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Revijalni članak **Review article**

INDIRECT CALORIMETRY: REVIEW BASED ON CURRENTLY AVAILABLE LITERATURE
(LITERATURE REVIEW ON INDIRECT CALORIMETRY)

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Summary

Background: *Indirect calorimetry (IC) is recognized as the gold standard for measuring energy expenditure (EE) in clinical settings. Accurate assessment of EE is critical for optimizing nutritional therapy, particularly in critically ill patients, cancer patients, patients following major surgical procedures, and those requiring specialized metabolic care. Traditional methods of estimating EE, such as predictive equations, often result in inaccurate estimations due to variations in metabolic demands, disease states, and patient-specific factors. Indirect calorimetry provides a more individualized approach by directly measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2), enabling tailored nutritional support. This review aims to summarize the principles, methodologies, applications, advantages, and limitations of indirect calorimetry while comparing it to predictive equations and other methods of energy expenditure estimation. This study is a comprehensive review of the currently available literature on indirect calorimetry and its application in clinical nutrition. A structured literature search was conducted using electronic databases, including PubMed, Scopus and Google Scholar. The search strategy included searching by terms such as: "nutrition therapy", "indirect calorimetry," "energy expenditure measurement," "clinical nutrition," "metabolic assessment," and "critical care nutrition" in various combinations with the AND or OR operator connecting them. Indirect calorimetry provides a precise measurement of EE by assessing oxygen consumption (VO_2) and carbon dioxide production (VCO_2), applying the Weir equation for calculations. However, practical barriers such as cost, equipment availability, and the requirement for specialized training limit its widespread use.* **Conclusion:** *Indirect calorimetry remains the most accurate method for determining energy requirements in critically ill and surgical patients.*

Keywords: *Indirect calorimetry; energy expenditure; medical nutritional therapy; metabolic rate measurement.*

Nutrition therapy

The main goals of nutrition therapy are prevention or treating malnutrition. According to the European Society for Clinical Nutrition and Metabolism – ESPEN guidelines, nutrition therapy includes screening, assessment, and provision of nutrition either orally (hospital diet, food fortification, oral nutritional supplements-ONS) or via enteral nutrition (EN) or parenteral nutrition (PN).[1] Nutrition therapy is mandatory in hospital settings; however, it is necessary for certain populations in settings beyond hospital (cancer patients, patients with short bowel syndrome, …). Moreover, nutritional therapy is a routine component of Enhanced Recovery After Surgery (ERAS) protocols.[2]

Currently, there are four states which can require nutrition therapy: malnutrition / undernutrition, over-nutrition (overweight and obesity), sarcopenia and frailty. Malnutrition includes disease-related malnutrition (DRM), and malnutrition/undernutrition without disease.[1] Malnutrition is frequently overlooked and has been described as a "silent epidemic".[3] The most vulnerable populations who can be at malnutrition risk or already in malnutrition are cancer and surgical patients,

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critically ill patients, neurological patients, elderly, frail and patients with chronic intestinal failure.[4]

In both general wards and Intensive care units (ICU), malnutrition is strongly linked to a higher risk of infections, impaired wound healing, pressure ulcer development, and extended hospital stays. Additionally, up to two-thirds of patients experience in-hospital weight loss, which frequently exacerbates malnutrition.[4,5] Due to the increased catabolic state associated with malignancies, the high incidence of malnutrition in cancer patients has been shown to have a substantial effect on overall survival. Regarding the optimal type of nutritional therapy for oncology patients, ESPEN recommends adherence to ERAS guidelines, with a strong preference for oral or enteral nutrition. EN has been shown to improve nitrogen balance and promote weight gain in cancer patients.[6,7] Dysphagia is a common issue among neurological patients due to their underlying conditions. Poor oral intake can lead to rapid weight loss.[8] Patients with acute or chronic intestinal failure are at high risk of malnutrition development due to malabsorption.[9] All these specific groups of patients are at high risk of malnutrition or already in malnutrition at hospital admission. The right dose of nutrition is essential for their treatment. In such varied conditions, assessing the appropriate daily energy requirements can be particularly challenging. An inappropriate nutrition therapy can lead to overfeeding or underfeeding and, in certain circumstances, may result in refeeding syndrome. As precision medicine is increasingly being adopted across various fields of medicine, nutritional therapy should likewise be tailored to the individual needs of each patient.

The importance of individualizing nutritional therapy

Optimal nutrition therapy plays a crucial role in the care of critically ill patients, influencing their recovery, morbidity, and survival. Effective nutritional management requires a comprehensive approach that includes thorough assessment, accurate estimation of energy needs, continuous monitoring, and individualized interventions. Nutritional strategies should be tailored to each patient's specific condition, diagnosis, ongoing treatments, and metabolic state during both their stay in the intensive care unit (ICU) or the recovery period. Critically ill patients often experience hypermetabolism, catabolism, and inflammation, which can exacerbate malnutrition and negatively impact clinical outcomes.[10]

According to expert opinion, personalized nutrition therapy should be tailored to the patient's phenotypes and endotypes. Patient phenotypes are defined by patient data and body composition, while endotypes identify disease-related mechanisms and metabolic processes.[11]

Phenotyping assessment should include medical history, evaluation of unintentional weight loss or decline in physical performance before hospital admission, physical examination, and, when feasible, assessment of body composition, muscle mass, and strength. Screening tools such as the Nutrition Risk Screening 2002 (NRS 2002), the Subjective Global Assessment (SGA) and Mini Nutritional Assessment (MNA) are recommended for routine practice. The choice of the most appropriate screening test depends on the characteristics of the population being assessed (e.g., NRS-2002 is best suited for surgical patients, while MNA is more appropriate for the elderly). Body weight and body mass index (BMI) alone are not reliable indicators of malnutrition, making it essential to detect muscle loss and sarcopenia, even in obese patients.[11,12] Nowadays, Global Leadership Initiative on Malnutrition (GLIM) seems more accurate than other scoring tests. According to the GLIM criteria, a malnutrition assessment should incorporate both an etiological factor, such as critical illness and a phenotypic component, such as the percentage of weight loss, BMI, decreased appetite or low muscle mass.[13,14]

For nutritional assessment we can use different strategies. Bioelectrical impedance analysis (BIA), computed tomography (CT), or ultrasound can be used to evaluate muscle mass, while handgrip dynamometry can be used to measure muscle function. BIA is particularly useful for evaluating body composition in hemodynamically stable patients without fluid imbalances, and phase angle measurements can help predict prognosis in critically ill individuals. Nowadays, body water analyzers (e.g. InBody BWA 2.0), represent advanced bioelectrical impedance analysis technology, providing accurate and detailed insight into body water, muscle mass, and fat.[15] Estimated body composition is important, particularly in elderly patients

due to high incidence of sarcopenia.[16] Patients who are present with low muscle mass on CT scans at hospital or ICU admission are at increased risk of prolonged hospital stays and higher mortality rates.[17]

Ideally, nutrition therapy should be personalized using real-time indicators to signal when energy delivery is optimized and protein is effectively utilized for lean mass (LM) maintenance. Additionally, it is essential to assess when energy intake reaches an appropriate level while avoiding the risks of overfeeding or underfeeding. Therefore, advancements in current and future technologies for measuring energy requirements and body composition are necessary to achieve these nutritional goals.[14] Indirect calorimetry could be useful tool for achieving optimal energy requirements.

Energy Requirements

Metabolic Response to critical illness

Critical illness triggers complex metabolic, hormonal, and immune responses. In 1942, Cuthbertson found two distinct metabolic phases: the ebb phase (early shock phase) and the flow phase (catabolic phase).[18] The ebb phase is characterized by hemodynamic instability, a decline in metabolism rate, and hormonal alterations, notably insulin resistance.[17,18] The flow phase is characterized by tissue breakdown, including lean muscle loss, to provide energy for the body's acute stress response while also reducing the risk of bleeding and infection.[18] More recently, a third phase—the anabolic recovery phase—has been recognized. During this stage, the body begins rebuilding lost tissue and becomes more metabolically efficient at utilizing nutrients for recovery.[18] The flow phase begins within 3 to 10 days and continues until the patient enters the recovering stage, during which metabolism returns to an anabolic state.[19,20]

In critically ill patients, endogenous glucose production is elevated and does not decrease in response to nutrient and insulin administration as it does in healthy individuals. Excessive glucose-based energy intake is linked to hyperglycemia, increased CO_2 production, enhanced lipogenesis, and higher insulin demands.[17] Critical illness leads to protein catabolism, which is marked by negative nitrogen balance, depletion of specific amino acids, and loss of skeletal muscle mass. However, there is no clear method to determine the transition from the acute to the post-acute phase, as no specific markers currently define the end of the acute phase.[17,18,20] Instead, a combination of metabolic markers (such as blood glucose levels, insulin requirements, and phosphate concentration) and inflammatory markers (such as C-reactive protein [CRP]), along with the patient's clinical progression, can help make a primarily subjective assessment of their current disease phase.[20]

Methods for estimated energy requirements - Indirect calorimetry, Predictive Equations, Guideline Recommendations

A key element of medical nutrition therapy (MNT) is providing energy specific to each patient's state of illness and metabolic stage during their hospital or ICU stay. Indirect calorimetry (IC) is widely recognized as the gold standard for measuring actual energy expenditure (EE) by assessing oxygen consumption (VO2) and carbon dioxide production (VCO2) using the Weir formula. When available and feasible, current clinical nutrition guidelines consistently recommend its use in routine practice.[16,20]

However, since indirect calorimetry (IC) and these alternative methods are often unavailable or impractical, weight-based equations remain a commonly used approach in clinical practice. Generally, in hemodynamic stable patients, weight-based equations can be used. According to these equations, The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends 20–25 kcal per kilogram of body weight (BW) per day, while the American Society for Parenteral and Enteral Nutrition (ASPEN) suggests 25–30 kcal/kg/day.[16,20] Both guidelines (ESPEN, ASPEN) recommended hypocaloric nutrition 70% estimated energy during the first week of septic shock or simple formula (14-20kcal/day).[16,20] Moreover, in early phase of sepsis (during the first three days), recommended trophic nutrition delivery is 10-20 mL/day (about 500kcal/day).[16,20] Although these formulas offer a practical and straightforward method for estimating EE, they have inherent limitations in accuracy.[16,20] Similar, as ESPEN and ASPEN weight-based equations, in 1997, American College of Chest Physicians (ACCP) published

consensus statement, and provide recommendations for the nutritional management of ICU patients. The guidelines suggest 25 kcal/kg of usual body weight/day for most patients for daily energy requirements.[21] For obese patients (BMI ≥ 25 kg/m²), they recommended using ideal body weight for estimation of daily energy needs. In severe malnourished patients (BMI < 16 kg/m²), initial daily energy requirements should be calculated based on the patient's current body weight for the first 7-10 days, after which the estimation should shift to ideal body weight.[21] However, validation study has shown that this equation is inaccurate in critically ill patients, with an accuracy rate of only 12%, and a low coefficient of determination (R^2) of 0.24.[22]

Besides weight-based equations, a substantial number of predictive equations (>200) have been performed to estimate energy expenditure (EE). Most of them have not been validated for critically ill patients. Commonly used equations in critical care include the Harris-Benedict equation, the Mifflin-St Jeor equation, Ireton-Jones equations, and the Penn State equation.[23,24] These equations aim to estimate resting energy expenditure (REE) to guide nutritional therapy and primarily rely on anthropometric data, such as height, weight, age, and sex, to predict daily caloric needs. Some predicted equations for hospitalized patients incorporate illness severity and whether the patient is receiving mechanical ventilation.[24] The Harris-Benedict equation was created in 1919 for healthy individuals with stable body weight, making it less applicable to critically ill patients. However, the Harris-Benedict equation is one of the most used in clinical practice for estimated energy requirements:[23]

Male: 66.473 + (13.7516 x weight [kg]) + (5.003 x height [cm]) - (6.755 x age [y])[23,24]

Female: 655.09 + (9.5634 x weight [kg]) + (1.8496 x height [cm]) - (4.6756 x age [y])[23,24]

The Penn State equation is well-suited for estimating resting energy expenditure (REE) in critically ill patients under stable conditions, but it is not valid for capturing acute fluctuations in energy metabolism. The original, and later modified Penn State equation through years is shown below: [23,25]

2003a: RMR (kcal per day) = 0.85 (Harris-Benedict equation) + (175x T_{max}) + (33xVe) -6433[23,25]

2003b: RMR (kcal per day) = 0.96 (Mifflin-St. Jeor) + 31(Ve)+167(T_{max}) – 6212 [23,25]

2010: RMR (kcal per day) = (for age ≥60 years, BMI≥30): 0.71(Mifflin-St. Jeor) + 85(T_{max}) + 64(Ve) – 3085 [23,25]

RMR- resting metabolic rate; T_{max}, maximum body temperature in past 24 hours (˚C); Ve, volume of exhaled gas (L/min).

When comparing with measured energy expenditure, the Penn State equation has demonstrated high accuracy (70–75%) in critically ill patients.[25] During critical illness, metabolic demands fluctuate significantly, necessitating cautious use of predictive equations. These models are not valid for capturing dynamic shifts in energy expenditure during various phases of illness or clinical intervention.[23]

Obesity (BMI > 30kg/m²) is a significant confounding factor, as predictive equations may underestimate or overestimate EE in obese critically ill patients.[24] Vest and co-workers have found that predictive equations can underestimated EE in obese ICU patients.[26] Critically ill patients can varying in body weight (obese or non/obese), ages, sex, and illness status which proposed that a single equation does not fit to all patients. The Penn State equation has demonstrated up to 70% accuracy when compared with measured EE in obese patients. However, results can vary based on factors such as age and obesity.[23,25]

Ireton-Jones equation is most suitable equation used for calculation of energy requirements in ICU settings. Ireton-Jones and Jones made a new version of equation which was more accurate for ventilated patients.[23]

Mechanically ventilated: 1784 - (11 × age [y]) + (5 × weight [kg]) + (244, if male) + (239, if trauma present) + (840, if burn present)[23]
Spontaneously breathing: 629 - (11 × age [y]) + (25 × weight [kg]) - 609 (when BMI > 27)[23]

What is indirect calorimetry?

Indirect calorimetry (IC) is regarded as the gold standard for measuring energy expenditure (EE), utilizing measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Also, IC can estimate other parameters besides REE such as utilization of carbohydrates, fat, and

protein.[27] In the context of personized medicine, indirect calorimetry is essential for precisely measuring EE in critically ill patients. Modern IC devices are highly advanced, non-invasive, easy to use, and capable accurately measuring resting energy expenditure (REE) in both mechanically ventilated patients, and patients with spontaneous breathing.[17,23,27]

What is the principle of indirect calorimetry?

Total energy expenditure (TEE) is the total amount of energy humans need for performing all functions and can be subdivided into basal energy expenditure (BEE) or basal metabolic rate (BMR), diet-induced thermogenesis (DIT) or thermic effect of feeding (TEF), and physical activity related energy expenditure (AEE). The resting energy expenditure (REE) or resting metabolic rate (RMR) encompasses BEE along with DIT.[27,29] REE reflects the energy requirements to maintain vital physiological processes like respiration, substrate metabolism, cardiac output, and thermoregulation during a 24-hour inactive period. In healthy sedentary adults, REE accounts for approximately two-thirds of total energy expenditure (TEE).[27,28,29]

It should be noted that while resting energy expenditure is sometimes referred to as basal energy expenditure, BEE is the primary component of REE. REE is influenced by a variety of factors (stress, inflammatory status, sepsis, brain activity, endocrine fluctuations, feeding state, mechanical ventilation, and pharmacological interventions). From these reasons, it can be challenging to predict nutritional requirements, especially in patients with acute or chronic conditions.[29,30]

In the presence of oxygen (O_2), nutrients – particularly carbon-based ones-undergo oxidation, resulting in release of adenosine triphosphate (ATP), carbon dioxide (CO_2), water (H_2O) and heat. Hence, indirect calorimetry is based on the principle that the oxidation of macronutrients (carbohydrates, fats, proteins), requires oxygen and produces carbon dioxide. By measuring the consumption of O_2, and the production of CO_2, energy expenditure (EE) can be accurately estimated. Unlike direct calorimetry, which estimates EE from measuring heat production in a controlled chamber (challenge to use in everyday practice), IC derives energy expenditure from gas exchange (easy to use, even in ICU settings).[29,30]

Resting energy expenditure (kcal/day) is typically calculated using the modified Weir equation:

EE (kcal/day) = 1.44 ([3.94 xVO_2] +[1.11xVCO_2] + [2.17 x uN2])[29,31]

VO_2-ml/min, VCO_2-ml/min, uN_2-g of urinary nitrogen/l

The urinary nitrogen component (uN_2) contributes only approximately 4% to total EE, and for simplicity is frequently omitted in EE calculations. The results of IC with no counting uN_2 show minor error of 1%–2% in both inpatient and outpatient settings. Consequently, a simple form of the equation is commonly used in every day pracitce.[29]

EE (kcal/day) = 1.44 ([3.94 xVO_2] +[1.11xVCO_2[29,31]

VO_2-ml/min, VCO_2-ml/min

The fundamental basis of IC is analyzing the exchange of respiratory gases, where the respiratory quotient (RQ) represents the ratio of VCO_2 to VO_2:

$RQ=VCO_2/VO_2$ [29-31]

RQ indicates the predominant substrate being metabolized (e.g., carbohydrates, fats, or proteins).[10,29,30] Generally, RQ physiologically tends to be between 0.67 to 1.3, and 0.86 is the number which is usual used for RQ in settings when measures of VO_2 is not possible.[29,31] The complete oxidation of glucose makes a RQ value of 1.0, while a RQ of 0.7 is characteristic for lipids, and 0.82 for proteins, and 1.33 for citrate oxidations.[10,29-31] Also, the respiratory quotient can offer valuable insight into nutritional status, showing underfeeding (RQ < 0.7), potential technical issues (such as leaks), or overfeeding (RQ > 1.0).[17,31]

Indirect calorimetry should be routinely performed from the third or fourth day from ICU admission and should be repeated at least once or twice per week during the ICU stay, especially for patients at malnutrition or in risk of malnutrition, or in those with prolonged ICU stays with the aim to optimize medical nutrition therapy.[17,30,33] Indirect calorimetry is recommended to use in critically ill patient on mechanical ventilation.[31,32,33]

Energy expenditure (EE) can be estimated by volumetric capnometry or circulatory calorimetry.

Volumetric capnometry is a widely used method in modified version, particularly when it drives EE from ventilators. The original equation is:

$EE \approx 8 \times [VCO_2]$[27,29]

VCO_2=ml/min

The equation which uses a modern ventilator for measuring REE using VCO_2 is:

$REEVCO_2$ (kcal/day) = 1.44x (3.941 x [VCO_2/RQ] + [1.106 x VCO2])[29,32]

VCO_2-ml/min, RQ is assumed to be 0.86

And can be simplified:

$REEVCO_2$(kcal/day) = 8.19 x VCO_2 [29]

REE measured by ventilator using VCO_2 (REE-VCO_2) (sometimes referred to as partial indirect calorimetry), cannot be precise as estimated as REE by IC (REE-IC) due to different measurements. For estimated REE using indirect calorimetry, both gases oxygen and carbon dioxide are measured, while in estimated REE using VCO_2 measure only VCO_2 and take into calculation RQ assumed as 0.85.[29,30] Kagan et co-workers showed that REE-VCO_2 is not precise as REE-IC.[34] The similar conclusion came from another study; REE-VCO_2 is overestimated in comparison with REE-IC, and some cases predictive equations are more accurate.[32] When compared to REE-IC in ICU patients, predictive equations often show poor agreement (more than 10% variability) in estimating REE. This discrepancy is especially higher in the presence of some factors such as body mass index, age, and illness severity.[35]

Energy expenditure (EE) can be estimated by circulatory calorimetry using Fick method, using oxygen consumption (VO2) from a pulmonary arterial catheter, and oxygen delivery form arterial blood. In this equation, consumption of O_2 is more important than in volumetric method:[27-30]

$EE \approx 7 \times [VO_2]$[30]

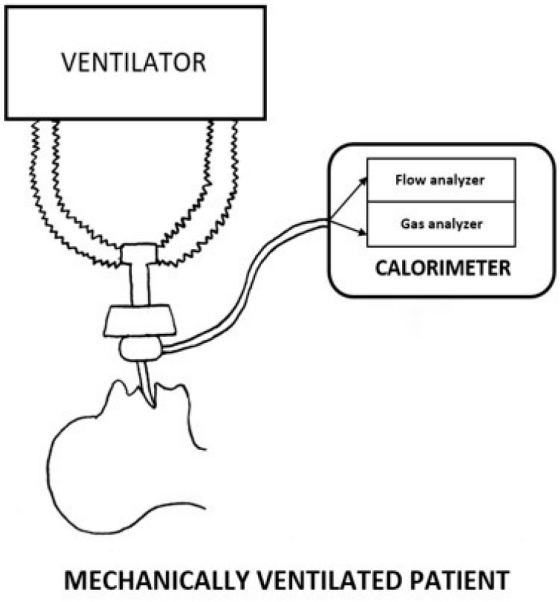
VO_2-ml/min

This method isn't popular due to the need for Swan-Ganz catheter placement.

How is indirect calorimetry performed?

IC can be performed in spontaneously breathing patients and patients who require mechanical ventilation. In mechanically ventilated patients, devices for sampling oxygen and carbon dioxide are integrated into the circuit between the endotracheal tube and the ventilator. Techniques for measurements are using either 'breath-by-breath' or mixing chamber method. (Figure 1). **'Breath-by-breath'**

Figure 1. Performing indirect calorimetry on a mechanically ventilated patient in intensive care unit A- resting energy expenditure by indirect calorimetry (IC-REE), B- resting energy expenditure by VCO_2



A



B

B



technology provides real-time gas exchange analysis but also shows short-term fluctuations. **Mixing chamber technology** shows averages gas concentration over time, offering more stable and precise measurements.[27,29,31]

For spontaneously breathing patients, a ventilated canopy hood or a fitted face mask is utilized to take respiratory gases (Figure 2). The canopy system (clear, rigid hood with a constant pull of air into) usually is used in healthy individuals. Fitting mask is more suitable for patients who are breathing in the air room. In spontaneous breathing IC continuously measures VO_2 and VCO_2 and keep minimal leakage to maintain accuracy.

In both mechanically ventilated or in patients with spontaneous breathing (canopy or mask), the respiratory gases are analyzed, and EE is subsequently calculated using Weir's equation (Figure 3).[27,31]

What are Advantages and Disadvantages of Indirect Calorimetry?

Advantages

1. Customization of Nutrition Therapy and accuracy

IC is the gold standard for measuring resting energy expenditure (REE) due to high accuracy. REE-VCO_2 and predictive equations often produce significant errors (overestimate or underestimate patient's energy needs) particularly in patients with variable metabolic states, such as critically ill or obese individuals.[29,31,33] Tailor nutritional therapy can be delivered more precisely according to measured REE and the patient's needs. Application of IC reduces the risk of complications associated with overfeeding (e.g., hyperglycemia, hepatic steatosis) or underfeeding (e.g., muscle wasting, prolonged recovery, infection). Application of IC reduction in short-term mortality.[29,35]

Figure 2. Performing indirect calorimetry on a patient with spontaneous breathing in intensive care unit

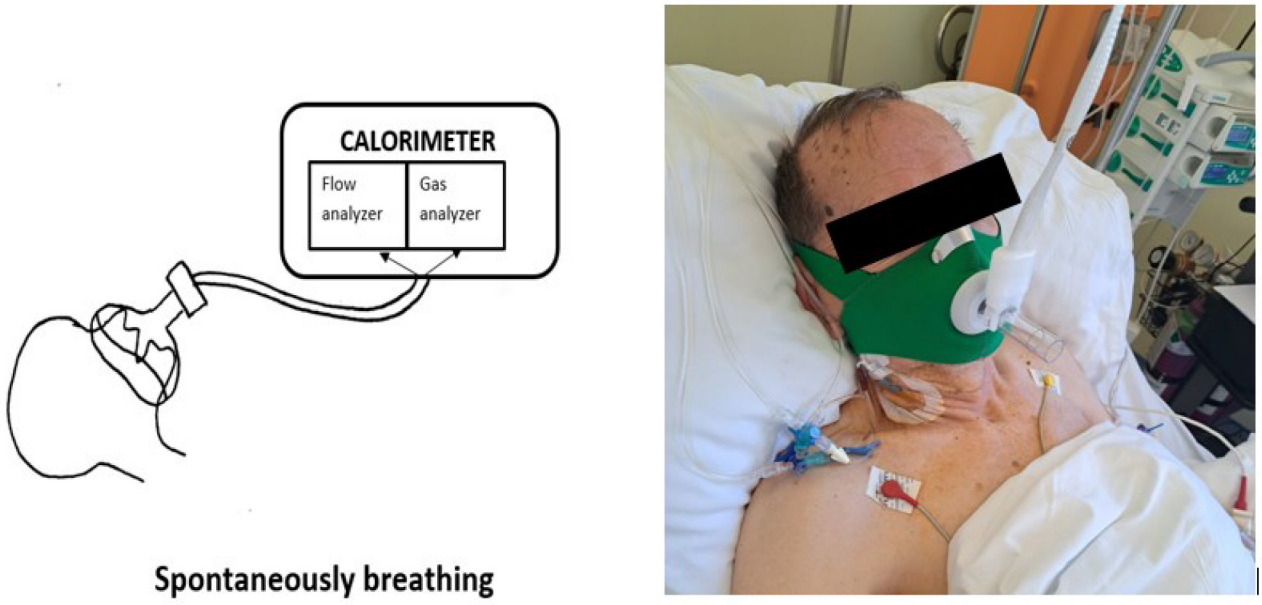
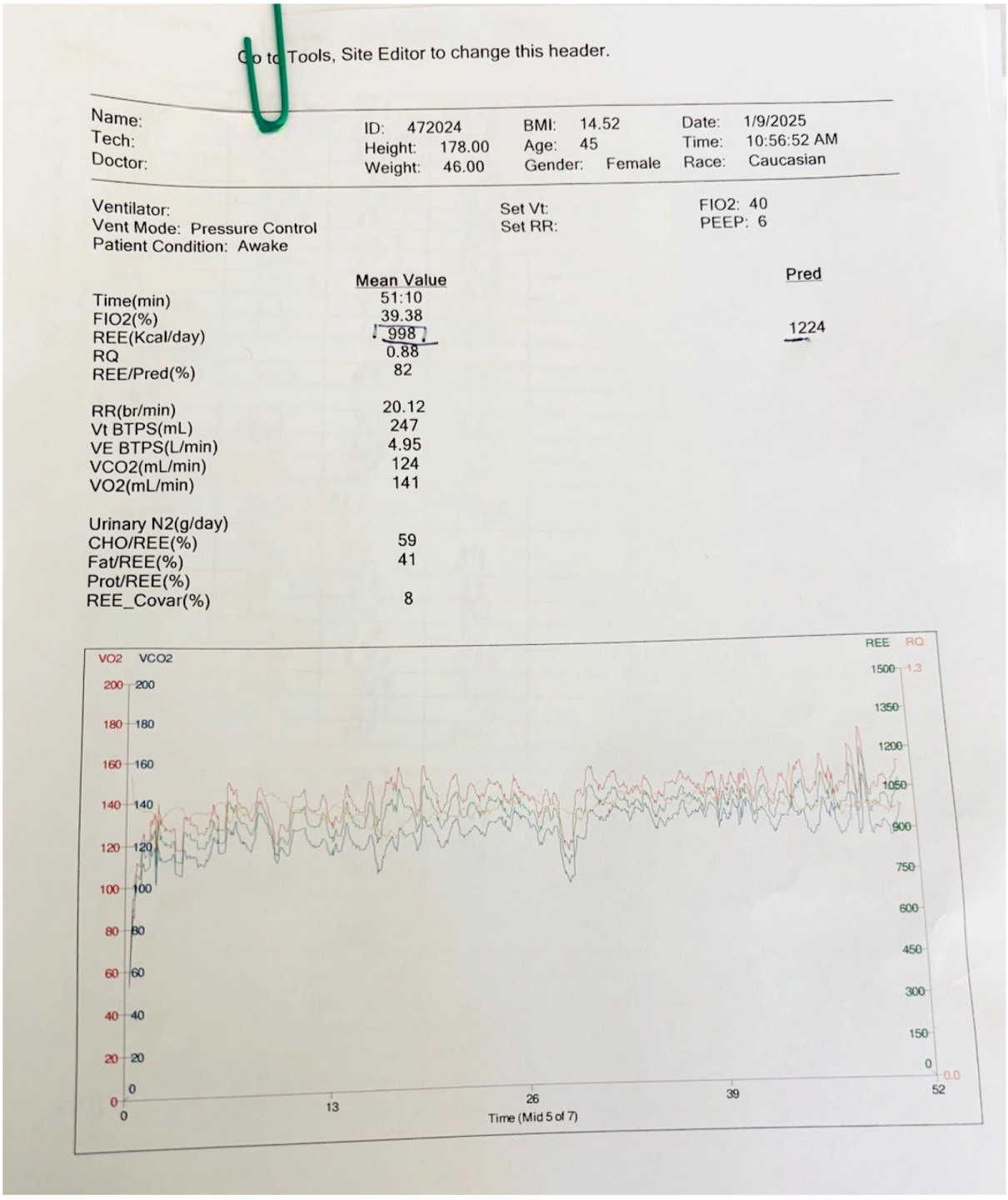


Figure 3. Numeric and graphic representation of the indirect calorimetry result



2. Non-invasive Measurement

Invasive techniques (the Fick principle or direct calorimetry) have been replaced by non-invasive indirect calorimetry (IC), which requires only the measurement of oxygen consumption and carbon dioxide production through gas sampling. This method is non-invasive, safe, and more acceptable for patients.[29,35]

3. Flexibility Across Clinical Settings

Given IC is suitable for both mechanically ventilated patients and those breathing spontaneously, can be used in vary settings: intensive care units, perioperative period, ambulatory setting in patients with chronic intestinal failure (CIF), in obese patients, in patients after bariatric surgery, and metabolic studies for diverse conditions (sepsis, organ failure, obesity, severe malnutrition).[36,37]

4. Adaptability to Changing Conditions

IC measurements can be repeated countless times as the patient's clinical status needs, enabling real-time adjustments to personalize nutrition therapy. Optimization of energy needs is of great impotency in critical ill patients with sepsis or burns, who have dynamic metabolic shifts.[37] Also, is very important in critically ill malnourished, obese patients.[32,37]

5. Reducing the Risk of Complications

Estimated accurate REE through IC reduces the risk of undernutrition or excessive caloric intake. These complications can further lead to developing infections, organ dysfunction, prolonged weaning from mechanical ventilation, and overall prolonged recovery, especially in patients in critically ill patients.[29,37]

Disadvantages

1. Influence of Patient-Specific Factors

The accuracy of IC can be compromised and so is contraindicated: in mechanically ventilated patients who needs for high oxygen (FiO_2 > 70%), PEEP > 12cmH_2O, in presence of air leak (pneumothorax, tracheal fistula), in patients on non-invasive ventilation, or high-flow nasal cannula, or non-ventilated patients who need oxygen therapy, using nebulization.[38] Also, some patient's conditions can influenced on accuracy of indirect calorimetry (fever, agitation, sedative use) and interpretation of this result should be done carefully.[37,38]

2. High Costs and Maintenance

IC equipment is expensive for investment and service. Trained staff for IC management (operation, calibration, and interpretation of results) are required, which influences healthcare budgets.[37,38]

3. Limited Accessibility

Despite IC is easy to use and portable, it is still not widely available, especially in resource-limited settings. At this moment, application of IC restricts to specialized centers.[27]

4. Dependency on Optimal Conditions

Accurate IC results demand strict adherence to procedural protocols (fasting, resting state, and steady physiological conditions). Deviations from these (early phase, non-nutritional calories, early phase of acute illness, and refeeding syndrome) can result in unreliable data, and misinterpretation of IC results.[37,38]

5. Technical Limitations

Due to technical limitations, patients with requirements of extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT) need adjustment before interpretation of IC results.[38,39] In general, at a standard CRRT effluent dose of up to 30 mL/kg/h, CO_2 losses through CRRT account for approximately 10% and may therefore be considered clinically relevant. For ECMO patients, modified IC can be applied in early phase of ICU admission.[40]

Dose of energy intake

Clinical guidelines in ICU settings advocate early initiation of enteral nutrition (EN), as early administration may help preserve intestinal barrier function and reduce the risk of ischemia, bacterial translocation, and dysbiosis. Recommendations suggest starting early EN within 24 to 48 hours of ICU admission (if oral intake is not possible). However, in cases of severe gastrointestinal intolerance (e.g., gastric residual volume > 500 mL/6h), mesenteric ischemia, gastrointestinal bleeding, intestinal obstruction, abdominal compartment syndrome, hemodynamic instability that has not been adequately resuscitated with high doses of vasopressors, severe hypoxemia, and acidosis, EN is contraindicated and recommended to postpone.[16,17,40.41] Also, in patients with high risk of aspiration, abdominal hypertension (abdominal pressure ≥ 15mmHg), high risk of developing refeeding syndrome, EN should be started carefully and monitored more frequently than usual. On the other hand, patients who have been resuscitated (e.g., normalized lactate), are on low-dose vasopressors (norepinephrine < 0.3 μg/kg/min), have an open abdomen, are on neuromuscular blockade, undergoing therapeutic hypothermia, ECMO, or are in prone position do not require a delay.[16,17,42,43] Nonetheless, until vasopressor support has been suitably reduced, patients on high-dose vasopressors (norepinephrine ≥ 0.3 μg/kg/min)

should not receive excessive EN or parenteral nutrition (PN).[16,17,43] In hemodynamically unstable patients, enteral nutrition, preferably as trophic feeding (10–20 mL/h), should be initiated once vasopressor doses are stable or decreasing and the patient has undergone adequate volume resuscitation.[16,17,20,43]

The clinical aspect of estimated daily energy intake is how much calculated or measured energy should be provided to patients. It mainly depends on patients' phase of disease and their own condition. Given that indirect calorimetry (IC) is gold standard for estimating energy expenditure (EE) and personalized ICU nutrition, data must be interpreted carefully in the context of patients' condition.[16,17] Critically ill patients should be started with trophic feeding within 48h of admission in ICU.[16,40,41] Full nutrition therapy (enteral, parenteral, or oral nutrition) should not be a goal in the early phase of critical illness so as to prevent overfeeding. However, full energy intake should be provided within three to seven days.[16,17,40,41,42] IC measurements should be performed after patients have been adequately resuscitated, in stable or steady hemodynamic state, typically around the third day in the ICU.[16,26,27,40] Current ICU nutrition guidelines recommend hypocaloric nutrition (initiating energy intake at approximately 10–15 kcal/kg or less than 70% of the IC-measured resting energy expenditure (REE)), whether enteral (EN) or parenteral nutrition (PN) is used, with gradual advancement as the patient stabilizes.[16] Minimal trophic enteral nutrition (20mL/hours) is recommended in the first 48 hours. After the third day, energy intake should cover 80%–100% of IC-REE and 70% of calculated EE. In the chronic phase, REE should reach 100%. During the rehabilitation phase, energy supply should exceed 100% of IC-REE or calculated EE.[16,42] When indirect calorimetry is available, isocaloric nutrition can be gradually introduced after the initial phase of acute illness. However, if energy needs are estimated using predictive equations, hypocaloric nutrition (providing less than 70% of estimated requirements) is recommended over isocaloric nutrition during the first week of the ICU stay.[16,42] According to the 2022 ASPEN guidelines, patients should receive 12–25 kcal/kg body weight/day during the first 7–10 days after ICU admission, due to mixed results about benefits energy intake (higher versus lower).[43] In cases of additional stress, such as new-onset sepsis, reducing energy intake to 10–15 kcal/kg or below 70% of IC-measured EE may be necessary, though further research is required to confirm this approach.[44]

Monitoring should track progress concerning the nutrition diagnosis, allowing for adjustments based on patient-centered outcomes, alongside any required healthcare provider or institutional measures. IC should be repeated every week to check patient fluctuation in energy requirements. In the later phase of treatment (recovery phase), choosing meaningful outcome indicators and using simple, clear language in goal setting can encourage patient engagement and self-monitoring in their nutritional care.[17]

To give a patient the ideal macronutrient composition is important as giving optimal energy. In the absence of acute disease, carbohydrates serve as the primary energy source, but in critically ill patients, stress-induced insulin resistance leads to non-utilization of glucose and results with hyperglycemia. Previous guidelines, based on expert recommendations, have suggested minimum carbohydrate requirements, though the precise optimal intake remains uncertain. During critical illness, the glucose (PN) or carbohydrates (EN) intake should not exceed 5 mg/kg/min.[18,44]

In critical illness, the metabolism of lipids is altered (low or high plasma triglyceride levels, low cholesterol). High-fat intake, especially unsaturated fats, due to lipid overload may impair lung function, and leads to immune suppression. Excessive intake of lipids and carbohydrates can cause hyperglycemia, liver steatosis and increased values in liver function tests. Regular monitoring of triglyceride levels and liver function tests is essential for guiding clinical decisions, particularly while propofol is used for sedation.[45]

The recommended daily maximum for intravenous lipids is 1 g/kg body weight, with a tolerance of up to 1.5 g/kg.[43] Emulsion with combination of more fatty acids should be used (medium chain triglycerides (MCTs), omega-9 monounsaturated fatty acids, and omega-3 polyunsaturated fatty acids).[43] Enteral formulae enriched in omega-fatty acids can be considered in specific groups of patients (acute respiratory distress syndrome, sepsis) with aim of immunomodulating properties. Parenteral eicosapentaenoic acid (EPA) and docosahexaenoic

acid (DHA) should be administered (fish oil in dose of 0.1-0.2 g/kg/day) in patients requiring parenteral nutrition.[16,43,44]

Special consideration is needed when administering propofol, as it serves as a source of fatty acids (FAs). This lipid-based anesthetic provides 1.1 kcal/mL and can contribute significantly to total energy intake, potentially exceeding nutritional requirements. Generally, doses of propofol should not exceed more than 75mcg/kg/day due to propofol infusion syndrome.[43,44]

Critical illness leads to protein catabolism, which is marked by negative nitrogen balance, loss of skeletal muscle mass, and depletion of specific amino acids. This catabolic state also increases the risk of ICU-acquired weakness (ICUAW), a clinical condition characterized by muscle dysfunction, which can be worsened by sedation, mechanical ventilation, and medications such as corticosteroids and muscle relaxants. In this setting, the body's ability to absorb the provided protein and amino acids, along with its capacity to synthesize new body proteins, plays a crucial role in mitigating and overcoming catabolism. Physiotherapy and mobilization are important as protein intake for muscle rehabilitation.[20]

The optimal dosing and timing of protein administration within medical nutrition therapy is still a topic of ongoing debate, as reflected in the varied recommendations found in current guidelines from international clinical nutrition societies. ESPEN suggests a target of 1.3 g/kg of body weight/day for adult critically ill patients, with the goal of gradually reaching this target throughout the ICU stay.[16,43] In contrast, ASPEN recommends a range of 1.2–2.0 g of protein/kilogram of body weight/day for adult critically ill patients.[43] Traditional monitoring of protein metabolism is calculating nitrogen balance, and novel methods are urea to creatinine ratio and 3-methylhistidine. No one of the method mentioned is accurate in clinical practice, and monitoring of protein metabolism has been investigated again.[20] Nitrogen balance, which reflects the equilibrium between protein intake and losses (via urinary urea), may be useful.[17] Studies have shown that achieving a positive nitrogen balance through higher protein intake.[45,46] Some indirect calorimeters include an option to input nitrogen balance data, which allows for the calculation of the proportion of energy obtained from protein metabolism.

For calculation of protein dose total body weight (TBW) is commonly used, but lean mass (LM) is more accurate. For sarcopenic obesity, TBW-based targets may result in protein overdosing, while in non-sarcopenic obesity, protein needs can be underdosed. Bioimpedance assessment (BIA), body water analyzer (BWA) are bedside tools that can estimate LM. Muscle ultrasound and CT scans also can assess body composition. The Gallagher predictive equation for estimation LM can be used, but with lower accurately.[17]

Biomarkers related to muscle breakdown, autophagy, inflammation, and insulin resistance could potentially help identify patients who would benefit from higher protein intake. For now, specific validated biomarkers and evidence of their impact on outcomes are still lacking.[17]

It is interesting to know resting metabolic rate among organs. Resting metabolic rates (RMRs) of adipose tissue are low (4.5 kcal/kg/day) compared with those for skeletal muscle (13 kcal/kg/day), liver (200 kcal/kg/ day), brain (240 kcal/kg/day), and heart and kidneys (440 kcal/ kg/day).[47]

Other non-nutritional calorie sources of energy, citrate (2.5 kcal/mg) and lactate (9 kcal/l) from solutions used in continuous veno-venous hemo(dia)filtration (CVVH, CVVHDF), influx calorie and should be accounted in daily energy intake. Fluid substitutions with different CRRT settings will be delivered various results.[40,43,48]

IC is feasible and safe to use in ICU. For modern ICU, measurement of IC-REE is necessary due to need for personalized approach treatment for every patient.[49,50] Using IC during CRRT is possible, but it requires some relevant pitfalls for interpretation of IC-REE. The most influenced pitfall during CRRT is VCO_2. Also, protein, glucose and lactate exchange, citrate anticoagulation, and potentially immunological activation and heat loss caused by extracorporeal circuit may alert results of IC.[48] However, loss of CO_2 from the circuit could be challenging, but affected energy expenditure by less than 5%.[51] It is more challenging with ECMO. De Waele et coworkers, show significant variation in IC-REE during ECMO.[52] Tatucu-Babet et al. showed that modified IC measurement during veno-arterial ECMO is feasible in early period after ICU admission.[40] TICACOS, multi-centric, randomized study showed

mild benefit of tight calorie intake measured by IC in critical ill patents.[53] However, some experts in the field of nutrition question this method, providing valid concerns and arguments.[54]

Conclusion

Indirect calorimetry is a crucial tool in modern clinical nutrition, providing precise energy expenditure measurements that enable personalized medical nutrition therapy. Its application in critically ill patients ensures appropriate caloric intake, preventing both underfeeding and overfeeding, which can significantly impact patient outcomes. Despite its advantages, widespread use is limited by availability, cost, and technical challenges. Predictive equations remain useful alternatives but lack the accuracy of direct measurements. Future advancements in technology may enhance the accessibility of indirect calorimetry, further improving nutritional management in critically ill patients.

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References

1. Cederholm T, Barazzoni R, Austin P et al. (2017). ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr 2017;36*(1): 49-64.

2. Weimann A, Braga M, Carli F et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clin Nutr, 2021;40*(7): 4745–4761.

3. Williams DGA, Molinger J, Wischmeyer PE. The malnourished surgery patient: a silent epidemic in perioperative outcomes? *Curr Opin Anaesthesiol 2019; 32*(3): 405-411.

4. Thibault R, Abbasoglu O, Ioannou E. et al. ESPEN guideline on hospital nutrition. *Clin Nutr 2021;40*(12): 5684–5709.

5. Weimann A, Braga M, Carli F et al. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr 2017;36*(3): 623–650.

6. Braga M, Sandrucci S. Perioperative nutrition in cancer patients. *Eur J Surg Oncol, 2016;42*(6):751–753.

7. Arends J, Bachmann P, Baracos, V et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr, 2017;36*(1):11–48.

8. Burgos R, Bretón I, Cereda E et al. ESPEN guideline clinical nutrition in neurology. *Clin Nutr 2018;37*(1): 354–396.

9. Pironi L, Cuerda C, Jeppesen PB et al. (2023). ESPEN guideline on chronic intestinal failure in adults – Update 2023. *Clin Nutr, 2023;42*(10):1940–2021.

10. Mat Nor MB. Optimal nutritional therapy in critically ill patients: a narrative review. *Malaysian Journal of Anaesthesiology, 2024;3*(1): 42–54.

11. van Zanten ARH. Editorial: Personalized nutrition therapy in critical illness and convalescence: moving beyond one-size-fits-all to phenotyping and endotyping. Curr Opin Crit Care. 2023;29(4):281-285.

12. Holdoway A, Page F, Bauer J, Dervan N, Maier AB. Individualized Nutritional Care for Disease-Related Malnutrition: Improving Outcomes by Focusing on What Matters to Patients. *Nutrients 2022;14*(17): 3534.

13. Jensen GL, Cederholm T, Correia MITD, et al. GLIM Criteria for the Diagnosis of Malnutrition: A Consensus Report from the Global Clinical Nutrition Community. JPEN J Parenter Enteral Nutr. 2019;43(1):32-40.

14. Wischmeyer PE, Bear DE, Berger MM. Personalized nutrition therapy in critical care: 10 expert recommendations. *Crit Care. 2023;27*(1): 261.

15. Mohan, Shruthi, Schablein RW, Krallman KA, Goldstein S, Stanski NL. Bioelectrical Impedance Analysis to Assess Fluid Balance in Children Undergoing Continuous Kidney Replacement Therapy: SA-PO041. Journal of the American Society of Nephrology. 2024;35(10S):10.1681/ASN.2024jaax8f8r.

16. Singer P, Blaser AR, Berger MM. ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. *Clin Nutr, 2023;42*(9): 1671-1689.

17. Wischmeyer PE. Nutrition Therapy in Sepsis. Crit Care Clin. 2018;34(1):107-125.

18. Ndahimana D, Kim EK. Energy Requirements in Critically Ill Patients. *Clin Nutr Res, 2018;7*(2): 81-90.

19. Dresen E, Notz Q, Menger J et al. (2023). What the clinician needs to know about medical nutrition therapy in critically ill patients in 2023: a narrative review. *Nutr Clin Pract, 2023;38(3):* 479-498.

20. McClave SA, Taylor BE, Martindale RG, et al. Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E-.N.). JPEN J Parenter Enteral Nutr. 2016; 40(2): 159-211.

21. Cerra FB, Benitez MR, Blackburn GL, et al. Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. Chest. 1997;111(3):769-778.

22. *de Waele E, Opsomer T, Honoré PM, Diltoer M, Mattens S, Huyghens L, Spapen H. Measured versus calculated resting energy expenditure in critically ill adult patients. Do mathematics match the gold standard? Minerva Anestesiol. 2015;81:272–282.*

23. Cordoza M, Chan LN, Bridges E, Thompson H. Methods for Estimating Energy Expenditure in Critically Ill Adults. *AACN Adv Crit Care, 2020;31*(3): 254-264.

24. Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci USA. 1918;4(12):370–373.

25. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. JPEN J Parenter Enteral Nutr. 2011;35(2):264-269.

26. Vest MT, Newell E, Shapero M, McGraw P, Jurkovitz C, Lennon SL, Trabulsi J. Energy balance in obese, mechanically ventilated intensive care unit patients. Nutrition. 2019; 66:48-53.

27. Delsoglio M, Achamrah N, Berger MM, Pichard C. Indirect calorimetry in clinical practice. *J Clin Med 2019;8*(9):1387.

28. Byerly SE, Yeh DD. The Role of Indirect Calorimetry in Care of the Surgical Patient. *Curr Surg Rep, 2022;10*(11): 186–191.

29. Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care. 2021;9(1):8.

30. Gupta RD, Ramachandran R, Venkatesan P, Anoop S, Joseph M, Thomas N. Indirect calorimetry: From bench to bedside. *Indian J Endocrinol Metab, 2017;21*(4), 594–599.

31. Ferrannini E. The theoretical bases of indirect calorimetry: a review. Metabolism. 1988;37(3):287-301.

32. Koekkoek WAC, Xiaochen G, van Dijk D, van Zanten ARH. Resting energy expenditure by indirect calorimetry versus the ventilator-VCO_2 derived method in critically ill patients: The DREAM-VCO_2 prospective comparative study. Clin Nutr ESPEN. 2020;39:137-143.

33. Oshima T, Berger MM, De Waele E, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr. 2017;36(3):651-662.

34. Kagan I, Zusman O, Bendavid I, Theilla M, Cohen J, Singer P. Validation of carbon dioxide production (VCO_2) as a tool to calculate resting energy expenditure (REE) in mechanically ventilated critically ill patients: a retrospective observational study. Crit Care. 2018;22(1):186.

35. Flancbaum L, Choban PS, Sambucco S, Verducci J, Burge JC. Comparison of indirect calorimetry, the Fick method, and prediction equations in estimating the energy requirements of critically ill patients. Am J Clin Nutr. 1999;69(3):461-466.

36. Singer P, Singer J. Clinical Guide for the Use of Metabolic Carts. *Nutr Clin Pract, 2016;31(1)*:30-38.

37. Berger MM, Reintam-Blaser A, Calder PC et al. Monitoring nutrition in the ICU. *Clin Nutr* 2019;38(2):584-593.

38. Haugen HA, Chan LN, Li F. Indirect Calorimetry: A Practical Guide for Clinicians. *Nutr Clin Pract, 2007;22(4):* 377-388.

39. De Waele E, van Zanten ARH. Routine use of indirect calorimetry in critically ill patients: pros and cons. Crit Care. 2022;26(1):123.

40. Tatucu-Babet OA, Diehl A, Kratzing C, Lambell K, et al. Modified indirect calorimetry for patients on venoarterial extracorporeal membrane oxygenation: a pilot feasibility study. Eur J Clin Nutr. 2023;77(9):888-894.

41. Reintam Blaser A, Starkopf J, Alhazzani W, et al.; ESICM Working Group on Gastrointestinal Function. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43(3):380-398.

42. Hill A, Elke G, Weimann A. Nutrition in the intensive care unit - a narrative review. *Nutrients 2021;13*(8):2851.

43. Compher C, Bingham AL, McCall M, et al. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr. 2022;46(1):12-41. Erratum in: JPEN J Parenter Enteral Nutr. 2022;46(6):1458-1459.

44. Shah U. Nutritional practices in critically ill patients – A review. *Vidarbha Journal of Internal Medicine, 2022;32:* 42-49.

45. Bousie E, van Blokland D, Lammers H et al. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. *Eur J Clin Nutr, 2016;70(12)*: 1443–1450.

46. Kim TJ, Park SH, Jeong HB, et al. Optimizing Nitrogen Balance Is Associated with Better Outcomes in Neurocritically Ill Patients. Nutrients. 2020;12(10):3137.

47. Elia, M. Organ and tissue contribution to metabolic rate. In: Kinney, JM.; Tucker, HN., editors. Energy Metabolism: Tissue Determinants and Cellular Corollaries. Raven Press; New York: 1992. p. 61-80.

48. Jonckheer J, Spapen H, Malbrain MLNG, Oschima T, De Waele E. Energy expenditure and caloric targets during continuous renal replacement therapy under regional citrate anticoagulation. A viewpoint. Clin Nutr. 2020;39(2):353-357.

49. De Waele E, Jonckheer J, Wischmeyer PE. Indirect calorimetry in critical illness: a new standard of care? Curr Opin Crit Care. 2021;27(4):334-343.

50. De Waele E, van Zanten ARH. Routine use of indirect calorimetry in critically ill patients: pros and cons. Crit Care. 2022;26(1):123.

51. Singer P, Statlender L. Beyond the limits of indirect calorimetry. Eur J Clin Nutr. 2023;77(9):925-926.

52. De Waele E, Jonckheer J, Pen JJ, Demol J, Staessens K, Puis L, et al. Energy expenditure of patients on ECMO: A prospective pilot study. Acta Anaesthesiol Scand. 2019;63:360–364.

53. Singer P, De Waele E, Sanchez C, et al. TICACOS international: A multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study. Clin Nutr. 2021;40(2):380-387. Erratum in: Clin Nutr. 2023;42(3):440-441.

54. Casaer MP, Van den Berghe G, Gunst J. Indirect calorimetry: A faithful guide for nutrition therapy, or a fascinating research tool? Clin Nutr. 2021;40(2):651.