Sepsis and Nutrition

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Introduction

Sepsis continues to be a common and serious problem. As the population ages, the incidence of sepsis in the United States continues to climb. It is estimated that in the United States, there are greater than 1.1 million cases of sepsis per year [1] at an annual cost of $24.3 billion [2]. Sepsis remains the leading cause of death in non-cardiac intensive care units (ICUs) [2]. In spite of extensive research, sepsis related mortality remains prohibitively high [3–5]. In recent years, multiple professional organizations have developed evidence-based guidelines for the management of sepsis. The intent of such guidelines is to improve patient outcomes by aiding clinicians in the delivery of evidence-based care. Providing adequate nutritional support of critically ill patients, including those with sepsis, is a key factor in improving patient outcomes. The provision of early nutritional support via the enteral route can attenuate the metabolic response to stress, favorably modulate the host's immune response, reduce the risk nosocomial infections, and reduce the risk organ dysfunctions associated with critical illness [3]. In this chapter, we will review the current literature as it relates to the nutritional support of critically ill patients with sepsis.

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The Pathophysiology of Sepsis

In order to understand the potential impact of nutritional intervention in the septic patient, an understanding of the physiologic changes that occur in sepsis is required. The initial clinical manifestations of sepsis are the result of a complex series of interactions between the inciting organism and the host's innate immune response. This intricate cellular interaction involves numerous signaling pathways as well as the production of cytokines and chemokines. A detailed discussion of each of these pathways is beyond the scope of this text. However, a few key elements will be discussed.

Definition of Systemic Inflammatory Response Syndrome and Sepsis

In the early descriptions of multiple organ failure (MOF) in the late 1970s by Eiseman, Polk, and Fry, it was concluded that MOF occurred as a result of uncontrolled infection [4–6]. However, in the early 1980s, reports out of Europe by Faist and Goris showed that MOF could occur after

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severe blunt trauma without identifiable source of infection [7, 8]. Sepsis syndrome became a "junk" term to describe this type of patient. The key question became if it is not infection, what is the driving force behind the over exuberant inflammatory response that is causing organ injury. Popular theories in the mid-1980s included bacterial translocation, shock-induced whole body ischemia/reperfusion (I/R), and unrecognized impaired flow dependent oxygen consumption [9]. However, in 1989, Roger Bone defined this term "sepsis syndrome" to be an infection plus the presence of systemic illness [10]. This description was followed by the American College of Chest Physicians and the Society of Critical Care Medicines Consensus Conference in 1991 that defined the Systemic Inflammatory Response Syndrome (SIRS) as having two or more of the following criteria: (1) a temperature < 96 °F or >100.4 °F, (2) a heart rate of >90 beats/min, (3) a respiratory rate of >20 breaths/min or a $paCO_2$ of <32 mmHg, (4) a white blood cell count of >12,000 or <4,000 cells/mm^3 or >10 % bands. Sepsis was then defined as an infection plus SIRS [11].

In response to ongoing criticism from experts in the field, a second consensus conference was convened in 2001 to revise the original definitions. The updated consensus conference definitions included an expanded list of the signs and symptoms of sepsis [12]. The definitions of sepsis are listed in Table 9.1.

Table 9.1 SIRS and sepsis definitions

Systemic inflammatory response syndrome (SIRS) must have two or more:	1. Temperature >38 or <36 °C 2. Heart rate >90 beats/min 3. Respiratory rate >20 breaths/min or $paCO_2 < 24$ 4. White blood cell count >12,000 or <4,000 cells/mm^3 or >10 % bands
Sepsis	SIRS due to infection
Severe sepsis	Sepsis with evidence of organ dysfunction or hypoperfusion. Hypoperfusion abnormalities may include lactic acidosis, oliguria, or an acute alteration in mental status
Septic shock	Severe sepsis with hypotension (systolic blood pressure <90 mmHg) despite adequate fluid resuscitation or the requirement for vasopressors/inotropes to maintain blood pressure

Response to Infection: Characteristics of the Pathogen

The host response to infection can be triggered by bacterial, viral, and/or fungal infection. The specific characteristics of the inciting organism play a role in the body's response to the infectious stimuli. Each organism has specific virulence factors that enable the organism to evade the host's defenses. These virulence factors include antigenic variation of surface molecules, inhibition of complement activation, resistance to phagocytosis, production of exotoxins, and scavenging of reactive oxygen intermediates [13]. Cell-to-cell communication between organisms allows for signaling and up regulation of virulence factors. Perhaps one of the best described virulence factors is lipopolysaccharide (LPS), also known as endotoxin, which is a component of the outer cell wall of all gram negative bacteria. The presence of LPS provokes local and systemic inflammation, including proliferation of cytokines and activation of macrophages. The presence of LPS is essential to maintaining the integrity of the outer membrane of gram negative bacteria, acting as a protective barrier against lysozymes, antimicrobial agents, and host phagocytic cells.

Response to Infection: Characteristics of the Host

The human body is equipped with a variety of defense mechanisms against microorganisms. These include physical barriers such as the skin and mucosal surfaces, the innate immune response, and the adaptive immune response. Dysfunction of any of these components can lead to the development of sepsis. The recognition of pathogens by the innate immune response initiates a complex cascade of events that are intended to remove the pathogen from the host. This includes the release of reactive oxygen metabolites to destroy the pathogen, release of chemokines to

recruit additional neutrophils and lymphocytes, and the generation of a variety of systemic cytokines to further activate the host immune response. We are just beginning to understand the potential impact of genetic polymorphisms and the impact these may have on patient survival.

The immune response to sepsis represents a complex series of interactions characterized by the proliferation of both pro and anti-inflammatory mediators. A complete description of this process is beyond the scope of this manuscript but a brief explanation of the process is helpful to understanding the clinical manifestations of sepsis. The early phase of sepsis is generally considered to be a pro-inflammatory state. In response to infection, activated macrophages and CD4+ T cells systemically release tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and gamma interferon (IFN-γ). This inflammatory response is necessary for the host to overcome the infectious organism. Unfortunately, in a subset of sepsis patients this inflammatory response is not well balanced and can lead to an overwhelming SIRS response with resultant early MOF and a fulminant death.

Recognition of the Compensatory Anti-inflammatory Response Syndrome

Throughout the 1980s and into the 1990s, prominent investigators identified multiple defects in adaptive immunity that occurred as patients progressed through their critical illnesses that were associated with poor outcomes. In the mid-1990s, Roger Bone coined the term "compensatory anti-inflammatory response syndrome" (CARS) to describe the post-SIRS anti-inflammatory response and subsequent immunosuppression [14–16]. CARS was associated with late infections, which, in turn, were assumed to precipitate a second peak in late MOF [17]. In the late 1990s, the SIRS/CARS paradigm of early and late MOF had become the conceptual framework to explain the immunological trajectory of a complicated ICU course. Research focused on treating SIRS and better characterizing CARS. Multiple contributing mechanisms that characterized CARS were described including increased number of regulatory T cells [18], macrophage paralysis with resultant decreases in cytokine production [19], lymphocyte apoptosis [20], T cell anergy [14], suppressed T cell proliferation [21], and shifting from the Th1 to Th2 phenotype [22]. It is important to note that CARS is not merely the cessation of SIRS. In fact, CARS can exist days to weeks after the resolution of SIRS when pro-inflammatory cytokines are no longer present [23]. Some of the anti-inflammatory effects of CARS occur through enhanced apoptosis with resultant loss of CD4 and CD8 T cells, B cells, and lymphocytes that are responsible for the proliferation of pro-inflammatory mediators [24]. Loss of these immune effector cells leads to sepsis-induced immunosuppression which is responsible for the development of delayed secondary infections.

With improvements in SIRS management in the ICU, the number of patients that survive this initial SIRS-CARS phase of sepsis has dramatically increased. The result is that we are seeing increasing numbers of patients that stay in the ICU for weeks with a syndrome of moderate organ dysfunction, secondary infections, respiratory failure, and progressive protein catabolism with resultant loss of lean body mass and strength. This has led to the recognition of new clinical phenomenon named persistent inflammation, immunosuppression, and catabolism syndrome (PICS). First described by Moore and colleagues in 2012, PICS is characterized by simultaneous chronic low level inflammation and adaptive immunosuppression [25]. The clinical criteria for diagnosing PICS are presented in Table 9.2. The management of patients with PICS is challenging and requires a multidisciplinary approach includes developing anabolic nutritional interventions to modulate the patient's nutritional status, enhance immune responses and to push physical therapy with active strength training exercising.

Table 9.2 Persistent inflammation, immunosuppression, and catabolism syndrome (PICS)

Clinical determinants of PICS	Measurements
Persistent	Prolonged ICU stay > 14 days
Inflammation	C-reactive protein > 100 kg/dL
Immunosuppression	Total lymphocyte count $< 0.80 \times 10^9$ L^{-1}
Catabolism	Weight loss > 10 % during hospitalization of body mass index < 18
	Creatinine height index < 80 %
	Albumin level < 3.0 g/dL
	Pre-albumin level < 10 mg/dL
	Retinol binding protein level < 10 μg/dL

The Role of the Gastrointestinal Tract in the SIRS/CARS Paradigm

Septic shock is a prime inciting event for MOF. The lack of perfusion that defines shock states, directly injures the gut and with resuscitation causes a reperfusion injury that releases pro-inflammatory mediators that can amplify SIRS. This also initiates a local inflammatory response that results in a variety of gut dysfunctions (e.g., gastroparesis, gastric alkalization, ileus, duodenogastric reflux, impaired mucosal blood flow, epithelial apoptosis, increased permeability, impaired local gut immunity). Early isotonic crystalloid resuscitation can amplify inflammation, cause problematic edema, and promote ileus. Early laparotomy with bowel manipulation promotes gut inflammation, mucosal injury, and ileus. Standard ICU interventions worsen these gut dysfunctions, including vasopressor agents (decrease mucosal perfusion), stress gastritis prophylaxis (worsens gastric alkalization), narcotics (worsen ileus), antibiotics (promote bacterial overgrowth), and parenteral nutrition (gut disuse decreases local gut immunity that contributes to worsening Cars). Over a short period of time, the normally sterile upper GI tract becomes heavily colonized with potential pathogens, and the gut becomes the reservoir for bacteria and toxins that escape the gut via pulmonary aspiration of gastric contents or bacterial translocation that contribute to late nosocomial infections and late MOF [26].

How Early Enteral Nutrition Interrupts This Sequence of Events

The gastrointestinal tract is the largest immune organ in the body. As a result, it plays a significant role in the immune response to infection and sepsis. The provision of enteral nutrition (EN) stimulates splanchnic perfusion thereby support gut-associated lymphoid tissue (GALT) [27]. The delivery of EN helps maintain the functional and structural integrity of the intestinal epithelium, stimulates intestinal contractility thus preventing bacterial overgrowth, and aids the processing of naive CD4 lymphocytes with a resultant release of anti-inflammatory mediators into the systemic circulation [28].

In a variety of models (i.e., sepsis, hemorrhagic shock, and gut ischemia and reperfusion) intraluminal nutrients have been shown to reverse shock-induced mucosal hypoperfusion [29, 30]. In the lab, we showed that early EN also reverses impaired intestinal transit when given after a gut I/R insult [31]. Improved transit should decrease ileus-induced bacterial colonization [32]. Moreover, EN (specifically glutamine) improves the gut permeability defect that is induced by critical illness [33]. Finally, the gut is a very important immunologic organ and the severity of CARS can be lessened by feeding the gut [34]. A recent series of innovative lab studies has nicely documented that EN supports the function of the mucosal associated lymphoid tissue (MALT) that produces 70 % of the body's secretory IgA [35]. Naive T and B cells target and enter the GALT where they are sensitized and stimulated by antigens sampled from the gut lumen and thereby become more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes, the thoracic duct, and into the vascular tree for distribution to GALT and extra intestinal sites of MALT. Lack of enteral stimulation (i.e., use of TPN) causes a rapid and progressive decrease in T and B cells within GALT and simultaneous decreases in intestinal and respiratory IgA levels. Previously resistant lab animals, then challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects and susceptibility to infection are reversed within 3–5 days after restarting EN.

Perhaps more important than the benefits of provision of EN in critical illness are the negative physiologic consequences of withholding EN. Failure to provide luminal nutrients to the intestinal epithelium results in loss of both structural and functional integrity of these cells. This results in loss of the normal barrier function of the gut. Lack of EN results in decreased gut contractility with resultant bacterial overgrowth and the potential emergence of pathogenic organisms in the lumen. Proliferation of the pathogenic organisms within the gut can lead to attachment to the intestinal epithelium with resultant release of cytokines and programmed cell death [36]. Death of the intestinal epithelial cells leads to further defects in the gut barrier and increases permeability. This increase in permeability permits luminal bacteria to interface the gut's immune system resulting in diffuse activation of macrophages. The end result of these changes is the generation of a systemic pro-inflammatory state, thereby worsening the SIRS response already initiated by the inciting infection.

Development of Chronic Critical Illness

In the early 2000s, mortality from trauma-induced MOF decreased substantially, and the second peak of late MOF deaths disappeared [37, 38]. This was a result of fundamental changes in the initial care of trauma patients arriving with severe bleeding and consistent delivery of evidence-based-guideline (EBG)-driven standard operating procedures (SOPs) in the ICU [39, 40]. The same decrease in mortality and MOF was not observed with sepsis, however, for two reasons. First, early diagnosis of sepsis is difficult, allowing many patients to progress into septic shock, which has a prohibitively high mortality, despite aggressive interventions. This provided the rationale for routine sepsis screening [41]. Second, many interventions that are known to have an impact on outcome in sepsis were haphazardly administered. One approach to consistently implement EBG-driven SOPs is computerized clinical decision support (CCDS) [42]. Using the combination of sepsis screening and CCDS for sepsis management in our surgical ICU, we documented a surprising decrease in inhospital mortality for severe sepsis/septic shock from 34 % in 2006 to 14 % in 2009 [43]. However, when we studied the epidemiology of these patients, we recognized that many of the survivors lingered in the ICU with manageable organ dysfunctions [44]. Their clinical course was characterized by recurrent inflammatory insults (e.g., repeat operations and nosocomial infections), a persistent acute-phase response with ongoing loss of lean body mass despite optimal nutritional support, poor wound healing, and decubitus ulcers [25]. These patients (especially the elderly) are commonly discharged to long-term acute care facilities (LTACs) and skilled nursing facilities (SNFs) with significant cognitive and functional impairments from which they rarely fully rehabilitate.

Advances in critical care medicine have significantly improved patient survival during the acute phase of sepsis. This improvement in patient survival is due to ongoing performance improvement efforts that ensure the timely delivery of evidence-based guidelines for the management of sepsis [43, 45, 46]. An unexpected result of this improved survival is a growing population of patients that develop a condition referred to as chronic critical illness (CCI). CCI is defined by a prolonged dependence upon life support. This has classically been defined as a prolonged need for mechanical ventilation (>2 weeks) but additional features have also been described. These include profound weakness secondary to myopathy and neuropathy, increased vulnerability to infection, brain dysfunction manifesting as coma or delirium, and changes in body composition including loss of lean body mass, anasarca, and increased adiposity [47, 48]. Several risk factors have been identified for the development of CCI. These include Glasgow Coma Score < 15, the presence of sepsis, inadequate caloric intake, and elevated body mass index (BMI) [49]. It is estimated that 5–10 % of critically ill patients will develop CCI [50]. The long-term outcomes for patients that develop CCI are poor. One year mortality rates for CCI patients are estimated at 40–50 % [51]. Those patients that do survive beyond the 1 year mark are reported to have poor functional status and require substantial caregiver support and ongoing care in SNFs [52].

A key component in the prevention and management of patients with CCI is the delivery of adequate nutritional support. As mentioned above, failure to deliver adequate nutritional support at the onset of critical illness is an independent risk factor for the development of CCI. Patients that develop CCI are often malnourished and in a persistent catabolic state. The malnutrition that accompanies CCI is mediated by the inflammatory response to critical illness and is characterized by tissue proteolysis and reduction of free amino acids and glutamine in skeletal muscle [50]. The provision of nutritional support in CCI reverses the catabolic state and is essential to restoring muscle function. The primary goal of nutritional support in CCI is to provide adequate nitrogen to compensate for the significant nitrogen losses that have occurred during the acute phase of critical illness. Patients also commonly have neuroendocrine imbalances, with hyperglycemia, bone resorption, and vitamin D deficiency. This constellation of problems requires clinicians to carefully manage the nutritional support to avoid over and underfeeding as well as refeeding syndrome. The enteral route is recommended as first line therapy and should be utilized in all patients with a functional gastrointestinal tract. Patients with CCI that will require enteral nutritional support for >30 days benefit from the placement of a percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ) tube for long-term nutritional support.

Guidelines for Provision of Nutritional Support in the ICU

In 2009, The American Society for Parenteral and Enteral Nutrition (ASPEN) in cooperation with the Society of Critical Care Medicine (SCCM) published guidelines for the provision and assessment of nutritional support in the critically ill patient. These practice guidelines were developed through a systematic review of all available literature, primarily utilizing prospective randomized controlled trials to support the recommendations. The guidelines are designed to provide clinicians with a comprehensive summary of the best available evidence for the provision of nutritional support in the critically ill adult patient.

Initial Assessment of Nutritional Status

The traditional assessment of nutritional status involves a combination of anthropometric and biochemical variables. Due to extreme derivations in patient physiology due to the inflammatory response to critical illness, many of these traditional methods of nutritional assessment are not as useful. As a result, nutritional assessment in the ICU population presents a unique set of challenges to the clinician. In the setting of acute critical illness, hepatic protein synthesis shifts toward the production of acute-phase proteins. This shift in protein synthesis limits the value of utilizing the traditional constitutive protein markers (albumin, pre-albumin, retinol binding protein, and transferrin) utilized for nutritional assessment. Nutritional assessment in the ICU population should begin with a thorough history and physical exam focused on identifying clinical signs of malnutrition. A recent history of weight loss or poor oral intake signals the need for aggressive nutritional support.

Another key component in the nutritional assessment of the critically ill patient is an evaluation of the status of the gastrointestinal tract. While provision of enteral nutrition is the preferred method of delivery, the overall hemodynamic status of the patient must be taken into consideration. The development of ischemic bowel is a rare but potentially fatal complication of enteral nutrition, occurring in <1 % of all patients [53, 54]. Intravascular volume status must be assessed and hypotension must be reversed prior to the initiation of enteral nutrition. Infusion of nutrients into the gut in the setting of visceral hypoperfusion poses a significant risk of non-occlusive mesenteric ischemia. The absorption of intraluminal nutrients increases the metabolic demands of the enterocytes with a resultant risk of mesenteric ischemia in patients suffering from systemic hypoperfusion. It is not safe to

initiate enteral nutrition in patients with ongoing evidence of hypoperfusion. This is especially true in patients that are receiving high doses of vasopressors to support blood pressure, as this may precipitate bowel ischemia. The delivery of EN should be avoided in patients who are hypotensive [mean arterial pressure (MAP) of <60 mmHg] and in patients that are receiving catecholamines (norepinephrine, phenylephrine, epinephrine, dopamine) particularly if the dose of catecholamines is escalating to MAP [55].

Delivery of Early Enteral Nutrition

The initiation of early enteral nutrition (EN) should begin as soon as fluid resuscitation is complete and hemodynamic stability has been restored. Initiation of EN within the first 24–48 h is optimal. The provision of early EN results in a multitude of benefits for the critically ill patient. When feeds are initiated within 48 h of the onset of critical illness, there is attenuation of the inflammatory response, decreased gut permeability, and diminished levels of TNF-α [56]. As mentioned previously, the GI tract plays a significant role in the immune response to sepsis via the GALTs. The GALT contains 70–80 % of all immunoglobulin-secreting cells [57]. The functional and structural integrity of the gut epithelium is affected presence or absence of luminal nutrients. When nutrients are not provided to the gut, there is shortening of microvilli of the intestinal wall with resultant impairment of nutrient absorption. There is also impairment of the functional and structural integrity of intestinal epithelium which results in increased risk for systemic infection and greater likelihood for the development of MOF [27]. These deleterious effects are amplified as disease severity worsens. The delivery of early EN is beneficial because it helps to maintain gut epithelial integrity, modulates the systemic immune response, decreases the risk of developing secondary infection, and decreases mortality [58, 59].

The initiation of early EN in the ICU population is not dependent upon clinical evidence of bowel function (i.e., flatus, passage of stool). The presence of GI dysfunction in the critically ill population ranges from 30 to 70 % and is dependent upon multiple factors including premorbid conditions, mechanical ventilation, and medications. GI dysfunction may also be due to mucosal barrier disruption, altered motility, or mucosal atrophy. The presence of bowel sounds, often used to assess for clinical evidence of bowel function, is only indicative of GI contractility. The presence or absence of bowel sounds does not tell the clinician anything about mucosal integrity, gut epithelial barrier function, or absorptive capacity. Therefore, in the hemodynamically stable patient, EN should be initiated and advanced using standard EN protocols. The target goal rate of EN should be determined at the time of initiation of nutritional support. Energy requirements should be calculated through the use of predictive formulas or through the use of indirect calorimetry. The delivery of small volume trophic feeds may not be sufficient to maintain gut mucosal integrity. In order to achieve maximal benefit of EN, 50–65 % of the caloric goal should be achieved within the first 7 days of hospitalization.

The choice of gastric vs. small bowel feeding is dependent upon patient-specific factors. There is some evidence to suggest that small bowel feedings are associated with less gastroesophageal reflux [60]. There is also some evidence that small bowel feedings as compared to gastric feedings are associated with a decreased incidence of ventilator-associated pneumonia [61]. In those patients deemed to be at high risk for aspiration or those patients that have demonstrated intolerance to gastric feeding, small bowel feeding is preferred.

Enteral Nutrition vs. Parenteral Nutrition

The administration of early EN vs. parenteral nutrition (PN) has been debated in the medical literature for over 30 years. There is now a substantial body of clinical evidence that clearly demonstrates the benefits of EN over PN [3, 62, 63]. Most studies comparing EN to PN have not

demonstrated significant differences in patient mortality. However, the use of early EN has been shown to reduce infection complications, including the development of secondary infections. In a prospective, randomized controlled trial comparing early EN to early PN, Moore and colleagues showed that early EN was associated with reduced infections, specifically a reduction in pneumonia [64]. Similar decreases in infectious complications have been reported by others [65]. Additional benefits seen in patients receiving early EN include reduced hospital length of stay [56], decreased cost of nutritional therapy [56], and improved return of cognitive function [66].

Significant controversy still exists about the timing of initiation of PN in critically ill patients that cannot reach their caloric needs with EN alone. In a recent randomized, multicenter trial, Van den Berghe et al. compared early PN (within 48 h of ICU admission) to late PN (after day 8). This study showed that late initiation of PN was associated with a faster recovery and fewer complications as compared to the early initiation group [67]. The current ASPEN/SCCM guidelines recommend that the use of PN should be reserved for those patients in whom EN is not feasible after the first 7 days of ICU admission [55]. In the event that a patient that is unable to tolerate EN presents to the ICU with evidence of protein-calorie malnutrition (defined as recent weight loss of >15 % of actual body weight OR actual body weight <90 % of ideal body weight) then it is appropriate to initial PN as soon as SIRS has resolved. In this subset of patients, a meta-analysis by Heyland reported that the use of PN was associated with significantly fewer overall complications when compared to delivering no nutritional support [68]. Therefore, in severely malnourished patients with a contraindication to EN, early PN should be initiated.

Monitoring for Nutritional Adequacy

After the initial nutritional assessment, clinicians should determine each individual patient's nutritional goals to include caloric requirements. This is often expressed as a goal rate or goal volume of enteral nutrition to be delivered. Once nutritional support has been initiated, it is important to perform routine monitoring to assess the adequacy of the nutritional support that is being delivered and make modifications when necessary.

There are multiple diagnostic tests that can be utilized to assess nutritional adequacy. These include body measurement testing (weight change, anthropometric measures), body composition testing (determination of percent body fat, lean body mass, etc.), and laboratory testing (urine analysis, pre-albumin, etc.). In the setting of critical illness there can be short-term alterations in patient's fluid status, rendering the body composition modalities and monitoring based off of changes in patient weight useless in this population. The biochemical indices that are used are also affected by critical illness.

Serum proteins are often measured to help assess for nutritional adequacy. Pre-albumin is commonly used due to its short half-life of 2.5 days. Due to this relatively short half-life, one would expect to see a more rapid change in pre-albumin levels in response to nutritional intervention. However, in the critically ill patient, it is important to note that the serum pre-albumin level may be increased in patients with renal failure, in patients receiving corticosteroids, and those who have a persistent acute response. With ongoing stress the body reprioritizes hepatic protein synthesis after stressful insults away from reverse-phase reactants (e.g., pre-albumin) to acute-phase reactants (e.g., CRP). Additionally, serum pre-albumin levels may be decreased in patients with liver disease, those patients receiving hemodialysis, and patients with severe hyperglycemia. Given all of the alterations to serum protein markers in the setting of critical illness, the use of serum pre-albumin to assess nutritional adequacy is of limited use until there is resolution of the acute-phase response which can be monitored by weekly CRP determinations.

Immunonutrition

Optimal function of the immune system is dependent upon the presence of adequate nutrition. In the presence of malnutrition, the host's immune response to infection is impaired. Recent

advances in our understanding of the role of the gut in the host's immune response have led to increased interest in the concept of immunonutrition. The term immunonutrition refers to the delivery of a particular nutrient in order to induce a specific metabolic or immunologic function. The addition of specific substances to enteral nutrition formulas could potentially modulate the immune response, improve wound healing, and reduce the oxidative stress associated with sepsis. As a result, specific immune enhancing formulas have been developed by adding compounds such as L-glutamine, L-arginine, omega-3 fatty acids, and supraphysiologic doses of selenium, vitamins A, C, and E. In this section, we will review the potential benefits of immunonutrition in sepsis.

Arginine

Under normal conditions, arginine is considered to be a nonessential amino acid that is derived from oral protein intake or synthesized endogenously in the proximal renal tubule by the conversion of citrulline to arginine. Citrulline is primarily derived from the intestinal conversion of arterial and luminal glutamine via the glutamate-to-ornithine pathway. Under stressed conditions, arginine becomes an essential amino acid because the normal quantities produced to maintain muscle mass are insufficient due to increased turnover. Arginine is an essential component for the stimulation and release of growth hormone, prolactin, insulin, and glucagon. It is also a critical substrate for the synthesis of nitric oxide (NO) by the enzyme nitric oxide synthase (NOS). NO is an important mediator of vascular dilation, protein synthesis in the liver, and mitochondrial electron transport. L-Arginine is also an essential compound for T-lymphocyte proliferation and some cytokines.

In patients with sepsis, both plasma and muscle arginine levels are markedly decreased as compared to health individuals [69–71]. This state of arginine deficiency in sepsis is due to inadequate nutritional intake of protein as well as increased utilization by the liver and immune cells. In addition, the de novo production of arginine from citrulline in the proximal renal tubule is decreased to one third of the normal level during sepsis [72]. Low levels of plasma arginine have been correlated with worse prognosis in patients with sepsis [73], suggesting there may be a role for arginine supplementation in sepsis.

In studies of arginine supplementation in animal models and healthy volunteers, nutritional supplementation with arginine can enhance immune parameters following stress and elective surgery. However, the use of arginine supplementation in patients with sepsis has been associated with negative outcomes. In the setting of severe sepsis/septic shock, the delivery of immunonutrition containing arginine has been implicated in an intensification of the systemic inflammatory response with a resultant increase in patient morbidity [74]. A potential explanation for the adverse effects seen with high dose arginine supplementation in sepsis is an increase in NO production with resultant tissue injury and cardiovascular collapse [75]. In patients who are in septic shock requiring vasopressor, arginine administration could result in excessive NO production which could be deleterious. However, there is also evidence to suggest that arginine supplementation in patients with sepsis has a positive impact on patient outcomes [46, 47]. Recently Dr. Ochoa's and Dr. Moldawer's laboratories have recognized that surgical trauma and sepsis results in a persistent "emergency myeloipoesis" response with persistent expansion of myeloid derived suppressor cells (MDSCs) [76–79]. These immature innate immune cells are being released from the bone marrow and are honing to other hemopoeitic organs (e.g., lymph nodes and spleen). These cells express arginase-1 which diverts arginine away from nitric oxide metabolism. As a result arginase-1 activation depletes arginine in the local environment and without arginine lymphocytes become dysfunctional. This provides the rationale for administering supraphysiologic amounts of arginine after septic shock has resolved. Ongoing investigation into the role and mechanism of arginine supplementation in sepsis is needed. The lack of clarity regarding the metabolism of L-arginine in sepsis and the conflicting evidence with the current medical literature has led to a great degree of controversy

over the use of arginine supplementation in sepsis. In light of this, the current ASPEN/SCCM guidelines recommend that L-arginine supplementation be used with extreme caution in patients with severe sepsis/septic shock.

Glutamine

Under normal physiologic conditions, glutamine is the most abundant nonessential, free amino acid in the body. Glutamine is primarily stored in skeletal muscle and plays a role in protein synthesis and acid-base homeostasis in the kidney. In addition, glutamine is a critical nitrogen donor for rapidly dividing cells, such as those found in the gut and immune system. Other beneficial effects of glutamine include antioxidant effects (glutamine is a substrate for glutathione production), maintaining the gut barrier function by fueling enterocytes, and serving as an energy substrate for lymphocytes and neutrophils. In states of catabolic stress, such as sepsis, the bodies' stores of glutamine become rapidly depleted, rendering glutamine a "conditionally essential" amino acid during catabolic stress. This depletion of glutamine impairs the immune response thereby contributing to infections. Patients also experience weight loss and significant loss of muscle mass. Low circulating levels of glutamine during critical illness have been associated with increased mortality [80, 81].

Over the past decade, there has been substantial evidence that glutamine supplementation may improve outcomes in critically ill patients. Debate has continued to exist over the preferred route of glutamine administration (parenteral vs. enteral). The administration of enteral glutamine is well tolerated in critically ill patients with no known side effects [82]. The gut and liver metabolize the majority of enterally administered glutamine which may limit the systemic benefits of enteral glutamine administration in critically ill patients. Enteral administration of glutamine does have beneficial effects in the gut by repairing damaged intestinal epithelial cell layers and maintaining the gut barrier function of the GI tract. The addition of enteral glutamine to an enteral nutrition regimen has been shown to reduce hospital and ICU length of stay [83–85]. Given these potential benefits, it is recommended that enteral glutamine supplementation be administered to critically ill patients with sepsis. The recommended dose of enteral glutamine is 0.3–0.5 g/kg/day administered in two or three divided doses.

There have been several recent studies evaluating the potential use of parenteral glutamine supplementation. In 2008, Ziegler et al. conducted a double-blind, randomized, controlled study of alanyl-glutamine dipeptide supplemented parenteral nutrition in surgical ICU patients requiring parenteral nutrition. The primary outcome in this study was the development of nosocomial infections. While the administration of parental glutamine was shown to increase serum glutamine levels, there was no difference in infection rates between those patients that received supplemental parenteral glutamine and those that did not [86]. This study was followed by a large, multicenter, blinded 2-by-2 factorial study funded by the National Institutes of Health (NIH) evaluating glutamine and antioxidant supplementation in critically ill patients. This study assigned 1,223 critically ill adults to receive supplements of glutamine, antioxidants, both, or placebo. In this trial, there was a trend toward increased mortality among patients that received glutamine as compared to those that did not [87]. It is important to note, that in a subgroup analysis of 66 patients that had serum glutamine levels drawn, only 31 % of patients had low serum glutamine levels prior to supplementation. As a result of this trial, the authors concluded that any patient in MOF in the ICU should not receive glutamine [88]. However, in those critically ill patients without MOF, there may still be a role for glutamine supplementation. A meta-analysis by Novak et al. demonstrated the greatest beneficial effects to glutamine supplementation were seen in those patients that received high dose (>0.20 g/kg/day) of parenteral glutamine [89]. Unfortunately, at the time of preparing this manuscript, a parenteral formulation of glutamine is not currently available in the United States.

Omega-3 Fatty Acids

The term omega-3 fatty acids refers to three fatty acids: (1) alpha-linoleic acid (ALA), (2) eicosapentanoic acid (EPA), and (3) docosahexanoic acid (DHA). Both EPA and DHA are metabolites of ALA. These omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) which are a major component of cellular membranes. Dietary supplementation with PUFAs has been shown to reduce platelet aggregation, slow blood clotting, and limit the production of pro-inflammatory cytokines [90]. Ingestion of plant oils serves as our primary source of ALA, while EPA and DHA are derived from cold water fish such as sardines, mackerel, and tuna. Humans possess limited capacity to metabolize ALA to EPA and DHA, therefore dietary intake is the main source of these fatty acids.

During critical illness, there is significant downregulation in the enzymatic pathway that converts ALA to EPA and DHA and results in negligible production of EPA and DHA during critical illness. Both EPA and DHA produce anti-inflammatory effects that could be beneficial in patients with sepsis. These include inhibition of inflammatory gene expression, reduction of oxidative injury by stimulating glutathione production, and reducing leukocyte and platelet adhesion to the endothelium [91]. Omega-3 PUFAs inhibit the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 [92].

In patients with sepsis, the administration of fish oil supplementation has yielded conflicting results. A recent systematic review by Marik showed an overall decrease in the number of infections, particularly secondary infections, in patients that received supplemental fish oil [93]. However, the administration of supplemental fish oil did not have any impact on length of stay or mortality. Another recent study by Pontes-Arruda et al. demonstrated that early administration of EN supplemented with EPA and antioxidant vitamins in patients with early sepsis resulted in a decreased incidence of progression to severe sepsis or septic shock [94]. However, once again there was no difference in mortality seen among patients that received supplemental omega-3 PUFAs. In contradiction to the above studies, Grau-Carmona compared septic patients that received standard enteral nutrition to those that received enteral nutrition plus omega-3 PUFA supplementation and did not find any difference in the development of secondary infections.

In spite of the lack of mortality benefit seen with omega-3 supplementation it is important to note that were no adverse effects associated with the administration of omega-3 PUFAs. While additional studies are needed, there does appear to be some benefit to the administration of supplemental omega-3 PUFAs with no known risk to the patient.

Antioxidant Vitamins and Trace Elements

During sepsis, free radical production is amplified and increased levels of reactive oxygen species are present. These reactive oxygen species can cause cellular injury through a variety of mechanisms. The host's endogenous antioxidant defense system includes the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. These enzymes all contain heavy metals including manganese, selenium, and zinc. During times of metabolic stress, these enzymatic defenses can become overwhelmed and cells must resort to alternate antioxidants to prevent further cellular damage. These nonenzymatic antioxidants include selenium, zinc, vitamin C, vitamin E, and beta carotene.

A recent meta-analysis evaluating the role of antioxidant supplementation during critical illness showed a significant reduction in mortality with administration of supplemental antioxidants [95]. Of particular benefit was the administration of parenteral selenium which has shown a trend toward reducing mortality in patients with severe sepsis and septic shock. Additional studies are needed to further identify the optimum dose and ratio of administration of these substances during critical illness.

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