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REVIEW

Inflammatory Response and Anti-Inflammatory Treatment in Persistent Inflammation-Immunosuppression-Catabolism Syndrome (PICS)

Dacheng Xiong[1,2], Huixian Geng[1,2], Xuechun Lv[1,2], Shuqi Wang[1,2], Lijing Jia[1,2]

[1]Department of Intensive Care Medicine, Hebei Medical University, Shijiazhuang, People's Republic of China; [2]Department of Intensive Care Medicine, Hebei General Hospital, Shijiazhuang, People's Republic of China

Correspondence: Lijing Jia, Department of Intensive Care Medicine, Hebei General Hospital, Shijiazhuang, Hebei Province, People's Republic of China, Tel +86 31185989925, Fax +86 31185989925, Email 90030200@hebmu.edu.cn

Abstract: Many patients now survive their initial critical events but subsequently develop chronic critical illness (CCI). CCI is characterized by prolonged hospital stays, poor outcomes, and significant long-term mortality. The incidence of chronic critical illness (CCI) is estimated to be 34.4 cases per 100,000 population. The incidence varies significantly with age, peaking at 82.1 cases per 100,000 in individuals aged 75–79. The one-year mortality rate among CCI patients approaches 50%. A subset of these patients enters a state of persistent inflammation, immune suppression, and ongoing catabolism, a condition termed persistent inflammation, immunosuppression, and catabolism syndrome (PICS) in 2012. In recent years, some progress has been made in treating PICS. For instance, recent advancements such as the persistent expansion of MDSCs (myeloid-derived suppressor cells) and the mechanisms underlying intestinal barrier dysfunction have provided new directions for therapeutic strategies, as discussed below. Persistent inflammation, a key feature of PICS, has received comparatively little research attention. In this review, we examine the potential pathophysiological changes and molecular mechanisms underlying persistent inflammation and its role in PICS. We also discuss current therapies about inflammation and offer recommendations for managing patients with PICS.

Keywords: persistent inflammatory-immunosuppressive-catabolic syndrome, chronic critical illness, inflammation, immunosuppression, anti-inflammatory therapy

Introduction

With the advancements in critical care medicine, an increasing number of critically ill patients are receiving adequate treatment in the ICU and surviving. Approximately 7.6% of these patients develop chronic critical illness (CCI),[1] which is defined as an ICU stay of at least 14 days with persistent organ dysfunction.[2] Despite receiving appropriate supportive treatment, about 30–50% of these patients continue to exhibit chronic low-grade inflammation, immunosuppression, and hypercatabolism.[3,4] In 2012, Gentile et al introduced the concept of Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) to describe patients with chronic critical illness (CCI).[5] Since its introduction, this syndrome has garnered widespread attention due to its complex pathophysiological mechanisms and profound impact on patient outcomes.

Persistent inflammation in PICS is characterized by elevated levels of systemic inflammatory markers, such as C-reactive protein (CRP), indicating ongoing inflammation. Sustained acute-phase responses, including increased levels of IL-6 and neutrophilia with a higher proportion of immature granulocytes, further highlight this persistent pro-inflammatory state.

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Immunosuppression in PICS is marked by adaptive immune dysfunction, as evidenced by a decreased absolute lymphocyte count (ALC). Lymphocytes, the key effector cells mediating adaptive immune responses, are significantly reduced in both number and function, reflecting profound adaptive immune suppression.[6] Furthermore, impaired antigen presentation, commonly referred to as "immune paralysis", is frequently observed and is manifested by reduced HLA-DR expression on monocytes.[7] This immunosuppressive state is further exacerbated by elevated levels of anti-inflammatory cytokines, such as IL-10 and soluble TNF receptors. Catabolic State is reflected by severe protein depletion, as indicated by a serum albumin level below 3.0 g/dl. Profound metabolic derangements, including significant weight loss exceeding 10% of baseline body weight or a body mass index (BMI) below 18, underscore the marked loss of lean body mass. These catabolic processes lead to poor functional outcomes and prolonged recovery.

The pathophysiological mechanisms underlying PICS provide a comprehensive explanation for the occurrence of CCI, which frequently develops following major trauma, burns, acute pancreatitis, or sepsis. Poor baseline health and advanced age (over 65) are significant risk factors for the development of PICS.[8–10] However, despite the growing recognition of this syndrome, its diagnostic criteria remain unstandardized. The following Table 1 summarizes the proposed diagnostic criteria by various authors.

The clinical parameters presented in the table are not direct measures of inflammation, immunosuppression, or protein catabolism. However, they can serve as surrogate markers and are easily obtainable in most intensive care unit (ICU) settings.

It has been over a decade since the diagnostic criteria for PICS were proposed, yet among the indicators reflecting the state of immunosuppression in patients, only the absolute lymphocyte count (ALC) has been consistently utilized.

While measuring absolute lymphocyte count (ALC) is logistically straightforward, cost-effective, and provides a direct indicator of adaptive immune function, it does not directly represent innate immune function.[15] Lymphopenia alone is insufficient to fully reflect the immune status of the body. In addition to ALC, incorporating additional indicators can provide a more comprehensive assessment of a patient's immune status. TNF-α secretion and monocyte HLA-DR (mHLA-DR) are also commonly used biomarkers and are suitable for evaluating the immune status of critically ill patients.[16–18] LPS-induced TNF-a production from peripheral blood cells reflects innate immune system function via myeloid cell capacity to respond to an inflammatory stimulus[16]. Previous studies have found that the dynamic changes in mHLA-DR expression within the first week after sepsis are a reliable predictor of mortality in sepsis patients.[19] Measuring the temporal dynamics of mHLA-DR expression holds significant clinical value. In healthy individuals, the expression levels of HLA-DR on monocytes and macrophages typically range between 15,000 and 60,000 antibody-binding sites (Ab/c) per cell.[20,21] The widely accepted lower limit of HLA-DR expression in healthy individuals is 15,000 Ab/c per cell.[22]

By assessing the expression levels of HLA-DR on the surface of monocytes and measuring ex vivo TNF-α secretion by blood cells, it is possible to further evaluate the immunosuppressive state of PICS patients. This quantification of immune dysfunction provides critical guidance for diagnosis and clinical management.

Table 1 Diagnostic Criteria for PICS

Authors	ICU Stay (Days)	C-reactive Protein (mg/L)	Total Lymphocyte Count (× 10^9/L)	Serum Albumin (g/dL)	Prealbumin (mg/dL)	Weight Loss (%)	BMI (kg/m²)
Gentile et al[5]	>10	>1.5	<0.8	<3.0	<10	>10	<18
Mira et al[11]	>14	>0.5	<0.8	<3.0	<10	>10	<18
Hu et al[12]	>10	>1.5	<0.8	<3.0	<10	>10	<18
Nakamura et al[13]	>14	>30	<0.8	<3.0	<10	>10	<18
Hesselink et al[3]	>14	>50	<0.8	<3.0	<10	>10	<18
Varela et al[14]	≥10	>1.5	<0.8	<3.0	<10	>10	<18

Notes: After unifying the units, there are some differences in ICU stay, C-reactive protein (CRP) levels, and retinal binding protein levels among these criteria.
Abbreviations: PICS, persistent inflammation, immunosuppression, and catabolism syndrome; ICU, intensive care unit; CRP, C-reactive protein; BMI, body mass index.

Methods

Data were acquired from PubMed, MEDLINE, Scopus, and OVID using the following search terms: persistent inflammation, immunosuppression, and catabolism syndrome, (persistent inflammation, immunosuppression, and catabolism syndrome) AND (inflammation OR persistent inflammation), (chronic critical illness OR sepsis) AND (inflammation OR persistent inflammation), (persistent inflammation, immunosuppression, and catabolism syndrome OR chronic critical illness OR sepsis) AND (persistent inflammation, immunosuppression, and catabolism syndrome OR chronic critical illness) AND (therapy). There was no restriction on the type of article and the study design. Articles from all years were considered.

Research Progress on Mechanisms Related to Persistent Inflammation in PICS

Both infectious and non-infectious injuries can induce a persistent inflammatory response in PICS patients. Elevated inflammatory markers can persist for at least 28 days after sepsis.[23] The production and activation of inflammatory mediators, the generation of autoimmunity, and alterations in the gut microbiota are significant contributors to this persistent inflammation (Figure 1).

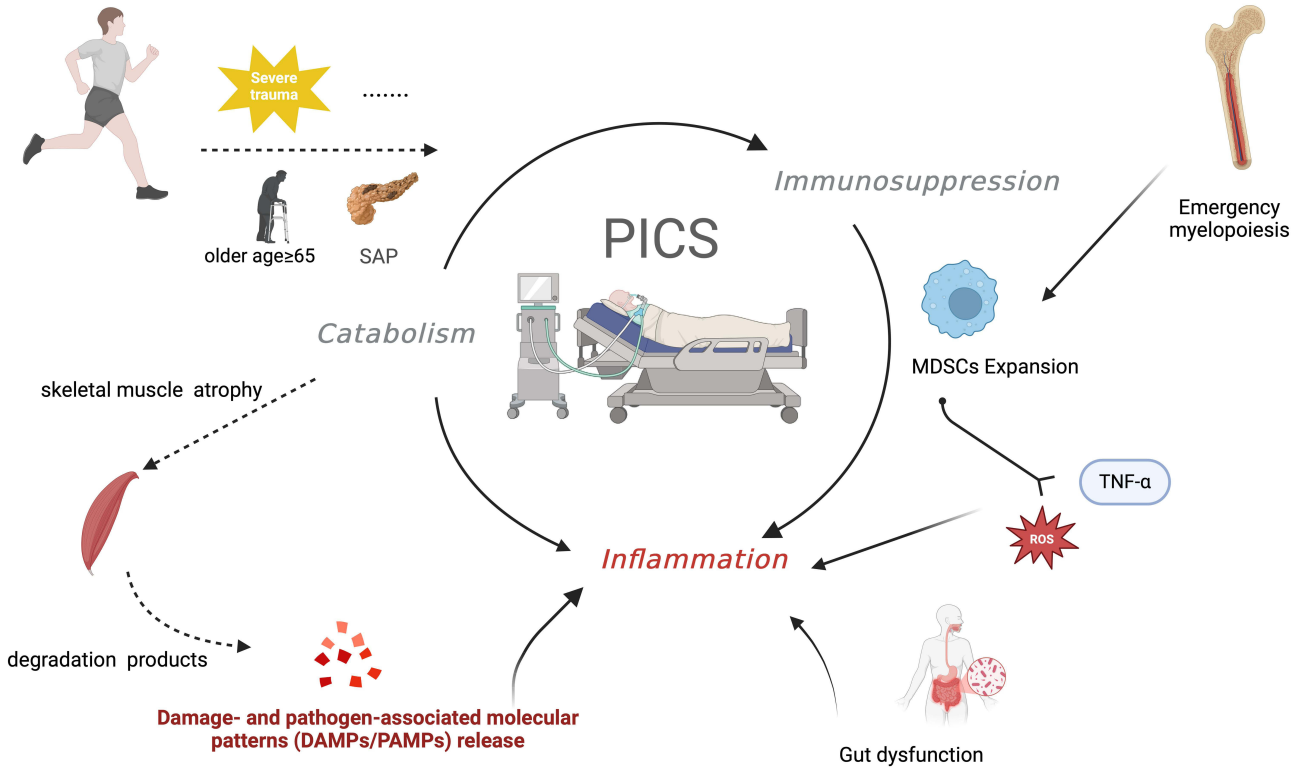

Figure 1 Athophysiological mechanisms of persistent inflammation in PICS. This figure illustrates the pathophysiological mechanisms underlying Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) following severe trauma. Key risk factors for PICS include severe trauma, advanced age (≥65 years), and severe acute pancreatitis (SAP). In patients with PICS, ongoing catabolic processes result in malnutrition, muscle wasting, and immune suppression. Concurrently, muscle breakdown products and exogenous pathogens stimulate the release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), perpetuating a chronic inflammatory state. SAP or trauma can also drive the migration of granulocytes from the bone marrow to sites of injury or infection, promoting the expansion of myeloid cells. This immune suppression contributes to recurrent infections and inflammatory responses, leading to further depletion of energy and nutrient stores. (Created with BioRender.com).

Abbreviations: PICS, persistent inflammation, immunosuppression, and catabolism syndrome; MDSCs, myeloid derived suppressor cells; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TNF-α, Tumor Necrosis Factor-alpha; ROS, reactive oxygen species; SAP, Severe Acute Pancreatitis.

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Persistent Proliferation of Myeloid-Derived Suppressor Cells (MDSCs)

In patients with PICS, an emergency myelopoiesis occurs in response to severe injuries such as sepsis or trauma, leading to the migration of granulocytes from the bone marrow to the site of injury or infection, which drives the expansion of bone marrow cells. Among these, the persistent expansion of MDSCs is considered to play a critical role.[4,24] During this emergency myelopoiesis, the differentiation of immature bone marrow cells into mature immune cells is blocked, resulting in the expansion of these heterogeneous populations of immature bone marrow cells, which possess immunosuppressive and inflammatory properties, known as Myeloid-Derived Suppressor Cells (MDSCs).[25–28] In animal models with chronic inflammation, we frequently observe MDSC infiltration in secondary lymphoid organs and the reticuloendothelial system.[29,30] MDSCs can produce inflammatory mediators, nitric oxide (NO), and reactive oxygen species (ROS), contributing to persistent inflammation, and are significantly expanded in conditions such as cancer, autoimmune diseases, inflammation, and sepsis.[24,29] In murine sepsis models, studies have shown that activated MDSCs can produce various pro-inflammatory factors, such as TNF-α, RANTES, and MIP-1β, in response to LPS stimulation. Similarly, in clinical studies, we have observed that in patients with severe sepsis, the proportion of MDSCs in peripheral blood correlates with the degree of inflammatory response, and can predict hospital stay duration and long-term clinical outcomes.[11,24] Compared to patients whose MDSC levels returned to baseline within two weeks, those with persistent MDSC expansion had longer ICU stays, higher in-hospital mortality, and a greater likelihood of being discharged to rehabilitation facilities.[11] Thus, this persistent expansion of MDSCs appears to be associated with the development of inflammation in PICS and may contribute to a deeper understanding of the pathophysiology of chronic critical illness (CCI) and PICS.

Recognition and Activation of DAMPs and PAMPs

In patients with PICS, hypercatabolic characteristics are often manifested by increased skeletal muscle atrophy, during which pro-inflammatory degradation products are released into the circulation, triggering a series of inflammatory responses.[31] Muscle biopsies from PICS patients show infiltration by neutrophils and macrophages, as well as muscle necrosis, which may contribute to the ongoing inflammation seen in PICS.[32] Additionally, insufficient energy supply and muscle damage can stimulate the release of damage-associated molecular patterns (DAMPs),[33] such as mitochondrial DNA and mitochondrial transcription factor A.[34] Both hospital-acquired infections and the reactivation of latent viral infections generate exogenous pathogen-associated molecular patterns (PAMPs)[35] and cause the continued release of endogenous DAMPs from damaged organs and inflammatory cells.[36] These molecules are recognized by the same pattern recognition receptors (PRRs) on immune cells, perpetuating inflammation. DAMPs bind to PRRs, including toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs),[36,37] acting as alarmins.[38] When the host recognizes these DAMPs, PRRs initiate a complex cascade of downstream signaling events that induce inflammatory responses.[36] Moreover, the persistent hypercatabolic state leads to malnutrition and even cachexia, making PICS patients more susceptible to infections. Recurrent infections, in turn, facilitate pathogen invasion and induce the release of PAMPs, further triggering inflammatory responses via PRR signaling pathways in the host.[33,35]

Impaired Intestinal Barrier Function

The gut is a motor of organ system dysfunction.[39] The gastrointestinal tract has long been recognized as playing a critical role in the pathophysiology of sepsis, acting as a driving factor for multiple organ dysfunction syndrome (MODS).[40] Impaired gut integrity, dysbiosis of the microbiota, and the release of toxic substances can exacerbate systemic inflammation and organ dysfunction.[41] Intestinal injury and impaired intestinal barrier function contribute to the translocation of bacteria and pathogen-associated molecular patterns (PAMPs), which subsequently induce pro-inflammatory pathways and distal organ dysfunction.[40,42] These findings indicate that intestinal dysfunction may play a key role in the development of persistent inflammation, immunosuppression, and catabolism syndrome (PICS). In clinical models of sepsis in mice, alterations in intestinal epithelial tight junctions occur as early as 1 hour after the onset of sepsis, and the increased intestinal permeability persists for at least 48 hours. Sepsis in mice can induce significant functional impairment of the intestinal barrier, leading to hyperpermeability.[43–46] This

allows luminal contents, including intact microbes and microbial products, to more easily escape their natural environment, where they can cause local or distant tissue damage. Recent research has revealed an interorgan pathway in mouse models of sepsis, where the gut releases a secreted phospholipase (PLA2G5) into the bloodstream, resulting in hemolysis and multi-organ failure. This pathway is detrimental to the host. PLA2G5 is associated with various cell types, including macrophages, adipocytes, endothelial cells, bronchial epithelial cells, and cardiomyocytes, and exhibits multiple local pathogenic effects. Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) may disrupt the intestinal epithelial barrier, impair gut integrity, and facilitate the release of PLA2G5 into the circulation, converting it into an "intestinal toxin" harmful to the host.[47] Simultaneously, we have found that intestinal lymph is also associated with the development of PICS-related inflammation, with substantial evidence supporting the gut-lymph hypothesis. Studies have shown that lymph collected from animals subjected to traumatic hemorrhagic shock, when injected into untreated mice, induces acute lung injury similar in toxicity to the injured animals themselves.[48] Gut-derived lymph drains directly into the pulmonary circulation via the mesenteric lymphatic vessels. Ligation of the mesenteric lymph vessels has been shown to prevent neutrophil-driven lung injury and acute respiratory distress syndrome (ARDS) in various critical illness models, including burns, trauma, and shock in both small and large animal models.[49] It has been confirmed that mesenteric lymph typically does not contain bacteria, endotoxins, or cytokines, but rather proteins and lipid factors that signal through a Toll-like receptor 4 (TLR4)-dependent pathway in the lungs. This suggests that inflammatory damage in distant organs can occur via pattern recognition receptor pathways stimulated by endogenous inflammatory proteins released from the gut. Intestinal dysfunction is receiving increasing attention, and further research is needed to clarify its exact role in PICS.

Research Advances in the Treatment of Persistent Inflammation in PICS

Reconstruction of Immune Homeostasis

In the early management of sepsis and systemic inflammatory response syndrome (SIRS), therapeutic strategies predominantly focused on improving patient outcomes by suppressing the early pro-inflammatory response. However, these approaches often failed to deliver the expected results. The introduction of persistent inflammation, immunosuppression, and catabolism syndrome (PICS), a condition characterized by profound immunosuppression, has provided new insights and directions for research. This has shifted the therapeutic focus toward restoring immune system homeostasis, aiming to reduce excessive inflammation in PICS patients and improve the efficacy of single-agent anti-inflammatory therapies. Several investigational drugs are currently under study, including leukocyte growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF); immune-modulating cytokines, such as interleukin-7 (IL-7), interleukin-15 (IL-15), and interferon-gamma (IFN-γ); and inhibitors targeting negative co-stimulatory pathways, such as anti-PD-1/PD-L1 antibodies. While some of these therapies showed limited success when used as standalone interventions, many have demonstrated partial efficacy and hold potential for improving outcomes when incorporated into more comprehensive treatment strategies. Furthermore, recent findings have revealed that the immunosuppressive state characteristic of severe trauma or PICS is closely associated with an increased population of regulatory T cells (Tregs). These findings offer new perspectives for understanding the mechanisms underlying PICS and provide a foundation for the development of novel therapeutic approaches. A detailed summary of these findings is presented as follows:

Cytokine-Based Therapies

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) have demonstrated the ability to restore monocyte antigen-presenting function, regenerate functional myeloid cell populations, enhance immune responses, and reduce the length of ICU stays. In a clinical trial involving immunosuppressed pediatric patients with sepsis, GM-CSF was shown to restore tumor necrosis factor (TNF) production in lymphocytes, resulting in fewer hospital-acquired infections, reduced duration of mechanical ventilation, and shorter hospital stays.[50] However, a meta-analysis of 12 randomized controlled trials (RCTs) revealed that while GM-CSF

and G-CSF improved infection clearance rates, they did not significantly reduce 28-day mortality compared to placebo.[51] This lack of significant mortality benefit may be due to the failure of these growth factors to address the pathological activation and expansion of myeloid-derived suppressor cells (MDSCs) caused by their stimulation. Interferon-gamma (IFN-γ) is a critical cytokine for activating monocytes and macrophages, but its production is often diminished during sepsis. Both animal and clinical studies have shown that recombinant IFN-γ therapy can enhance the expression and function of monocyte human leukocyte antigen-DR (mHLA-DR).[52] Moreover, IFN-γ therapy has been reported to reduce infection-related mortality in patients with sepsis-induced immunosuppression.[53] However, its maximal therapeutic benefit appears to be limited to specific subgroups of patients, particularly those with significantly reduced monocyte HLA-DR expression. PICS patients, who often exhibit such immune profiles, may be an ideal candidate group for this therapy. Interleukin-7 (IL-7) and interleukin-15 (IL-15) are anti-apoptotic cytokines that prevent lymphocyte apoptosis and help restore immune function. These cytokines promote T-cell survival, proliferation, and receptor diversity, all of which are compromised during sepsis.[54–56] In sepsis models of sepsis, IL-7 has been shown to significantly increase the number of CD4+ and CD8+ T cells and improve survival rates.[57,58] A recent randomized clinical trial in critically ill septic patients demonstrated that IL-7 as an immunoadjuvant therapy reversed sepsis-associated lymphopenia, enhanced T-cell proliferation and activation, and exhibited sustained effects lasting up to 28 days after administration[59,60] Inoue et al observed that IL-15 treatment reduced splenic cell apoptosis in a murine model of polymicrobial sepsis.[61] Additionally, IL-15 therapy increased survival rates threefold in septic mice when administered postoperatively. Similar improvements in survival rates were observed in a murine model of Pseudomonas aeruginosa-induced pneumonia.[61] While IL-15 has not yet been evaluated in human clinical trials for sepsis, these findings highlight its strong potential as a therapeutic agent for managing sepsis-related immunosuppression.

These cytokine-based approaches represent promising strategies for addressing the immune dysregulation characteristic of PICS and sepsis. However, further clinical studies are required to confirm their efficacy and determine their optimal use in broader clinical practice.

Based on Regulatory T Cells (Tregs)

The regulatory T cell (Treg) population, including both CD4+ and CD8+ Tregs, was first described and promoted by Sakaguchi et al.[62] Current evidence indicates that naturally occurring Tregs play a critical role in suppressing immune responses in various diseases.[63] This immunoregulatory function is essential for maintaining immune system homeostasis. However, in conditions such as sepsis or severe trauma, an abnormal increase in Tregs may exacerbate immunosuppression, leading to secondary infections and further weakening of host defense mechanisms. Monneret et al were the first to report that sepsis increases the relative proportion of Tregs in the blood of septic patients.[64] Recent studies have shown that Treg cells can function within established severe inflammation to reverse all known types of inflammatory responses and restore long-term immune homeostasis. The enhanced function of Tregs in resolving inflammation provides a theoretical foundation for their application in complex immunopathologies. Additionally, a single population of Tregs has been shown to persist in the periphery after systemic inflammation is reversed, providing lasting protection against autoimmune diseases. These cells remain functionally stable for months without showing signs of functional decline, offering a strong theoretical basis for the development of Treg-based adoptive therapies. Enhancing Treg stability and function through gene editing or cell therapy approaches represents a promising potential strategy to address sepsis-associated immunosuppression.[65]

Immune Checkpoint Inhibitors

In sepsis and PICS, the expression of programmed death-1 (PD-1) is typically upregulated on CD4+ and CD8+ T cells to prevent excessive T-cell activation. However, high levels of PD-1 expression are associated with increased infection rates and higher mortality in patients. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have demonstrated success in cancer immunotherapy and have also shown potential in extending survival in animal models of sepsis. These findings highlight their promise as a therapeutic strategy in the management of sepsis and PICS, though further clinical investigation is required to validate their efficacy.[66,67]

Regulation of Inflammation by Myeloid-Derived Suppressor Cells (MDSCs)

In chronic inflammation models in animal studies, chronic inflammation has been shown to promote the activation of myeloid-derived suppressor cells (MDSCs). These activated MDSCs further suppress adaptive immune responses, leading to elevated levels of pro-inflammatory cytokines and increased mortality rates.[68] We believe that the persistent expansion and infiltration of MDSCs is a key factor contributing to the sustained inflammation in PICS. The prolonged presence of MDSCs can induce significant pathophysiological changes, leading to chronic critical illness (CCI) and subsequent PICS.[69,70] Modulating the activation and expansion of MDSCs at specific time points, such as during the immunosuppressive phase after day 14 of sepsis, may represent a potential therapeutic approach for PICS.[71]

Direct Regulation

Other strategies to regulate MDSCs may involve genetic modification or inhibition of MDSC byproducts. Genetically, microRNAs (miRs), which are small non-coding RNAs, are significant in cell transcription and epigenetic modification. These miRs regulate the expression of genes involved in cell development and differentiation, and altered miR expression can affect the expansion of immature myeloid cell populations. At the molecular level, miRs function by targeting proteins involved in myeloid differentiation and maturation, making them an easily modifiable potential therapeutic target for MDSC regulation.[72] In a burn-induced mouse model, administration of gemcitabine (a ribonucleotide reductase inhibitor) on day 6 was observed to reduce MDSCs in mice injected with a lethal dose of lipopolysaccharide (LPS), which was associated with a reduction in mortality rates.[73]

Indirect Regulation

MDSC byproducts, such as arginase-1, nitric oxide (NO), or inducible nitric oxide synthase (iNOS) 71 74,[51] play a role in this process. In mouse cancer models, phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, were able to inhibit NOS, arginase-1, and MDSC function, thereby reducing mortality in mice.[73,74]

Anti-Inflammatory Agents

Anti-inflammatory and Antioxidant Therapies Targeting IL-1 Receptors as Potential Approaches for Suppressing PICS-Associated Hyperinflammation While Preserving Tissue Integrity and Function. IL-1 receptor-targeted anti-inflammatory and antioxidant therapies are considered promising approaches to suppress excessive inflammation associated with PICS while maintaining tissue integrity and function. Anakinra, an IL-1 receptor antagonist, inhibits pro-inflammatory signaling pathways and was initially tested in clinical trials based on the hypothesis that blocking the IL-1 receptor could counteract the cytokine storm linked to sepsis, thereby reducing the incidence of multiple organ failure and improving survival rates.[75] This research demonstrated potential mortality benefits in a subset of patients with macrophage activation syndrome (MAS). Subsequently, in a Phase III clinical trial focusing on septic patients with MAS characteristics, IL-1 blockade was associated with reduced mortality.[76] Patients with PICS exhibit persistent inflammation and immunosuppression similar to septic patients with MAS, prompting further trials of anakinra in MAS, such as the PROVIDE trial. While anakinra showed promising effects during treatment, the trial did not show a statistically significant mortality benefit. This lack of long-term benefit may be attributed to premature discontinuation of treatment, as patients remained in a highly inflammatory state. Shorter treatment durations may obscure the potential benefits of this therapeutic approach.[77] Larger sample size and extended-duration trials are currently underway. Blocking IL-6-mediated pathways can also reduce inflammatory responses, and using IL-6 receptor antagonists, such as tocilizumab, has improved survival rates in critically ill COVID-19 patients. Anakinra and tocilizumab, which block IL-1 and IL-6 receptors respectively, are examples of promising therapies potentially capable of improving survival in adult sepsis. While IL-6 receptor antagonists can improve survival and organ function in critically ill COVID-19 patients[78], IL-6 receptor blockade may carry risks, such as increased susceptibility to opportunistic infections and potential neurotoxicity, which pose potential hazards in sepsis treatment and may even result in adverse outcomes.[79,80] IL-6 is a core cytokine with diverse biological effects. Beyond its role in driving inflammation, fever, cytokine storms, and tumorigenesis, IL-6 is critical for regulating metabolism and hematopoiesis, as well as both innate and adaptive immunity. In the liver, IL-6 contributes to tissue

regeneration, lipid homeostasis, and the induction of the acute phase response. Additionally, it is essential for the proliferation of intestinal epithelium.[81] Tocilizumab, by blocking IL-6 receptor (IL-6R) signaling, inhibits the protective and reparative functions mediated by IL-6 through classical signaling pathways. In patients receiving tocilizumab therapy, an increased incidence of bacterial infections has been reported, along with elevated serum transaminase levels, lipid abnormalities, pancreatitis, and intestinal perforation, particularly in those concurrently treated with corticosteroids.[82,83]

Antioxidant and Catabolic Therapies

Muscle biopsies from PICS patients reveal neutrophil and macrophage infiltration as well as muscle necrosis.[32] Preventing this necroptosis may represent a therapeutic approach for addressing the persistent inflammation in PICS. Muscle atrophy caused by critical illness primarily results from increased muscle protein degradation and decreased protein synthesis. Early exercise therapy (ET) and rehabilitation may play a preventive and therapeutic role in such patients. ET encompasses passive activities (eg, range-of-motion exercises, neuromuscular electrical stimulation), assisted activities (eg, upper and lower limb-assisted movements), and active activities (eg, respiratory muscle training, standing and walking, or functional activities). ET not only counteracts the physiological consequences of critical illness on physical function and recovery but also exerts positive effects on cognitive and psychological functioning.[84] Mechanistically, early exercise therapy promotes muscle regeneration by activating muscle protein synthesis pathways, such as the mTOR signaling pathway, and inhibiting protein degradation pathways, such as the ubiquitin-proteasome system.[85] Additionally, exercise stimulates satellite cell activity, which is essential for muscle regeneration. Furthermore, exercise has been shown to reduce inflammation,[86] thereby effectively modulating immune function, which is particularly significant for patients experiencing chronic inflammatory states.[87] Receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed-lineage kinase domain-like protein (MLKL) are key components of the necroptosis signaling pathway. Potential small-molecule inhibitors targeting these pathways have been comprehensively reviewed in recent studies.[88] Inhibiting these targets could help to further suppress the progression of inflammation.

Additionally, certain anti-catabolic agents can alleviate the hypercatabolic state in PICS patients and suppress further inflammation. Studies have shown that insulin-like growth factor-1 (IGF-1) can mitigate the hypercatabolic state associated with severe burns.[89] Exogenous testosterone supplementation promotes protein synthesis, reduces protein degradation, and inhibits autophagy through androgen signaling pathways, thereby improving muscle catabolism in patients with severe burns.[90] Mitochondria-targeted antioxidants containing ubiquinone or vitamin E have been employed to counteract excessive reactive oxygen species (ROS) production caused by mitochondrial dysfunction.[91] Among these, mitochondria-targeted ubiquinone (MitQ) has been shown to reduce mitochondrial damage, organ dysfunction, and severe inflammatory responses during the treatment of sepsis in animal models.[92] Melatonin, known for its anti-inflammatory properties, acts as a scavenger of reactive oxygen and nitrogen species. In animal models of sepsis, melatonin has been shown to inhibit mitochondrial damage and stimulate ATP production.[93–95] Another therapeutic strategy involves increasing mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor gamma (PPARγ) agonists, such as pioglitazone and rosiglitazone, or through sirtuin-activating compounds like resveratrol.[93] A systematic review indicated that pioglitazone administration can reduce intramuscular inflammation and increase markers of ATP biosynthesis within muscle tissue.[96] In summary, anabolic and anti-catabolic agents are promising in attenuating the hypercatabolic status in patients with PICS, and further studies on this subject are necessary.

Gastrointestinal Regulation of Inflammation

PICS patients often suffer from varying degrees of gastrointestinal dysfunction, leading to reduced nutrient absorption.[36] Additionally, alterations in both the structure and function of the gut microbiota have been observed in PICS patients, impacting the host's metabolic processes.[37] Malnutrition impairs immune cell metabolism and suppresses the host immune response.[38] In this context, dysfunction in the gut microenvironment may serve as a critical initial event contributing to the vicious cycle of PICS. Over the past few decades, there has been growing interest in modifying

the gut microbiome through fecal microbiota transplantation (FMT), probiotics, or prebiotics to improve outcomes for critically ill patients. Probiotics, thus far the most extensively researched microbiome-based therapy, have shown promise in preventing sepsis. Studies have found that probiotics can help reduce ventilator-associated pneumonia, diarrhea, and infections in critically ill patients requiring mechanical ventilation.[97] Previous research on probiotic interventions has primarily focused on Lactobacillus and Bifidobacterium genera,[98,99] with other probiotics showing potential in animal studies and preclinical research. Recently, Akkermansia muciniphila (Akk), known as a key regulator of chronic systemic inflammation, has gained attention. Both live and pasteurized Akk have been shown to modulate the gut microbiota, reduce serum FD-4 levels, normalize gut mucus thickness, increase goblet cell numbers, and upregulate tight junction protein (claudin-1) expression, thereby enhancing gut mucosal barrier function, restoring gut microecology, and alleviating PICS-related inflammation and multi-organ dysfunction.[100,101] In addition, the nutrition support mentioned above and fecal microbiota transplantation[102] are also important means of promoting the recovery of gut function in patients with PICS.new probiotics such as *Akkermansia muciniphila* have shown potential as therapeutic agents for the treatment of Persistent inflammation-immunosuppression-catabolism syndrome.[100]

Nutritional Support

Nutritional support has become a routine and essential intervention in the treatment of critical illnesses. Appropriate nutritional support has been shown to improve persistent inflammation and gastrointestinal function in patients with post-intensive care syndrome (PICS). The 2016 guidelines from the Society of Critical Care Medicine (SCCM) recommend that early enteral nutrition (EEN), initiated within 48 hours of ICU admission, can benefit critically ill patients by effectively improving nutritional status, alleviating inflammatory responses, preventing bacterial translocation, and mitigating gastrointestinal dysfunction.[103,104] However, recommendations regarding protein intake in ICU patients remain inconsistent. The Protein Summit (2017) suggests that 1.2–2.5 g/kg/day of protein supplementation can preserve muscle mass and reduce mortality in patients with chronic critical illness (CCI).[105] In contrast, the European Society for Clinical Nutrition and Metabolism (ESPEN, 2019) recommends at least 1.3 g/kg/day of protein for critically ill patients.[106] Despite these differences, both guidelines agree that providing more than 1.3 g/kg of protein is a key factor in CCI care, as it improves long-term outcomes and offers benefits for PICS patients. In addition, the selection of an appropriate nutritional strategy is crucial. In recent years, immunonutrition (IED) has become a recommended intervention for many surgical patients to enhance their prognosis.[107] IED, which consists of arginine, glutamine, omega-3 fatty acids, nucleotides, fish oil, and vitamins, has been shown to prevent infections, enhance adaptive immunity, and reduce ICU length of stay.[103] In PICS, arginine depletion may occur due to the expression of arginase-1 induced by the expansion of myeloid-derived suppressor cells (MDSCs). Since lymphocytes cannot proliferate in the absence of arginine, this can lead to immunosuppression and increased infection risk during PICS.[108] Furthermore, omega-3 fatty acids and specialized pro-resolving mediators (SPMs) offer promising therapeutic potential for PICS patients. Omega-3 fatty acids have been reported to regulate inflammatory responses, minimize systemic inflammation, and inhibit oxidative damage.[109] Omega-3 fatty acids are metabolized within the body to produce resolvins, protectins, and maresins, which belong to the family of specialized pro-resolving mediators (SPMs). These mediators facilitate the resolution of inflammation and promote tissue and organ recovery, potentially mitigating the progression of PICS.[110–112]

Conclusion

Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) is a significant subtype of chronic critical illness (CCI) and has posed a substantial challenge in the ICU since it was first identified. This review highlights the sources of persistent inflammation in PICS and suggests that proliferation of bone marrow-derived cells, a hypermetabolic state, and gut dysfunction may serve as key underlying mechanisms of inflammation. Targeted interventions aimed at these pathways hold promise for improving patient outcomes. However, research indicates that inappropriate timing of interventions to block inflammatory mediators may inadvertently stimulate or inhibit other related signaling pathways, potentially leading to adverse effects. Thus, the inflammatory factors in PICS require further investigation. In addition, multimodal therapies—including immunomodulators, anti-inflammatory drugs, anabolic and anti-catabolic agents, antioxidants, microbiome modulators, and nutritional support—are essential and may provide benefit to PICS patients (Figure 2).

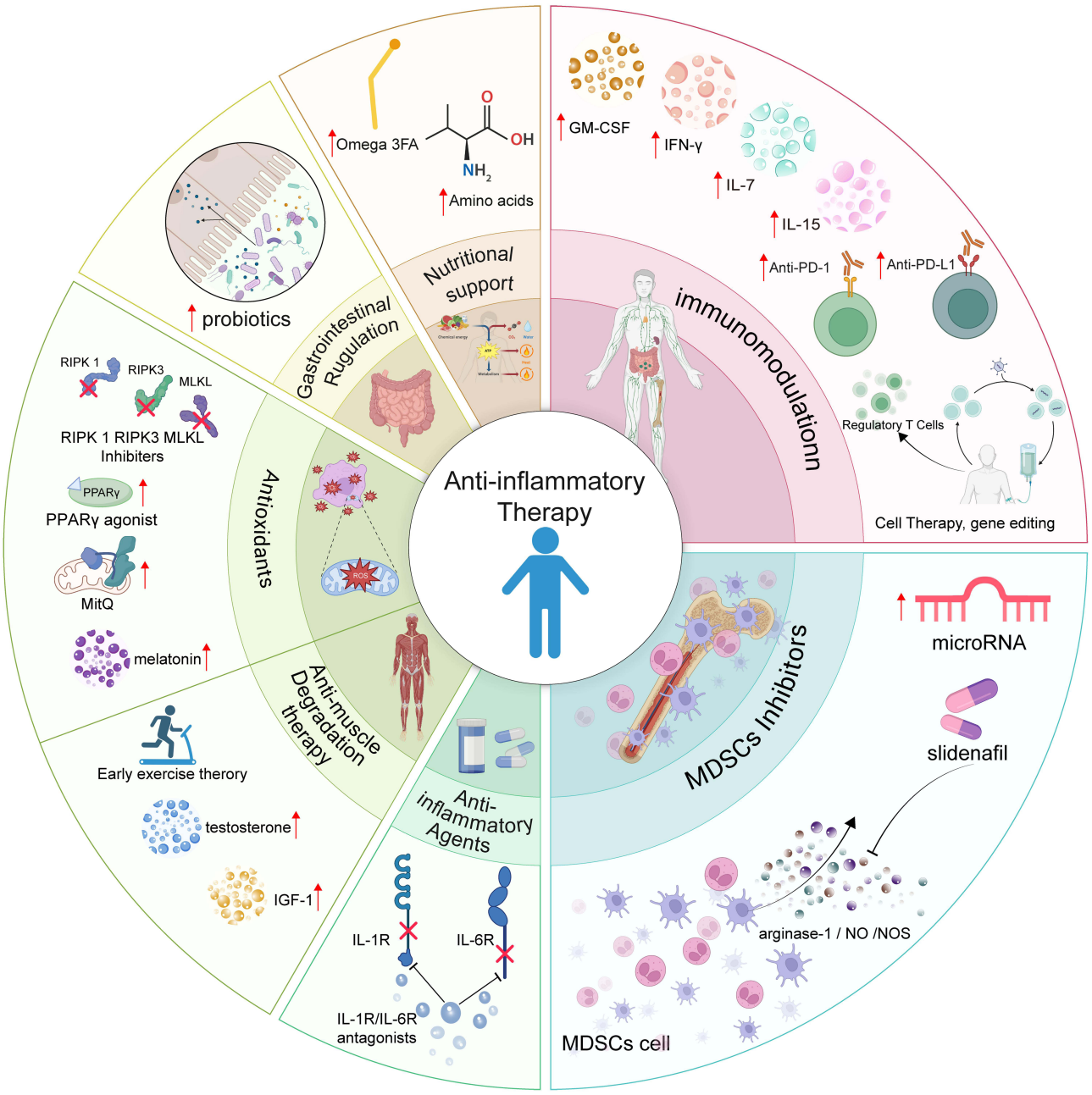

Figure 2 Summary diagram of potential anti-inflammatory treatments for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS). This diagram illustrates a multifaceted approach to anti-inflammatory therapy for PICS, incorporating immunomodulation, nutritional support (amino acids, Omega-3), gastrointestinal regulation (probiotics), antioxidants, and MDSC inhibitors (microRNA, sildenafil, IL-1R/IL-6R antagonists). It also features cell death pathway inhibitors (RIPK1, RIPK3, MLKL) aimed at reducing inflammation. Additionally, the therapy includes immunomodulatory cytokines (GM-CSF, IFN-γ, IL-7, IL-15), cell therapy and gene editing related to the regulatory T Cells, and early exercise therapy as preventative measures. Collectively, these strategies represent comprehensive interventions at the nutritional, immune, and molecular levels to enhance anti-inflammatory effects.

Abbreviations: NOS, nitric oxide synthase; RIPK1, Receptor-interacting protein kinase 1; RIPK3, Receptor-interacting protein kinase 3; MLKL, mixed lineage kinase domain-like protein; IL-1R, interleukin-1 receptor; IL-6R, interleukin-6 receptor; MDSC, myeloid-derived sup-pressor cell; omega-3FA, omega-3 fatty acids; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFN-γ, Interferon-gamma; IL-7, Interleukin-7; IL-15, Interleukin-15; MicroRNA, MicroRNAs; Sildenafil, A phosphodiesterase-5 inhibitor; IGF-1, Insulin-like growth factor-1; PPARγ, Peroxisome proliferator-activated receptor gamma; MitQ, Mitochondria-targeted ubiquinone; Anti-PD-1, Anti-programmed cell death protein 1; Anti-PD-L1, Anti-programmed cell death ligand 1.

Discussion and Outlook

PICS typically occurs in ICU patients following severe trauma or infection, characterized by an initial strong inflammatory and immunosuppressive response, which subsequently transitions into persistent organ damage, sustained

inflammation, and immune suppression, along with continuous muscle loss and poor wound healing. This leads to a reduced quality of life, often requiring long-term care post-discharge, and may ultimately result in chronic wasting and death. The importance and value of defining PICS lie in its provision of an overarching mechanism to explain prolonged low-grade inflammation and adaptive immune suppression, thereby offering a viable direction for clinical treatment. The inflammatory sources in PICS comprise a complex process, including the expansion of myeloid-derived suppressor cells (MDSCs), persistent pro-inflammatory factor release due to DAMP and PAMP recognition and activation, immunosuppression and gastrointestinal dysfunction, with the interactions between these mechanisms still lacking systematic investigation. The timing of immunotherapeutic interventions for patients with PICS (persistent inflammation, immunosuppression, and catabolism syndrome) remains a critical but under-researched area. In the early stages of severe trauma or sepsis, therapeutic interventions are often initiated hours after the rapid activation of innate immune responses, the release of early inflammatory mediators, and the initiation of the inflammatory cascade. This delay often renders single-agent anti-inflammatory therapies ineffective.[113] A meta-analysis conducted by Eichacker demonstrated a positive correlation between the efficacy of anti-TNF-α therapy and mortality in patients with severe sepsis.[114] While anti-TNF -α therapy showed some benefits in the most critically ill patients, it appeared to be harmful in patients with milder conditions.[115] These findings suggest that treatment strategies for PICS patients must take into account the severity of the disease and the phase-specific characteristics of the inflammatory response. Single-targeted anti-inflammatory therapies may fail to meet the complex pathophysiological demands of PICS, as such treatments could further alter the patient's immune state, leading to unpredictable therapeutic outcomes. This phenomenon is primarily due to the unclear understanding of the intrinsic link between persistent inflammation and immunosuppression in PICS. The inflammatory response represents the immune system's reaction to infections or injuries. Without the regulation of immune cells and immune molecules, an inflammatory response cannot occur. The hallmark of PICS is the coexistence of immunosuppression and persistent inflammation. In clinical practice, peripheral blood markers are most commonly used to assess immunosuppression due to their convenience, reliability, and ease of repeated sampling. However, relying solely on peripheral blood data may not fully reflect the systemic immune status. Blood merely serves as a "conduit" for immune cells, whereas many immune responses take place in tissues or organs such as lymph nodes, the spleen, bone marrow, and gut-associated lymphoid tissue. Therefore, relying exclusively on blood markers risks overlooking the dynamic changes within the local immune microenvironment.[116] Complementing peripheral blood assessments with evaluations of immune status in other tissues and sites is critical for a more comprehensive understanding of immune function. This may include histological analysis, immunohistochemistry, and other approaches. Elucidating the relationship between immunosuppression and inflammation in PICS is essential for the implementation of targeted immunomodulatory therapies. Immunosuppression is likely a major cause of recurrent infections and persistent inflammation. Restoring immune homeostasis may represent a key therapeutic strategy for PICS. Meanwhile, anti-inflammatory treatments should focus on restoring organ function to reduce or prevent the release of damage-associated molecular patterns (DAMPs), thereby alleviating inflammation. When immunotherapy is applied in this context, its impact on the inflammatory response must be carefully considered. Ultimately, precise and personalized therapeutic strategies will be critical. The absence of clearly defined diagnostic criteria for PICS underscores the complexities of its pathophysiology and the challenges it presents in treatment. Detection of biological markers related to inflammation, immune suppression, and metabolism such as glucagon-like peptide (GLP-1)[117] may assist clinicians in identifying PICS patients and potentially preventing its onset, although further research is required to identify specific, valuable biomarkers. There are some potential therapeutic approaches for PICS, including probiotics, anakinra, and melatonin, though their clinical efficacy and long-term impact require further investigation. Additionally, the IL-6 inhibitor tocilizumab is still in the early stages of exploration. Future research should focus on further understanding the inflammatory characteristics of PICS, building on current knowledge to establish effective and standardized interventions aimed at improving long-term outcomes.

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Disclosure

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