

Nutritional Therapy in Abdominal Sepsis

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The term sepsis encompasses a spectrum of disease ranging from systemic inflammatory response syndrome (SIRS) to severe sepsis and multiple organ failure. Numerous conditions can be sources of infection in patients who have sepsis. Many surgical diseases may cause intra-abdominal sepsis, including intra-abdominal abscesses; severe acute necrotizing pancreatitis; and some common diseases that have taken a complicated turn (e.g., acute gallstone disease, acute appendicitis).

The American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference of 1992 agreed on a new set of definitions that could be readily applied to patients in different stages of infection or inflammation. These definitions help clarify the difference between two commonly misused terms, infection and sepsis. The exact definitions of sepsis are variable but generally defined as the presence or presumed presence of an infectious source accompanied by the systemic response syndrome described above. Severe sepsis is defined as the presence of sepsis with one or more organ dysfunction. Septic shock is defined as the presence of sepsis and hemodynamic instability. This is primarily refractory hypotension with systolic peak pressures less than 90 mm Hg, mean arterial pressures less than 65 mm Hg, or a drop of greater than 40 mm Hg from baseline.⁽¹⁾

Sepsis is the systemic response to infection. Historically, sepsis described a life-threatening condition characterized by fever, tachycardia, tachypnea, and organ dysfunction, and was frequently associated with shock and death. It was also frequently associated with a bacterial, fungal, or virus infection, which could be either localized or systemic in nature. However, other conditions, such as severe trauma, pancreatitis, hemorrhage, ischemia, and burn injury, can produce the same clinical findings in the absence of an identified infectious source. This constellation of fever, tachycardia, tachypnea, and organ dysfunction has come to be known as the systemic inflammatory response syndrome. That is, SIRS is a clinical syndrome that can be caused by a variety of insults, including sepsis.

A series of events requiring multiple organ systems are required for the progression from localized infection to sepsis, severe sepsis, and septic shock. The initial reaction of the host is localized to the site of infection or injury. The process begins with cellular activation at the endothelial level of macrophages, monocytes, and neutrophils. Various microbial components such as cell wall structures, proteins, or DNA bind to specific receptors on the white cells surface called Toll Receptors. These cells then start a cascade of events, including activation of the complement system leading to vasodilatation, increased capillary permeability, which leads to increased interstitial fluid and chemoattractants in the local area. Additional macrophages are attracted to the area; these, in turn, then orchestrate the intensity of the inflammatory response. In the presence of the infection, the macrophages undergo accelerated phagocytic activity with of

elaboration of tumor necrosis factor (TNF) and other proinflammatory cytokines which can, if in high enough concentration, spill over into the systemic circulation to influence the entire systemic response. Once systemic activation has begun, micro vascular coagulation is noted platelets, mast cells, and local vasodilators results in generalized edema, accelerated oxygen free radical production, and eventual organ injury. ⁽²⁾

During the onset of sepsis, the inflammatory system becomes hyperactive, involving both cellular and humoral defense mechanisms. Endothelial and epithelial cells, as well as neutrophils, macrophages and lymphocytes, produce powerful pro-inflammatory mediators, specially tumor necrosis factor (TNF), interleukin 6 (IL-6), IL-1, and IL-8. Simultaneously, robust production of acute phase proteins, such as C reactive protein, occurs and humoral defense mechanisms such as the complement systems are activated, resulting in production of pro inflammatory mediators, including C5a. C5a ultimately enhances cytokine and chemokine production. Furthermore, the coagulation system becomes activated through various mechanisms, often resulting in disseminated intravascular coagulopathy. Phagocytic cells (neutrophils and macrophages) respond to many of these mediators by releasing granular enzymes and producing reactive oxygen species (ROS) such as H₂O₂, which is a crucial product for the killing of bacteria. H₂O₂ is also capable of causing tissue damage, which ultimately leads to increased vascular permeability and organ injury. In later stages of sepsis, anti-inflammatory mediators are produced (such as IL-10, transforming growth factor Beta and IL-13), leading to abatement in the production of many of the pro inflammatory mediators. In this phase, various innate functions are suppressed, especially the functions of neutrophils, leading to a hypo reactive host defense system and immunoparalysis. ⁽³⁾

This initial septic response is pro-inflammatory. This pro-inflammatory phase is followed by a compensatory anti-inflammatory response. Virtually all major organs are involved but cardiac, pulmonary, renal and hepatic are most commonly observed clinically. Although at first glance it would appear that the systemic response is destructive to the host, these systemic manifestations of the septic response are in effect related to attempts to contain the infection. It is important to remember that immune suppression is a major part of the later phases of sepsis.

Activation of coagulation by monocytes and endothelial injury, make the coagulation and inflammatory cascades work together, enhance the effects of one with another, so that the process is markedly stimulated coagulation (DIC) and characterized by a large increase in deposits of fibrin micro thrombi as at the level of the microcirculation, leading to organ and tissue ischemia.

On the other hand, the last time the process of coagulation, fibrinolysis that is, is blocked by the presence of (PAI-1) Plasminogen activator inhibitor type-1, produced by the injured endothelium, which inhibits the conversion of plasminogen tissue in plasmin. This process anti fibrinolytic ads another block more of the same, dependent on the thrombin: TAFI (Fibrinolysis Inhibitor Derived from Activated Thrombin).

So, that the homeostatic imbalance that arises as a result of sepsis is summarized joint participation and amplified each of three groups of metabolic disorders and their consequences.

- a) The activation of the inflammation cascade.
- b) Activation of the Coagulation Cascade
- c) Blocking the Way of Fibrinolysis

The result is the successive presentation in order of severity from micro vascular thrombosis, hypo perfusion, ischemia and tissue injury. Severe sepsis, septic shock, MODS.

METABOIC RESPONSE DURING SEPSIS

CARBOHIDRATE METABOLISM: Under normal conditions, glucose homeostasis is regulated by several control mechanisms to match the uptake and production of glucose. These mechanisms maintain “normal” blood glucose concentrations under a wide range of conditions. However, hyperglycemia and significant insulin resistance is a characteristic clinical finding in sepsis.

Pro-inflammatory cytokines potentiate the release of catabolic hormones (glucagon, cortisol and catecholamines). These catabolic hormones stimulate glycogenolysis and gluconeogenesis to mobilize glucose. Following the onset of sepsis, glycogen stores are depleted within hours, and endogenous lipids and protein become the major source of oxidative energy substrate.

Sepsis results in hyperglycemia secondary to alterations in endogenous glucose production, decreased glucose uptake, and insulin resistance. As sepsis progresses, reduced splanchnic blood flow and severe hepatic dysfunction eventually lead to hypoglycemia and decreased glucose production in the final stages of life.⁽²⁾

Protein Metabolism: The accelerated peripheral muscle protein breakdown noted in sepsis is accompanied with diminished amino acid uptake by muscle, leading to the net flux amino acid away from the peripheral to the liver. The urea genesis rate is increased, as well as the synthesis rate of creatinine, uric acid, and ammonia. All are excreted in increased amounts in the urine during sepsis. The nitrogen loss of severe sepsis complicating recovery from trauma may exceed 30 g/day. The primary sites of this amino acids efflux are from the labile amino acids pools in skeletal muscle, connective tissue, and unstimulated gut. The hepatic uptake of amino acids and hepatic protein synthesis are increased. However, the increase in hepatic protein synthesis is not uniform. Although positive acute phase proteins, such as haptoglobin and C-reactive protein concentrations in serum increase in response to stress, synthesis of negative acute phase proteins such as albumin and pre albumin falls. This concept is often referred to as hepatic reprioritization.

Under these catabolic circumstances, patients who receive adequate exogenous amino acids to maintain production of acute phase proteins are more likely to survive. Nonetheless, adequate nutrition support will not completely ablate the catabolic effects and response.

As the systemic response to sepsis progresses, protein catabolism increases, and the failure of synthetic process to keep up with the breakdown rate results in severe losses of skeletal and visceral proteins. In addition to supplying amino acid for acute phase protein synthesis, a driving force for the mobilization of amino acid during sepsis and other significant stress is thought to be the host attempting to provide glutamine to enterocytes and leukocytes. Unfortunately,

prolonged catabolism of skeletal muscle protein compromises respiratory function, impair wound healing, exacerbates immunosuppression, accelerates the loss of strength and endurance necessary for recover, and ultimately increases the risk of death. ⁽²⁾

Lipid Metabolism: The catabolic hormones epinephrine, norepinephrine, and glucagon are the predominant stimulators of the hydrolysis of stored triglycerides (Lipolysis) via hormone sensitive lipase. In early sepsis, catabolic hormones outweigh the effects of anabolic hormones such as insulin and result in breakdown of stored triglycerides to glycerol and free fatty acids (FFAs). In addition to the increased rate of lipolysis of peripheral adipose stores observed in sepsis, intracellular transport metabolism is also affected. The ability of the cell to transport long chain FFAs into mitochondria via the acyl-carnitine carrier is impaired. Consequently, long chain FFAs esters accumulate within the cell and can inhibit the function of pyruvate dehydrogenase complex directly, resulting in intracellular acidosis and the accumulation of lactate and pyruvate.

This, in effect, decreases aerobic respiration and the cells ability to use the Krebs cycle for efficient energy production. Finally, the activity of lipoprotein lipase, which is responsible for the conversion of triglycerides to FFA in peripheral cells, is suppressed in sepsis. Consequently, hyperlipidemia, hyperglycemia, hyperlactatemia and high levels of circulating B-hydroxybutyrate often are present in severe sepsis. ⁽²⁾

The hallmark of the management of sepsis includes the timely use of appropriate antimicrobial agents and early drainage or removal of purulent foci to achieve rapid bacterial or fungal eradication. Support of the septic patient also includes administration of early goal directed therapy with crystalloid and colloid solutions, blood products (including red blood cells and fresh frozen plasma), inotropic and vasoactive agents, and mechanical ventilation to ensure hemodynamic stability and oxygenation of vital tissues. Recent data would also support use of activated protein C, intense management of hyperglycemia, and corticosteroids for the appropriate patient. ⁽⁴⁾

Recently, the understanding of sepsis has become somewhat more complicated than describe above as an initial pro inflammatory phase followed by compensatory anti-inflammatory stage. In fact, anti-inflammatory cytokines (interleukins 4 and 10) may predominate rather than pro-inflammatory cytokines (TNF, interleukin 2, interferon gamma) depending on the initial stimulus of inflammation, polymorphisms in genes for cytokines, and clinical status, including age. Thus, susceptible patients may be immunosuppressed causing host inability to eradicate the pathogen adequately.

Appropriate nutritional therapy during sepsis and severe infections is essential because it plays a key role in modulating the inflammatory response, maintenance of immune function, the abrogation of skeletal muscle catabolism, wound healing, and the maintenance of mucosal barrier function.

Appropriate nutritional support is an important but challenging part of standard supportive care during critical illness. Patients with severe sepsis or septic shock commonly suffer from

compromised gastrointestinal function, including enhanced intestinal permeability and reduced motility. Underlying malnutrition is often encountered in these patients. Intestinal stimulation by enteral nutrients helps to maintain bowel integrity and decreases translocation, resulting in less infectious sequelae and decreased length of hospital stay. Still, the debate about what type of nutrition is appropriate in critically ill patients continues. Elke conducted a study aimed to identify current clinical practices regarding nutrition and its association with morbidity and mortality in patients with severe sepsis or septic shock in Germany. The study included 454 intensive care unit and 415 patients. The data showed that 20.1% of patients received exclusively enteral nutrition, and 35.1% exclusively parenteral nutrition, and 34.6% mixed nutrition; 10.3% were not fed at all. Patients with gastrointestinal/intra-abdominal infection, pancreatitis or neoplasm of the gastrointestinal tract, mechanical ventilation, or septic shock were less likely to receive exclusively enteral nutrition. Overall hospital mortality was 55.2%. Hospital mortality was significantly higher in patients receiving exclusively parenteral (62.3%) or mixed nutrition (57.1%) than in patients with exclusively enteral nutrition (38.9%). Conclusions: Patients with severe sepsis or septic shock on German intensive care units received preferentially parenteral or mixed nutrition. The use of parenteral nutrition was associated with an increased risk of death. ⁽⁵⁾

Enteral Nutrition: Dr. Moore in the “The evolving rationales for early enteral nutrition based on paradigms of multiple organ failure” ascertain that shock combined with delayed enteral feeding impairs the gut barrier, allowing endotoxins and bacteria to escape the bowel lumen through the portal vein, which then stimulates the hepatic Kupffer cells to elaborate inflammatory mediators that cause immunosuppression, via prostaglandin E₂; increase the stress response via interleukin-6; and directly injure multiple remote organs, via tumor necrosis factor, including the kidneys, manifested as acute tubular necrosis, and the lungs, manifested as adult respiratory distress syndrome. ⁽⁶⁾

In brief, traumatic shock and septic shock are 2 prime inciting events for MOF. Both injure the gut, with resuscitation, cause a reperfusion injury that release proinflammatory response that results in a variety of gut dysfunctions (eg, impaired mucosal blood flow, gastroparesis, gastric alkalinization, ileus, duodenogastric reflux, 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; vasopressors decrease mucosal perfusion, stress gastritis prophylaxis worsen gastric alkalinization, opiates worsen ileus, antibiotics promote bacterial overgrowth, and parenteral nutrition results in gut disuse, which decreases local gut immunity and contributes to worsening systemic 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. These toxic products escape the gut via aspiration or translocation when the host has progressed into CARS to cause late nosocomial infections and late MOF.

Based in tis conceptual framework, we can now explain hoe early enteral nutrition interrupts this sequence of events to prevent late nosocomial infections and MOF. In a variety of models (sepsis,

hemorrhagic shock) intraluminal nutrients have been shown to reverse shock-induced mucosal hypoperfusion.

In recent years, the recognition of abdominal compartment syndrome and intraabdominal hypertension has led to an increase in the use of decompressive laparotomy. Intraabdominal sepsis is one of the main indications for open abdomen. Some authors report their results of early enteral nutrition in patients with open abdomen.

There are few reports of enteral nutrition in patients with open abdomen; Dr. Tsuey reported enteral nutrition in 14 patients with open abdomen. The most common underlying diagnoses were traumatic abdominal injuries, bowel perforation, and ischemic bowel. Eight patients (57%) met at least an average of 80% or greater of the predicted energy expenditure ⁽⁷⁾ In the work of Dr. Collier not covered patients with abdominal sepsis, only trauma patients, however, in patients with early enteral nutrition (less than 4 days) was achieved early closure wall and a lower percentage of fistulas as a complication ⁽⁸⁾. In a paper published by our group, 33% of patients with open abdomen had abdominal sepsis, early enteral nutrition was used in 21% of cases, mixed nutrition in 46%, 69% of patients achieved the target on the fourth day ⁽⁹⁾

Specific nutrients in abdominal sepsis: Major abdominal surgery usually exacerbates the systemic inflammatory response and carries an increased risk of life-threatening complications that can result in multiple organ failure for several reasons, including excessive inflammatory cytokine production, ischemia-reperfusion injury, and organ damage. Therefore, it is important to maintain a balance between proinflammatory and anti-inflammatory mediator levels in patients who have undergone major abdominal surgery. Maintaining such a balance also seems to improve the prognosis of surgical patients.

Several epidemiological observations and clinical trials have provided evidence that a fish oil (FO)-enriched parenteral nutrition regimen could modulate the production of proinflammatory cytokines, ameliorate the course of infections, and restore liver function. To evaluate the safety and efficacy of a fish oil-enriched parenteral nutrition regimen in patients undergoing major abdominal surgery, a meta-analysis of randomized controlled trials was conducted.

In the meta-analysis conducted by Chen, the results supporter that the use of FO emulsions improved serum concentrations of liver enzymes on post operative day (POD) 6 and reduced the duration of hospital and ICU stays more effectively than did the use of conventional fat emulsions in patients who underwent major abdominal surgery. FO also improved the rate of complications due to postoperative infection, including septicemia, pneumonia, wound abscess, intra-abdominal abscess, and urinary tract infection. These results might be explained by the improvement of immune functions and down regulation of discordant inflammatory responses after trauma and surgery. However, they t found no significant reduction in postoperative mortality in patients receiving postoperative FO compared with receiving standard parenteral nutrition. ⁽¹⁰⁾

Molecular mechanisms proposed for the action of glutamine ⁽¹¹⁾

Tissue protection, increased expression of HSP, minimizes intestinal barrier dysfunction, decreases apoptosis

Anti-inflammatory and immune-regulatory

Attenuation of cytokines and activation of NF- κ B

Preservation of metabolic functions in the stress

Maintains ATP levels in sepsis and ischemia – reperfusion

Antioxidant effect

Increases GSH levels and reduces the expression of iNOS in sepsis

Selenium: Selenium is an essential micronutrient for humans. The most significant biological role currently attributed to selenium is its well-known antioxidant, which is secondary to the selenoenzyme calls within these the most studied are the glutathione peroxidase (GPx) and selenoprotein P (SEPP). The states of systemic inflammatory response (SIRS) and multiple organ dysfunctions (DOM) such as severe sepsis, severe trauma, burns, severe pancreatitis and critical are characterized by the existence of oxidative stress. In this context, depletion of selenium nutritional status is a distinctive feature; the same is reflected by reduced serum levels of selenium and different selenoenzymes, especially glutathione peroxidase and selenoprotein P. These antioxidant selenoproteins play a protective role against lipid peroxidation of cell membranes also participating in the process of regulating the inflammatory response.

SIC German multicenter study (Selenium in Intensive Care) led by Angstwurm et al enrolled 238 patients with severe SIRS, severe sepsis / septic shock and APACHE II score > 70. In the therapeutic group (1000 μ g sodium selenite load and then infusion of 1000 mg / day for 14 days) demonstrated a significant reduction in mortality at 28 days of 14.3% compared to the control group, the greater the decline in mortality in patients with septic shock and disseminated intravascular coagulation (DIC), as well as in patients with more than three or malfunctions with the highest score of APACHE III score on the other hand, the use of sodium selenite at high dose was safe and inexpensive.⁽¹²⁾

Manzanares published a prospective, randomized study in patients with SIRS investigating the action of two doses of selenite and selenious acid, the objective was to determine the pharmacokinetic and pharmacodynamics profiles of selenium and try to estimate the dose to optimize the selenium status of vision to study their clinical effects and metabolic and pharmaco. The two dose levels of selenium were as follows: group A (low dose) received a bolus loading dose at a rate of 1200 g (15.18 mmol) for 2 hours and then 800 μ g per day (10.12 mmol / day) as continuous infusion for 10 days, the second group (group B) or high dose group received a loading dose of 2000 μ g (23.5 mmol) for 2 hours and then 1600 μ g per day (20.24 mmol) as a continuous infusion for 10 days. The results showed that the pharmacokinetic profile evaluated for GPx-3 shows an optimal GPx-3 with the high dose of selenious acid. The maximum concentration of selenium and GPx activity maximum-3 were well tolerated and therefore were in the range well tolerated, clinical outcomes were similar in both groups. The authors conclude that this high dose

of selenite parenterally (1600µg per day) and the mode of administration (bolus followed by continuous infusion at a rate of 20 mmol per day for 10 days) optimize selenium status and GPx-3 maximizes in the physiological range and no observable clinical effects. ⁽¹³⁾

In patients with severe sepsis and septic shock, transient early pro oxidant effect of selenium can be used as a therapeutic strategy. A loading bolus dose in the early phase of septic shock may have the following effects: direct reversible inhibition of NF-κB binding controlling the synthesis of pro-inflammatory cytokines in the early stage of SIRS, induction of apoptosis and cell cytotoxicity pro activated circulating inflammatory microcirculation level and a direct effect virucidal and bactericidal.

Studies evaluating the use of PN supplementation in those with low doses of NE might change clinical practice. If the results of these studies are positive, the addition of NP to low doses of NE could help mitigate some of the pressures of clinical experiences with tolerance to the flow of aggressive NE infusion

CONCLUSIONS

- **Nutritional Therapy plays an important role in the management of patients with sepsis**
- **Specific nutrients such as selenium, other anti-oxidants, glutamine, omega 3 fatty acids could have a significant therapeutic effects in patients with sepsis**

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