



Persistent Inflammation, Immunosuppression, and Catabolism Syndrome in Sepsis

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Abstract: Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection. Early recognition and appropriate management improve in-hospital mortality in patients with sepsis. However, many patients progress to chronic critical illness (CCI). Persistent inflammation, immunosuppression, and catabolic syndrome (PICS), a new phenotype of CCI, is characterized by chronic low-grade inflammation, host immunosuppression, and catabolic-dominant weight loss. Due to the complexity of the pathophysiologic mechanisms of PICS, there is no effective treatment available. The aim of this review is to increase understanding of the pathophysiological mechanisms of PICS in sepsis, to summarize the diagnostic criteria and potential treatments for PICS, and to help clinicians adopt more comprehensive measures to improve the long-term prognosis of patients with PICS.

Keywords: sepsis, persistent inflammation, immunosuppression, and catabolism syndrome, pathophysiology, treatment

1. Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated immune response to host infection[1], is an important clinical problem facing critical care medicine today. With the continuous development of critical care medicine and the "Surviving Sepsis Campaign", the survival rate of septic patients has been greatly improved, and many patients can be discharged from the intensive care unit (ICU) alive[2, 3]. Nevertheless, certain observational studies have indicated that a subset of individuals afflicted with sepsis do not achieve a full restoration of normal physiological function and progress to a state of chronic critical illness (CCI). These patients are predisposed to heightened complications, sustained organ dysfunction, and notably elevated long-term mortality rates[4]. In 2012, Gentile et al.[5]proposed the new concept of PICS. Their clinical features are usually characterized by recurrent nosocomial infections, chronic mild organ insufficiency, malnutrition, and a high mortality rate[6], which increases both the consumption of social resources and the burden on families. The precise mechanism underlying PICS in sepsis patients remains incompletely elucidated, and clinicians continue to exhibit a relative dearth of understanding concerning PICS, thereby impeding the recovery process for patients who develop PICS. This review aims to delineate the pathophysiological mechanisms, diagnostic approaches, therapeutic modalities related to PICS in sepsis patients. The ultimate objective is to improve the prognostic outcomes for individuals impacted by this condition.

2. Pathophysiology

2.1 Persistent Inflammation

A key driver of sustained inflammation in individuals suffering from PICS are alarmins[4], predominantly identified by common pattern recognition receptors (PRRs) present on immune cells and histiocytes, thereby perpetuating the inflammatory process. There are two sources of alarmins, including exogenous pathogen-associated molecular patterns(PAMPs)[7] and endogenous damage-associated molecular patterns (DAMPs)[8]. The PRRs with PAMPs or DAMPs initiates intracellular signaling pathways, triggering a protective response in the host. PAMPs are discharged during both early and late nosocomial infections in sepsis, while DAMPs are initially liberated from tissues experiencing primary infectious injury[9]. Research has indicated that DAMPs are continuously released due to prolonged mitochondrial impairment in the kidneys, lungs, and intestines of patients with CCI, consequently resulting in persistent low-grade inflammation following sepsis in these individuals[10]. This results in a continuous cycle of inflammation-induced organ damage and damage-induced inflammation.

2.2 Immunosuppression

In sepsis, the body produces an "emergency myelopoiesis"[11], leads to the expansion of a heterogeneous population of immature bone marrow cells exhibiting immunosuppressive and inflammatory properties, identified as "myeloid-derived

suppressor cells (MDSCs)"[12, 13]. Studies have demonstrated a substantial and persistent elevation in the abundance of MDSCs among septic patients[14, 15]. MDSCs exhibit dual functionality as they not only exert immunosuppressive effects on macrophages, CD4+ T cells, and CD8+ T cells, but also possess pro-inflammatory properties. They generate reactive oxygen species, tumor necrosis factor alpha, and nitric oxide, which can all inflict tissue cell damage and elicit an inflammatory response. The interplay between immunosuppression and persistent inflammation contributes to prolonged hospitalization and diminished quality of life in patients.

2.3 Catabolism

Studies propose that a reduction in protein synthesis and an elevation in catabolism among septic patients contribute to muscle breakdown and the liberation of muscle-derived DAMPs. Concurrently, chronic low-grade inflammation and oxidative harm to the mitochondria can perpetuate the release of DAMPs throughout the body, consequently fostering sustained inflammation and skeletal muscle catabolism[9]. Further suggestions propose that the continual low-grade inflammatory response observed in patients with PICS stimulates the substantial release of catecholamines and counter-regulatory metabolic hormones. This phenomenon, in turn, engenders a heightened state of catabolism surpassing anabolism, impairing the utilization of energy-providing substrates, and leading to manifestations such as nutritional intolerance and related sequelae.

3. Diagnosis

Since the inception of the concept of PICS in 2012, there has been a lack of standardized diagnostic criteria. In the original delineation provided by Gentile, persistence was characterized as a prolonged hospitalization exceeding 14 days, inflammation was identified by C-reactive protein (CRP)>150 ug/dl, immunosuppression was indicated by a total lymphocyte count<0.80*10⁹ /L, and catabolism was defined by a creatinine height index<80%, serum albumin <3.0 g/dl, retinol binding protein <10 ug/dl, or weight loss >10%, BMI <18 during hospital admission. Hesselink et al. proposed clinical and laboratory diagnostic criteria for PICS[16], defining PICS clinically as an ICU stay of ≥14 days, presence of ≥3 infectious complications and evidence of a catabolic state. Additionally, markers for PICS were considered positive if patients exhibited ≥2 days of immunosuppression (lymphocyte count <0.8 × 10⁹/L), ≥2 days of inflammation(CRP >50 mg/L) and a catabolic state. A catabolic state was defined as either weight loss >10%, Body Mass Index (BMI) <18 or albumin <30 g/L during hospitalization. In recent years, the investigation of microRNAs as biomarkers for tissue injury, inflammation, and various diseases has emerged as a prominent area of research[17]. In the future, the specific diagnosis of PICS is anticipated to be accomplished through the utilization of microRNAs.

4. Treatment of PICS

4.1 Etiologic Treatment

Numerous studies have demonstrated that prompt surgical intervention to effectively drain infected foci in septic patients with well-defined focuses of infection contributes to a significant reduction in in-hospital morbidity and mortality rates[18]. Consequently, early intervention plays a crucial role in these patients, involving targeted treatment of the disease's etiology, comprehensive management of infected foci, appropriate utilization of antibiotics based on drug sensitization results, timely removal of inflammatory mediators, control over the inflammatory response.

4.2 Medication

Pharmacological intervention seeks to disrupt the cascade of inflammation, immunosuppression, and proteolytic metabolism. All-trans retinoic acid can effectively inhibit the expansion of MDSCs and induce their differentiation into neutrophils, monocytes-macrophages and dendritic cells, thus improving the immunity of patients[19]. Immunomodulator Thymosin α-1 can promote the differentiation and maturation of lymphocytes, enhance the immune function of the body. Studies have shown that treatment with thymosin α1 alone or in combination can reduce the sepsis mortality rate and the incidence of secondary infections[20]. Granulocyte-macrophage colony stimulating factor (GM-CSF), an immunostimulant, has been shown to reduce the rate of reinfection and hospitalization[21]. IL-7 restores lymphocyte function in patients, preventing opportunistic infections[22]. In conclusion, the enhancement of immune function in sepsis patients can avoid the occurrence of many clinical adverse events.

4.3 Nutritional support

The intestinal tract is an important immune organ, and sepsis can cause a variety of intestinal impairments. Nutritional support has become a routine and important intervention in the treatment of critical illnesses, and has been shown to help

improve the intestinal dysfunction and hypercatabolic state of patients with PICS[23]. The ESPEN suggests that proper protein supplementation is an important factor in improving the long-term prognosis of critically ill patients[24]. Supplementation with arginine may allow patients with PICS to restore lymphocyte numbers and promote wound healing and tissue repair. Leucine can reduce muscle protein catabolism and induce protein synthesis[25]. Glutamine supplementation can enhance cellular immunity and inhibit systemic inflammation[26], which may help to reduce the inflammatory response and re-infection rate in patients with PICS[27]. Supplementation with Omega 3 fatty acids may improve patient prognosis by attenuating the hypermetabolic response in critically ill patients, reducing muscle atrophy, inhibiting oxidative damage, and providing anti-inflammatory mediators.

4.4 Rehabilitation

Limb restriction restraints and lack of functional exercise contribute to muscle atrophy and dysfunction in ICU patients. Early performance of functional muscle exercise has been shown to be beneficial for critically ill patients[28]. A study have found that early functional exercise improves sepsis-induced catabolism and induces a systemic anti-inflammatory response[29]. It has also been shown that neuromuscular electrical stimulation can promote muscle protein synthesis and prevent muscle atrophy in critically ill patients[30]. At the same time, during the clinical process, clinicians need to control the depth of sedation to ensure that patients are lightly sedated and ready to wake up and perform appropriate physical rehabilitation activities[31].

5. Conclusion

With significant advances in medical understanding of the pathophysiologic mechanisms of sepsis and therapeutic options, sepsis morbidity and mortality have now declined significantly, but many of those who survive still experience persistent organ dysfunction. PICS has a high incidence in the clinic and severely affects the prognosis of critically ill patients. Although there is a preliminary understanding of the pathophysiological mechanisms of PICS in terms of inflammation-immunosuppression and catabolism, more animal models and clinical trials are needed to further improve and explore the pathophysiological mechanisms in depth, to develop precise treatment plans and personalized strategies for PICS patients, and to improve the survival and long-term prognosis of patients.

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