Early Feeding in Critical Care - Where Are We Now?

Mette M. Berger, MD, PhD[a,*], Annika Reintam Blaser, MD, PhD[b,c], Orit Raphaeli, PhD[d], Pierre Singer, MD[e,f]

KEYWORDS

• Enteral nutrition • Target • Gastrointestinal dysfunction • Gastric residual volume • Refeeding syndrome • Endogenous glucose production

KEY POINTS

- The critical illness journey is characterized by different phases with predominance of catabolism during the first days, which progressively shifts over to anabolism when inflammation fades: feeding tolerance is low during this phase.
- Full early feeding is deleterious whatever the route of feeding (enteral or parenteral).
- Enteral feeding intolerance (EFI), most often defined as increased gastric residual volumes (GRV), has repeatedly been shown to be associated with adverse patient-relevant outcomes that may justify continuing the measurements of GRV during initiation of enteral nutrition (EN), unless replaced by ultrasound or new technologies.
- Machine learning may be helpful to identify the risk of EFI and predict complications of EN.
- Early recognition of at-risk patients is a step toward personalized intensive care unit (ICU) nutrition that has the potential to improve outcomes across ICU patient journey.

INTRODUCTION

Medical nutrition therapy (MNT) has evolved considerably over the last 2 decades[1,2]; several high-quality trials were published, generating the need for a practical revision of the European guidelines.[3] The term MNT encompasses oral nutritional supplements, enteral nutrition (EN), and parenteral nutrition (PN). Despite recent studies having shown that PN is not inferior to EN when similar doses of nutrients are administered,[4,5] EN is still considered the next most physiologic after the oral intake,

[a] Faculty of Biology & Medicine, Lausanne University, Lausanne, Switzerland; [b] Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia; [c] Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland; [d] Department of Industrial Engineering and Management, Ariel University, Ariel, Israel; [e] Department of Anesthesia and Intensive Care, Faculty for Medical and Health Sciences, Tel Aviv University, Herzlia Medical Center; [f] General Intensive Care Department, Beilinson Hospital, Rabin Medical Center, Petah Tikva 49100, Israel
* Corresponding author.
E-mail address: mette.berger@unil.ch

Crit Care Clin ■ (2024) ■–■
https://doi.org/10.1016/j.ccc.2024.09.002 **criticalcare.theclinics.com**

leaving the PN at the end of the "feeding hierarchy" in the critically ill in the most recent guidelines.[1,3,6] But in the 2019 guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), for the first time, the existence of different metabolic phases of critical illness was recognized,[1] underlining the importance of dose rather than route, as the key player in the early MNT, explaining the results of randomized controlled trials (RCTs).

Accordingly, a question arises: is this strong encouragement of early EN really optimal in the sickest patients? Next to overall negative effect of full dose nutrition in the early acute phase of critical illness, recent evidence has outlined rare but life-threatening complications related specifically to early full EN, such as mesenteric ischemia and Ogilvie's syndrome,[5,7] and showed association of the commonly occurring enteral feeding intolerance (EFI) with impaired outcome.[8] It is not entirely clear what are the associated metabolic changes and mechanisms worsening the clinical outcome related to early full feeding.

Hereafter, we will explore the different trials that have investigated the impact of different feeding strategies on outcome, discuss possible mechanisms behind the findings, and address aspects that have not been studied sufficiently. We discuss definitions of EFI as a reflection of gastrointestinal (GI) dysfunction during acute illness and respective management of EFI.

RECENT HISTORY OF NUTRITIONAL INTERVENTIONS IN THE CRITICALLY ILL

The "enteral nutrition mantra" became dominant after the demonstration in the late 1980s that 5 days of PN compared to EN in healthy subjects resulted in an exacerbated inflammatory response to an endotoxin injection.[9] And indeed, the lipid emulsions used in PN were limited to n-6 fatty acids, which were proinflammatory.[10] Further overfeeding was the rule at that time, the first name of PN being "hyperalimentation." EN could only be better: thus an intense controversy resulted,[11] with authors writing articles entitled "Death by parenteral nutrition."[12] But the strong encouragement of EN as the "only accepted feeding route" has also potentially resulted in iatrogenic malnutrition.[13,14]

Importance of Energy Balance

Twenty years ago, 2 prospective observational studies using the same methodology[13,14] showed in 100 critically ill patients that growing negative energy balances caused by insufficient EN were linked to increasing number of complications. Both studies also showed that a modest energy deficit generated by the progressive feeding strategy was well tolerated: a cumulated deficit of −4′000 kcal (−50 kcal/kg) had no consequence. But with the progression of the deficit beyond −8′000 kcal (−100 kcal/kg) assumably malnutrition-related complications increased, affecting 100% of patients when −10′000 kcal (−130 kcal/kg) were reached. The complications presented as ventilator-associated pneumonia (VAP), wound dehiscence and infection, sepsis, pressure sores, and renal failure. Similarly Faisy and colleagues[15] showed that a *large negative energy balance (based on predictive equation)* during the first 14 days of the intensive care unit (ICU) stay was an independent determinant of mortality in a very sick medical oncological population with prolonged mechanical ventilation and ICU stay: the threshold for increasing mortality was 5021 kJ/d (−1200 kcal/d). A few years later, Yeh and colleagues[16] confirmed these data, showing in 213 surgical ICU patients that those who had negative energy balances exceeding −6′000 kcal were 3 times less likely to be discharged to home. More recently, similar consequences were shown in children: energy deficit, low serum albumin, and elevated C-reactive protein (CRP)

were also associated with length of mecahnical ventilations and length of stay.[17] A prospective cohort study in 100 ICU patients identified a critical cutoff for complications of 480 kcal/d, which was present in 72% of patients, and was associated with higher mortality ($P = .03$).[18] Both energy and protein deficits increased the length of hospital stay, and protein deficit greater than 20 g/d was an independent factor for ICU mortality.[18]

Negative energy balances also impact the type of microorganisms causing infection, as shown by Faisy and colleagues.[19] In their second study, they first confirmed the link between deficit and severe infections. Then they showed that the largest cumulated energy deficits were associated with a higher incidence of *Staphylococcus aureus* ventilator associated pneumonia (VAP) than those with VAP caused by other pathogens ($-10{,}275 \pm 4211$ kcal vs -7376 ± 4013 kcal from ICU admission to the day of balance, $P < .01$). Taken together, information from these observational studies and physiologic rationale provided a base for RCTs comparing targeted (higher) versus nontargeted (or targeted lower) provision of energy and protein in critically ill to improve outcomes.

Randomized Controlled Trials on Early Nutrition

Having demonstrated the link between growing energy deficit and outcome,[13,14] early full feeding using a combination of EN and PN was considered the best preventive approach, but proved wrong.

Several "negative trials" attempted immediate full feeding from day 1 by EN, PN, or a combination. The randomized trials EPaNIC[20] and PEPaNIC[21] were conducted with similar protocols in adults and in children. The studies compared early supplemental PN within 24 hours of ICU admission introduced to a fixed target of 25 kcal/kg from day 01 on, or to receive PN after 7 days (late): EN was initiated during the first weeks in both groups, and insulin was infused to achieve normoglycemia. The higher insulin requirements in the early PN group likely reflected overfeeding. Both trials showed no mortality difference, but a higher rate of infectious complications, with prolonged mechanical ventilation, and delayed ICU and hospital discharge.[22]

The randomized EDEN trial compared initial "trophic" feeding with full feeding for up to 6 days, in patients with acute lung injury (ALI)[23] to test the hypothesis that trophic enteral feeding would be better. The trophic strategy did not improve ventilator-free days, 60 day mortality, or infectious complications but was associated with less GI intolerance.

The randomized INTACT study tested intensive feeding (ie, provision of >75% of estimated energy [25–30 kcal/kg]) and protein needs from ICU admission for ALI to hospital discharge compared with standard nutrition.[24] A significantly higher mortality (40% vs 16%, $P = .02$) in the early full feeding group was observed with first deaths occurring on day 4, and the study was stopped for futility. Of note the early full feeding group had been in hospital with poor/nil feeding for 8 days before ICU admission. While no phosphate data were available, the likeliness of a refeeding syndrome ranks high among possible causes of death.

In summary, no RCT has shown benefit from early full feeding in critically ill patients, and several studies have even shown potential harm. Accordingly, early full feeding by any route is clearly not advocated anymore.[1,3] The progressive delivery of enteral feeds with an individual adjustment of targets seems to be the safe way but the optimal timing, dose, and slope of progression for individual patient remain unclear.

The Swiss randomized supplemental PN trials, SPN1[25] and SPN2[26] used an individualized strategy while targeting a measured energy target only from day 4 of the ICU admission, addressing the question of tolerable energy deficit. Eligibility criterion was to be a patient on EN who was not receiving 60% of the initially prescribed target on

day 3 (mean cumulated deficit −4000 kcal). The energy expenditure (EE) was measured by indirect calorimetry (IC) to adjust the feeding target. The intervention patients received SPN to complete the measured EE value, while control patients continued on EN only. The individually optimized energy completion with SPN starting on day 4 was associated with a significant reduction of nosocomial infections and reduced inflammatory response (TNF-α tumor necrosis factor-α).[26] That there might be a maximal of 3 to 4 days before energy deficit becomes deleterious is also supported by a surgical study[27]: in 230 major abdominal surgery patients with identified high nutritional risk and poor EN tolerance, early SPN, that is, introduced by day 3 versus day 7, resulted in higher energy delivery (26.5 $\pm$ 7.4 vs 15.1 $\pm$ 4.8 kcal/kg daily), and fewer nosocomial infections (10 out of 115 [8.7%] vs 21 out of 114 [18.4%]; $P = .04$). In the TICACOS International study,[28] energy target was guided by daily IC measurements. When compared to standard therapy using predictive equations, the study group received significantly more energy, despite measured and estimated energy targets being similar, and showed a trend to decrease in the infection rate and the mortality rate without reaching significance. A meta-analysis of studies comparing energy targeted using IC and standard therapy found a significantly improved short-time survival without differences in other outcomes.[28]

Importantly, underfeeding is even more difficult to detect at bedside as compared to overfeeding. There is a relevant risk that recent evidence on the harm of early full feeding will cause feeding practices worldwide switching from early overfeeding to prolonged underfeeding. Therefore, careful interpretation of available studies and possible mechanisms for harm is needed. It will be a big challenge to design the next relevant and meaningful large study on nutrition, and it would thereby be important to avoid a research question "when is a lower energy delivery not enough during early and later phases?"

METABOLIC CONSEQUENCES OF THE EARLY FULL FEEDING

The metabolic consequences of achieving a full energy target determined by a predictive equation faces four types of risks that may explain their disappointing and even negative results: (1) the risk of early overfeeding due to the low metabolic rate during shock phase, and the persistence of the endogenous substrate production as long as the inflammatory response persists; (2) the risk of refeeding syndrome in patients who had low or nil intakes for several days before the ICU admission[29]; (3) the suppression of adaptive mechanisms that are evolutionary developed to cope with severe illness (autophagy and ketogenesis); and (4) aggravating GI dysfunction by high feed volumes with EN.

Overfeeding

Providing excessive amounts of energy is deleterious but is an easily modifiable factor. Mainly 2 mechanisms cause it: prescribing feeds higher than needs and not respecting adaptive mechanisms to disease. A delivery of feeds in excess of the EE is a consequence of the full feeding strategy[30]: it is frequent with predictive equations,[31] and the IC is useful.[32] However, in the early phase, the elevated endogenous glucose production (EGP), which is present during the acute phase of inflammation is not quantified by IC and is not repressed by feeding.[33] EGP cannot be measured at the bedside (measure requires isotopic methods), but it is indirectly reflected by high insulin requirements and high VCO_2.[34] Full coverage of estimated energy requirements with feeding in addition to an elevated EGP is potentially deleterious as it generates overfeeding.[30] In young patients with major trauma, starved by day 3 for undue reasons,

Tappy and colleagues[35] showed that EGP generated the 3.1 mg/kg/min of glucose, equivalent of 1200 kcal/d: this occurred at the expense of protein catabolism, amino acids being used for gluconeogenesis. Similar results were observed in partially fed 65 year old patients: the mean amount of EGP by day 4 was still 180 g/d glucose (720 kcal/d).[26]

The metabolic processes leading to nonsuppressible EGP and clinical harm from more energy in the early phase are not entirely understood. The purpose of EGP is to provide a continuous glucose supply to the glucose-dependent organs (brain, blood cells, and kidney medulla) to enable ATP production, while not preventing the consequences of persisting energy deficit. By providing too much extrinsic energy, that is, feeding, we disturb some protective adaptive mechanisms developed during evolution. The progressive feeding strategy has the advantage of not overwhelming the organism.

This early phase is generally characterized by an intense inflammation during which there is resistance to nutrition.[36] Intramuscular inflammation and altered substrate utilization have been shown to be present during the first week of critical illness,[37] potentially impeding beneficial effects of nutrition and exercise. Accordingly, inflammation markers (even the simple CRP) may provide an interesting research tool in fine-tuning of nutritional interventions as well as exercising in the ICU.

Refeeding Syndrome

The transition from fasting to eating is a physiologic process that can malfunction,[38] and early full feeding is a major risk factor: a small intake of glucose from feeding or drug dilution is sufficient to initiate it. When nutrition begins, insulin not only transports glucose but also moves potassium and phosphate to intracellular space. Glucose oxidation increases the demand for thiamine and phosphate, resulting in hypokalemia, hypophosphatemia, hypomagnesemia and may lead to fatal arrhythmias, muscle weakness, congestive heart failure, lactic acidosis, and acute abdominal symptoms. Prevention resides in a progressive delivery of feeding (whatever the route), and in case of development of hypophosphatemia (Pi < 0.65 mmol/L for ESPEN[3] and for Doig and colleagues,[39] or a 0.16 mmol/L decrease for the latter),[39] to slow down the process by temporary reduction of feeding.[3]

Impact on Mitochondrial Adaptive Mechanisms

Mitochondrial function is strongly altered in the early phases of shock.[40] These functions include the production of ATP by oxidative phosphorylation, regulation of programmed cell death, calcium homeostasis, and the generation and control of reactive oxygen species.[41] In vitro their morphology changes in response to metabolic inputs. Mitochondrial fragmentation occurs in response to nutrient excess and cellular dysfunction, and it has been observed in cardiovascular and neuromuscular disorders, cancer, and obesity. It facilitates the autophagic clearance of mitochondria and allows the adaption to physiologic demands.[41]

Autophagy is a housekeeping mechanism,[42] a catabolic process induced under conditions of cellular stress, which prevents cell damage and promotes survival in the event of energy or nutrient shortage[43]: it is deregulated in the context of various human pathologies including critical illness. It serves to eliminate large protein aggregates and as a survival mechanism in starvation for generating energy (ATP) and promoting protein synthesis to maintain cell structure.[44] The effect of feeding on autophagy is complex, poorly understood, and difficult to predict.[45,46] Some authors consider that early PN and proteins might inhibit autophagy.[47] However, the argument to withhold feeding to preserve autophagy is poorly substantiated.[42]

Ketogenesis

Starvation initiates an integrated metabolic response to prevent hypoglycemia and energy depletion, and the generation of ketone bodies (ketone-3-hydroxybutyrate and acetoacetate) by the liver is the normal response to fasting in healthy subjects. The nonesterified fatty acids released during lipolysis triggered by fasting are degraded through β-oxidation within liver mitochondria, resulting in the production of acetyl-CoA, which is then either incorporated into the tricarboxylic acid cycle or channelled into the ketogenesis pathway.[48] Insulin typically inhibits ketogenesis as does full feeding.

In critical illness utilization of glucose and fatty acids is impaired, which may contribute to organ dysfunction. A pilot study including 29 critically ill patients randomized them to either ketogenic (n = 14) versus standard enteral feeding for 10 days[49]: the ketogenic high lipid diet proved to be safe and well tolerated and resulted in a modest but significant ketosis in all patients. This was associated with lower insulin requirements, fewer hypoglycemic events, but more diarrhea. The interest of this strategy remains to be confirmed.

Overloading the Gastrointestinal Tract

The impact of early EN on the GI tract is described in "Obstacles to Enteral Feeding" and "Impact of EFI on Clinical Outcomes" sections. Overloading with EN may result in gastric overfilling, intestinal dilatation and/or diarrhea, all with potentially severe consequences. In a study including 278 patients and 1595 patient-days, diarrhea was observed in 38 patients (14%) and 83 patient-days.[50] Diarrhea risk factors were EN covering greater than 60% of energy target (relative risk, 1.75 [1.02–3.01]), antibiotics, and antifungal drugs.

ENTERAL FEEDING INTOLERANCE AND GASTROINTESTINAL DYSFUNCTION

Definitions

There is no unique consensus definition available for EFI, with different approaches being proposed.[51–53] A systematic review[53] largely confirmed the results of an earlier review[54] with still the same wide variation of definitions being used in studies. Different studies have measured EFI by assessing gastric residual volumes (GRV), a variety of GI signs and symptoms (eg, vomiting, abdominal distension, and diarrhea) including or excluding GRV, or the amount of EN received compared to an estimated full energy target.[53,54]

- GRV alone is of limited use due to different cutoffs[53,54] and measurement strategies[55] with some ICUs not using this technique at all. Moreover, gastric intolerance may not be clinically as significant as postpyloric intolerance that may remain undetected or even mismanaged with focusing solely on GRV.[51,52,56]
- GI signs and symptoms may reflect GI dysfunction caused or aggravated by EFI, but the assessment is observer dependent. Studies suggest that number of concomitant symptoms is important and considering different aspects necessitate a complex scoring system.[57]
- The amount of energy target reached with EN. Practically, EFI indeed means that EN cannot be administered in a planned amount due to GI dysfunction. However, several other definitions and decisions influence the amount of EN (**Fig. 1**).[56]

GRV and IAP are the only numerical variables on the list of variables possibly reflecting GI dysfunction, but their respective value is disputed.[51,53] A broad approach covering all different mechanisms of EFI is advocated by the third group of authors.[52]

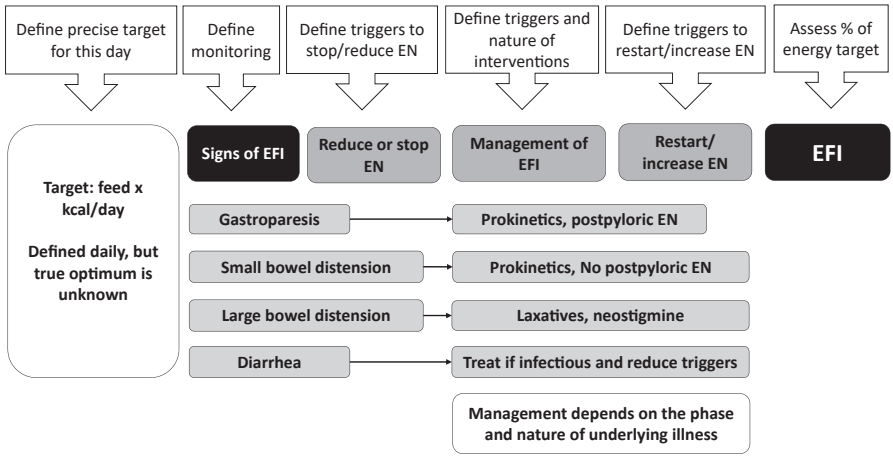

Fig. 1. Definitions and decisions before using the proportion of energy target as definition for EFI.[56] (Reproduced with permission.[56])

The latter is complicated and includes several observer-dependent features but is supported by the evidence showing that inclusion of all available aspects of GI dysfunction results in better prediction of mortality.[57] A recent consensus process on daily monitoring of GI function (Core Outcome Set of daily MOnitoring of GastroIntestinal function in critically ill patients—https://cosmogi.site) united researchers and physicians worldwide for a joint effort in this area. McClave and colleagues[51] importantly pointed out that a new definition of EFI is probably not helpful if it does not lead to a correct therapy, or even leads to a wrong therapy.

The main difference between EFI and GI dysfunction is application of EN, considering EFI as worsening of GI dysfunction in response to EN, whereas GI dysfunction can also occur without application of EN. Current assessment of GI dysfunction is limited to mainly signs of GI dysmotility, not enabling accurate measurement of digestion and absorption, endocrine, immunologic, and barrier functions. Accordingly, while clinical assessment can be used in the absence of biomarkers,[51,52,58] search for biomarkers, mainly focusing on absorption of nutrients and on barrier function, needs to be continued. In the future, a score of GI dysfunction should ideally enable the identification of patients with a greater likelihood for EFI upon initiation of EN and, at the same time, enable the identification of patients at an increased risk for adverse outcomes related to EFI.[51]

Obstacles to Enteral Feeding

Multiple obstacles to achieve enteral feeding targets have been observed in different studies.[59] They include inadequate tube position, missing energy target due to unadjusted time, speed or body position, nutrition interruptions due to investigations and interventions, GI complications, and missing protocols. Nasogastric tube malposition is relatively common: around 24,000 cases of pulmonary malposition occurred for 1.2 million nasogastric tubes inserted in the United States.[60] This complication may induce around 5000 pulmonary complications and increase length of stay and hospital costs.[61] A small study in 61 patients showed 115 EN interruptions occurring mainly due to a computed tomography scan (n = 27), gastric paresis with high GRV (n = 19), nasogastric tube dysfunction (n = 16), and planned extubation (n = 10). Most

interruptions occur within the first 3 days of ICU admission, lasting the longest in case of tube malfunction.[62,63] A nurse-driven study in 87 patients showed that the main reasons for not introducing and progressing EN were recent GI surgery, shock, and large GRV.[64]

Impact of Enteral Feeding Intolerance on Clinical Outcomes

EFI has repeatedly been shown to be associated with adverse patient-relevant outcomes.[8,53,54,65,66] The most recent and largest study including 15,918 patients used a broad approach identifying EFI as interruption of EN due to either high GRV, increased abdominal girth, distension, subjective discomfort, emesis, or diarrhea.[8] One-quarter of patients developed EFI, and adjusted hazard of death increased by 1.5 (95% CI 1.4–1.6) after the development of EFI. High GRV increased the risk of having another day with EFI compared to patients in whom EFI was diagnosed without high GRV.[8] Another large study observed a GRV of 250 mL or greater in 46% of patients, more often in patients receiving energy-dense feeds, and an increase in adjusted 90 days mortality in patients presenting with high GRV.[66] It is not clear whether this finding should be attributed to a different composition (energy density) of the EN causing EFI or rather supports the hypothesis that higher energy dose provided by EN results in both more EFI and worse outcome. Prevalence and mortality of EFI are obviously highly dependent on the definition of EFI that is applied.[53,54,67]

Measuring GRV is a matter of discussion since Reignier and colleagues demonstrated that not measuring GRV contributed to improve feed delivery[68] without increasing the incidence of VAP in medical ICU patients receiving full EN.[69] However, 3 large observational studies showed its association with adverse outcomes,[8,66,70] suggesting that measurements should not be abandoned without a robust substitute for monitoring gastric feeding intolerance. Two large RCTs compared full EN versus PN initiated within 24 to 36 hours of ICU admission: the CALORIES trial with 2400 patients (target 25 kcal/d),[4] and the NUTRIREA-2 trial with 2410 patients (20–25 kcal/kg/d).[5] In both studies, more GI complications and increased use of prokinetics were shown in the EN group.

The question whether EFI is reflecting severity of illness and the applied organ support therapies rather than the result of GI dysfunction or inappropriate EN, is matter of debate.[51,52] Clearly, EFI occurs more often in more severely ill patients, who also receive more treatments potentially causing or aggravating GI dysfunction such as vasopressors, opioids, sedatives, mechanical ventilation, and broad-spectrum antibiotics. However, recent studies using adjusted analyses suggest that GI dysfunction itself may influence patient-relevant outcomes independently.[8,57,65,66]

Why EFI or its management may impact outcomes has not been widely studied and discussed. Assessment of EFI is performed at the bedside by ICU health care professionals without robust monitoring tools and also decisions to manage EFI are subjective and probably widely variable. When considering definition of EFI based on achieved energy target via EN, this obviously may include several interventions to increase provision of EN, which potentially may have impact on outcome beyond the effect of EFI itself.

Dose of Enteral Nutrition as a Target of Nutritional Intervention

Recent evidence suggesting harm from full energy dose provided in the early phase[7,71] supports the hypothesis that EFI may be an adaptive mechanism. Indeed, earlier studies comparing EN versus PN consistently showed worse outcomes in patients with PN: more recent knowledge attributes this effect to the lower energy administered with EN and higher with PN, leading to overfeeding in the latter. Accordingly,

EFI might be seen as a protective mechanism against overfeeding. EN may result in specific complications, leading to not only a higher number of GI symptoms but also potentially life-threatening conditions such as Ogilvie's syndrome and acute mesenteric ischemia, as shown in studies administering an early full dose of EN, especially in patients receiving vasopressors.[5,7,71] On one hand, this may appear logical because EFI can occur only in patients receiving EN. On the other hand, the provision of EN would be expected to have positive effects on GI motility, enterocyte function, intestinal mucosal integrity, and microbiome.[72–74]

The effect of difference in dosing between EN and PN was only realized more recently.[75] This hypothesis, may have important implications for feeding practices, suggesting that EFI should, maybe, not always be "aggressively" treated, but that a reduction of EN might be a more appropriate intervention. With this concern, the recent update of ESPEN guidelines already revised the suggestion to treat EFI with reasonable measures, instead of maximizing EN.[3]

Some important questions remain.

- Does early trophic EN exhibit beneficial effects on GI motility, enterocyte function, mucosal integrity, and microbiome, while balanced against potential negative metabolic effects of nutrients in the early acute phase, and accordingly, should early trophic EN be aimed in majority of patients?
- How to differentiate negative effect of too much nutrition from negative effect of GI dysfunction, and accordingly, how large energy deficit should be accepted before SPN becomes indicated?

The hypothesis that EFI might be adaptive at some stages of critical illness, but become maladaptive with time, if left untreated, similar to many other adaptive mechanisms (eg, tachycardia and tachypnea) requires validation. Future studies assessing different dose and progression of EN should also integrate assessment of GI dysfunction and possibly treatment of EFI.

Achievement of nutrition targets via EN should probably not be seen as an alone-standing treatment goal and is rather not a patient-relevant outcome. The strategy is summarized in **Fig. 2**. As the first attempt to combine nutrition targets with assessment of GI function and its management, a recent single-center RCT demonstrated that progressive targets of EN were more appropriately reached with a novel system allowing automated regulation of the dosage of EN with concomitant reflux control.[76] Whether this translates to improved patient-relevant outcomes remains to be clarified.

PERSONALIZED NUTRITION WITH NEW TECHNOLOGIES AND ARTIFICIAL INTELLIGENCE

Machine-Learning Models to Predict Enteral Feeding Response

Machine learning (ML), a subfield of artificial intelligence (AI), uses statistical analysis and computational technologies to learn from experience and detect patterns from datasets.[77] ML is valuable when predictors are numerous and/or their effects are complex and nonlinear. Studies have applied ML to predict clinical outcomes and complications in the ICU, including identifying nutrition-related issues (**Table 1**). Wang and colleagues[77] created a model to identify ICU populations needing EN by applying 6 ML algorithms to a dataset of 53,150 patients. The eXtreme Gradient Boosting (XGBoost) algorithm had the best performance with an Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.90 (95% CI 0.89–0.91). Key predictors were sepsis, Sequential Organ Failure Assessment (SOFA) score, and acute kidney injury.

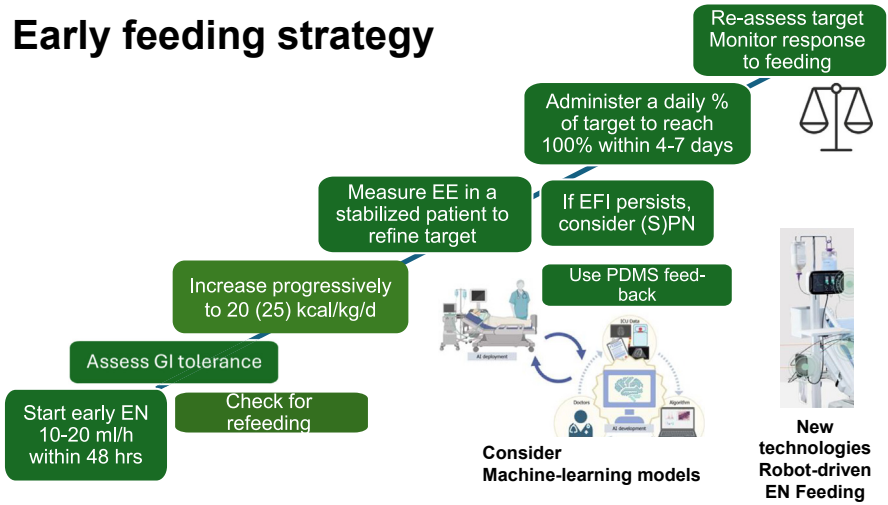

Fig. 2. In critically ill patients, the feeding strategy should be individualized from start: proceed stepwise over the first days, while carefully monitoring intestinal and metabolic responses, and adapting to those responses. Protein delivery should be monitored, but it will progress according to your available feeding products. EFI, enteral feeding intolerance; EE, energy expenditure; PN, parenteral nutrition; SPN, supplemental PN; PDMS, patient data management system.

Lu and colleagues[78] developed a clinical prediction model for EFI risk in ICU patients receiving EN using a cohort of 203 patients. A logistic regression algorithm achieved an AUCOC of 0.70 (95% CI 0.63–0.77), with age, GI disease, and early feeding as important predictors. Hu and colleagues[79] validated a model to predict EFI in ICU patients with sepsis using a dual-center, retrospective, case–control study of 195 patients. The artificial neural network algorithm had an AUCOC of 0.79 (95% CI 0.68–0.89), with respiratory infections, peptide EN, and shock as the main factors. Raphaeli and colleagues[70] examined EFI markers during early ICU in a retrospective single-center study, using seven ML algorithms on data from 1584 patients. The gradient boosting algorithm had the highest predictive value with an AUCOC of 0.71 (95% CI 0.67–0.74), with BMI, high GRV on day 2, and high SOFA on day 1 as the main factors for early EN failure. Choi and colleagues[80] used an ML model to identify patients at risk for refeeding syndrome in a study of 806 patients. The XGBoost algorithm had an AUCOC of 0.95 (95% CI 0.92–0.97), with low initial phosphate, recent weight loss, and high creatinine as the main factors to predict refeeding syndrome. Overall, these studies show ML can support nutritional therapy decisions, but methodological differences in designs, endpoint definitions, and risk factors limit generalization. More research is needed to improve ML model generalization.

New Technologies

A large gap between EN prescription and delivery has been described in numerous observational studies,[81] the most efficient centers achieving 80% of the prescribed value.[82,83] Computerized information systems can or are customized to enable visualization of nutrition quantity being delivered.[61] Technological help to monitor the actual feeding in an individual patient has been available since a while, but it is still rarely requested/used.

Table 1
Main characteristics of machine learning-based predictive models of enteral nutrition response

Study	N patients	Primary Endpoint	ML Algorithms Compared	Best Algorithm	Main Predictors
Wang et al,[77] 2023	N = 53,150, n = 7210 (13.5%) initiated EN at early phase	EN initiation	XGBoost, SVM, KNN, RF, LR, and DT	XGBoost	Sepsis, SOFA score, AKI, and body temperature
Lu et al,[78] 2022	N = 203, n = 77 (37.9%) with EFI	EFI	LR	LR	Age, GI disease, early feeding, mechanical ventilation before EN started, and abnormal serum sodium
Hu et al,[79] 2022	N = 195, n = 86 (44.1%) with EFI	EFI	ANN, GB, RF, LR, and NB	ANN	Infection of the lower respiratory tract, peptide EN, and shock
Raphaeli et al,[70] 2023	N = 1584, n = 1019 (64.3%) with early EN failure	Early EN failure	GB, KNN, DT, RF, XGBoost, LR, and AdaBoost	GB	BMI, high GRV (>250 mL) on second day of ICU admission, SOFA, and age
Choi et al,[80] 2021	N = 806, n = 367 (45.5%) with hypophosphatemia	Refeeding syndrome	XGBoost, LR, L1, and L2	XGBoost	Low initial phosphate, recent weight loss, high creatinine, diabetes mellitus with insulin use, low HbA1c, furosemide use, ICU admission, blood urea nitrogen level of 19–65 mmol/L, PN, magnesium below or above the normal range, low potassium, and older age

Abbreviations: AdaBoost, Adaptive Boosting; ANN, artificial neural networks; DT, decision tree; GB, gradient boosting; KNN, K-nearest neighbor; L1, lasso regression; L2, ridge regression; LR, logistic regression; ML, machine learning; NB, Naïve Bayes; RF, random forest; SVM, support vector machines; XGBoost, eXtreme Gradient Boosting.

Intragastric balloon monitoring

A technique to assess gastric motility by measuring the pressure in a low-volume intragastric balloon mounted on a gastric feeding tube was presented by Goelen and colleagues.[84–86] This device might serve to detect GI motility disorders but requires validation in ICU patients.

An integrative platform

A new platform to improve feeding has been developed aiming at overcoming frequent problems of EN,[76] called smART+ (ART Medical, Netanya, Israel): its originality resides in the integration of tube positioning confirmation, reflux and gastric residual volume monitoring using a nasogastric tube equipped with sensors, and EE calculation from an integrated VCO_2 measurement.[87,88] Accordingly, the system should facilitate achieving the EN target. EN is administered or stopped according to the detection of refluxes, ensuring a high feeding efficiency in case of the absence of refluxes and safety in case of presence of refluxes, accordingly.[76] It may confirm Reignier's hypothesis[69] that gastroesophageal reflux is independent of the actual GRV.

The performance of this platform was compared with conventional feeding. The EE was calculated from VCO_2 in the intervention group versus measured by IC in the controls—the latter patients having a higher prescribed energy target (2030 vs 1725 kcal). Kagan and colleagues[76] showed close to a 100% feeding efficiency (ie, reaching prescribed value), overfeeding, defined as exceeding of estimated and prescribed needs was avoided and underfeeding minimalized (**Fig. 3**, **Table 2**). The prescribed target was reached only in 34% of control patients. Whether the targets, set in a progressive way with starting low and not exceeding 70% of targets, were entirely appropriate for each individual patient considering EGP and refeeding, is not known. However, adjusted length of stay and length of ventilation were significantly reduced (by 3 or more days) in the intervention group, supporting a benefit.[76] Whether this benefit might have occurred largely due to the prevention of regurgitation remains to be answered. In a post hoc analysis, most feeding interruptions (80%) were related to diagnostic/therapeutic interventions.[89] These results are promising and must be confirmed in further studies including cost–benefit analysis and nurse acceptance.

This integrative platform and the use of AI are tools to personalize EN in critically ill patients.[90] Whereas the guideline recommendations[3] suggest using the gastric route, to determine energy and protein target, to administer EN continuously and only react to GI intolerance and vomiting, AI might become a tool enabling prediction of EN success and preventing complications.

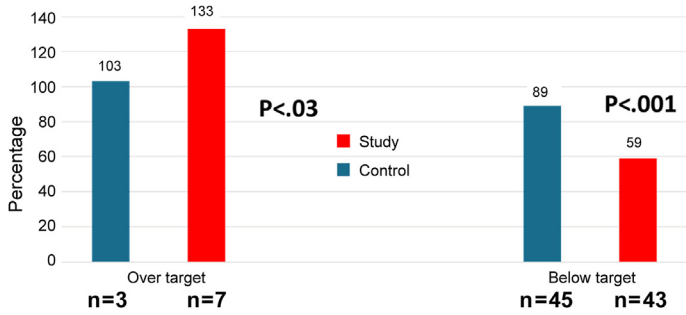

Fig. 3. Average deviation from 100% feeding efficacy defined as reaching prescribed target using a robot-guided enteral feeding system.[76]

Table 2
Main differences observed in 100 critically ill patients between enteral standard therapy and the use of the integrative platform.[76]

	Standard Therapy	Integrative Platform[76]	Pro/con
NGT position	Intermittent by radiography[59,60]	Continuously by sensors	NGT misplacement is easier recognized with platform: Sensors are alerting for misplacement and radiography is not required
Energy target determination	By predictive equation and calculation	Target based on EE calculated from VCO_2[87,88]	Automatic adjustment according to VCO_2 with progressive targets facilitates planning and delivery of EN
Choice of the formula	Dietician (or by protocol in many ICUs)	Computerized[a] according to the energy requirements and the hospital availability	Facilitates the dietician work but is more expensive
GI intolerance (reflux)	Not detected except vomiting, or if GRV is measured	Sensors detecting massive and minor refluxes	Reflux is difficult to detect clinically, and small reflux has been shown to be frequent. The tool could potentially replace GRV measurements
Energy target reached	Around 70% of the target[83]	Around 90% of the target	Progressive energy targets difficult to reach without automatization
Interruptions	Not compensated[32]	Compensated	Automatic compensation enables to nearly reach the target
Nonnutritional energy intake	Often not measured	Integrated manually[b] in the calculation of the energy target	May prevent overfeeding

Abbreviations: NGT, nasogastric tube, GRC, gastric residual volume.
[a] The platform enables customization of locally available formula, including special formula.
[b] The platform is not yet connected to the data management system or to pumps.

SUMMARY

After 3 decades of controversies regarding the feeding route and timing, a more physiologic approach to MNT is emerging. The recognition of different phases of critically illness is paramount for understanding apparently contradictory evidence. Critical illness in its early phase is associated with catabolism and inability to use nutrients for anabolism, and aggressive achievement of energy targets during this period may worsen GI dysfunction, delay recovery, and worsen outcome. PN is a decent alternative to EN in presence of EFI, whereas the main challenge remains to identify the appropriate dynamic targets avoiding overfeeding, refeeding, and underfeeding. It is possible and even likely that strong recommendations in favor of EN including aggressive treatment of EFI might be softened in future guidelines.

CLINICS CARE POINTS

- Education of staff (residents and registrars, nurses) regarding the complex nutritional needs of critically ill patients should be embedded into hospital orientation for ICU, and wards.
- Early assessment of the patient should be included the ICU protocols, and the specific tasks be precisely assigned to the different caregiver types.
- While an early progressive initiation of EN is desirable, the high incidence of EFI should be particularly emphasized in the teaching, as it informs about the severity of the metabolic alterations.
- Reporting of the indicators of intestinal function and indicators of feeding tolerance should belong to the medical visit.
- Collaborative multidisciplinary research is required to ensure appropriate delivery and monitoring of nutrition therapy.

DISCLOSURE

M.M. Berger received speaker honoraria from Abbott, Baxter, Fresenius Kabi, Nestlé Health; Support for attending meetings from Baxter and Fresenius Kabi Int. A. Reintam Blaser received speaker fees from Nutricia Danone and consultancy fee from VIPUN Medical and is holding a grant from the Estonian Research Council (Grant PRG1255). O. Raphaeli: declares no COI. P. Singer received Honoraria for lectures from Abbott, Baxter, Fresenius Kabi, Nestlé Health; Support for attending meetings from Baxter, Nestle Health and Fresenius Kabi Int.; Research grant to institution from Baxter, United States, Fresenius Kabi, Germany, Nestle, Switzerland, ART MEDICAL. Advisory board: Fresenius Kabi, ART MEDICAL.

REFERENCES

1. Singer P, Reintam-Blaser A, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48–79.
2. McClave SA, Taylor BE, Martindale RG, et al. 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 Enter Nutr 2016;40:159–211.
3. Singer P, Reintam Blaser A, Berger MM, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive care unit. Clin Nutr 2023;42:1671–89.

4. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults - calories Trial. N Engl J Med 2014;371:1673–84.
5. Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391:133–43.
6. 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 Enter Nutr 2022;46:12–41.
7. Reignier J, Plantefeve G, Mira JP, et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3). Lancet Respir Med 2023;11:602–12.
8. Heyland DK, Ortiz A, Stoppe C, et al. Incidence, risk factors, and clinical consequence of enteral feeding intolerance in the mechanically ventilated critically ill: an analysis of a multicenter, multiyear database. Crit Care Med 2021;49:49–59.
9. Fong YM, Marano MA, Braber A, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg 1989;210:449–57.
10. Calder PC. Hot topics in parenteral nutrition. Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults. Proc Nutr Soc 2009;68:252–60.
11. Jeejeebhoy KN. Total parenteral nutrition: potion or poison? Am J Clin Nutr 2001;74:160–3.
12. Marik PE, Pinsky M. Death by parenteral nutrition. Intensive Care Med 2003;29:867–9.
13. Villet S, Chioléro RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24:502–9.
14. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr 2006;25:37–44.
15. Faisy C, Lerolle N, Dachraoui F, et al. Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. Br J Nutr 2009;101:1079–87.
16. Yeh DD, Fuentes E, Quraishi SA, et al. Adequate nutrition may get you home: effect of caloric/protein deficits on the discharge destination of critically ill surgical patients. JPEN - J Parenter Enter Nutr 2016;40:37–44.
17. Carvalhal FB, Ferreira Peres WA, Fontes Lima GC, et al. Impact of energy deficit during hospitalization and biomarkers at admission on clinical outcomes in critically ill children: a longitudinal study. Clin Nutr ESPEN 2019;32:70–5.
18. Siqueira-Paese MC, Dock-Nascimento DB, De Aguilar-Nascimento JE. Critical energy deficit and mortality in critically ill patients. Nutr Hosp 2016;33:253.
19. Faisy C, Llerena M, Savalle M, et al. Early ICU energy deficit is a risk factor for Staphylococcus aureus ventilator-associated nneumonia. Chest 2011;140:1254–60.
20. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–17.
21. Vanhorebeek I, Verbruggen S, Casaer MP, et al. Effect of early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments in the PEPaNIC trial. Lancet Respir Med 2017;5:475–83.
22. Casaer MP, Wilmer A, Hermans G, et al. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247–55.

23. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307:795–803.
24. Braunschweig CL, Freels S, Sheean PM, et al. Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis. Am J Clin Nutr 2017;105:411–6.
25. Heidegger CP, Berger MM, Graf Set al, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385–93.
26. Berger MM, Pantet O, Jacquelin-Ravel Net al, et al. Supplemental parenteral nutrition improves immunity with unchanged carbohydrate and protein metabolism in critically ill patients: the SPN2 randomized tracer study. Clin Nutr 2019;38:2408–16.
27. Gao X, Liu Y, Zhang L, et al. Effect of early vs late supplemental parenteral nutrition in patients undergoing abdominal surgery: a randomized clinical trial. JAMA Surg 2022;157:384–93.
28. Duan JY, Zheng WH, Zhou H, et al. Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis. Crit Care 2021;25:88.
29. Koekkoek WAC, Van Zanten ARH. Is refeeding syndrome relevant for critically ill patients? Curr Opin Clin Nutr Metab Care 2018;21:130–7.
30. 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;36:651–62.
31. Zusman O, Kagan I, Bendavid I, et al. Predictive equations versus measured energy expenditure by indirect calorimetry: a retrospective validation. Clin Nutr 2019;38:1206–10.
32. Page A, Langan A, Wan YI, et al. Association between energy surplus and intensive care unit length of stay in critically ill patients: a retrospective cohort study. JPEN - J Parenter Enter Nutr 2024;48:206–14.
33. Wolfe RR. Sepsis as a modulator of adaptation to low and high carbohydrate and low and high fat intakes. Eur J Clin Nutr 1999;53(Suppl 1):S136–42.
34. Udin I, Habisreutinger M, Tappy L, et al. Magnitude of gluconeogenesis and endogenous glucose production: are they predictable in clinical settings? Clin Nutr 2021;40:3807–14.
35. Tappy L, Schwarz JM, Schneiter P, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, *de novo* lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med 1998;26:860–7.
36. Merker M, Felder M, Gueissaz L, et al. Association of baseline inflammation with effectiveness of nutritional support among pPatients with disease-related malnutrition: a secondary analysis of a randomized clinical trial. JAMA Netw Open 2020;3:e200663.
37. Jameson TSO, Caldow MK, Stephens F, et al. Inflammation and altered metabolism impede efficacy of functional electrical stimulation in critically ill patients. Crit Care 2023;27:428.
38. van Zanten ARH. Nutritional support and refeeding syndrome in critical illness. Lancet Respir Med 2015;3:904–5.
39. Doig GS, Simpson F, Heighes PTet al, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943–52.
40. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med 2007;35:S441–8.

41. Wai T, Langer T. Mitochondrial dynamics and metabolic regulation. Trends Endocrinol Metabol 2016;27:105–17.
42. McClave SA, Weijs PJ. Preservation of autophagy should not direct nutritional therapy. Curr Opin Clin Nutr Metab Care 2015;18:155–61.
43. Dikic I, Elazar Z. Mechanism and medical implications of mammalian autophagy. Nat Rev Mol Cell Biol 2018;19:349–64.
44. Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol 2010;221:3–12.
45. Wesselink E, Koekkoek WAC, Grefte S, et al. Feeding mitochondria: potential role of nutritional components to improve critical illness convalescence. Clin Nutr 2019;38:982–95.
46. Abate M, Festa A, Falco M, et al. Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol 2020;98:139–53.
47. Wernerman J, Christopher KB, Annane D, et al. Metabolic support in the critically ill: a consensus of 19. Crit Care 2019;23:318.
48. Fukao T, Lopaschuk GD, Mitchell GA. Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. Prostaglandins Leukot Essent Fatty Acids 2004;70:243–51.
49. McNelly A, Langan A, Bear DE, et al. A pilot study of alternative substrates in the critically Ill subject using a ketogenic feed. Nat Commun 2023;14:8345.
50. Thibault R, Graf S, Clerc A, et al. Diarrhoea in the intensive care unit: respective contribution of feeding and antibiotics. Crit Care 2013;17:R153.
51. McClave SA, Gualdoni J, Nagengast A, et al. Gastrointestinal dysfunction and feeding intolerance in critical illness: do we need an objective scoring system? Curr Gastroenterol Rep 2020;22:1.
52. Reintam Blaser A, Deane AM, Preiser JC, et al. Enteral feeding intolerance: updates in definitions and pathophysiology. Nutr Clin Pract 2021;36:40–9.
53. Jenkins B, Calder PC, Marino LV. A systematic review of the definitions and prevalence of feeding intolerance in critically ill adults. Clin Nutr ESPEN 2022;49:92–102.
54. Reintam Blaser A, Starkopf J, Kirsimagi U, et al. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand 2014;58:914–22.
55. Lindner M, Padar M, Mandul M, et al. Current practice of gastric residual volume measurements and related outcomes of critically ill patients: a secondary analysis of the intestinal-specific organ function assessment study. JPEN - J Parenter Enter Nutr 2023;47:614–23.
56. Reintam Blaser A, Bachmann KF, Deane AM. Gastrointestinal function in critically ill patients. Curr Opin Clin Nutr Metab Care 2023;26:463–9.
57. Reintam Blaser A, Padar M, Mandul M, et al. Development of the Gastrointestinal Dysfunction Score (GIDS) for critically ill patients - a prospective multicenter observational study (iSOFA study). Clin Nutr 2021;40:4932–40.
58. Jenkins B, Calder PC, Marino LV. A scoping review considering potential biomarkers or functional measures of gastrointestinal dysfunction and enteral feeding intolerance in critically ill adults. Clin Nutr ESPEN 2022;52:331–9.
59. Hoffmann M, Schwarz CM, Furst S, et al. Risks in management of enteral nutrition in intensive care units: a literature review and narrative synthesis. Nutrients 2020;13.
60. Motta APG, Rigobello MCG, Silveira Rccp, et al. Nasogastric/nasoenteric tube-related adverse events: an integrative review. Rev Lat Am Enfermagem 2021;29:e3400.

61. de Aguilar-Nascimento JE, Kudsk KA. Clinical costs of feeding tube placement. JPEN - J Parenter Enter Nutr 2007;31:269–73.
62. van Nieuwkoop MM, Ramnarain D, Pouwels S. Enteral nutrition interruptions in the intensive care unit: a prospective study. Nutrition 2022;96:111580.
63. Onuk S, Ozer NT, Savas N, et al. Enteral nutrition interruptions in critically ill patients: a prospective study on reasons, frequency and duration of interruptions of nutritional support during ICU stay. Clin Nutr ESPEN 2022;52:178–83.
64. Kuslapuu M, Jogela K, Starkopf J, et al. The reasons for insufficient enteral feeding in an intensive care unit: a prospective observational study. Intensive Crit Care Nurs 2015;31:309–14.
65. Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN - J Parenter Enter Nutr 2015;39:441–8.
66. Arunachala Murthy T, Chapple LS, Lange K, et al. Gastrointestinal dysfunction during enteral nutrition delivery in intensive care unit (ICU) patients: risk factors, natural history, and clinical implications. A post-hoc analysis of the Augmented versus Routine approach to Giving Energy Trial (TARGET). Am J Clin Nutr 2022;116:589–98.
67. Reintam Blaser A, Starkopf L, Deane AM, et al. Comparison of different definitions of feeding intolerance: a retrospective observational study. Clin Nutr 2015;34:956–61.
68. Poulard F, Dimet J, Martin-Lefevre Let al, et al. Impact of not measuring residual gastric volume in mechanically ventilated patients receiving early enteral feeding: a prospective before-after study. JPEN - J Parenter Enter Nutr 2010;34:125–30.
69. Reignier J, Mercier E, Le Gouge Aet al, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013;309:249–56.
70. Raphaeli O, Statlender L, Hajaj C, et al. Using machine-learning to assess the prognostic value of early enteral feeding intolerance in critically ill patients: a retrospective study. Nutrients 2023;15.
71. Pardo E, Lescot T, Preiser JC, et al. Association between early nutrition support and 28-day mortality in critically ill patients: the FRANS prospective nutrition cohort study. Crit Care 2023;27:7.
72. Nguyen NQ, Besanko LK, Burgstad C, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. Crit Care Med 2012;40:50–4.
73. Piton G, Le Gouge A, Brule N, et al. Impact of the route of nutrition on gut mucosa in ventilated adults with shock: an ancillary of the NUTRIREA-2 trial. Intensive Care Med 2019;45:948–56.
74. Ralls MW, Demehri FR, Feng Y, et al. Enteral nutrient deprivation in patients leads to a loss of intestinal epithelial barrier function. Surgery 2015;157:732–42.
75. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117.
76. Kagan I, Hellerman-Itzhaki M, Bendavid I, et al. Controlled enteral nutrition in critical care patients - a randomized clinical trial of a novel management system. Clin Nutr 2023;42:1602–9.
77. Wang YX, Li XL, Zhang LH, et al. Machine learning algorithms assist early evaluation of enteral nutrition in ICU patients. Front Nutr 2023;10:1060398.

78. Lu XM, Jia DS, Wang R, et al. Development of a prediction model for enteral feeding intolerance in intensive care unit patients: a prospective cohort study. World J Gastrointest Surg 2022;14:1363–74.
79. Hu K, Deng XL, Han L, et al. Development and validation of a predictive model for feeding intolerance in intensive care unit patients with sepsis. Saudi J Gastroenterol 2022;28:32–8.
80. Choi TY, Chang MY, Heo S, et al. Explainable machine learning model to predict refeeding hypophosphatemia. Clin Nutr ESPEN 2021;45:213–9.
81. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35:1728–37.
82. Soguel L, Revelly JP, Schaller MD, et al. Energy deficit and length of hospital stay can be reduced by a two-step quality improvement of nutrition therapy: the intensive care unit dietitian can make the difference. Crit Care Med 2012;40:412–9.
83. Ridley EJ, Davies AR, Hodgson CL, et al. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: a systematic review and meta-analysis of randomised controlled trials. Clin Nutr 2018;37:1913–25.
84. Goelen N, Tack J, Janssen P. Erythromycin stimulates phasic gastric contractility as assessed with an isovolumetric intragastric balloon pressure measurement. Neuro Gastroenterol Motil 2021;33:e13991.
85. Raymenants K, Huang IH, Goelen N, et al. Clinical validation of the VIPUN gastric monitoring system versus manometry for the evaluation of gastric motility. Neuro Gastroenterol Motil 2024;e14783.
86. Goelen N, de Hoon J, Morales JF, et al. Codeine delays gastric emptying through inhibition of gastric motility as assessed with a novel diagnostic intragastric balloon catheter. Neuro Gastroenterol Motil 2020;32:e13733.
87. Stapel SN, de Grooth HJ, Alimohamad H, et al. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. Crit Care 2016;19:370.
88. Kagan I, Zusman O, Bendavid I, et al. 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;22:186.
89. Kagan I, Hellerman Isthaki M, Singer P. Evaluation and compensation of patient related and diagnostic/therapeutic related interruptions of enteral nutrition using the smART + platform. a post hoc computerized analysis. Clin Nutr ESPEN 2024;63:980.
90. Wischmeyer PE, Bear DE, Berger MM, et al. Personalized nutrition therapy in critical care: 10 expert recommendations. Crit Care 2023;27:261.