/min), providing an upper limit for delivery before de novo lipogenesis occurs, whereas diabetic diets experience provide us with the minimum intake,

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Table 2. Summary of randomized clinical trial studies basing the prescription of energy (energy goals) on indirect calorimetry measurements

Study name/year	Authors	Patients (*N*)	General design	Results and comment
TICACOS [9]/2011	Singer *et al.*	112	RCT comparing equation based (25 kcal/day) versus daily indirect calorimetry -driven energy goals. Enteral nutrition completed with parenteral if goals not met	Mean age: 61 years. indirect calorimetry in both groups showed important daily variation of energy expenditure. Lower mortality in the intervention group ($P=0.02$), but more infectious complications ($P=0.05$) and longer ventilation time and ICU stay ($P=0.03$). Energy prescription did not integrate no nutritional energy sources resulting in overfeeding in the intervention group.
SPN1 [35] / 2013	Heidegger *et al.*	305	RCT comparing groups fed from day 4 for 5 days to individually indirect calorimetry adapted and completed feeding using supplemental parenteral nutrition to cover energy goals, versus absence of this adaptation. Patients were selected on insufficient enteral feeding on day 3	Mean age: 61 years. Reduction of nosocomial infectious complications after day 9 in the SPN group
Hypocaloric versus normocaloric [36]/2016	Petros *et al.*	100	RCT investigating the impact on infectious complications of the delivery of 100% (normocaloric) versus 50% (hypocaloric) of the measured indirect calorimetry energy expenditure value for the first 7 days	Mean age: 66 years. Delivery of energy was lower than planned with 80 and 40% respectively of measured energy expenditure. Significant reduction of infectious complications in patients of the upper goal
EAT-ICU [10]/ 2017	Allingstrup *et al.*	199	RCT comparing groups fed to repeated indirect calorimetry measures for energy goals, and urinary urea calculated protein goals. Full feeding from day 1 using enteral and/or parenteral feeding	Mean age: 65 years. No impact on the quality of life at 6 months (principal outcome), nor on infectious complications or mortality
SPN2 [5▪▪]/ 2018	Berger *et al.*	23	RCT using the same design as SPN1 with indirect calorimetry-based energy goals, completing it with tracer studies, immunologic investigations and muscle mass measurements	Mean age: 65 years. Absence of significant difference in glucose and protein turnover. Endogenous glucose production of 180 g/day on day 4 decreasing to 110 g/day on day 9. Improved immunity

RCT, randomized controlled trial.

which is then connected with blood glucose. Excessive glucose intakes result in de novo lipogenesis [25,28], and excessive CO_2 production [29]. Hyperglycemia and increasing insulin requirements, or a new need for insulin, to maintain blood glucose less than 8 mmol/l usually signal excessive doses. Of course, insulin resistance can be generated by inflammation; therefore, changes in insulin requirements should integrate this differential diagnosis.

Lipids: In 1981 [29], John Kinney's group advocated the use of high fat proportion (55% of 'non-protein' intake) in patients with respiratory failure to facilitate weaning from ventilator. The metabolic study included five severely malnourished patients and six critical care septic patients. REE was carefully measured, and 1.5 times the measured energy expenditure was then delivered: both groups received 510 kcal from amino acids. During the glucose phase of the study, the patients received 1550–1995 g glucose per day (25–30 g/kg), which resulted in an excessive CO_2 production compared with the phase where half of this excessive energy was delivered as fat, with a logical lower VCO_2. With the disappearance of the hyperalimentation

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concept, their results were never reproduced. Other studies have since shown de novo lipogenesis (DNL) to occur when lipids represent greater than 50% of energy intakes [25,28].

But there is a minimal need for essential fatty acids to cover to prevent deficiency: parenteral nutrition studies have shown the minimal intakes preventing essential fatty acid deficiencies to be 0.3 g/kg/day. Blood triglycerides and liver tests generally increase reflecting this excess after 2–3 days already [30,31].

Proteins/amino acids: No blood marker is available for proteins needs, as urine urea has too many limitations to truly reflect needs. The investigators of very well conducted study (EAT-ICU) [10] tried to adapt nitrogen intakes to urinary urea losses, but were confronted with expected difficulties. Indeed, urinary urea nitrogen agrees poorly with isotopic estimates of protein balances (differences in ureagenesis between patients, losses of nitrogen as ammonia and creatinine, impact of urinary pH, impaired excretion in renal failure, and stools or other losses not included). For the time being, this strategy remains the simplest indicator for tailoring the prescription of protein.

In the SPN2 study [5▪▪], which compared enteral nutrition that was insufficient regarding energy delivery compared with measured goal feeding from day 4 using supplemental parenteral nutrition, prealbumin change over time (every 5 days) was used to assess response to feeding, an increase of 0.02 g/week or more being considered significant, and reflecting adequate feeding.

The recent large retrospective cohort studies in medical critical care patients ($n = 801$) by Weijs *et al.* [32▪] and in mixed ICU patients ($n = 2263$) by Bendavid *et al.* [33▪] suggest the safety of early protein delivery, and support the hypothesis of a protein provision greater than 1 g/kg/day to achieve a mortality beneficial effect. The advantage of large studies is their power, but the individual patient is not well served by these statistical assessments. Concepts, such as calorie/protein ratios have been discussed [34], but a bed-side tool is still missing. Recent development in ultrasonography may allow to repeatedly measure the muscle mass of one or more muscles (e.g. quadriceps): the ultrasound imaging enable evaluation of the decline of the muscle mass known to be strongly correlated to the energy and protein balances.

CONCLUSION

A reliable and easy-to-handle indirect calorimetry is required to enable adaptation of feeding to energy expenditure as a point-of-care device: a device integrating a new technology has appeared on the market and seems able to make this objective real [21▪]. Regarding proteins, a reliable marker of needs is still missing. We still do not know, which parameter of protein metabolism should be considered as a reliable indicator of needs in clinical practice: research is urgently required to find such a biomarker and enable an objective determination of protein needs during the early and later phases of acute disease.

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