Recent recommendations in Nutritional support to patients with sepsis in ICU

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Abstract

Background: Despite recent advances in detection and treatment approaches, sepsis remains a significant cause of mortality globally. According to the Third International Agreement for Sepsis (Septic-3) consensus, the term "septic shock" is a subset of the more general term "sepsis" since it includes hypotension or an elevated lactate level despite attempts to revive the patient. Sepsis is caused by a variety of organisms, including Gram-positive and Gram-negative bacteria that produce toxins, an immune-compromised host, and maybe a genetic predisposition. When sepsis strikes, the body's response is immune-inflammatory, accompanied by the release of pro-inflammatory cytokines, which in turn triggers a neuro-endocrine cascade that leads to metabolic dysfunction and organ dysfunction. Cellular abnormalities such as mitochondrial damage and cytopathic hypoxia are also present. Taking 200 mg thiamine for a week post-ICU with high-dose short-term vitamin C and a 5-day Vitamin D supplementation for deficient individuals appears to be the most sensible course of action. It is a series of coordinated efforts used to establish the best kind, dosage and duration of nutrition treatment to achieve the highest therapeutic result, prevent side effects, and save costs.

The following: Nutritional Stewardship and pharmaconutrition play a critical role in the treatment of sepsis, as well as the implementation of Nutritional Stewardship in the clinical context.

Key words: Nutritional support, recommendations, sepsis, ICU.

1. Introduction

Despite its high prevalence, little is known about the pathophysiological dysregulations that define Sepsis, a disease condition marked by a variety of complicated and time-dependent symptoms. The mortality rate for patients with sepsis remains high despite advances in diagnostic tools, monitoring, and therapy. Severe sepsis and multiple organ dysfunction syndromes are examined in this study in an effort to better manage treatment in sepsis patients and find potential targets for new therapies. It is difficult to meet the dietary needs of individuals with septic shock or sepsis since the typical technique of feeding critically sick patients does not apply. [1]

1. Highlighting Definitions

Third International Consensus in 2016 has defined sepsis as an infection-induced dysregulation of the host response, resulting in the release of inflammatory mediator and cell dysfunction in the affected host, and associated with profound microvascular, hemodynamic, metabolic and endocrine abnormalities that lead to life-threatening organ dysfunction.

While adequate volume resuscitation to prevent volume depletion, patients in septic shock are at significantly increased risk for death because the condition is exacerbated by hypotension and necessitates the use of vasopressors to keep their MAP (mean arterial blood pressure) above 65 mm Hg and a serum lactate concentration of more than 2 mmol/L. [2].

Systemic Inflammatory Response Syndrome (SIRS):

Two of the four clinical criteria for a diagnosis of SIRS are met: heat or hypothermia; tachypnea; and, in the case of leucocytosis, the presence of immature neutrophils in the bloodstream.

It’s important to highlight that SIRS has been identified as a non-specific response to sepsis and discovered to be related with many other illnesses in which there is extensive tissue insult, such as acute pancreatitis, significant trauma, severe tissue ischemia/reperfusion damage and burns. One of the most often used terms in the past, severe sepsis, has been deemed outdated and is now used to describe sepsis coupled with severe organ dysfunction.

2. Etiology and Risk Factors.

Sepsis may be brought on by almost any pathogen. In turn, this leads to a wide range of symptoms. A nosocomial infection (one obtained in the hospital) or a community-acquired illness may both lead to sepsis.

More than 80% of all sepsis cases occur in the general public. The respiratory tract is the most common cause of infection that leads to sepsis, followed by the abdomen-peritoneal (20%), bloodstream (15%), renal and genitourinary tracts (10%), and the bloodstream (14 percent ). [4].

Sepsis Occurrence in Acutely Ill Patients (SOAP) research found that Gram-positive and Gram-negative bacteria were approximately evenly distributed among sepsis patients. Illnesses caused by Gram-negative bacteria are currently less prevalent than infections caused by Gram-positive bacteria. [5]

3. Pathophysiology, A Double-Faced Immune-Inflammatory Condition.

Molecular theories in sepsis

The pathogenesis of SIRS and sepsis syndrome could be explained by three mechanisms, all of which involve the release of mediators that triggers systemic inflammatory response.
A) The Pro-inflammatory Response,
Clinical manifestations of SIRS is attributed primarily to excessive release of pro-inflammatory mediators (cytokine storm) that causes overwhelming inflammation.

Following phases are involved in the pathogenesis of SIRS accompanying sepsis:
Release of bacterial toxins, Pathogen associated molecular patterns (PAMS) are toxins that are generated by invading organisms that interact with innate immune cells, triggering an inflammatory response. Lipopolysaccharide (LPS), Lipoteichoic acid (LPA), and Superantigens such as Staphylococcal Toxic Shock Syndrome Toxin are only a few examples (TSST). [6]

Production of Mediators in Response to Infections,
On Macrophage cells of the innate immune system (Macrophages), PAMS that are identified by pattern-recognition receptors (TLR)-2 and TLR-4. When a super antigen activates T cells, it causes the body to produce IL-2 and IFN-gamma.

Anti- and pro-inflammatory mediators
An overabundance of pro-inflammatory mediators is hypothesised to be responsible for sepsis-associated inflammation when the compensatory anti-inflammatory response (CARS) falls short of providing adequate immunosuppression. When CARS takes over, the immune system is paralysed, enabling existing infections to deteriorate (cytokine storm). There is a need to update existing information on nutritional support for sepsis, focusing on energy and protein needs, supplementation routes, and the role of pharmaconutrition and application of Nutritional Stewardship in the current literature.

Nutritional Management Objectives in Sepsis
A) The method of feeding: Enteral or parenteral.
While parenteral nutrition (PN) is more costly, it lacks the physiological benefits of enteral nutrition (EN).

- Prevent stress ulcers, preserve intestinal mucosal structure; stimulate enzymatic processes; minimise bacterial translocation; and improve gastrointestinal blood flow are just some of the benefits of this supplement.
- Because it does not need central venous access and does not have the same side effects as PN, such as hyperglycemia, EN may be preferable to PN.
- Full EN feeding should be avoided during the acute phase of septic shock, according to recommendations. PN may be a better option for these people. It’s still up for debate as to when the best time is to begin PN.
- Patients at risk of malnutrition should have supplementary PN considered if EN fails to provide calorie requirements after 3 to 7 days.
- Uncontrolled shock, uncontrolled hypoxemia, and acidosis remain contraindications for early enteral feeding in the European Society of Intensive Care Medicine (ESICM) practise guideline.

B) Calorie and Protein Management.

1. Acute Phase "Adequate Protein and Moderated Non-Protein Calories"
The acute phase of sepsis is distinguished by a significant mobilization of the body's calorie reserves as skeletal muscles, glycogen, and fat stores are broken down to produce glucose to sustain production of ATP. [9]

This metabolic response to stress can generate up to 75% of glucose needs during illness, which is not suppressed by feeding or intravenous glucose infusion. [10]

B. Chronic and recovery phase of sepsis: significant increase in protein and calorie needs.
1. Chronic phase – "post-resuscitation increase in nutrition delivery"
Protein (1.2–2.0 g/kg/d; 25–30 kcal/kg/d) and calories (25–30 kcal/kg/d) must be increased to avoid additional LBM breakdown, allow for early ambulation, and boost functional recovery as the patient stabilises.

For patients who have been on mechanical ventilation for more than eight days, a recent research found that providing enough protein and calories improved quality of life. [11]

At the end of the first week of care in the ICU, patients who received insufficient nutrition had a greater mortality rate than those who got adequate nutrition (>80% of calorie/protein demands).

2. Recovery phase - continued increased nutrition delivery requirements?
The caloric intake of patients will need to be raised in tandem with the intensity of their rehabilitation exercises as they go through the healing period.

As World War II came to an end, an important study was done called the "Minnesota Starvation Study," which provided significant information on post-sepsis nutrition.

In order to properly recover from muscle mass and weight loss, this research found that a fit 70 kg person needing significant weight loss needs an average of 5000 kcal/day for 6 months to 2 years. [13] and [12].

- Vitamins, minerals, and other nutrients from a pharmaceutical perspective
  - There is a considerable body of information that identifies nutrients that may or may not have been delivered in the early phase of sepsis in addition to the maintenance of calorie and protein needs. Below, we’ll go into further depth on each of these topics.
  - It's called pharmaconutrition, and it refers to supplementing conventional nutrition with nutrients that have specific beneficial effects (such as antioxidant action) in order to boost the gut mucosal and systemic immune defence mechanisms and limit an exaggerated pro-inflammatory response during the catabolic phase of disease.
  - Deficiencies in vitamins may lead to sepsis, since they play a role in several biological processes. Biochemical systems such as antioxidant and anti-
inflammatory effects, protein synthesis and energy generation are only a few examples. Vitamin therapy has also been associated to improved results in certain adult and paediatric studies in which patients were sepsis patients. Vitamin therapy has been associated to improved outcomes in various observational and randomised control studies of adult and paediatric sepsis patients, as well as during sepsis there are relative vitamin shortages in plasma.

**Thiamine is a vitamin (Vit B1)**

As a water-soluble vitamin involved in the Krebs cycle and the pentose-phosphate shuttle, thiamine, vitamin B1, is critical for aerobic metabolism and cellular respiration. TPP enters the Krebs cycle through a TPP/thiamine antipporter and serves as a cofactor for pyruvate dehydrogenase, which converts pyruvate to acetyl-coenzyme A, and as a key component in -ketoglutarate dehydrogenase and branched-chain ketoacid dehydrogenase complexes, respectively.[14].

The electron transport chain generates more lactate and less adenosine triphosphate when any of these phases is blocked. By weakening glutathione and other redox activities, TPP deficiency also contributes to the development of oxidative stress. As an additional benefit, thiamine has other direct antioxidant qualities and may have an effect on the overall inflammatory response; [15]

Using thiamine as a sole treatment for sepsis is not recommended

Patients with sepsis, high lactate, and fluid resistant shock who were given thiamine 200 mg IV twice day for seven days showed a significant improvement in their condition, according to a new randomised, double-blind research. 4 Thirty-five percent of thiamine-deficient individuals had a significantly decreased death rate following 24 hours of treatment with thiamine. Mortality overall, severity of illness score, days without a ventilator, ICU stay, and duration of stay in the hospital did not improve. Overall mortality, however. [16].

Combination treatment with thiamine.

Vitamin C in combination treatment will be discussed more in the chapter on thiamine in combination therapy.

**Recommendation**

To enhance outcomes, all septic shock patients should be given 200 mg of thiamine for one week post-ICU admission, with the caveat that further research is needed.

**A source of vitamin c (Ascorbic acid)**

Fruits and green leafy plants are rich sources of water-soluble vitamin C, sometimes referred to as ascorbic acid. Upon absorption, it breaks down into ascorbate at a pH of 7.0. Vitamin C’s most prevalent redox state in cells. VitC protects the cardiovascular system by reducing oxidative stress, regulating intracellular signal pathways, and preserving nitric oxide homeostasis. Antioxidant vitamin C is also essential for the formation of the vasoactive polypeptides (VPPs), supra renal hormones (noradrenalin and adrenaline), as well as vasopressin. [17, 18]

Depletion of vitamin C is associated with an increased risk of organ malfunction and death in patients with sepsis and other life-threatening conditions. This correlation is dose-dependent. [19].

**Safety**

All of these probable adverse effects of high IV Vitamin C dosages include pro-oxidant effects, increased iron absorption, and interference with blood glucose readings. High-dose. Oxalate crystals may also develop in tissues and the kidneys as a result of vitamin C deficiency. Short-term high-dose vitamin C administration has not been shown to cause this problem in controlled studies. Glyoxylate is broken down to carbon dioxide rather than oxalate by Thiamine Pyrophosphate, which is a coenzyme that has been utilised for decades in combination treatment for sepsis. Due to an increased incidence of severe hypernatremia in patients receiving HAT treatment, a recent RCT in adults with sepsis was prematurely halted. Animal and human studies show that high-dose IV vitamin C is safe and has little to no harm. To prevent hemolysis, high-dose vitamin C should be avoided by patients with oxalate nephrolithiasis, lack of glucose-6-phosphate dehydrogenase and paroxysmal nocturnal hemoglobinuria. [20]

Monotherapy with Vitamin C

High-dose IV vitamin C has been demonstrated to be effective in the treatment of sepsis in critically sick people in most clinical studies. IV vitamin C treatment improved organ dysfunction and lowered inflammatory indicators such as vascular damage and endothelial injury in a dose-dependent way in a 2014 clinical study of 24 persons with sepsis. [21].

Vitamin C as part of a larger treatment plan.

Combination treatment studies incorporating vitamin C have had mixed outcomes. Antioxidant treatment for patients at risk of sepsis after major surgery or trauma was shown to reduce organ failure and length of stay in the intensive care unit, according to a prospective, randomised research. When given an enteral diet high in eicosapentaenoic acid, omega-3 fatty acids, and vitamin E as part of their treatment, patients in a Brazilian study saw comparable outcomes. There was a lower death rate and fewer organ damage in those who took vitamin C and E. With an enteral diet, patients spent fewer days on a ventilator and in the intensive care unit. [22].

**Recommendations**

Using large doses of vitamin C in the early stages of sepsis has been shown to be risk-free and useful for reducing morbidity, even if there is no good evidence of a decrease in death.

**Selenium**

Antioxidant, anti-inflammatory, and immunomodulatory properties are all attributed to selenium, a trace mineral found in seleno-proteins. Neutrophil and macrophage function is hindered when
selenium levels are low in those who have inflammatory processes or sepsis. [23].

Recommendation,

Various factors, including dosage, mode of administration, combination with other nutrients, and the kind of patients being examined, may influence how well selenium works as a therapy.

Various forms of Vitamin A.

Vitamin A is an essential nutrient.

Precursors (such as beta-carotene from plants or fruits) and animal sources (such as dairy, fish, and meat) provide vitamin A, which is then digested in the small intestine and stored as retinol (also known as vitamin A). It's a part of the oxidative phosphorylation process in the mitochondria and the retina. Vitamin A has also been shown to improve innate and adaptive immunity and to reduce the production of pro-inflammatory cytokines. During an acute infection, vitamin A metabolism may be altered in critically sick individuals, leading to increased renal clearance. Study participants with ARDS had lower levels of retinol than healthy controls, and daily vitamin A doses failed to repair the shortfall.

B. Vit E.

Tocopherols, the most common type of vitamin E, are present in plant oils and are a potent antioxidant.

Scavenging reactive oxygen species (ROS), inhibiting nuclear factor-kappa B, and reducing proinflammatory cytokine levels are just a few of the biological qualities that vitamin E has to offer. In preclinical animal models of sepsis, vitamin E has been shown to impact macrophage function and to be inversely related with oxidative stress [24].

C. Vitamin B2.

Dietary sources of vitamin B2 include eggs, dairy products, and green vegetables. It aids in cellular respiration. The bulk of evidence for the anti-inflammatory and antioxidant properties of vitamin B2 comes from studies in animals used in preclinical settings. Pro-inflammatory cytokines and NO have inflammatory and antioxidant properties of vitamin B2.

Electrolytes and Water as a System

Patients with haemodynamic instability, as defined by either hypotension (systolic blood pressure <90 mm Hg, MAP <70 mm Hg, or a fall in systolic blood pressure of >40 mm Hg from baseline) or increased lactate (4 mmol/L), should receive a bolus of 30 mL/kg crystalloid fluids. This is the SSC's recommendation.[25].

Pediatric sepsis requires an initial fluid infusion of 20 millilitres per kilogramme of body weight (crystalloids or albumin), which may be repeated three times up to 60 millilitres per kilogramme of body weight. [26].

With no clear advantage to colloids, several research have investigated the efficacy of colloidal and crystalloid-based resuscitation. [27].

First-line resuscitation should employ crystalloid fluids rather than colloid fluids because of the greater costs and the increased risk of nephrotoxicity. Human albumin would be the primary option over synthetic solutions if a colloid fluid is required. [28].

Further stabilisation of the hemodynamics and evaluation of the fluids

Responsiveness

Following the initial fluid resuscitation, fluid responsiveness should be evaluated in patients who continue to have haemodynamic instability. Assessing fluid responsiveness has been done using many different methods throughout the years, including cardiac output and stroke volume monitoring, central venous pressure measurement, respiratory fluctuations in inferior vena cava diameter, pulse pressure variation and stroke volume variation.

Aside from the limitations in accuracy in predicting fluid responsiveness (as with central venous pressure and central venous oxygen saturation [ScvO2]), the need for technological advancements (such as pulse pressure variation and stroke volume variation), or the requirement for sedation, sinus rhythm, and positive pressure ventilation with respiratory volumes greater than or equal to eq, all currently available methods for assessing fluid responsiveness have limitations (as with inferior vena cava). Even though they may be difficult to conduct at the bedside, dynamic tests such evaluating responses to a passive leg lift in stroke volume or cardiac output may be beneficial. In the event that these functional haemodynamic indicators cannot be used to predict fluid responsiveness, a fluid challenge should be done to ensure that fluid is only given to individuals who respond favourably to fluid administration.

Recommendations
Although data shows that balanced solutions have some benefits in severely sick persons, there does not seem to be enough evidence to urge a wholesale switch to balanced solutions over saline. In the meantime, it looks fair to evaluate chloride concentrations while using normal saline, and to transition to a balanced crystalloid if hypo-chloremia emerges and additional fluids are necessary.

**Electrolytes**

According to current study, a considerable number of ICU patients may be low in trace elements upon admission or grow deficient over their stay. [29].

The malnourished ICU patient is at risk of refeeding syndrome. This must be verified by electrolyte measurement (potassium, phosphate, magnesium) and replenishment as necessary. [30].

**Recommendation**

"Regular treatment of intravenous minerals and vitamins with electrolyte replacement is helpful during the acute period of critical illness until normal enteral intake is achieved.". [29].

**Glycemic control**

The ideal blood glucose levels to strive for remain unclear. Hyperglycemia has been related to a poor outcome. If a severe protocol is followed, tight glucose control is attainable in patients receiving parenteral nutrition. [31].

A 2001 investigation in Leuven, Belgium, demonstrated that rigorous glycemic control was connected with substantial improvements in morbidity and mortality in postsurgical ICU patients when compared to usual care. In a second Leuven investigation, benefits in terms of morbidity (but not mortality) were established in a medical ICU scenario. [32].

**Recommendation**

The current consensus is to maintain glycemia at 180 mg/dL while avoiding rigorous glycemic control.

**Nutrition Stewardship**

Nutrition stewardship is characterized as a series of coordinated measures, similar to fluid stewardship, that are used to determine the optimal form of nutrition, dosage, and duration of treatment for the highest therapeutic result, avoiding adverse effects, and decreasing cost. The 6 D’s (diagnostic, drug, dosage, duration, de-escalation, and discharge) may assist to achieve this. [33].

1. **Diagnosis**

Correct nutrition treatment starts with a comprehensive analysis of the patient’s nutritional health and metabolic condition utilizing indirect calorimetry in combination with other monitoring modalities such as BIA and nitrogen balance. [34; 35]

2. **Drug**

Nutrition should be considered as a drug with indications and contraindications, as well as probable side effects, by critical care doctors, who should pay careful attention to the numerous elements and their specificities (calories, nitrogen, protein, glucose, lipids, and micronutrients) (calories, nitrogen, protein, glucose, lipids, and micronutrients). There are distinct signals and bad consequences for each form of nourishment. [36]

**3. Dose**

"Sola dosis facit venenum," or "the dosage makes the poison," is a Latin phrase that meaning "the dose causes the poison." As previously discussed, there are several important considerations for nutritional prescription, as calorie and protein dosage are directly linked with mortality, and pharmacokinetics and dynamics, as well as volume kinetics, must be taken into account, as nutrition may also relate to fluid retention. [37; 38]

4. **Duration**

The time of full or supplemental nutritional treatment is equally critical, and parenteral feeding must be tapered after shock has been treated and the gastrointestinal tract is acting correctly. [39].

5. **De-escalation**

When artificial EN or PN nutrition therapy is no longer essential, the final step is to consider withholding or stopping them.

6. **Discharge**

Correct (dis)continuation or tapering of nutritional therapy and (where appropriate and justified) prescription after ICU or hospital discharge is aspect of the nutritional treatment plan and should meet quality requirements. [35]

**References**


