

Clinical treatment for persistent inflammation, immunosuppression and catabolism syndrome in patients with severe acute pancreatitis (Review)

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Received January 27, 2023; Accepted July 28, 2023

DOI: 10.3892/etm.2023.12194

Abstract. Severe acute pancreatitis (SAP) is a severe disease with a high prevalence and a 3-15% mortality worldwide, and premature activation of zymogen for any reason is the initial factor for the onset of SAP. Gallstone disease and heavy alcohol consumption are the two most common etiologies of SAP. Persistent inflammation, immunosuppression and catabolism syndrome (PICS) is a life-threatening illness, and there are no effective treatments. The relapse state of PICS mainly leads to high mortality due to septic shock or severe trauma, both of which are dangerous and challenging conditions for clinicians. Thus, it is important for medical staff to identify patients at high risk of PICS and to master the prevention and treatment of PICS in patients with SAP. The present review aims to increase the understanding of the pathogenesis of PICS, produce evidence for PICS diagnosis and highlight clinical treatment for PICS in patients with SAP. With this information, clinical workers could implement standardized and integrated measures at an early stage of SAP to stop its progression to PICS.

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1. Introduction

Acute pancreatitis is a common acute abdominal disease characterized by abnormal activation of pancreatic proteases and a secondary local inflammatory response in the pancreas due to multiple etiologies (1). Systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) can occur from onset to 2 weeks after onset (2). Among acute pancreatitis cases, 80% are mild acute pancreatitis and 20% can progress to severe acute pancreatitis (SAP), which can lead to persistent inflammation, immunosuppression and catabolism syndrome (PICS) in the later stage due to abdominal infection (2-3). The immune system is preactivated after the onset of SAP, resulting in SIRS and antagonistic compensatory anti-inflammatory response syndrome (CARS) (4). If the disease is uncontrolled, CARS and SIRS antagonize each other and progressively worsen, resulting in mixed antagonistic response syndrome (MARS) (5). Progression on the 'SIRS-CARS-MARS' immune axis continues, and the control of the proinflammatory response slowly declines, with ~43.1% of patients developing PICS at a later stage (6). The immune model of SIRS-CARS-MARS is formed after trauma. After further development, the advantages of the pro-inflammatory response against the anti-inflammatory response are gradually reversed, and persistent inflammation and severe immunosuppression are finally formed (6). The evolution of PICS is shown in Fig. 1. Organ dysfunction syndrome refers to the occurrence of dysfunction or failure of more than two organs or systems successively or simultaneously after various traumas and infections, so that the body cannot maintain the stability of the internal environment (7). PICS can be regarded as a new clinical subtype of late organ dysfunction syndrome, a chronic critical illness (CCI) characterized by immune paralysis (8). CARS was first used to describe phenomena that could explain the initial response of the host to a variety of infectious and noninfectious conditions (8). CARS was proposed to follow SIRS and appeared to explain this increased susceptibility to

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Key words: SAP, persistent inflammation, immunosuppression, catabolic syndrome, clinical treatment

infection and bimodal distribution of multiorgan failure (4,9). CARS was viewed as progressive suppression in adaptive immunity, resulting in secondary infections (8). PICS came after CARS and was used to summarize the refractory CCI population with immune paralysis as the main feature, which is characterized by persistent severe immune paralysis and high catabolism (7). Even with good treatment and nutritional support, it is inevitable to have repeated nosocomial infection, malnourishment and other problems, which eventually lead to death from chronic organ failure (10). Compared with CARS, PICS has a more complex mechanism and a worse prognosis (11). There are numerous similarities between PICS and CCI, for example, both focus on the pathophysiological process of critically ill patients after 14 days of onset. Inflammation, nutrition and high catabolism are the common concerns of both (10). CCI covers a wider range of problems, including ventilator dependence, brain dysfunction, neuromuscular dysfunction, neuroendocrine disorders and malnutrition, which are related to the chronic phase of critically ill patients (6). PICS focuses on inflammation, immunity and nutrition, which are closely related to infection, and its core feature is immune paralysis. Therefore, to a certain extent, PICS is a special type of CCI, and it is a CCI with immune paralysis (7). Patients with PICS are prone to pulmonary insufficiency, acquired muscle weakness, decreased immunity, malnutrition and dyspnea, which in turn affects the quality of life of patients (11). PICS is the key point difficulty in the clinical treatment of CCI due to its high susceptibility to infection and organ damage and poor prognosis; early warning and treatment of PICS is the key to improve the long-term prognosis of patients with CCI (11). Over the years, previous studies have explored treatment methods for SAP and its complications, which consume enormous medical resources and are associated with prolonged intensive care unit (ICU) hospitalization and poor mortality rates (12,13). The term PICS is used to describe the newly observed phenotypes of persistent inflammation, immunosuppression and proteolytic metabolism, which represents the next challenge in surgical intensive care (11). It is important for clinical staff to establish a collaborative partnership with patients and to help them identify complications. The purpose of the present review is to elucidate the pathogenesis, diagnosis and possible treatment methods of SAP combined with PICS.

2. Pathogenesis of PICS in SAP

Trypsinization. The early activation of the enzyme for any reason is the initiating factor for SAP (13). Abnormal activation of trypsin can not only cause bleeding and necrosis of the pancreas itself but also disrupt the vascular endothelial barrier through venous reflux, causing a large amount of blood to seep out of the blood vessels, leading to capillary leakage syndrome, multiple organ bleeding and abdominal fluid accumulation (13). Some protein kinases can induce the release of various pro-inflammatory factors through transduction signals, regulate inflammatory reactions, promote inflammatory reactions generated by pancreatic enzyme digestion and ultimately lead to PICS (14).

Inflammatory factor release. Activated trypsin can stimulate mononuclear macrophages and damaged pancreatic acini in

the pancreas to produce inflammatory mediators, leading to a cascade of white blood cell overactivation and increased inflammatory mediators levels referred to as the ‘waterfall effect’ (13). If not corrected in a timely manner, the ‘waterfall effect’ can further develop into a persistent inflammatory response state, ultimately leading to PICS (14). TNF- α and IL-6 are the earliest and core inflammatory factors that are upregulated during the onset of acute pancreatitis (15). They can act on various inflammatory cells, promote the release of inflammatory mediators such as IL-1 and IL-8, exacerbate inflammatory reactions, and cause tissue damage (14).

Immunosuppression. In the early stage of SAP, the body is in a state of coexistence of SIRS and CARS, which is a mixed type of anti-inflammatory response syndrome, leading to immune suppression (16). With the progression of SAP, the number of peripheral blood CD4⁺ T lymphocytes and the CD4⁺/CD8⁺ ratio decreases, the balance of T helper (Th)1/Th2 cells shifts in the direction of Th2 cells, and when Th2 cells are dominant, they secrete inflammatory response inhibitors such as IL-4 and IL-10, which leads to a decline in cellular immune function, a systemic inflammatory response state, and PICS (17,18). In patients with SAP, the expression of human leukocyte antigen on the surface of monocyte macrophages is markedly reduced, antigen presentation is impaired, and the levels of the proinflammatory factors IL-1 and IL-6 are reduced, all of which impair the activation of the immune response of the body, leading to immunosuppression (19).

Intestinal bacterial translocation. Intestinal bacterial translocation is the main cause of SAP, and the destruction of the intestinal barrier is a prerequisite for bacterial translocation (20). The main mechanisms of intestinal bacterial translocation are intestinal wall ischemia, hypoxia and ischemia-reperfusion injury (20). Following the translocation of intestinal bacteria and their endotoxin, the activated mononuclear-macrophages are further stimulated to produce more inflammatory factors, which constitute a ‘second strike’ to organs such as the pancreas and even aggravate MODS (13,21). Inflammatory factors produced by intestinal bacterial translocation and MODS aggravate each other, forming a vicious cycle and exacerbating the sustained inflammatory response state of the body, eventually leading to PICS (21).

Microcirculation disturbance. Early SAP is often accompanied by pathological changes, including capillary ischemia, increased permeability and microthrombus formation (13). Excessive activation of neutrophils and macrophages promotes the secretion of inflammatory factors, which not only induces capillary leakage syndrome but also disrupts the endothelial function of capillaries, leading to impaired coagulation mechanisms. This is closely related to inflammatory cascade reactions, including coagulation factor Xa promoting the excessive release of inflammatory factors such as IL-6 and IL-8, increasing the number of adhesion factors, and activating inflammatory reactions (13). When the pancreatic artery is complicated with spasm and embolism, it can lead to ischemia and necrosis of the pancreatic segment supplied by the blood vessel, resulting in microcirculation disturbance (13).

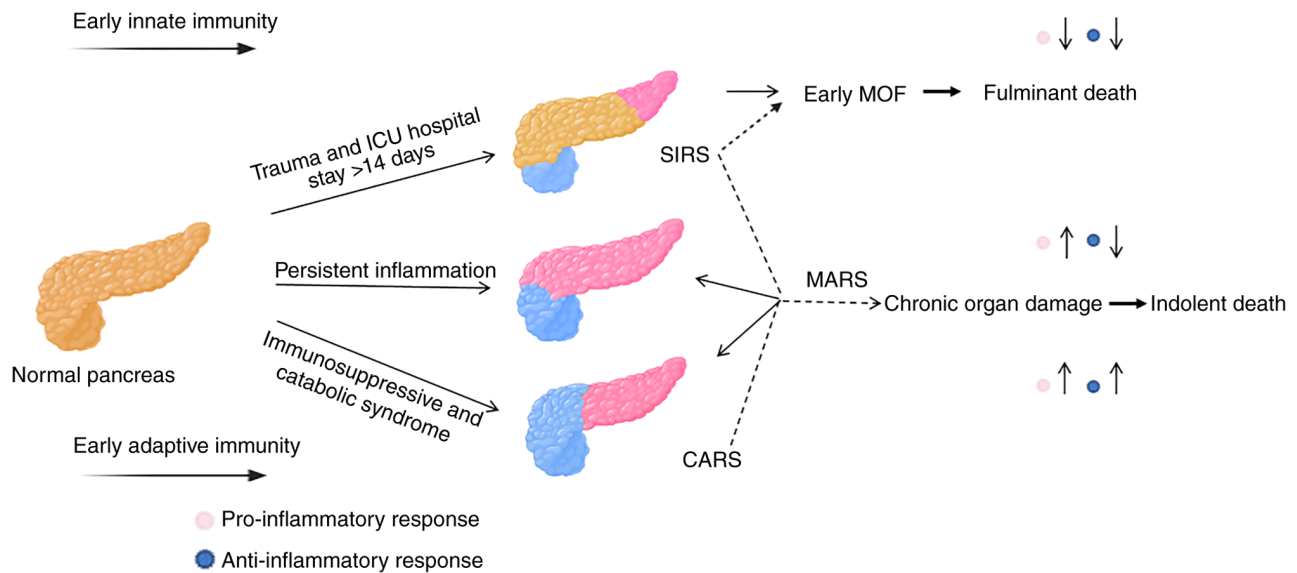


Figure 1. Evolution of persistent inflammation, immunosuppression and catabolism syndrome in severe acute pancreatitis. CARS, compensatory anti-inflammatory response syndrome; ICU, intensive care unit; MARS, mixed antagonistic response syndrome; MOF, multiorgan failure; SIRS, systemic inflammatory response syndrome.

Internal relationship. Patients with PICS have impaired immune function, which makes it difficult to clear infectious pathogens or induce recurrent infections. Multidrug-resistant infections often occur, resulting in pathogen-associated molecular patterns (PAMP) or persistent antigen release. Furthermore, PAMP or antigen acts on the pattern recognition receptors (PRR) of immune cells or induces adaptive immune activation, leading to a persistent inflammatory response (22). When the inflammatory response persists, not only a large number of pro-inflammatory factors are released, but also anti-inflammatory factors and high expression of immunosuppressive molecules are secreted to try to restore the balance with the pro-inflammatory response (23). However, improper synthesis, secretion or expression of these anti-inflammatory factors and immunosuppressive molecules can lead to or aggravate the immunosuppression of the body (23). Myeloid-derived suppressor cells are an important mechanism mediating immune dysfunction in PICS (24). When activated, myeloid-derived suppressor cells synthesize a large amount of $\text{TNF-}\alpha$, IL-10 , nitric oxide and reactive oxygen species, inhibits the function of various T cells (mainly CD4^+ and CD8^+ T cells), promotes the proliferation of regulatory T cells, and exerts pro-inflammatory and immunosuppressive effects (22,25). Clarifying the relationship between immunity and inflammation in PICS is crucial for the implementation of goal-directed immunomodulatory therapy targets. Persistent inflammation in PICS can lead to the imbalance of substance and energy metabolism. During inflammation, a large number of cytokines and stress-related hormones are released, resulting in high catabolism, increased energy consumption and muscle protein decomposition. High catabolism is mainly manifested as malnutrition, weight loss and hypoproteinemia (11). Pro-inflammatory cytokines can act on mitochondria to reduce the activity of respiratory chain enzymes, resulting in insufficient energy metabolism, reduced production of adenosine triphosphate, and aggravation of the imbalance of

energy supply and demand, which may lead to tissue and cell damage (26,27). High catabolism leads to muscle protein and fat decomposition, muscle atrophy, and muscle weakness (11). Tissue decomposition can induce the release of damage associated molecular patterns (DAMP) and induce the inflammatory response via the DAMP-pattern recognition receptors (PRRs) signaling pathway (28,29). Therefore, regulation of inflammation and intervention of metabolism are expected to become novel targets for PICS treatment. Metabolic abnormalities in PICS are not only limited to solid cells in organs and tissues of the whole body, but also involve various immune cells (30). A previous study (31) has reported that after peripheral blood monocytes were incubated with lipopolysaccharide or *Candida albicans*, not only was the secretion of $\text{TNF-}\alpha$, $\text{IL-1}\beta$ and IL-6 markedly reduced, but the activities of the glycolysis pathway, oxidative phosphorylation and fatty acid β oxidation pathway of monocytes were also markedly reduced, and the metabolic pathway activity was restored after recovery. Patients with malnutrition lack the corresponding metabolic substrates and enzymes, resulting in insufficient ATP production and aggravating immunosuppression (32). Immune imbalance in PICS can induce metabolic disorders (30). Abnormal metabolism of immune cells may mediate immune inflammatory response disorders; however, to the best of our knowledge, the metabolic patterns of immune cells in PICS, such as metabolic substrates, pathways, key enzymes and regulatory mechanisms, remain to be elucidated. Targeted intervention of immune cell metabolic molecules may open up a novel field of immunomodulatory therapy.

3. Diagnosis

Due to advances in intensive care technology, an increasing number of patients with SAP have avoided early death (33). However, despite the comprehensive treatment of active nutritional support and minimally invasive or surgical drainage,

Table I. Clinical determinants of PICS.

Diagnostic criteria	Numerical value	Existing problems of diagnostic criteria	Suggestion
ICU hospitalization days	Prolonged hospitalization >14 days (6,11)	ICU time is not uniform (40)	Evidence-based medicine may be used to clarify the issue of ICU length of stay, such as meta-analysis

PICS, persistent inflammation, immunosuppression and catabolism syndrome; ICU, intensive care unit.

there are still critically ill patients who stay in the ICU for a prolonged period of time and develop CCI (11). Therefore, identifying and appropriately managing patients at high risk of death directly affects the prognosis of PICS (34). Elderly patients with systemic infection and severe trauma are at high risk of PICS (35). Elderly individuals are susceptible to PICS due to multiple common diseases and a gradual decline in immune function as they age (6,36). Therefore, with an aging population, PICS will become a novel challenge for critically ill patients. In addition, patients with obesity and biliary pancreatitis have a higher incidence of PICS than patients with pancreatitis of other etiologies (34,37). Patients with SAP require long-term supportive care in the ICU and are prone to ventilator dependency and malnutrition, which mainly presents with recurrent nosocomial infections, acquired debility, cognitive dysfunction and psychosomatic impairment (anxiety, depression and sleep disorders) (38). The diagnosis of PICS relies on the following four indicators (Table I) (6,11,39,40): i) ICU hospitalization >14 days; ii) persistent inflammatory response: C-reactive protein (CRP) >3.0 mg/dl or retinol-binding protein <10 mg/l; iii) immunosuppression: Lymphocyte count <0.80x10⁹/liter; and iv) catabolism: Serum albumin <30 g/l, prealbumin <10 mg/dl, creatinine/height index <80% or body mass decline during hospitalization >10% or body mass index <18 kg/m². The diagnostic criteria for PICS have not been standardized (41), and PICS symptoms are numerous but nonspecific. The selection of current indicators, such as C-reactive protein, lymphocytes, neutrophils and albumin, is reasonable although it has a certain degree of subjectivity. One study applied this diagnosis in examining outcomes of SAP (14). Another study reported that the criterion of day 14 CRP for PICS should be 3.0 mg/dl with lower Barthel Index, albumin and total lymphocyte counts (39). We hypothesized that PICS diagnosis needs to satisfy at least one of each aspect. ICU stay >14 days is a prerequisite, inflammatory indicators such as CRP, immunosuppression indicators such as lymphocytes and catabolism indicators such as prealbumin should also be present. Molecular biology detection technology has made great progress, and the determination of the inflammatory response and immune status could be realized by direct detection at the cellular and molecular levels (42). Enzyme-linked immunosorbent assays (ELISA) could reflect the inflammatory state of the body by directly detecting the expression levels of IL-6, IL-10, IL-1 receptor antagonist and soluble tumor necrosis factor receptor 1 in plasma (43). Flow cytometry could make the phenotype of the microcytic population clearer than can ELISA and further

improve the observation index of PICS (44). These methods may help identify PICS early. In clinical practice, the diagnosis of PICS should be based on laboratory tests and clinical manifestations. Larger samples and more rigorous prospective studies are required in the future (11). Therefore, clinical staff should pay attention to the etiology and severity of SAP and lymphocyte count measurements (6). In addition, they should strengthen symptom recognition in patients with SAP to raise awareness of self-monitoring and avoid worsening of symptoms.

4. Importance of clinical treatment for PICS

Patients with PICS experience a multi-level and multi-step cycle of immunosuppression, persistent inflammation and high metabolic rate, which eventually affects the outcome of disease, leading to a long hospital stay and poor clinical prognosis (3). Therefore, it is necessary to investigate PICS prevention, early identification and timely intervention (45). However, a survey on the readiness for discharge of patients with SAP indicated that the readiness for discharge of patients with SAP is low (46). Clinical staff should have an understanding of PICS, know the early warning of high-risk patients and strengthen health education during hospitalization, which can improve compliance and help in managing PICS.

5. Clinical treatments for PICS in patients with SAP

There is a complex interactive dialogue among immunosuppression, persistent inflammation and hypercatabolism in patients with PICS (11). The body undergoes a cycle of immunosuppression, repeated infection, persistent inflammation and hypercatabolism, which ultimately affects the outcome of patients with PICS, leading to a long hospital stay and poor clinical prognosis (3). It is important to determine how to carry out early warning, risk stratification and prognosis assessment for patients with PICS. The Modified Early Warning Score (MEWS) is an objective indicator tool that can be used for early warning of patients and rapid assessment of the severity and potential changes in the condition (47). It evaluates the condition of the patient by scoring five indicators, including heart rate, systolic blood pressure, respiratory rate, temperature and consciousness, and assigns certain scores to physiological indicators within a certain range (47). The temperature is scored as 0-2 points and the other items are scored as 0-3 points and the maximum possible score was 14. The higher the score, the more serious the condition of the patient. It is of great

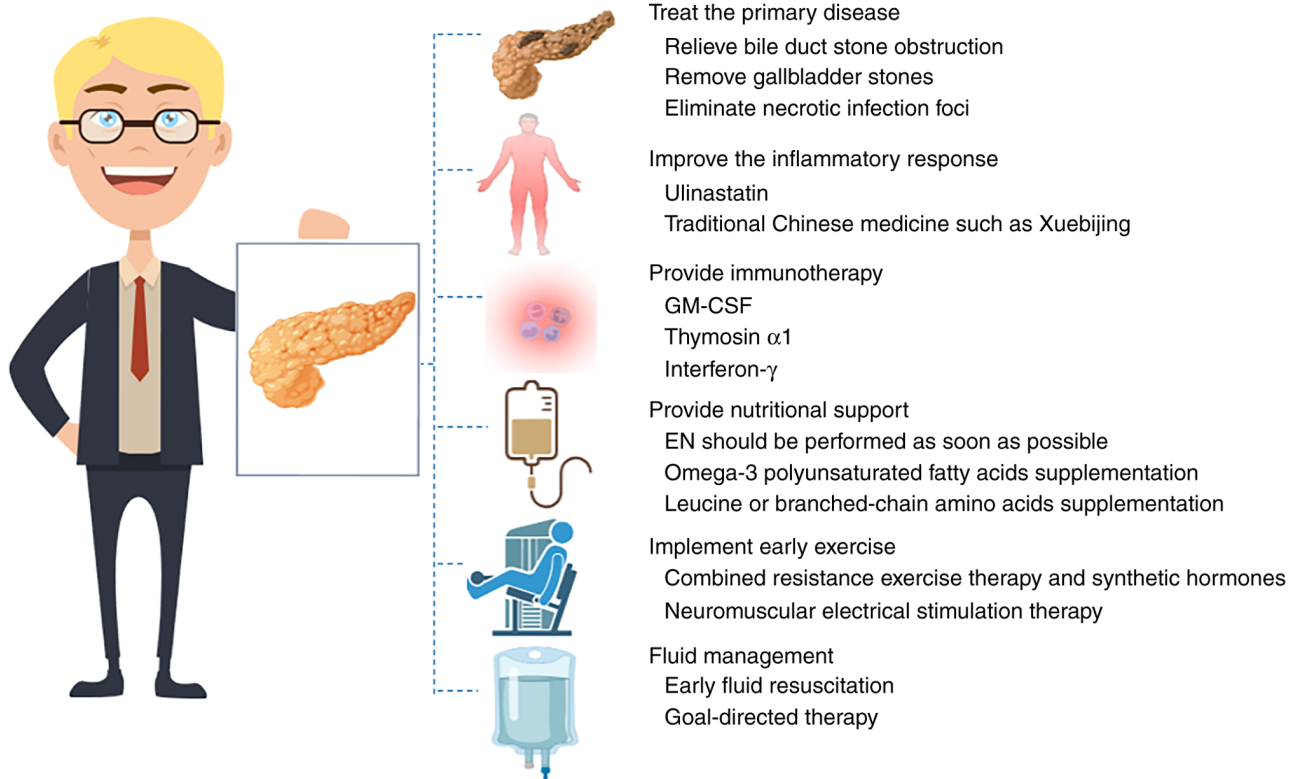


Figure 2. Interventions for persistent inflammation, immunosuppression and catabolism syndrome. EN, enteral nutrition; GM-CSF, granulocyte-macrophage colony stimulating factor.

significance for identifying potentially critical patients (48,49). The combination of MEWS and some related indicators such as serological indicators, inflammatory factors, acute physiology of intra-abdominal pressure and chronic health score (APACHE) IIScore, sequential organ failure (SOFA) score, CRP, pro-calcitonin and Bedside Index for Severity, improves the prediction of the severity and prognosis of patients with PICS. The possible treatment measures targeting the pathogenesis are shown in Fig. 2 and the possible pathogenesis and corresponding treatment methods are summarized in Table SI.

Treat the primary disease. Several studies (50,51) have demonstrated that the mortality rate of SAP ranges between 10 and 33%. Peripancreatic necrotic infection is the main cause of death (37), which may occur in the later stage of the disease and is also a major contributor to PICS. Active treatment of primary disease should be implemented to weaken SIRS in patients with SAP, thereby preventing secondary PICS (37). For patients with bile duct stone obstruction, the obstruction should promptly be relieved (37). Individuals with gallbladder stones should undergo cholecystectomy as soon as possible once the condition is under control (13). Patients afflicted with necrotizing acute pancreatitis can be treated with necrotic tissue removal surgery (13). Individuals suffering from hyperlipidemic SAP should avoid fat emulsions and refrain from utilizing medications that may potentially elevate blood lipids (13). Small dosages of such drugs are recommended. Hypercalcaemia SAP is frequently associated with hyperparathyroidism, which requires calcitonin therapy (37). Symptomatic treatment should be provided

for patients with pancreatic anatomical and physiological abnormalities, medication-induced conditions and pancreatic tumors (37). Furthermore, for patients with co-infections, it is imperative to actively eliminate necrotic infection foci and enhance drainage care through appropriate fixation of the drainage tube and improved quality of care (37). This not only ensures efficient drainage and mitigates inflammation but also reduces recurrence rates and enhances the quality of life of patients (13).

Improve the inflammatory response. At present, there is no effective approach to mitigate PICS by inhibiting the systemic proinflammatory response from the source (11). The primary obstacle lies in the rapidity of innate immune response and the difficulty of intercepting early-stage release of inflammatory factors or maintaining optimal levels thereof (52). Nevertheless, certain medications may be explored as potential remedies. Ulinastatin is a versatile protease inhibitor that stabilizes lysosomal membranes, antagonizes oxygen free radicals, regulates the release of inflammatory factors and promotes recovery of specific immune functions (53). It has been widely used in the treatment of SAP. A study established a rat SAP model to investigate the therapeutic efficacy of ulinastatin, and the results demonstrated that ulinastatin effectively suppressed the expression of inflammatory factors such as TNF- α , IL-1 and IL-6, which subsequently mitigated the inflammatory response of the body and enhanced the survival rate of rats (54). Some traditional Chinese medicine preparations, such as safflower flavin A in Xuebijing injection (55), have been demonstrated to effectively inhibit the activity of the transcription factor κ B

signaling pathway and reduce endotoxin levels. This can help alleviate SAP symptoms by reducing inflammatory factors and delaying the progression of PICS (55,56).

Provide immunotherapy. Immunomodulatory imbalance in the body is an important cause of death in patients with SAP with PICS (24). Immunotherapy focuses on restoring the homeostasis of the immune system (57). PICS is associated with alterations in immune effector cells, and acquired immune agonists can be utilized for the treatment of immunosuppression (24). Several studies on immunomodulatory therapy have demonstrated the beneficial effects of granulocyte-macrophage colony stimulating factor (GM-CSF), thymosin $\alpha 1$, IL-7, IL-15, programmed cell death protein 1/programmed death-ligand 1 antibody, anti-cytotoxic T-lymphocyte-associated protein 4 antibody, anti-lymphocyte activation gene 3 antibody, anti-T lymphocyte immunoglobulin mucin 3 antibody and interferon- γ in enhancing the immune function of patients (19,58). Thymosin $\alpha 1$ is a bioactive peptide secreted by the thymus gland, which can induce T lymphocyte differentiation and maturation, enhance the phagocytic function of monocytes and macrophages, promote the activation, proliferation and antigen presentation function of dendritic cells, and regulate immune balance (59). GM-CSF is a powerful immune stimulator (60). When combined with its receptor, it can not only promote the proliferation and differentiation of hematopoietic progenitor cells, and enhance hematopoietic function, but also regulate the proliferation and differentiation of monocyte macrophages and dendritic cells to serve an immunoregulatory role (61). Interferon- γ is an inflammatory factor, which can induce the expression of major histocompatibility complex I and II, activate monocyte macrophages and natural killer cells, and regulate the function of dendritic cells and B lymphocytes (62). Interferon- γ combined with granulocyte macrophage colony-stimulating factor can markedly reduce the serum TNF- α level, and improve monocyte macrophage dysfunction and the immunosuppression status (58). These results suggest that immunotherapy may become a key approach for the treatment of patients with SAP with PICS. It has been found (63,64) that continuous blood purification (CBP) therapy can rapidly and effectively improve the condition of patients with SAP, mainly by correcting acid-base balance disorders, removing excessive inflammatory factors in the body, and maintaining the homeostasis of the immune system of the body. However, the timing and effect of CBP in treating SAP remain contentious (63). Excessive reliance on CBP may even heighten the risk of infection (65). Therefore, CBP should be used in moderation according to the condition of the patient. Furthermore, during the implementation of CBP, it is customary to employ anticoagulation measures to ensure CBP vascular access patency. Heparin and sodium citrate solution are the two main tube sealing solutions in clinical practice. The catheter will be pumped back before the central venous catheter and the pumping volume is mainly twice the catheter capacity (66). The pulse tube flushing technique combined with the positive pressure tube sealing technique is used to seal the tube to reduce the blood return of the catheter lumen (67). Through effective anticoagulant care, the effect of CBP is ensured, which can reduce the

inflammatory response of the patient, enhance the immune function and improve survival rates (68).

Provide nutritional support. Patients with SAP and with PICS enter a state of continuous consumption early, and the duration of catabolism is longer than that of anabolism (11). Based on the pathogenesis of PICS, nutritional support is an important part of the treatment of PICS (10). At present, there is no unified standard for nutritional support plans for patients with SAP with PICS. Research results have demonstrated that in patients with severe infections and persistent inflammatory status similar to SAP pathological changes, administering enteral nutrition (EN) preparations rich in fat and protein could markedly reduce serum TNF- α , IL-6 and IL-8 levels, inhibit early inflammatory reactions and improve immune status (69). An increasing number of studies have demonstrated that EN can not only provide essential nutrients but also help improve intestinal mucosal barrier function, reduce endotoxin and bacterial translocation, and alleviate the inflammatory response (50,51). It was hypothesized that EN should be performed as soon as possible for patients without contraindications, and the transition from parenteral nutrition to EN should be performed as soon as possible for patients with contraindications after the body function recovers because the severity of systemic immunosuppression can be reduced (70). Patients with high nutritional risk (The Nutrition Risk in Critically ill score ≥ 5) and malnutrition should supplement EN within 2-3 days to achieve calorie and protein levels $>80\%$ of the target value. After 7-10 days, if the energy level does not meet the standard, supplementation of parenteral nutrition should be considered (71). A prospective randomized controlled study (10) has indicated that early and rational EN (with special attention to protein intake) markedly reduced the incidence of SAP with PICS. However, there are differences in the recommended guidelines such as ESPEN Guidelines and The 2016 American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine (ASPEN/SCCM) guidelines for protein intake in patients in the ICU (70,72). A protein summit recommends that protein supplementation of 1.2-2.5 g/kg/day can reduce the mortality of critically ill patients (73). It has been previously suggested that supplementation with higher proteins inhibits endogenous protein breakdown in a dose-dependent manner (74). Enteral immunomicroecological nutrition can effectively improve the nutritional status of patients with PICS, protect their intestinal barrier function and improve immune function, which is conducive to preventing patient regression and improving prognosis (7). A meta-analysis has demonstrated that supplementation of parenteral nutrition with omega-3 polyunsaturated fatty acids reduced the 28-day mortality and length of ICU stay in patients with sepsis (75). Leucine supplementation can improve muscle protein synthesis by stimulating the mTOR signaling pathway in elderly patients (≥ 60 years) and patients with cancer (24). Therefore, the addition of leucine or branched-chain amino acids to nutritional support may be beneficial for patients with SAP with PICS. Furthermore, compounds derived from natural products with antiviral activity and antioxidant activity, such as oligosaccharides, can also be used to attempt adjuvant therapy (76). However, EN often leads to symptoms of feeding intolerance (77). Therefore,

more attention should be paid to possible risk factors, such as APACHE and whether soluble fiber serum albumin is added, while performing effective EN nursing (78,79). It has also been demonstrated that there is an association between the nutrition infusion rate and symptoms of feeding intolerance (80). The guidelines of the American Society for Parenteral and Enteral Nutrition recommend that when the intra-abdominal pressure of the patient is 12-15 mmHg, routine EN should be continued, when the intra-abdominal pressure is 16-20 mmHg or continuously increased, nutritional feeding should be adopted, and when the intra-abdominal pressure is >20 mmHg, EN should be suspended (72).

Implement early exercise. In critically ill patients, the quadriceps femoris cross-sectional area can be reduced after the onset of the disease (81). Severe muscle decomposition is accompanied by the decline of body movement and organ function and is closely related to the increase in mortality (81). Early activity and resistance exercise are important to prevent the loss of fat-free mass, strength failure and loss of function in patients with PICS (82,83). After evaluating the cardiopulmonary function of patients, they can be encouraged to carry out appropriate physical recovery exercise, supplemented by psychological counseling when necessary (84). Combined resistance exercise therapy and synthetic hormones can effectively inhibit muscle breakdown and even reverse muscle loss in patients (85). In addition, a study has found that neuromuscular electrical stimulation therapy was helpful in stimulating muscle protein synthesis and relieving disuse muscle atrophy (86). Clinicians should pay attention to the fact that excessive sedation is often an important factor for long-term bed-rest and ventilator dependence in patients with PICS (87). In clinical practice, it is best to implement continuous intravenous drip or syringe pump administration managed by bedside nurses to control the depth of sedation to ensure that patients are in a light sedation state, and can wake up at any time and carry out corresponding physical rehabilitation activities (88).

Fluid management should be emphasized. Fluid resuscitation is the key to the early treatment of SAP with PICS. Severe blood volume deficiency within 72 h after SAP onset can rapidly activate the renin-angiotensin-aldosterone system and cause sympathetic nervous system excitement, thus it is critical that we get the timing right for fluid resuscitation (89). Isotonic crystals are the preferred liquid and the rate of fluid infusion ($5-10 \text{ ml} \cdot \text{kg}^{-1} \text{ h}^{-1}$) should be strictly controlled (90). Early fluid resuscitation can use an infusion pump to continuously infuse at a constant rate, and the nurse should dynamically monitor the amount of inflow and outflow (91). Early goal-directed therapy (92) is recommended for initial fluid management in SAP, which achieves resuscitation goals within 6 h, including central venous pressure of 8-12 mmHg, mean arterial pressure $\geq 65 \text{ mmHg}$, hourly urine volume $\geq 0.5 \text{ ml/kg}$ and central venous oxygen saturation $\geq 70\%$. However, there is a debate about how to perform early resuscitation (93). Patients with early shock begin infusion at a rate of 150-600 ml/h and appropriate fluid replacement (130-150 ml/h) is applied for non-dehydrated patients. However, for patients with organ failure, it is necessary to evaluate the circulatory capacity before determining the infusion speed. For most patients, the

total infusion volume of 2,500-4,000 ml is enough to reach the recovery goal within the first 24 h. Effective fluid management can reduce the inflammatory response of the patient, enhance immune function and improve survival rates (94). Furthermore, microcirculatory monitoring can help diagnose occult shock (95). Compared with standard hemodynamic guided treatment, patients with septic shock who undergo resuscitation based on peripheral perfusion indicators have a lower infusion volume, shorter hospital stay, lower mortality rate and lower scores of SOFA (95). Corresponding clinical studies have demonstrated the type of fluid resuscitation, starting time, speed and target of fluid resuscitation (93,96,97); however, the specific plan needs to be carried out in clinical practice combined with monitoring. Fluid resuscitation for SAP with PICS follows the principle of 'timely and sufficient but not excessive'. It is important to carry out multi-center studies to provide a suitable resuscitation protocol for SAP with PICS.

6. Conclusions

The present review highlights the importance of clinical treatment for patients with SAP with PICS. Although the pathophysiological mechanism of PICS has not been elucidated, most scholars hypothesize that it is preventable and treatable. Therefore, it is important for medical staff to identify populations at high risk of PICS and to master the prevention and treatment of patients with SAP with PICS.

The selection of appropriate patients for rigorously designed controlled studies, clinical evaluation of existing diagnostic criteria and screening of novel specific biomarkers are crucial for accurate early warning and prognostic assessment of PICS. Ultimately, under the guidance of high-level evidence, treatment should move from experience to standardization to achieve goal-oriented precision treatment, and standardized and integrated measures could be taken at an early stage of SAP to stop its progression to PICS, which is of great significance for improving the long-term prognosis of patients with CCI.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82072699).

Availability of data and materials

Not applicable.

Authors' contributions

BZ, QX, QM and LH conceived, drafted and directed the study. BZ, QX and LH designed the study. BZ, QX, QM and LH wrote the article. BZ, QX, QM and LH critically revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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