Overcoming challenges to enteral nutrition delivery in critical care

Paul E. Wischmeyer

Purpose of review
Existing data and all ICU nutrition guidelines emphasize enteral nutrition (EN) represents a primary therapy leading to both nutritional and non-nutritional benefits. Unfortunately, iatrogenic malnutrition and underfeeding is virtually ubiquitous in ICUs worldwide for prolonged periods post-ICU admission. Overcoming essential challenges to EN delivery requires addressing a range of real, and frequently propagated myths regarding EN delivery.

Recent findings
Key recent data addresses perceived challenges to EN including:

(1) Adequately resuscitated patients on vasopressors can and likely should receive trophic early EN and this was recently associated with reduced mortality;
(2) Patients paralyzed with neuromuscular blocking agents can and should receive early EN as this was recently associated with reduced mortality/hospital length of stay;
(3) Proned patients can safely receive EN;
(4) All ICU nutrition delivery, including EN, should be objectively guided by indirect calorimetry (IC) measures. This is now possible with the new availability of a next-generation IC device.

Summary
It is the essential implementation of this new evidence occurs to overcome real and perceived EN challenges. This data should lead to increased standardization/protocolization of ICU nutrition therapy to ensure personalized nutrition care delivering the right nutrition dose, in the right patient, at the right time to optimize clinical outcome.

Keywords
ICU nutrition, indirect calorimetry, metabolic cart, neuromuscular blocking agents, prone position, vasopressor

INTRODUCTION

As brilliantly summarized by the dear recently-departed clinical nutrition pioneer Dr Stanley Dudrick [1], enteral nutrition (EN) delivery in illness has been utilized for over 3500 years dating back to 1500 BC, when ancient Egyptians, according to Herodotus, tied animal bladders to small clay and ceramic pipes allowing nutrition and medication delivery by rectal enemas. Over a millennium later, around 400 BC Hippocrates used apparatus similar to that used by the Egyptians to administer wine, milk, and whey via rectum. In 1790, John Hunter reported the ingenious innovation of using a small eelskin, drawn over a flexible whalebone to advance eelskin 'tube' through the oesophagus into the stomach. The proximal end of 'tube' was attached to a hollow wooden tube connected to an animal bladder. With this hybrid apparatus, he fed a 50-year-old stroke patient with eggs, milk, wine, sugar, and jellies until his paralyzed pharynx recovered swallowing function allowing him to eat orally. In the middle of the 20th century, the modern era of

Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina, United States

Correspondence to Paul E. Wischmeyer, MD, EDIC, FASPEN, FCCM, Professor of Anesthesiology and Surgery, Duke University School of Medicine DUMC, Box 3094 Mail # 41; 2301 Erwin Road, 5692 HAFS, Durham, North Carolina 27710, United States. Tel: +919 681 6646; e-mail: Paul.Wischmeyer@duke.edu

Curr Opin Crit Care 2021, 26:000–000
DOI:10.1097/MCC.0000000000000801

KEY POINTS

- Existing data and all ICU nutrition guidelines emphasize enteral nutrition (EN) as a primary therapy leading in the ICU, however real and perceived 'myths' challenges to EN have contributed to iatrogenic malnutrition and underfeeding remaining virtually ubiquitous in ICUs worldwide for prolonged periods post-ICU admission
- Adequately resuscitated patients on vasopressors can receive EEN safely and likely should receive trophic EEN (within 48 h of ICU admission) to improve clinical outcomes as EEN on vasopressors was recently associated in a large health outcomes study with reduced mortality at doses of NE < 0.3 ug/kg/min.
- Patients paralyzed with neuromuscular blocking agents can and should receive EEN (within 48 h of admission) as this was recently associated with reduced mortality/hospital length of stay in a large health outcomes study
- Patients in the prone can safely receive EN and should receive EEN as recommended by recent ASPEN/SCCM COVID-19 Guidelines.
- All ICU nutrition delivery, including EN, should be objectively guided by metabolic cart/indirect calorimetry measures obtained every 3–5 days in the ICU and likely weekly in post-ICU setting, which is now possible with the new availability of a simple, practical, affordable, and highly accurate new generation IC device.

EN began in conjunction with the discovery of parenteral nutritional therapy by pioneers in the field including legends like Stanley Dudrick. In the last 20 years, meaningful evidenced-based research has finally begun to address optimal delivery of nutritional strategies, like EN, in intensive care unit (ICU) patients. This has allowed the opportunity to finally begin to address a range of real and perceived challenges to ICU EN delivery.

ENTERAL FEEDING IN THE MODERN ICU-CHALLENGES AND OPPORTUNITIES

All current major societal critical care nutrition guidelines recommend early enteral nutrition [2▪▪,3]. Despite universal recommendations for early EN (EEN), iatrogenic malnutrition and underfeeding is virtually ubiquitous in most ICUs worldwide [4]. Review of current practise demonstrates the actual amount of nutrition delivered primarily via EN in the ICU is < 50% of prescribed goal even in our most malnourished patients [5]. In an era of heightened concern about patient safety and medical error, we and others have consistently documented that ICU patients receive, on average only 40–60%, of prescribed goal nutritional requirements for prolonged periods (>1 week) post-ICU admission [6,7]. Further, it takes >60 h on average for any nutrition to be started in U.S. ICUs and often >48 h in ICU's worldwide. [5] This is particularly concerning as the average protein delivery for first 12 days of ICU stay is only 0.6 g/kg/d, which is one-third of guideline recommendations of 1.5–2.0 g/kg/d via American Society of Parentetal and Enteral Nutrition (ASPEN) Society guidelines and < one-half of European Society of Parenteral and Enteral Nutriton (ESPEN) guidelines suggesting 1.3 g/kg/d in ICU [2▪▪,3,8]. This is an urgent patient safety crisis that must be addressed.

To address this, many challenges to ICU EN delivery need to be addressed, far more than can be covered in this focused review. This review will focus on recent data for overcoming and addressing a number of key challenges EEN in critically ill patients as shown in Table 1. These include:

(1) Feeding on vasopressors,
(2) Feeding the paralyzed patient on neuromuscular blocking agents (NMBA)
(3) Feeding in the prone position
(4) Essential of measurement of nutritional requirements via a new generation indirect calorimetry (IC) device

ENTERAL NUTRITION FEEDING ON VASOPRESSORS: COULD IT BE SAFE AND REDUCE MORTALITY?

A common question in ICU rounds is: 'Can I feed the patients on vasopressors?' As summarized in a recent review of EN delivery on vasopressors [9▪▪], the gut has long been believed to be fundamental in pathogenesis and progression of critical illness [10,11]. Past seminal papers have described the gut as the 'motor of systemic inflammation and organ failure' [10,11]. The central role of the gut in critical illness is believed to be related

Rapid loss of normal gut microbial ecology or the microbiome, known as dysbiosis [12];

Increased intestinal permeability leading to activation of gut immune system and subsequent systemic inflammation [10,11];

Impaired vagus nerve-related systemic inflammatory signalling [13]; and

Effects on mesenteric lymph toxicity to lung and other organs [14,15].

All these factors are believed to drive systemic inflammation leading to gut-related downstream organ dysfunction and multiple organ failure (MOF) in the ICU patient. As described in a recent

Table 1. EN delivery challenges/barriers. EN, enteral nutrition

Challenges in EN Delivery	Recommendation	New Data	Key Refs
EN Delivery on Vasopressors	Adequately resuscitated patients on vasopressors (< 0.3 μg/kg/min) can and likely should receive trophic EEN (within 48 h of admit)	EEN associated with ↓ mortality at doses of NE < 0.3 μg/kg/min NE in > 52,000 patient health outcome study Patients on > 0.5 μg/kg/min NE receiving EEN may be at ↑ risk of bowel ischemia	[9▪▪,16▪▪,17▪▪]
EN Delivery on Neuromuscular Blocking Agents (NMBA's)	Patients paralyzed with NMBA's can and should receive EEN (within 48 h of admit)	EEN associated with ↓ mortality and hospital length of stay in patients on NMBA's in large health outcome study	[21▪▪]
EN Delivery in Patients in Prone Position	Proned patients can safely receive EN	ASPEN/SCCM COVID-19 Guidelines recommend EEN in patients in prone position	[22▪▪]
Objective Measurement of EN Calorie Needs via Indirect Calorimetry (IC)	All ICU nutrition delivery, including EN, should be objectively guided by metabolic cart / IC measures obtained every 3–5 days in the ICU and likely weekly in post-ICU setting	LEEP-COVID study clinical findings showing inaccuracy of predictive equations over ICU stay Universal Societal Guideline recommendations calling for use of IC to determine energy requirements in ICU Longstanding data showing prediction of resting energy expenditure (pREE) using standardized formulas, or bodyweight calculations correlates poorly with measured REE (mREE) This is now possible with new availability of a simple, practical, affordable, and highly accurate new generation IC device (Q-NRG)	[2▪▪,3,26,27,34,35▪▪,37▪▪]

ASPEN/SCCM, American Society of Parentetal and Enteral Nutrition/Society of critical care medicine; EN, enteral nutrition; EEN, early enteral nutrition; NMBA, neuromuscular blocker agent.

review [9▪▪], modulation of the gut's role as the 'motor of systemic inflammation and organ failure' require key goals of good gut management in the ICU including:

Prevention of dysbiosis and maintenance of normal microbiome;

Maintenance of gut barrier function to attenuate gut immune activation and creation of potential toxic lymph drainage; and

Nutrient-mediated activation of gut vagal pathways for maintenance of anti-inflammatory vagal tone. EEN can be beneficial in achieving all of these goals [9▪▪]. *It is essential to note these are all believed to be achieved by taking advantage of the non-nutritional benefits of EN* [9▪▪].

Our most severely ill ICU patients, at greatest risk for gut-driven MOF, often require vasopressors which have often led to patients not receiving EN until vasopressors were stopped. The concern for feeding on vasopressors is nonocclusive bowel necrosis or bowel ischemia from EN increasing gut oxygen demand beyond delivery [9▪▪]. Unfortunately, limited reliable clinical indicators exist to allow for early accurate diagnosis, however commonly used markers such as increased gastric residual volumes (GRVs) and unexplained lactate increase with initiation of feeding can be helpful [9▪▪]. Despite these concerns, a majority of past data implies potential clinical outcome benefits of early initiation of EN in adequately resuscitated patients, with declining or normal lactates, who are on declining or stable doses of vasopressors [9▪▪]. These previous small studies imply trophic feeding may be of greater beneficial then early full EN dose delivery, thus supporting hypothesis of potential non-nutritional benefits of EEN in patients recovering from conditions such as septic shock requiring vasopressors [9▪▪].

A recent large health outcome study supporting this concept of EEN demonstrating safety and clinical benefit in ICU patients on vasopressors was recently published. This study compared outcomes in EEN and late enteral nutrition (LEN) in ventilated patients with shock requiring low-(<0.1 mcg/kg/min), medium-(0.1–0.3 mcg/kg/min), or high-dose (>0.3 mcg/kg/min) norepinephrine (NE) [16▪▪]. A total of 52,563 eligible patients were included with results showing 28-day mortality rate was significantly lower in EEN group in the low-dose NE group

Table 2. Overcoming barriers to EN in patients on vasopressors

Resuscitation Markers For EN Delivery	Vasopressor Choice[a] (To optimize splanchnic 02 delivery/gut perfusion)	Vasopressor Dose Norepinephrine doses (equivalents)	Feeding Strategy	Signs of Intolerance
Lactate normalized or falling rapidly Vasopressor dose decreasing or stable Mixed Venous 02- WNL or elevated Fluid requirements stabilizing, no ongoing active bleeding. Limit crystalloid fluid over-resuscitation to reduce bowel edema (especially in septic shock – with more pronounced vascular leak)	First Choice Norepinephrine, Norepinephrine / Dobutamine & Phenylephrine 2nd Choice Epinephrine 3rd Choice Vasopressin/Dopamine	< 0.1 μg/kg/min (more optimal and data exists for reduced mortality) 0.1- 0.3 μg/kg/min (may be acceptable and data exists for reduced mortality) 0.3 - 0.5 μg/kg/min (Feed EN with great caution: data equivocal for risk versus benefit) > 0.5 μg/kg/min (Do not feed EN: may pose significant risk of bowel ischemia/ necrosis)	Initiate *gastric* delivered trophic EN (10–20 cc/ h) (DO NOT USE postpyloric feeding) Advance EN slowly and watch for signs of intolerance Check residuals on vasopressors Consider elemental or peptide formula to minimize gut O2 consumption and improve absorption	Increased gastric residual (ONLY > 500 cc's) Nausea/Vomiting Abdominal distension New abdominal pain Unexplained elevation in lactate with feeding initiation or escalation Intra-abdominal hypertension or abdominal compartment syndrome

[a]Observational data and animal data supporting recommendation based on gut perfusion/blood flow/splanchnic O_2 delivery/extraction. EN, enteral nutrition.

(risk difference, 2.9%; 95% confidence interval [CI], 4.5%, 1.3%) and in the medium-dose NE group (risk difference, 6.8%; 95% CI, 9.6%, 4.0%) versus LEN group. Mortality did not differ significantly between EEN and LEN arms in the high-dose NE group. The study authors conclude results suggest EEN is associated with a reduction in mortality in ventilated ICU patients treated with low- or medium-dose NE, with no signal of benefit, *or signal of risk for adverse outcomes,* seen in high-dose NE group.

Conversely, a recent study also demonstrates we must utilize caution when considering the use of full-dose, rapidly escalated EEN in severe shock patients on high vasopressor doses. The NUTRIREA-2 trial [17▪▪] studied 2,410 mechanically ventilated adults receiving vasopressor agents randomized to PN or EN with a goal to achieve nutrition goals within 24 h. It is key to note the patients received a quite high NE dose, with a mean of 0.53 mcg/kg/min, a dose that is higher than exclusion limits for many similar large nutrition RCTs (including PermiT and EDEN trials). Results reveal no differences in primary 28-day mortality or ICU-acquired infections. Unfortunately, a significant increase in bowel ischemia ($P = 0.007$), and acute colonic pseudoobstruction ($P = 0.04$) was observed with aggressive EEN (at goal within 24 h). This study is the first ever-described evidence from a large RCT that aggressive EEN can be associated with bowel ischemia and authors concluded rapidly escalated, full-feeding with EN should be avoided until patients are hemodynamic stabile. This trial also implied that early in shock, PN may be a better and safer option then full dose EEN.

In summarizing this data, almost all recent studies show EEN, particularly when delivered initially via trophic feeding, can be safely delivered to adequately resuscitated patients on reasonable doses of vasopressors [9▪▪]. Data seem to support a reasonable range of doses of NE (or equivalent) that are safer, and perhaps beneficial, to provide EEN is between 0.14 and 0.3 mcg/kg/d NE [9▪▪]. It is also essential to realize that slow advance of trophic feeds, perhaps supplemental parenteral nutrition until full stability is achieved. Further, randomized trial data is urgently needed to address this question. Suggestions for safety and optimization of EN delivery in critically ill patients receiving vasopressors are summarized in Table 2.

Enteral nutrition feeding in the patient on neuromuscular blockers: safe. . .and reduces mortality?

Another common question ICU rounds is: 'Can I feed my paralyzed (neuromuscular blocker agent (NMBA) receiving) patients?' The concern often heard is 'gut peristalsis will be paralyzed/impaired?' This, of course, is not correct. It is key to understand NMBA's relax skeletal muscle but do not relax smooth muscle, like that found in stomach and gut. Skeletal muscle is controlled by action of acetylcholine on nicotinic acetylcholine receptors at neuromuscular junctions, whereas smooth muscle

is controlled by acetylcholine acting on muscarinic receptors. Nondepolarizing NMBAs are competitive antagonists acting on nicotinic receptors only [18]. Previous data shows NMBAs do not affect gastric peristalsis following an EN bolus [19]. Other studies show that underlying illness, (i.e., prolonged immobility, opiates, or fluid overload) not NMBA use, are associated with poor GI peristalsis, gastroesophageal reflux, and vomiting, associated with increased aspiration and ventilator-associated pneumonia risk [20]. A recent study from the same research group who studied EEN in vasopressor-receiving patients [21▪▪], examined outcomes in EEN versus LEN in ventilated patients undergoing sustained NMBA's treatment. This study examined 2,340 eligible patients of whom 378 patients (16%) received EEN. The in-hospital mortality rate was significantly lower in EEN versus LEN patients (risk difference, –6.3%; 95% CI, –11.7% to –0.9%). No significant difference in rate of hospital pneumonia was observed between two groups. Length of hospital stay among survivors was markedly and statistically significantly shorter in EEN compared with LEN group (risk difference, –11.4 d; 95% CI, –19.1 to –3.7 d). No significant difference between groups in length of ICU stay (LOS) or length of mechanical ventilation was observed. Authors concluded EEN may be associated with lower in-hospital mortality with no increase in-hospital pneumonia in patients undergoing sustained treatment with NMBA's [21▪▪]. Thus, EEN can be safely delivered in patient's paralyzed with NMBA's and data supports EEN is associated with reduced mortality and hospital LOS. Thus, EEN can and should be delivered in patients paralyzed with NMBA's.

Enteral nutrition feeding in the proned patient

Another common question, especially during the recent COVID-19 pandemic, has been: 'Is it safe, or possible, to feed the prone patient'? Prone positioning reduces mortality in patients with acute respiratory failure (ARF) with a PaO_2/FiO_2 ratio of <150 and has become a standard of care in ICU's worldwide. This practice has become much more common as a result of SARS-CoV-2 infection leading to increasing numbers of patients with severe ARF. This led to the SCCM/ASPEN Guidelines addressing this in their updated ICU nutation recommendations for COVID-19 [22▪▪]. These guidelines state: *'Retrospective and small prospective trials show EN in prone patients is not associated with increased risk of GI or pulmonary complications, thus we recommend early EN in prone patients'*. Guidelines encourage when EN is introduced during prone positioning, if possible, the head of the bed should be elevated (reverse Trendelenburg) to at least 10–25 degrees to decrease risk of aspiration of gastric contents, facial oedema and intra-abdominal hypertension.

Role of new generation metabolic carts in improving dosing, safety, and efficacy of enteral nutrition in ICU

One of the major drivers of the lack of emphasis on improved nutrition delivery in ICU and Post-ICU patients is lack of objective energy requirement data which is known to change throughout the course of illness. *ICU physicians would not deliver vasopressors without a continuous blood pressure measure from an arterial line; thus, the ICU community has not embraced a focus on nutrition delivery due to lack of objective data to guide nutrition care*. This is essential to address to bring objective nutrition care in-line with other aspects of ICU care.

The definition of an ICU patient's nutritional targets/needs is a critical first task of an ICU clinician prior to prescribing nutrition therapy. However, it is difficult to estimate the caloric needs of ICU patients due to the complex and dynamic metabolic alterations observed in critical illness [23,24]. Energy expenditure (EE) in ICU patients is highly variable and based on a range of features including initial injury/illness, severity of illness, nutritional status and medical treatment [25▪,26,27]. It is also known EE can change from day-to-day quite significantly as clinical status changes [25▪,26,27]. A number of studies have shown predictive formulas developed to calculate EE in ICU patients are not accurate nor clinically relevant [26,27]. Recently, it has become clear ICU clinicians need to be objectively measuring EE via indirect calorimetry (IC) as both over-/underfeeding is associated with increased ICU mortality [2▪▪,28]. The most recent international ICU nutrition guidelines recommend use of IC to measure the EE in ICU patients for accurate determination of caloric needs [2▪▪,28]. Further use of metabolic cart data to optimize nutritional support has been associated with improved clinical outcomes from nutrition therapy [29,30]. Unfortunately, recent studies have shown that the current commercially available IC's are inaccurate [31,32] and the inconvenience of the measurement (large device size, long warm-up duration and calibration, complex maintenance, etc.) have led to a very limited use of IC in clinical practice [33].

Recently, an ambitious and essential project was launched joining leaders in the ICU clinical nutrition field with innovative industry leaders to address this critical deficiency in ICU nutrition care. The group, the International Multicentric Study

Group for Indirect Calorimetry (ICALIC) led a project to develop an accurate, reliable, cost affordable, and user-friendly indirect calorimeter (IC) to measure energy expenditure (EE) in ICU and other hospitalized patients. The result of this project was the development of the next-generation Q-NRG indirect calorimeter (IC) device [34].

The new Q-NRG device was validated in the recently published ICALIC project paper [35▪▪]. This multicenter study evaluated the ease of clinical use of the new IC device in ICU patients. The study tested the device in six international academic ICU centres on three continents. The results of the study showed the Q-NRG IC required a much shorter time (with reliable measurements in ~10 min) to determine EE in mechanically ventilated ICU patients versus other ICs. The authors concluded the new Q-NRG is the only commercially available IC tested against mass spectrometry to ensure gas accuracy, while being easy-to use. These characteristics should allow for a much broader use of IC in order to optimize the prescription of nutritional support by limiting the risk of under- or overfeeding.

In response to the recent worldwide COVID-19 pandemic [36▪], the new Q-NRG IC device was recently utilized to conduct the first longitudinal study of the metabolic phenotype and measured resting EE (mREE) of this novel pandemic disease. In this very recently published paper [37▪▪], the LEEP-COVID study group demonstrated that during the 1st ICU week in intubated COVID-19 patients mREE was observed to fall between 15 and 20 kcal/kg (for Actual body weight (ABW) in BMI < 30 and Adjusted BW (AdjBW) in obese subjects. [2▪▪]). Increasing hypermetabolism and wider variability in mREE were observed post1st ICU week. Unlike data from smaller studies in other ICU populations [38], observed hypermetabolism persisted, and in fact increased during 3rd ICU week (Mean mREE = 150% predicted REE (pREE) in 3rd ICU week). Certain individuals exhibited metabolic rates greater than two-times predicted via Harris-Benedict equation (HBE), which significantly underpredicted REE post1st ICU week. Changes in mREE may not be significantly related to severity of organ failure, and only minorly affected by paralysis/prone positioning, as these were not significantly different over study period. These data suggest personalization of nutrition delivery, including IC use [2▪▪,35▪▪], should be strongly considered as the new standard of care to provide accurate assessments of energy expenditure and help guide nutrition delivery in COVID-19 ICU patients. Given: 1) LEEP-COVID study clinical findings of inaccuracy of predictive equations throughout ICU stay; 2) Universal guideline recommendations calling for use of IC to determine energy requirements in ICU; and 3) Data showing prediction of resting energy expenditure (pREE) using standardized formulas, or bodyweight calculations correlates poorly with measured REE (mREE) [2▪▪] the use of this new generation metabolic cart (Q-NRG) device should be considered the new standard of care for objective delivery of all nutrition, including EN, PN, and oral nutrition in the ICU and post-ICU patient.

CONCLUSION

Existing data and all ICU nutrition guidelines nutrition [2▪▪,3] emphasize enteral nutrition (EN) represents a primary therapy leading to both nutritional and non-nutritional benefits. EN therapy should be considered a critical part of the initial resuscitative efforts, which immediately follows acute resuscitation measures to restore adequate oxygen delivery and address shock. Unfortunately, iatrogenic malnutrition and underfeeding is virtually ubiquitous in ICUs worldwide for prolonged periods post-ICU admission. [5,6,7]. This is often due to a range of real, and unfortunately frequently propagated myths around barriers and challenges to ICU EEN delivery. Key findings beginning to dispel these perceived barriers and challenges to EN delivery are summarized in Table 1. Finally, to ultimately overcome fundamental challenges in delivering EN, in addition to objective measurement of EN requirements, a structured approach to nutrition delivery must be achieved in ICU nutrition therapy, as it has in other areas of critical care. A structured nutrition delivery strategy that optimally incorporates the latest evidence-based practice has been described in a recent review on ICU and post-ICU nutrition [39▪▪]. Another excellent algorithm is described in the recently published EFFORT trial. This large multicenter randomized trial in acutely ill hospitalized patients at high nutrition risk [40▪▪] found a structured nutrition algorithm led to significant reductions in mortality, complications at 30 days, and significant improvements in recovery and functional independence ($P < 0.006$) and EQ-5D QoL at 30 d ($P = 0.018$). Importantly, this nutrition algorithm can be adapted for both ICU and post-ICU care. In conclusion, it is essential that implementation of this new evidence to overcome real and perceived challenges to EN, as well as standardization and protocolization of ICU nutrition therapy occurs to ensure each ICU patient receives personalized nutrition care delivering the right nutrition dose, in the right patient, at the right time to optimize clinical outcomes.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

PEW has received grant funding related to this work from NIH, Canadian Institutes of Health Research, Abbott, Baxter, Fresenius, Nutricia, and Takeda. PEW serves as a consultant to Abbott, Fresenius, Baxter, Nutricia, and Takeda for research related to nutrition in surgery and ICU care; received unrestricted gift donation for surgical and critical care nutrition research from Musclesound and Cosmed; received honoraria or travel expenses for CME lectures on improving nutrition care in surgery and critical care from Abbott, Baxter, Nestle, Nutricia, and Fresenius.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Dudrick SJ, Palesty JA. Historical highlights of the development of enteral nutrition. Surg Clin North Am 2011; 91:945–964.
2. ■■ Singer P, Blaser AR, Berger MM, *et al.* ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019; 38:48–79.

Recent comprehensive guidelines on nutrition delivery in critically ill patients.

3. Taylor BE, McClave SA, 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.). Crit Care Med 2016; 44:390–438.
4. 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; 35:1728–1737.
5. Cahill NE, Dhaliwal R, Day AG, *et al.* Nutrition therapy in the critical care setting: what is 'best achievable' practice? An international multicenter observational study. Crit Care Med 2010; 38:395–401.
6. Heyland DK, Schroter-Noppe D, Drover JW, *et al.* Nutrition support in the critical care setting: current practice in Canadian ICUs–opportunities for improvement? J Parenter Enteral Nutr 2003; 27:74–83.
7. Krishnan JA, Parce PB, Martinez A, *et al.* Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest 2003; 124:297–305.
8. Taylor BE, McClave SA, 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 (ASPEN). Crit Care Med 2016; 44:390–438.
9. ■■ Wischmeyer PE. Enteral nutrition can be given to patients on vasopressors. Crit Care Med 2020; 48:122–125.

Recent comprehensive overview of rationale, pathophysiology, and literature review of data for EN delivery in critically ill patients on vasopressors. Review concludes most all recent studies show EEN, particularly when delivered initially via trophic feeding, can be delivered safely to adequately resuscitated patients on reasonable doses of vasopressors.

10. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the 'motor' of critical illness. Shock 2007; 28:384–393.
11. Hassoun HT, Kone BC, Mercer DW, *et al.* Postinjury multiple organ failure: the role of the gut. Shock 2001; 15:1–10.
12. Wischmeyer PE, McDonald D, Knight R. Role of the microbiome, probiotics, and 'dysbiosis therapy' in critical illness. Curr Opin Crit Care 2016; 22:347–353.
13. Lubbers T, de Haan JJ, Luyer MD, *et al.* Cholecystokinin/Cholecystokinin-1 receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. Ann Surg 2010; 252:376–382.
14. Magnotti LJ, Upperman JS, Xu DZ, *et al.* Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. Ann Surg 1998; 228:518–527.
15. Yi J, Slaughter A, Kotter CV, *et al.* A 'clean case' of systemic injury: mesenteric lymph after hemorrhagic shock elicits a sterile inflammatory response. Shock 2015; 44:336–340.
16. ■■ Ohbe H, Jo T, Matsui H, *et al.* Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: a propensity-matched analysis. Clin Nutr 2019; 39:460–467.

Recent large health outcomes study comparing outcomes in EEN and late enteral nutrition (LEN) in ventilated patients with shock requiring low-(<0.1 ug/kg/min), medium-(0.1–0.3 ug/kg/min), or high-dose (>0.3 ug/kg/min) norepinephrine (NE). 52,563 eligible patients were included with results showing 28-day mortality rate was significantly lower in EEN group in the low-dose NE group and in the medium-dose NE group versus LEN group. Mortality did not differ significantly between EEN and LEN arms in the high-dose NE group. Study concludes results suggest EEN is associated with a reduction in mortality in ICU patients treated with low-/medium-dose NE, with no signal of benefit, (or risk) for adverse outcomes, seen in high-dose NE group.

17. ■■ 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: 133–143.

The NUTRIREA-2 trial studied 2,410 mechanically ventilated adults receiving vasopressor agents randomized to PN or EN with a goal to achieve nutrition goals within 24 h. Results reveal no differences in primary 28-day mortality or ICU-acquired infections. Unfortunately, significant increase in bowel ischemia ($P = 0.007$), and acute colonic pseudoobstruction ($P = 0.04$) was observed with aggressive EEN (at goal within 24 h). This study is the first ever-described evidence from a large RCT that aggressive EEN can be associated with bowel ischemia and authors concluded rapidly escalated, full-feeding with EN should be avoided until patients are hemodynamic stabile.

18. Paton WD. Mode of action of neuromuscular blocking agents. Br J Anaesth 1956; 28:470–480.
19. Tamion F, Hamelin K, Duflo A, *et al.* Gastric emptying in mechanically ventilated critically ill patients: effect of neuromuscular blocking agent. Intensive Care Med 2003; 29:1717–1722.
20. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med 1999; 27:1447–1453.
21. ■■ Ohbe H, Jo T, Matsui H, *et al.* Early enteral nutrition in patients undergoing sustained neuromuscular blockade: a propensity-matched analysis using a nationwide inpatient database. Crit Care Med 2019; 47:1072–1080.

Large health outcomes study of EEN versus LEN in ventilated patients undergoing sustained NMBA's treatment. Authors concluded EEN appears to be associated with lower in-hospital mortality with no increase in-hospital pneumonia in patients undergoing sustained treatment with NMBA's. Thus, EEN can and should be safely delivered in patient's paralyzed with NMBA's

22. ■■ Martindale R, Patel JP, Taylor B, Warren M, McClave SA, Nutrition Therapy in the Patient with COVID-19 Disease Requiring ICU Care, https://www.sccm.org/COVID19RapidResources/Resources/Nutrition-Therapy-in-the-Patient-with-COVID-19-Dis: Published Online: 4/1/2020.

Key recent update to SCCM/ASPEN guidelines for nutrition delivery in COVID-19 ICU patients.

23. Oshima T, Graf S, Heidegger CP, *et al.* Can calculation of energy expenditure based on CO2 measurements replace indirect calorimetry? Crit Care 2017; 21:13.
24. Graf S, Pichard C, Genton L, *et al.* Energy expenditure in mechanically ventilated patients: The weight of body weight! Clin Nutr 2015; 36:224–228. doi: 10.1016/j.clnu.2015.11.007 (article in press).
25. ■ Wischmeyer PE. Nutrition Therapy in Sepsis. Crit Care Clin 2018; 34:107–125.

Recent comprehensive review of nutrition delivery in sepsis.

26. Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. JPEN J Parenter Enteral Nutr 2013; 37:705–713.
27. Guttormsen AB, Pichard C. Determining energy requirements in the ICU. Curr Opin Clin Nutr Metab Care 2014; 17:171–176.
28. 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 Enteral Nutr 2016; 40:159–211.
29. Heidegger CP, Berger MM, Graf S, *et al.* Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013; 381:385–393.
30. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. Crit Care Med 2014; 42:2600–2610.
31. Sundstrom M, Tjader I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr 2013; 32:118–121.
32. Graf S, Karsegard VL, Viatte V, *et al.* Evaluation of three indirect calorimetry devices in mechanically ventilated patients: which device compares best with the Deltatrac II((R))? A prospective observational study. Clin Nutr 2015; 34:60–65.

33. De Waele E, Spapen H, Honore PM, *et al.* Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care 2013; 28:884e881-886.

34. 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; 36:651–662.

35. Oshima T, Delsoglio M, Dupertuis YM, *et al.* The clinical evaluation of the new ■■ indirect calorimeter developed by the ICALIC project. Clin Nutr 2020; 39:3105–3111.

This multicenter study evaluated and validated use of the new indirect calorimeter (IC) device in ICU patients. Results of the study showed the Q-NRG IC required a much shorter time (with reliable measurements in ~10 min) to determine energy expenditure in mechanically ventilated ICU patients versus other ICs. The authors concluded new Q-NRG is only commercially available IC tested against mass spectrometry to ensure gas accuracy, while being easy-to use. These characteristics should allow for a much broader use of IC in order to optimize the prescription of nutritional support by limiting the risk of under- or overfeeding.

36. Berlin D, Gulick R, Martinez F. Severe Covid-19. N Engl J Med 2020. ■

Definitive early review of pathophysiology and initial treatment strategies in severe COVID-19 in critically ill patients

37. Whittle J, Molinger J, MacLeod D, *et al.,* Group L-CS. Persistent hypermeta-■■ bolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020; 24:581.

First description of longitudinal metabolic phenotype and energy expenditure in critically ill COVID-19 patients. Data shows COVID-19 ICU patients display a unique metabolic response of normo-metabolism in 1st week post-ICU admission and become markedly hypermetabolic in the 2nd and 3rd week post-ICU admission, further study showed consistent inaccuracy of predictive equations for energy need throughout ICU stay

38. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. Crit Care Med 1999; 27:1295–1302.

39. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical ■■ illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care 2019; 23:368.

Excellent and comprehensive review of ICU nutrition delivery across all phases of ICU and post-ICU care

40. Schuetz P, Fehr R, Baechli V, *et al.* Individualised nutritional support in medical ■■ inpatients at nutritional risk: a randomised clinical trial. Lancet 2019; 393:2312–2321.

Critical new large multicenter randomized controlled trial of a structured nutrition intervention in malnourished hospitalized patients led to significant reductions in mortality and complications at 30 days. The early malnutrition intervention also led to significant improvement in recovery and functional independence ($P < 0.006$) and EQ-5D QoL at 30 d ($P = 0.018$).