ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 November 14; 30(42): 4518-4596

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 42 November 14, 2024

World Journal of Gastroenterology

Weekly Volume 30 Number 42 November 14, 2024

Contents

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
November 14, 2024

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World J Gastroenterol 2024 November 14; 30(42): 4518-4522

DOI: 10.3748/wjg.v30.i42.4518

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Sepsis-associated liver injury: Mechanisms and potential therapeutic targets

Jia-Wen Chen, Chen-Yi Liu, Shu Li, Shi-Wen Wu, Chao Cai, Ming-Qin Lu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Liu YQ

Received: September 5, 2024

Revised: September 20, 2024

Accepted: September 26, 2024

Published online: November 14, 2024

Processing time: 55 Days and 21.4 Hours

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Abstract

In this editorial, we examined a recent article in the *World Journal of Gastroenterology* that focused on sepsis-associated liver injury (SLI) and its treatment. SLI is a serious complication of sepsis, primarily caused by microcirculatory disturbances, the gut-liver axis, and inflammatory responses. Specific treatment recommendations for SLI are lacking. The gut-liver axis represents a potential therapeutic target, with metformin showing promise in modulating the gut microbiome and enhancing intestinal barrier function. Although immunomodulatory therapies are being explored, anti-tumor necrosis factor agents and interleukin-1 receptor antagonists have not demonstrated significant clinical benefits. Statins may reduce liver inflammation and prevent injury in sepsis, but their clinical application is limited. Reduced D-related human leucocyte antigen expression on monocytes and lymphocytes suggests immune suppression in patients, indicating that corticosteroids could reverse clinical deterioration in severe infections and address adrenal cortical insufficiency. Current large-scale studies on glucocorticoid therapy for sepsis have yielded mixed results, likely due to inadequate assessment of the immune status of the host. Future research should prioritize the development of personalized immunotherapy tailored to patients' immune profiles, focusing on identifying novel indicators of immune status and advancing immunomodulatory targets and therapeutics for septic patients.

Key Words: Sepsis; Sepsis-associated liver injury; Gut-liver axis; Immunosuppression; Inflammation; Immune dysregulation; Glucocorticoid; Adrenal cortical insufficiency

Core Tip: Immunosuppression is a key aspect of progressive sepsis. Assessing this state is crucial for managing sepsis-associated liver injury and guiding therapeutic choices. Suppression of D-related human leucocyte antigen expression, along with changes in clinical presentation and tests, may indicate an immunosuppressive phase. Hormonal interventions based on D-related human leucocyte antigen levels could potentially alter outcomes in severe infections. However, large-scale studies on glucocorticoid therapy for sepsis show inconsistent results, likely due to inadequate assessment of the immune status of the host.

Citation: Chen JW, Liu CY, Li S, Wu SW, Cai C, Lu MQ. Sepsis-associated liver injury: Mechanisms and potential therapeutic targets. *World J Gastroenterol* 2024; 30(42): 4518-4522
URL: https://www.wjgnet.com/1007-9327/full/v30/i42/4518.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i42.4518

INTRODUCTION

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection, with high global incidence and mortality rates. Sepsis-associated liver injury (SLI) is a severe and common complication of sepsis, occurring in approximately 34% to 46% of patients. Although the liver possesses strong regenerative capacity and resilience against insults, the incidence of SLI remains lower than that of other organs. However, the mortality rate associated with SLI can be as high as 54% to 68%, significantly exceeding the mortality rates of patients with pulmonary dysfunction or failure, which are among the most commonly affected organs in sepsis[1]. Recently, Zhang *et al*[2] employed bibliometric methods to review research on SLI, summarizing its pathogenic mechanisms, signaling pathways, potential therapeutic targets, and possible treatment options. This article briefly discussed the pathogenic mechanisms of SLI as well as its therapeutic approaches and medications.

THE PATHOGENIC MECHANISMS UNDERLYING SLI

The pathogenic mechanisms underlying SLI are highly complex, with current theories primarily encompassing circulatory disturbances, inflammation, immune responses, and the gut-liver axis, among other factors. Notably, the mechanisms related to the gut-liver axis and inflammatory immune responses are receiving increasing attention.

During sepsis, hemodynamic disturbances in microcirculation and the inflammatory response result in increased vascular permeability and coagulopathy in the liver. This cascade of events leads to reduced hepatic blood perfusion and alterations in liver microcirculation and blood flow[3]. Ischemia-reperfusion and the influence of inflammatory mediators can cause damage and necrosis in hepatocytes, potentially resulting in liver failure. Additionally, the liver may initiate its own inflammatory response during sepsis, which can trigger complications such as hepatitis and liver fibrosis.

Increased levels of inflammatory cytokines, a diminished ability to clear bacteria, and the accumulation of metabolic products can lead to dysbiosis of the gut microbiota and disruption of the intestinal mucosal barrier[4] in the course of sepsis. Bacterial translocation and the resulting intestinal inflammation can trigger a systemic inflammatory response and acute liver injury. When the liver experiences inappropriate immune responses or overwhelming inflammation, its impaired ability to clear pathogens and metabolic dysfunction may further exacerbate damage to the intestinal barrier, leading to additional disruption of the gut microbiota[1]. Zhang *et al*[2] noted in their study that multiple articles have identified the gut-liver axis as a potential target for therapeutic intervention; simultaneously, the gut microbiota is considered an upstream regulatory factor in liver injury induced by polymicrobial sepsis, providing new insights for the treatment of SLI.

Zhang *et al*[2], in their study of SLI, found that frequently cited high-frequency keywords included tumor necrosis factor (TNF)-α, inflammation, oxidative stress, and NF-κB. All these keywords revolve around one important kind of molecule: Cytokines. The cytokines can be classified into two main categories: Immune-activating and immune-suppressive. However, in patients with sepsis, there is often an imbalance between immune-activating and immune-suppressive cytokines. Immune-activating cytokines can interact with transcription factors, further promoting the production of proinflammatory mediators through multiple signaling pathways and exacerbating tissue inflammatory damage.

Zhang *et al*[2] also discovered that NF-κB is a crucial intracellular nuclear transcription factor that regulates the transcription of various proinflammatory cytokine genes and serves as the most important trigger of inflammatory signaling pathways. As the disease progresses, excessively high levels of immune-activating cytokines can cause immune cell exhaustion, gradually leading the body into an immunosuppressive state, resulting in further uncontrolled inflammation. Immunosuppression is an important hallmark of progressive sepsis, characterized by decreased numbers of active immune cells and impaired function[5]. This suppression reduces the body's resistance to infection, making the liver more susceptible to bacterial, viral, or fungal infections, thereby triggering liver inflammation and damage. Furthermore, the release of inhibitory cytokines and the dysregulation of both the innate and adaptive immune systems also contribute to sepsis-induced immune dysregulation[6].

The literature indicates that in sepsis, hypoxic hepatitis and sepsis-induced cholestasis can lead to liver injury and subsequent dysfunction. Profound hemodynamic alterations, microthrombi formation, sinusoidal obstruction, and endothelial dysfunction impair liver perfusion, resulting in liver damage and hypoxic hepatitis. The definition of sepsis-induced cholestasis has not yet been standardized, and its prognostic relevance remains unclear. Sepsis-induced cholestasis is understood as impaired bile formation and defective flow caused by non-obstructive intrahepatic injury. Animal model studies have suggested that proinflammatory cytokines alter the expression of bile acid transporters in hepatocytes, thereby reversing the normal transport of bile acids into the bloodstream[7].

Currently, there are no specific therapeutic drugs for SLI. Zhang *et al*[2] found that most treatments and medications have not been clinically tested to verify their effectiveness. First, early antibiotic treatment and source control of the infection are crucial for improving liver function. Providing appropriate hemodynamic support can restore liver perfusion, which is also a key step in preventing liver damage[3].

Given the important role of the gut in the progression of liver injury caused by sepsis, targeting the microbiota may hold potential for the prevention and treatment of liver dysfunction[1]. Modulating the targeted microbiota in high-risk patients before the onset of sepsis can help reduce the incidence of sepsis. The use of probiotics and synbiotic formulations has been shown to decrease the incidence of infections in the intensive care unit[8-11]. Zhang *et al*[2] noted in their study that the gut-liver axis has been recognized as a potential target for therapeutic intervention, with the gut microbiota considered an upstream regulatory factor in SLI, providing new insights for the treatment of SLI. Furthermore, studies found that metformin may improve liver injury by modulating the gut microbiota and alleviating sepsis-related intestinal barrier dysfunction, which might be an effective approach for treating SLI[12]. The literature indicates that metformin can mitigate SLI by reducing levels of cytokines, high mobility group box 1, and mitogen activated protein kinase while simultaneously upregulating the expression of adenosine monophosphate activated protein kinase[13].

Immunomodulatory therapy is an important topic in current research. Initially, studies focused primarily on the proinflammatory aspects of immune responses in sepsis, as the typical early proinflammatory cytokines TNF and interleukin (IL)-1 were first shown to induce organ failure in animal models, making them primary targets for the development of anti-sepsis drugs. However, anti-inflammatory strategies, including anti-TNF drugs, IL-1 receptor antagonists, and numerous other medications, have not demonstrated significant effects in clinical trials for sepsis[5,14].

Zhang *et al*[2] found in their literature review that a study based on a lipopolysaccharide experimental model confirmed that simvastatin alleviated liver inflammatory damage *via* the NF-κB signaling pathway. Studies found that simvastatin can reduce liver injury induced by endotoxemia and plays a significant role in immune modulation during sepsis by decreasing the levels of IL-6, TNF-α, IL-1β, and microimmunoflurescence in the peritoneal cavity[15]. These findings may support the clinical application of statins in preventing SLI, although further clinical research is needed for validation.

While statins have the potential to reduce liver inflammatory damage, they also carry potential adverse effects, such as liver injury and rhabdomyolysis, indicating that there is still a distance to cover for clinical application. The key issue in sepsis lies in the imbalance between proinflammatory and anti-inflammatory mechanisms: Early on, there is a predominance of systemic inflammatory response, while later stages exhibit severe immunosuppression. The initial proinflammatory host response varies among individuals. According to a series of host-related factors, the immune system may evolve into a complex state of immune dysregulation, sometimes referred to as aggressive post-immunosuppression[16-18].

Many cytokines exhibit both proinflammatory and anti-inflammatory properties rather than being solely one or the other at any given stage. This partly explains why previous anti-inflammatory treatments have failed to significantly impact clinical trial outcomes. Therefore, determining whether a patient is in a state of hyperinflammation or dominant immunosuppression is crucial for treating SLI and provides important guidance for the choice of therapeutic agents. Biomarkers indicative of immune dysfunction in sepsis, such as the expression of D-related human leucocyte antigen (HLA-DR) on monocytes and lymphocytes, are often suppressed.

The suppression of HLA-DR expression, in conjunction with the dynamic changes in the patient's clinical presentation and auxiliary examinations, can indicate that the patient is in an immunosuppressive phase[4,19]. Currently, some studies assessed immune status based on the expression levels of HLA-DR. Severe infections can suppress adrenal function, leading to low levels of adrenocorticotropin, which may trigger relative adrenal cortical insufficiency, resulting in critical illness-associated glucocorticoid (GC) deficiency. This suggests that the use of GC in sepsis can be guided by adrenocorticotropin levels as well as the activity of the hypothalamic-pituitary-adrenal axis.

Research indicates that GCs play a critical role in the survival of sepsis, primarily due to their anti-inflammatory properties. The immunosuppressive effects of GCs extend beyond merely inhibiting the transcription of proinflammatory genes; they also involve the activation of anti-inflammatory gene expression through GC receptor (GR) dimers, along with the suppression of proinflammatory gene expression. The formation of GR homodimers is essential for the protective effects of GCs against acute inflammation. These GR dimers possess the potential to modulate acute inflammatory responses by inducing dimer-dependent genes whose products exhibit anti-inflammatory functions (such as sphingosine kinase 1 and mitogen-activated protein kinase phosphatase 1), or by inhibiting proinflammatory genes (such as signal transducer and activator of transcription 1 and *IL-1β*) in a dimer-dependent manner[20].

Current large-scale studies on GC therapy for sepsis have yielded mixed results, with some indicating efficacy, while others demonstrated no significant benefit[21,22]. This inconsistency may be related to inadequate assessment of the immune status of the host. The immune status of the host may reflect different subtypes of sepsis, with each subtype exhibiting a distinct response to GC. The failure to stratify sepsis patients by subtype during enrollment may contribute to the variability in the outcomes of the aforementioned studies. However, there remains a lack of effective and accurate biomarkers for assessing the immune status in sepsis. Zhang *et al*[23] employed machine learning techniques to derive a

disease axis through principal component analysis. They assessed its consistency across various cohorts of sepsis patients by examining patterns of feature loading and correlation[23]. This offers a novel tool for the classification of sepsis subtypes; however, its efficacy awaits validation through larger sample sizes and additional centers.

CONCLUSION

Immune imbalance is a primary cause and potential target of SLI, but specific immunomodulatory drugs for the effective treatment of SLI have yet to be integrated into current clinical practice. Therefore, future preclinical and clinical studies should prioritize the development of personalized immunotherapy based on the patient's immune status. Attention should be paid to the immune status of patients with sepsis, particularly in identifying novel indicators of the immune state and the development of immunomodulatory targets and drugs.

FOOTNOTES

Author contributions: Chen JW designed the outline of the manuscript; Chen JW, Liu CY, and Li S contributed to the writing of the manuscript; Cai C supervised and took responsibility for planning and executing the research activities; Lu MQ developed the concept for the article and provided writing ideas; All authors read and approved the final version of the manuscript to be published.

Supported by The Zhejiang Medical and Health Science and Technology Program, China, No. 2021KY205 and No. 2024KY139; and The Wenzhou Science and Technology Plan Project, China, No. Y2023111.

Conflict-of-interest statement: The authors declare that there are no financial or other conflicts of interest that could influence the content or conclusions of this manuscript.

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S-Editor: Luo ML
L-Editor: Filipodia
P-Editor: Yuan YY

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