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Organ-Specific Nutrition: One for the History Books or Still an Active Player?

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Abstract
Purpose of Review Critical illness frequently involves multi-organ failure and it can be difficult to treat nutritional derangements in these patients. Organ-specific formulas were initially created to meet the specific nutritional needs of critically ill patients. Formulas have been developed to augment pulmonary, pancreas, liver, and renal failure. There is overall minimal evidence evaluating these formulas and many of the studies are small.
Recent Findings A few large randomized trials have been done and the results are not supportive of widespread use of these enteral formulas.
Summary This review will evaluate the evidence and current guidelines of organ-specific nutritional formulas for the lung, pancreas, liver, and kidney.

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Introduction

Organ-specific nutrition has been marketed over the past several years as a method to improve nutritional status and potentially impact patient outcomes during critical illness. There are specific formulas for patients with lung injury, pancreatic and liver disease as well as acute renal injury. There is considerable variation in the quality of evidence evaluating these formulas and nutrition supplementation. Formulas for pulmonary organ failure have been studied in large randomized trials recently, but other organ systems have few studies and no large randomized trials to evaluate effectiveness. This review will evaluate the existing

evidence for organ-specific tube feeding formulas and the future of these formulas.

Pulmonary

The most studied formulas were designed to alter the nutritional status of pulmonary failure in critical illness. These include formulas with omega three fatty acids thought to potentially benefit hypoxic respiratory failure and reduced carbohydrate to reduce carbon dioxide production related to hypercapnic respiratory failure. Both of these situations will be reviewed separately.

Hypoxemic Respiratory Failure

In the intensive care unit (ICU), acute respiratory distress syndrome (ARDS) is a common cause of hypoxemic (type I) respiratory failure. First described in 1967 by Ashbaugh and colleagues, ARDS is a form of nonhydrostatic pulmonary edema [1]. The Berlin criteria defines ARDS as (1) acute (within 7 days) onset of respiratory symptoms, (2) diffuse bilateral infiltrates on radiograph consistent with pulmonary edema, (3) respiratory failure not explained by cardiogenic pulmonary edema, and (4) a moderate-to-severe oxygenation impairment must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (P/F ratio). When the positive end-expiratory pressure (PEEP) is $\geq$5 cm of water pressure, a P/F ratio of 200–300 is considered mild ARDS, 100–199 moderate ARDS, and <100 severe ARDS [2].

ARDS can be secondary to direct pulmonary injury or nonpulmonary causes. Pneumonia is the most common pulmonary injury leading to ARDS. Sepsis is the most common nonpulmonary cause of ARDS. Other nonpulmonary causes include acute pancreatitis, drug overdose, and trauma. The inciting event elicits an inflammatory response which leads to loss of endothelial–alveolar barrier function and widespread but inhomogeneous proteinaceous (exudative) edema formation. As a consequence, some lung units remain open while others are collapsed. Therefore, tenets of ARDS management are aimed at preventing overdistention of open lung units (potentially leading to barotrauma and biotrauma) and avoiding cyclic opening–closing of collapsed lung units (potentially leading to atelectrauma). First, low-tidal volume ventilation (4–6 milliliters (mL) per kilogram (kg) ideal body weight) is delivered during positive pressure mechanical ventilation to prevent barotrauma [3, 4]. Second, open-lung ventilation using positive end-expiratory pressure (PEEP) is initiated to recruit collapsed alveoli, prevent atelectrauma, and improve oxygenation [5–7]. Third, volume status management to induce a net negative daily fluid balance has been shown to improve outcomes such as duration of mechanical ventilation [8]. In severe ARDS, therapies such as neuromuscular blockade within 48 h, prone positioning, and extracorporeal membrane oxygenation have demonstrated improvements in outcome [9–11].

What is the role of immunonutrition in ARDS? To better understand the rationale for specialized enteral nutrition (EN) in ARDS, it is important to understand the three distinct stages in ARDS.

First is the exudative stage and is characterized pathologically as pulmonary edema with diffuse alveolar damage, the hallmark of which is hyaline membrane formation. Second is the proliferative stage (after 7–10 days) in which there is type II pneumocyte hyperplasia, squamous metaplasia, and myofibroblast infiltration with collagen deposition. Third is the fibrotic stage, marked by diffuse lung fibrosis and cyst formation leading to abnormal lung architecture [12]. The majority of patients recover after the proliferative phase [13].

The exudative phase of ARDS is associated with alveolar neutrophil accumulation, cytokine-mediated inflammation and injury, and oxidant-mediated injury [13]. Pro-inflammatory molecules initiate and perpetuate lung injury. During cellular stress, both omega-3 and omega-6 fatty acids are released from the cell membrane by phospholipases and converted to eicosanoid hormones, which serve to modulate the inflammatory response (Fig. 1) [14]. Omega-3s are polyunsaturated fatty acids found in cold-water fish, flaxseed, and canola oil and contain a carbon–carbon double bond at the third carbon [14]. The three most important omega-3 fatty acids are alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) [14]. Omega-6 fatty acids are found in animal fat and include linolenic acid, dihomo-gamma-linolenic acid, and arachidonic acid. Omega-6 fatty acids are enzymatically metabolized to the pro-inflammatory eicosanoids of the 2 and 4 series (e.g., leukotriene B4 (LTB4) and prostaglandin E2 (PGE2)), while omega-3 fatty acids are converted to anti-inflammatory eicosanoids of the 3 and 5 series [14]. Omega-6-derived eicosanoids are pro-inflammatory and mediate platelet aggregation, neutrophil activation and adhesion, cytokine production, and increased vascular permeability. Omega-3-derived eicosanoids exhibit anti-inflammatory properties by reducing pro-inflammatory eicosanoid production through arachidonic acid displacement, increase production of the anti-inflammatory lipids resolvins and protectins, decrease chemotaxis, and decrease adhesion molecule expression [14, 15]. An intermediate in the omega-6 pathway is gamma-linolenic acid (GLA). GLA is found in borage oil. When GLA is administered with EPA, the terminal enzyme is blocked resulting in less arachidonic acid production (Fig. 1) [16].

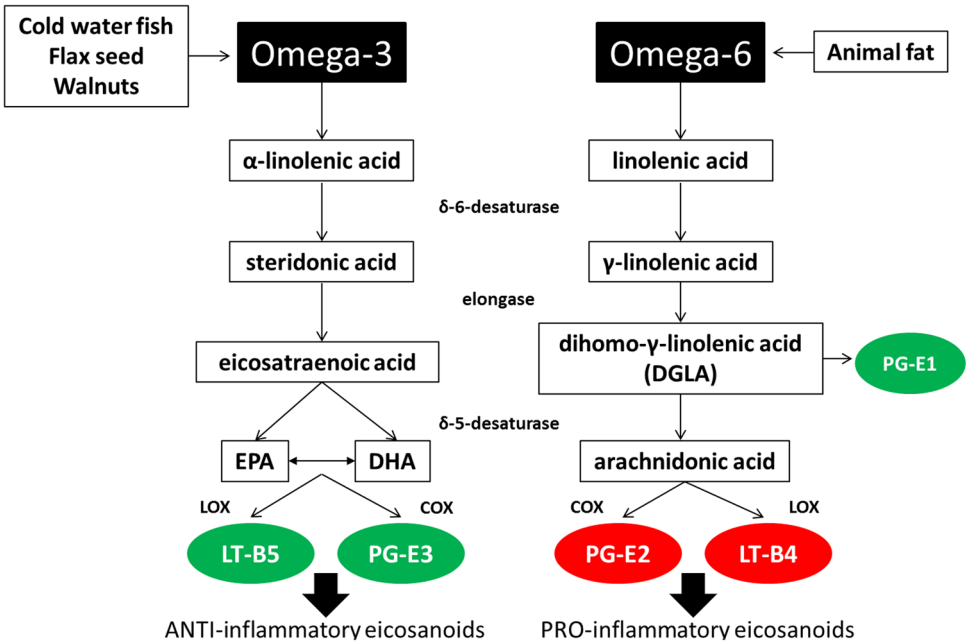

Fig. 1 Omega-3 fatty acid metabolism. The end products of the omega-3 pathway include eicosanoids of the 3 and 5 series, which are anti-inflammatory, inhibit cytokine production, and directly counteract the effect of 2 and 4 series eicosanoids. D-GLA is an intermediate in the omega-6 pathway which increases arachidonic acid levels; however, when D-GLA is administered with EPA, δ-6-desaturase is inhibited, thus reducing arachidonic acid production and increasing PG-E1, a potent pulmonary vasodilator. The end products of the omega-6 pathway are eicosanoids of the 2 and 4 series, which are pro-inflammatory, and lead to leukocyte adhesion, cytokine production, platelet coagulation, fever induction. *COX* cyclooxygenase; *DHA* docosahexaenoic acid; *EPA* eicosapentaenoic acid; *LOX* lipoxygenase; *LTB* leukotriene; *PG* prostaglandin

Modulation of the omega-3 and omega-6 fatty acid pathways by providing enteral immunonutrition with predominantly omega-3 fatty acids has been a focus of research to improve ARDS outcomes.

Animal studies demonstrated improvements in clinical and inflammatory markers with immunonutrition [17–19]. Murray et al. substituted enteral EPA and GLA for LA in an Escherichia coli-induced pig model of acute lung injury (ALI) and demonstrated that improvements in oxygen delivery reduced pulmonary vascular resistance and 7-fold less thromboxane B2 (TxB2) production in those pigs which received EPA alone and both EPA and GLA, as compared to LA alone [17]. Mancuso et al. prefed rats for 21 days with one of the following enteral formulas: 20 % corn oil, 20 % EPA, 20 % EPA, and 5 % GLA, or 20 % EPA and 20 % GLA. Endotoxin-induced ALI was established and the rats prefed with EPA and EPA plus GLA had a lower degree of hypotension, less pulmonary microvascular permeability, and reduced synthesis of pro-inflammatory arachidonic acid mediators LTB4, TxB2, and PGE2 [19].

Human studies using omega-3 fatty acids in ARDS have demonstrated variable outcomes. In a multicenter randomized controlled trial, Gadek et al. randomized 51 patients to receive EN enriched in EPA + DHA + GLA + antioxidants versus 47 to receive an isonitrogenous isocaloric control EN. Patients receiving EN-enriched diet had improvements in oxygenation (from baseline), fewer days of ventilatory support (11 vs. 16.3; p value = 0.011), and decreased length of ICU stay (12.8 vs. 17.5 days; p value = 0.016) [20]. The control group received EN with a high amount of omega-6 fatty acids, potentially widening the benefit for the experimental group receiving omega-3 fatty acids. Low-tidal volume ventilation to manage ARDS was not the standard of care, limiting external generalizability. In addition, the EN-enriched formula contained other antioxidants, limiting analysis of omega-3 formulation alone. Two subsequent trials using the same control EN formulation reported similar outcomes [21, 22]. A small randomized trial by Parish et al. used EN with omega-3 alone and demonstrated benefit in regards to oxygenation and ventilator-free days [23]. A small randomized trial by Stapleton et al. using EN with omega-3 alone demonstrated no benefit in regards to mortality or duration of mechanical ventilation [24]. The largest trial to date (n = 272 patients) was stopped early for potential harm [25•]. A meta-analysis of seven randomized controlled trials failed to demonstrate benefit of omega-3 fatty acid supplementation in ARDS in regards to mortality, ventilator-free days, and ICU-free days [26]. To date, the eight randomized controlled trials of omega-3 fatty acids in

ARDS are limited by heterogeneity with omega-3 formulation, infusion method, placebo formula used, inclusion of other anti-inflammatory compounds, duration of therapy, and primary outcomes (Table 1) [20–24, 25•, 27, 28]. Therefore, based on low- to very low-quality evidence, the 2016 American Society of Parenteral and Enteral Nutrition/Society of Critical Care Medicine (ASPEN/SCCM) nutrition therapy guidelines could not make a recommendation regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile in patients with ARDS [29••].

Hypercapnic Respiratory Failure

In hypercapnic (type II) respiratory failure, the patient is unable to sufficiently ventilate to excrete carbon dioxide. Conditions predisposing to hypercapnic respiratory failure include chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and neuromuscular disorders. The hallmark of acute hypercapnic respiratory failure is an elevated partial pressure carbon dioxide (PaCO2). The respiratory quotient (RQ) is the ratio of carbon dioxide produced to oxygen consumed. The RQ for fats is 0.7 and 1 for carbohydrates. The limited ability of these patients to ventilate raises concerns about excess PaCO2 production with nutritional supplementation, potentially making liberation from mechanical ventilation difficult.

Theoretically, enteral formulas with a high fat-to-carbohydrate (F/C) ratio ought to create a lower RQ and produce less PaCO2. Human studies have not demonstrated benefit of using EN with high F/C ratio. Instead, avoiding overfeeding is recommended to prevent excess PaCO2 production [29••].

Other Considerations

Other nutritional considerations for the patient in acute respiratory failure are monitoring and optimization of serum phosphate and using a calorie-dense formula in patients where volume restriction is warranted. Critical illness in general predisposes the patient to hypophosphatemia. Phosphate is required for adenosine triphosphate (ATP) production and thus muscle contraction. Hypophosphatemia may lead to diaphragmatic weakness and thus monitoring to maintain serum phosphate >2.2 milligrams (mg) per deciliter (dL) is recommended [29••]. Next, critical illness therapies such as fluid resuscitation predispose the patient to volume overload states. When volume restriction is employed, the 2016 ASPEN/SCCM guidelines recommend a calorie-dense formula (1.5–2 kcal/mL) be considered [29••].

In conclusion, acute respiratory failure is one of the most common indications for ICU admission. ARDS is a form of type I respiratory failure. Despite enthusiasm from animal data, human trials of EN formulas containing omega-3 FO, borage oil, and antioxidants have demonstrated conflicting data and a recommendation for routine use cannot be made [29••]. For hypercapnic respiratory failure, human studies have not demonstrated benefit in using an EN formula with high F/C ratio. Rather, avoiding overfeeding is recommended to prevent excess PaCO2 production. Since diaphragm and other respiratory muscle functions are dependent on ATP generation, it is important to monitor and replete serum phosphate to keep level >2.2 mg/dL. Critically ill patients are prone to volume overload. When a volume restriction strategy is undertaken, it is reasonable to use a calorie-dense (1.5–2 kcal/mL) enteral formula.

Pancreas

The pancreas has both exocrine and endocrine functions. It is responsible for producing digestive enzymes and producing insulin, glucagon, and somatostatin [30]. Pancreatitis, inflammation of the pancreas, can be acute or chronic. Catabolism is a result of the inflammatory response. This response is responsible for increased energy expenditure, justifying early nutrition support [31]. Historically, diseases of the pancreas required avoidance of pancreatic stimulation during inflammation to alleviate pain [32]. Enteral nutrition and solid food intake was assumed to stimulate the pancreas by activation of digestive enzymes [32]. For those cases requiring hospitalization, treatment protocol included NPO and bowel rest. Initiation of parenteral nutrition was previously deemed acceptable if unable to establish adequate solid food intake >5–7 days [33]. Recent studies have found early enteral nutrition may be initiated safely, replacing parenteral nutrition [33]. Benefits to initiating enteral nutrition include preservation of GI function which assists in decreasing systemic stress and immune response [33].

Although not largely studied, enteral nutrition typically recommended for pancreatitis were semi-elemental or elemental formulas. Semi-elemental formulas contain peptides of varying chain length, simple sugars, glucose polymers, or starch and fat primarily as medium-chain triglycerides [33]. Elemental formulas are completely predigested and consist of amino acids, simple sugars, and enough fat to prevent essential fatty acid deficiency [33]. Most recently, polymeric formulas have been found to be effective in managing pancreatitis. Polymeric formulas are those that contain nonhydrolyzed proteins, complex carbohydrates, and long-chain triglycerides [33]. Polymeric formulas had typically been avoided for use in pancreatitis due to the assumption that intact proteins require more effort to digest leading to increased pancreas stimulation [32].

Table 1 Randomized controlled trials of omega-3 fatty acid supplementation in acute respiratory distress syndrome

Author	Year	No. of patients	Intervention	Omega-3 delivery method	Control formula	Therapy duration	Ventilation strategy	Primary outcome	Mortality*
Gadek [20]	1999	146	EPA + GLA + antioxidants	Enteral formula	High-fat, omega-3 EN formula	7 days	NA	Duration of mechanical ventilation	6/51 vs. 9/47, p = NS
Singer [22]	2006	100	EPA + GLA + antioxidants	Enteral formula	High-fat, omega-6 EN formula	14 days	Tidal volume <7 mL/kg	Change in oxygenation	13/46 vs. 28/49, p = NS
Pontes-Arruda [21]	2006	165	EPA + DHA + GLA + antioxidants	Enteral formula	High-fat, omega-6 EN formula	NA	ARDSnet	28-day mortality	18/55 vs. 25/48, p = NS
Grau-Carmona [27]	2011	160	EPA + DHA + GLA + antioxidants	Enteral formula	Low-fat, high-cab EN formula	NA	ARDSnet	New organ dysfunction	11/61 vs. 11/71, p = NS
Stapleton [24]	2011	90	EPA + DHA	Single daily bolus	Low-fat, standard cab EN formula	14 days	ARDSnet	BAL lavage interleukin levels	9/40 vs. 11/45, p = NS
Rice [25•]	2011	272	EPA + DHA + GLA + antioxidants	Twice daily bolus	Low-fat, EN formula	21 days	ARDSnet	60-day or hospital mortality	39/143 vs. 21/129, p = NS
Elamin [28]	2012	22	EPA + DHA + GLA + antioxidants	Enteral	High-fat, omega-6 EN formula	7 days	NA	Modified lung injury score	0/9 vs. 1/8, p = NS
Parish [23]	2014	58	EPA + DHA	Enteral	NA	14 days	ARDSnet	Change in oxygenation	7/29 vs. 9/29, p = NS

* Reported as experimental versus control group mortality rate

ARDSnet acute respiratory distress syndrome network, *BAL* bronchoalveolar lavage, *DHA* docosahexaenoic acid, *EN* enteral nutrition, *EPA* eicosapentaenoic acid, *GLA* gamma-linolenic acid, *NA* not available, *NS* not significant

Semi-elemental formulas were the first to be compared to parenteral nutrition for those pancreatic patients requiring nutrition support. Semi-elemental formulas were preferred due to less stimulation using low-fat, medium-chain triglyceride-based or elemental formulas [34••]. Cost of enteral nutrition compared to parenteral nutrition was three times less [34••]. Although enteral nutrition is less expensive than parenteral nutrition, elemental formulas are more expensive than standard polymeric formulas.

By feeding 40 cm below the ligament of Treitz, enteral nutrition reflects nearly no stimulation of the pancreas [32]. Makola studied 126 pancreatitis patients managed at the University of Virginia Health System from August 2000 to June 2004. Standard polymeric formula delivered distal to the ligament of Treitz improved CT Severity Index by 79.2 % [32]. In addition, decreased hospital stay, increased BMI for those patients with BMI <18.5, and increased albumin were found. Of note, patients with BMI 18.5–25 had no weight change. Less complications were noted when compared to total parenteral nutrition [32]. Tiengou compared semi-elemental formulas to polymeric formulas. He conducted a randomized prospective pilot study, stratified according to pancreatic severity. This study included 30 acute pancreatitis patients requiring jejunal nutrition. Patients were given either Peptamen or Sondalis-Iso at 35 kcal/kg/days. Tiengou found no difference between the two groups in regards to pain, bloating, and tolerance. There was no difference in absorption of nutrition formula (24-h stool weight, 24-h creatorrhea, 24-h steatorrhea, and mean number of stools) [31]. In both groups, both formulas were successful in resolving pancreatitis as evidenced by abdominal CT scan results of favorable outcomes. Petrov et al. conducted adjusted meta-analysis that compared polymeric (standard) tube feeding formulas with semi-elemental formulas. This comparison demonstrated that the use of standard formulas does not lead to a significantly higher risk of feeding intolerance, infectious complications, or death in acute pancreatitis patients [35].

As of 2009, European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines explicitly state enteral nutrition as the preferred treatment for those patients unable to establish adequate PO intake within 5–7 days [34••]. Furthermore, it recommended that standard tube feeding formula be introduced initially. Specialized formulas to include semi-elemental and elemental formulas should only be used if standard formulas prove intolerable [30]. Pancreatitis induces increased metabolic rate and protein catabolism leading to the need for increased energy intake from both fat and carbohydrates [36]. Additionally, where EN was initiated with 48 h of admission to the hospital, EN was found to be well tolerated, associated with fewer septic complications than parenteral nutrition, and resulted in decreased systemic inflammatory response syndrome (SIRS) [36]. Additional benefits recognized were less need for surgical intervention, multiple organ failure, and mortality when compared to the use of parenteral nutrition [30]. Semi-elemental or elemental formulas should only be introduced as acceptable pancreatitis treatment if standard tube feeding formulas are poorly tolerated.

Liver

Malnutrition is very common in chronic liver disease with a prevalence ranging from 20 % to more than 80 % in patients with compensated and decompensated cirrhosis, respectively [37]. It has also been reported to be an independent risk factor for survival [38]. Many patients with liver disease are therefore either at risk for malnutrition or have already developed it. When patients are unable to gain these calories with normal food, the addition of supplementary enteral nutrition (EN) is recommended [39]. Currently, there are limited data regarding liver-specific EN, but several professional societies have provided guidelines and recommendations.

The energy recommendations in patients with liver disease, based on the 2006 ESPEN and 2016 ASPEN/SCCM guidelines, range from 25 to 40 kcal/kg/day [29••, 39]. The ESPEN guidelines recommend using a simplistic weight-based equation (35–40 kcal/kg/day) [38]. In critically ill patients with hepatic failure, energy needs are highly variable and difficult to predict by simple equations, and the ASPEN/SCCM guidelines recommend using indirect calorimetry (IC) instead. If IC is unavailable, a published predictive equation or simplistic weight-based equation at lower energy intake (25–30 kcal/kg/day) may be used. Dry weight is preferred over actual weight for calculating energy requirements because of cirrhosis-related complications arising from fluid shifts and volume status changes including ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia [29••].

Historically, protein restriction was recommended in patients with liver disease to reduce risk of hepatic encephalopathy (HE) [40], but studies have now shown no benefit from protein restriction as these patients are able to safely tolerate normal protein diets [41]. Conversely, protein restriction can lead to worsening of nutritional status, decreased lean muscle mass, and ironically decreased ammonia removal. The current consensus is that protein restriction should be avoided in all patients with liver disease, except in patients with severe protein intolerance (e.g., HE Grade III–IV) in which protein may be reduced for a short period of time [42]. The ESPEN guidelines recommend protein intake of 1.2–1.5 g/kg/day in all

cirrhotic patients [39]. The ASPEN/SCCM guidelines recommend a higher protein intake of 1.2–2 g/kg/day (calculated from dry weight) in liver patients in the medical and surgical intensive care units [29••]. In general, whole protein formulas are recommended for patients with all severities of liver disease. More concentrated high-energy formulas should be considered in patients with ascites because of fluid shifts [39]. In the ICU setting, the new ASPEN/SCCM guidelines recommend using a standard polymeric isotonic or near-isotonic 1–1.5 kcal/mL formula and avoiding the use of all specialty formulations in the medical intensive care unit and all disease-specific formulations in the surgical intensive care unit [29••].

Branched-chain amino acids (BCAA) are of particular interest in regards to liver-specific nutrition. These formulas are very expensive and contain higher proportion of BCAAs and reduced amounts of aromatic amino acids (AAAs) [43••]. Patients with cirrhosis have a low ratio of BCAA to AAA because AAA levels are increased secondary to impaired capacity for hepatic deamination. As a result, tryptophan, an AAA, outcompetes BCAA for increased uptake in the brain leading to an imbalance of neurotransmitter synthesis. This is the proposed mechanism leading to confusion and altered mental status. BCAA is also thought to reduce hyperammonemia [44]. Although there has been controversy in regards to benefit, the ESPEN guidelines recommend BCAA for patients with hepatic encephalopathy [39]. This was largely based on a large randomized control trial which showed that long-term supplementation (12 months) resulted in decreased frequency of hepatic failure and associated complications [45]. In a recent Cochrane systemic review evaluating 16 randomized clinical trials including 827 patients with hepatic encephalopathy, BCAA was found to have a beneficial effect on hepatic encephalopathy with a high quality of evidence (risk ratio (RR) 0.73, 95 % confidence interval (CI) 0.61–0.88). Compared to placebo, there were no differences in mortality, quality of life, or nutrition parameters, but the authors report that they need additional trials to evaluate these outcomes. In the same review, BCAA was also shown to be beneficial in sensitive analyses that excluded trials with lactulose or neomycin control (RR 0.76, 95 % CI 0.63–0.92). Additional sensitive analyses showed no statistical significance between BCAA and lactulose or neomycin (RR 0.66, CI 0.34–1.30) [46••]. The ASPEN guidelines therefore do not recommend BCAA in the intensive care setting as patients with encephalopathy are already on first-line medications (antibiotics and lactulose) [29••].

Preoperative transplantation and surgery patients with liver disease should follow the same nutrition guidelines for cirrhotic patients as described above. Postoperatively, normal food and/or enteral nutrition should be initiated within 12–24 h after liver transplantation. Early normal food or enteral nutrition should be initiated in all other surgical patients with liver disease. In addition, there is a recommendation for using nasogastric or catheter jejunostomy tubes to achieve early enteral nutrition [39].

Renal

Finally, we will focus on acute kidney injury (AKI) which can further complicate a patient's nutritional assessment, particularly in critically ill patients. AKI is defined by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) or the Acute Kidney Injury Network (AKIN) definition. Both definitions have several stages of kidney injury with the minimum being a 25 % or greater decrease in glomerular filtration rate or less than 0.5 mL/kg/h of urine for 6 h with the RIFLE definition, and a serum creatinine increase of 1.5–2 times that of the baseline or a similar decrease in urine output for the AKIN definition [47]. Development of AKI occurs in 30 % of patients who are admitted to the intensive care unit and approximately half of these patients will have a fatal outcome [48].

Many patients who develop AKI have other underlying diseases and organ dysfunction compounding any existing nutritional abnormalities and deficiencies. AKI may result in severe derangements in electrolyte and micronutrient balance. Several electrolytes are fully or partially regulated by renal function including potassium, phosphate, magnesium, and calcium. Potassium abnormalities can have severe consequences including arrhythmia and death, thus potassium should be closely monitored in AKI and should be managed via renal replacement therapy. Calcium, phosphate, and magnesium levels can be altered in AKI; although typically do not become life threatening, these should be monitored and adjusted as necessary [49•]. The ASPEN/SCCM recommends that specialized tube feeding formulas should only be used with severe electrolyte abnormalities. In the absence of abnormalities, standard tube feeding formulas may be used in patients with AKI [29••].

In addition to electrolyte abnormalities, AKI is associated with alterations in the metabolism of protein, carbohydrate, and lipids. There is an increase in protein catabolism secondary to critical illness that is exacerbated by AKI and will be discussed in detail below [50]. Altered lipid metabolism occurs with AKI secondary to impaired lipolysis. This results in an increase in low-density lipoproteins and triglycerides with a concurrent decrease in total cholesterol and high-density lipoproteins. Despite these changes, fatty acid oxidation is maintained and remains an essential energy source for these patients [49•].

Finally, carbohydrate metabolism is altered as patients with AKI have exacerbated insulin resistance which contributed partly to decreased renal gluconeogenesis. Patients with AKI and insulin resistance have a higher mortality rate compared to patients with AKI alone. The etiology of this is unclear and has been shown to be independent of illness severity, supplemental cortisol, or underlying diabetes [51]. The guidelines (both ESPEN and ASPEN/SCCM) recommend patients with AKI should receive a standard enteral formula unless there are severe electrolyte disturbances. There is some evidence that patients with AKI benefit from tube feeding and have improved ICU outcomes [52, 53]. Derangements in lipid and carbohydrate metabolism should be monitored and treated medically as indicated.

Protein metabolism is severely altered in patients with AKI as it is a catabolic state, and patients have high protein and calorie needs to meet baseline energy expenditures in this disease process. ASPEN/SCCM and ESPEN guidelines are based only on expert opinion but recommend standard protein and caloric intake for patients with AKI who are not receiving any form of renal replacement therapy. Protein requirements increase when patients are placed on any form of renal replacement therapy as protein losses are increased during this therapy. The exact amount of protein therapy required by patients with AKI is unknown and the catabolic rates may reach up to 1.5 g/IBW/day [54]. However, it is unclear if the replacement of this can be achieved through higher protein intake as one study showed that a diet of 2.5 g/day did not achieve nitrogen balance in 65 % of patients [55].

A separate study by Scheinkestel et al. showed that patients could achieve a positive nitrogen balance with protein supplements up to 2.5 mg/kg/day. This study showed that increased protein intake did improve nitrogen balance but there was no correlation with improved outcome from critical illness [53]. Overall, this study was small and has not been replicated, therefore the ESPEN guidelines note that there is no direct evidence regarding the safety of high protein intake above 2 g/kg/day in patients with AKI and hypercatabolism may not be overcome by increased enteral intake of protein alone. Both professional societies do not recommend withholding protein however in light of this paucity of evidence [50].

There is little evidence supporting the use of immune-enhancing enteral formulas for patients with AKI. Although previously thought that these may benefit patients given the loss of trace elements and water-soluble vitamins, studies show that these formulas may exacerbate the pro-inflammatory response in sepsis, which is a frequent comorbid condition in patients with AKI [56]. This increase in inflammation likely negates any benefit for patients with AKI. There are no separate randomized trials for patients with AKI without sepsis to recommend immune formulas for patients with AKI. Furthermore, the REDOX (A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients) trial showed that the treatment of patients with immune-modulating formulas should be considered with caution without medical evidence showing benefit [57••]. This trial was not specific for patients with AKI; however, approximately one third of patients in the trial had some level of renal dysfunction. The trial showed an increase in mortality with glutamine supplementation and no improvement with antioxidants. These supplements should not be considered in critically ill patients with multi-organ failure.

Conclusion

Critical illness and organ failure continue to have a high mortality rate associated with it. As the number of organs failing increased, mortality also increases. Organ-specific nutrition was initially introduced in an effort to improve outcomes for patients with organ failures and/or injuries. These formulas however have not been proven effective and in some circumstances there is some suggestion of harm related to the formula. There is at this time little evidence to recommend the use of organ-specific formulas and both ASPEN/SCCM and ESPEN recommend standard tube feeding formulas for critically ill patients. Although enteral nutrition remains an essential therapy for critically ill patients, unfortunately, specialized organ-specific formulas appear to be heading for the history books.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Patel, Kha, Butler, Kozeniecki, Martindale, and Karen Allen declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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