JOURNAL OF HEALTHCARE SCIENCES

Volume 5 Issue 12 2025, Article ID: JOHS2025001151

http://dx.doi.org/10.52533/JOHS.2025.51216

e-ISSN: 1658-8967

Review

Acute Gastrointestinal Complications in Patients with Severe Sepsis: Incidence, Recognition, and Outcomes

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Received: 18 December 2025, Accepted: 22 December 2025, Published: 23 December 2025.

Abstract

Sepsis refers to a life-threatening organ dysfunction that occurs due to a dysregulated systemic inflammatory response to infection. It is associated with high morbidity and mortality rates. Sepsis severity depends on the number of organ failures and the presence of septic shock. Acute gastrointestinal complications are common in severe sepsis patients due to reduced gastrointestinal microcirculatory blood flow, systemic inflammation, and disruption of the gut barrier. Gut barrier disruption is a central event in the pathophysiology of gastrointestinal complications in severe sepsis patients. It allows for bacterial translocation into the systemic circulation, which affects the liver and other organs, and further exacerbates systemic inflammation. The most frequent gastrointestinal complications in severe sepsis patients include gastrointestinal dysmotility, gastrointestinal bleeding, and acute liver injury. These complications, especially sepsis-induced liver injury, are associated with poor outcomes and higher mortality rates. Moreover, severe sepsis patients who develop such complications require tailored management, which further complicates sepsis treatment. Novel therapeutic approaches are required for effective management of sepsis-associated gastrointestinal complications. In this narrative review, we aim to outline current knowledge regarding the most common acute gastrointestinal complications encountered in severe sepsis patients, focusing on their incidence, recognition, and outcomes, highlighting the role of the gut barrier in the pathophysiology of these complications.

Keywords: *severe sepsis, septic shock, systemic inflammation, gut barrier disruption, bacterial translocation, sepsis-induced liver injury, gastrointestinal complications*

Introduction

Severe sepsis is considered an exaggerated inflammatory response. It is defined as life-threatening organ dysfunction that occurs because of a dysregulated systemic inflammatory response to infection (1). Sepsis is considered the leading cause of admission to the intensive care unit (ICU), as well as the leading cause of mortality in the ICU (2). Severe sepsis is increasingly common due to changes in population age, presence of comorbidities, increase in immunosuppressive treatments, use of invasive medical care devices, nosocomial infections, and rise of antimicrobial resistance (3-5). Estimates of severe sepsis incidence among ICU admissions range from 11% to 15%, with mortality rate ranges between 25% and 60% (6). However, due to inconsistencies in defining and diagnosing sepsis, the true incidence of sepsis is considered difficult to determine (7, 8). Sepsis severity depends on the number of organ failures and the presence of septic shock (9). Septic shock refers to a subset of sepsis in which the circulatory, cellular, and metabolic abnormalities involved are associated with a greater likelihood of mortality than sepsis alone. (1).

Sepsis-associated organ dysfunction comprises several organs and systems, including pulmonary dysfunction, particularly acute respiratory distress syndrome, cardiac dysfunction, kidney dysfunction, particularly acute kidney injury, and brain dysfunction (2). Moreover, sepsis-related immunosuppression contributes to the development of nosocomial infections, which are common after sepsis admission (10). The most frequent nosocomial infections include ventilator-associated pneumonia, catheter-associated bacteremia, catheter-associated urinary tract infections, surgical site infections, antibiotic-associated diarrhea, and Clostridium difficile colitis (11). Management of sepsis involves a combination of multi-faceted interventions in the form of bundle care approach as recommended by the Surviving Sepsis Campaign (SSC). The SSC bundle comprises administration of antimicrobials, vasopressors, fluid therapy, and corticosteroids, in addition to mechanical ventilation (12).

Acute gastrointestinal complications are common in severe sepsis patients due to reduced intestinal microcirculatory blood flow, systemic inflammation, and disruption of the gut barrier. Gut barrier disruption allows for bacterial translocation into the systemic circulation, which further exacerbates the systemic inflammation, leading to more injury and dysfunction in interconnected organs, including cardiovascular, pulmonary, renal, hepatic, and neurological systems. Consequently, each organ system contributes to the amplification and perpetuation of septic shock and multiorgan dysfunction syndrome, resulting in a bidirectional interaction (13, 14). The most frequent sepsis-associated gastrointestinal complications include disruption of gastrointestinal motility, gastrointestinal bleeding, and acute liver injury (13, 15, 16). This narrative review aims to summarize current evidence regarding the most frequent acute gastrointestinal complications in patients with severe sepsis, focusing on their incidence, recognition, and outcomes, highlighting the role of the gut barrier in the pathophysiology of these complications.

Methodology

This narrative review is based on an extensive literature search conducted on 18 November 2025 in PubMed, Cochrane, Scopus, and Web of Science databases using medical subject headings (MeSH) and relevant keywords. The search aimed to identify studies investigating current knowledge regarding acute gastrointestinal complications in severe sepsis patients. The review focused on articles that examine the incidence, recognition, and outcomes of sepsis-associated gastrointestinal complications, including disruption of gastrointestinal motility, gastrointestinal bleeding, and sepsis-induced acute liver injury, highlighting the role of the gut barrier in the pathophysiology of these complications. No restrictions were applied regarding publication date, language, or type of publication, to ensure a broad investigation of the available literature.

http://dx.doi.org/10.52533/JOHS.2025.51216

Discussion

Disruption of the gut barrier

The gastrointestinal microenvironment includes three key components: a single cell layer of epithelium, a local immune system, and the microbiome. Together, these components play a major role in maintaining homeostasis. During sepsis, this gastrointestinal microenvironment is disturbed, resulting in pathological events, leading to both local and distant injuries. Disruption of the gut barrier is considered a central event in the pathophysiology of sepsis-associated gastrointestinal complications and gastrointestinal dysfunction. Several mechanisms are involved in gut barrier disruption, including increased intestinal permeability, intestinal epithelium apoptosis, dysbiosis, and dysregulated immune signaling (17, 18).

Enterotoxins from microorganisms such as C. difficile, C. perfringens, Vibrio cholerae, Staphylococcus aureus, Yersinia enterocolitis, and Shigella dysenteriae can cause an increase in the intestinal membrane permeability through different modes of action according to the toxin type, ranging from the formation of transmembrane pores and disorganization of the actin cytoskeleton to degradation of the tight junction proteins (19, 20). Bacterial translocation occurs in severe sepsis patients as a result of a compromised gut barrier (14). Bacterial translocation refers to the phenomenon in which bacteria, their derivatives, or both cross the intestinal barrier, reach the systemic circulation, and colonize extraintestinal tissues, which further exacerbates the sepsis-related systemic inflammation (21).

Biomarkers for damage to the gut barrier are used for recognizing patients with intestinal damage, and those at risk of bacterial translocation. These biomarkers are elevated intestinal fatty acid binding protein (I-FABP), which is a biomarker of enterocyte damage, and decreased citrulline, which is a biomarker of enterocyte mass reduction (22). While biomarkers for bacterial translocation include elevated levels of soluble CD14 subtype (sCD14-ST) and decreased levels of lipopolysaccharide-binding protein (LBP) (23). Production of sCD14-ST is mediated by the binding of the membrane protein of the CD14 macrophages with bacterial cell wall components, namely, peptidoglycans from Gram-positive and lipopolysaccharides from Gram-negative bacteria. sCD15-ST, which is also known as presepsin, is considered a biomarker of the early phase of sepsis and a prognostic outcome factor in septic patients (24). LBP is a protein that is produced in the acute phase of bacteremia, and it binds with lipid A of bacterial lipopolysaccharides (LPS), leading to increased sensitivity of immune cell receptors to LPS and activation of the immune response by releasing proinflammatory cytokines. LBP is considered an effective biomarker of bacterial translocation and the development of septic complications (21, 23).

Gastrointestinal dysmotility

Disruption of gastrointestinal motility is a common complication during severe sepsis and septic shock. Impairment of neural and hormone-mediated regulation of gastrointestinal motility occurs during septic shock. This leads to dysregulation of peristaltic movements that are responsible for gastrointestinal propulsion (13). Intestinal dysmotility affects the absorption of nutrients and drugs, which impacts the outcomes of critically ill patients (25). Disrupted intestinal motility leads to bacterial overgrowth, potentially resulting in bacterial translocation, systemic inflammatory response, and multiple organ dysfunction syndromes. The most common clinical manifestation of small intestine dysmotility in sepsis patients is the presence of paralytic ileus (26).

Bacterial lipopolysaccharides (LPS), which are key components of the outer membrane of Gram-negative bacteria, can alter gastrointestinal motility. LPS-induced motility alterations are mediated by nitric oxide (NO) and prostaglandins. Several cell types are involved in the pathogenesis of sepsis-associated ileus. Residential muscular macrophages in the stomach and ileum have a role in NO production, in addition to mucosal macrophages that switch towards a pro-inflammatory mode due to the sepsis-related systemic inflammation. These events lead to recruitment of leukocytes and release of

http://dx.doi.org/10.52533/JOHS.2025.51216

inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor-α that play a role in inhibiting intestinal muscle function (27).

The enteric nervous system, which is composed of enteric glial cells, interstitial cells of Cajal, and neurons, plays a major role in the neuroimmunomodulation of intestinal motility. Enteric glial cells are involved in modulating neuromuscular transmission, gastrointestinal motility and secretion. Along with enteric neurons, they also control intestinal barrier functions and gut immune homeostasis (6). Damage to enteric glial cells and reduction in their number is associated with dysfunction in gastrointestinal motility (28). NO has been reported to cause disruption in the networks of interstitial cells of Cajal, leading to intestinal dysmotility (29). Moreover, injury to interstitial cells of Cajal due to activation of IL-17 signaling within the intestinal muscularis is associated with sepsis-related intestinal dysmotility (30). Furthermore, damage to the intestinal muscularis neurons has been reported in sepsis-induced intestinal dysmotility. Muscular neutrophil infiltration has been reported to result in neuronal loss in intestinal muscle, consequently, leading to disruption in intestinal motility (31).

Gastrointestinal dysmotility is very common in critical illness, with around 60% of critically ill patients experiencing intestinal dysmotility, however, the exact incidence among severe sepsis patients is undetermined (26). Early recognition and management of gastrointestinal dysmotility is crucial for improving patient outcomes in severe sepsis. Diagnosing gastrointestinal dysmotility in ICU setting involves manometry, gastric residual volumes, ultrasonography, magnetic resonance imaging, lactulose breath hydrogen test (32). Moreover, management of this dysfunction includes alteration of patient posture, adjustment of electrolyte imbalances, control of blood glucose, early enteral feeding, and administration of prokinetic agents such as metoclopramide, cisapride, and erythromycin (26, 33).

Gastrointestinal bleeding

Gastrointestinal bleeding (GIB) is considered one of the most serious and frequently occurring complications among sepsis patients, and it is often classified as upper gastrointestinal bleeding (UGIB) (34). UGIB is defined as bleeding along the gastrointestinal tract from the mouth to the duodenum proximal to the ligament of Treitz, and it manifests as hematemesis, which refers to vomiting blood, or melena, which refers to black and tarry stools (35). The sepsis-associated systemic inflammation leads to impairment of gastric mucosal blood flow, coagulopathy, and increased secretion of gastric acid. Moreover, deficits in the gastrointestinal mucosal microcirculatory perfusion have been associated with gut injury and disruption of gut barrier function. These factors contribute to UGIB occurrence and increase the likelihood of gastrointestinal dysfunction in sepsis patients (34, 36, 37).

The incidence of GIB among septic shock patients is 5.4%, with a 9% increase in mortality from 45% in septic shock patients without GIB to 54% in presence of GIB. Moreover, GIB significantly increases the days of hospital stay and further complicates sepsis management. Other comorbidities such as peptic ulcer and cirrhosis increase the incidence of GIB in sepsis patients (38). As sepsis is considered a critical condition, sepsis patients often require invasive procedures and mechanical ventilation, which increase the risk of UGIB occurrence (39). Another risk factor for UGIB in severe sepsis patients is the use of vasopressors for treatment of sepsis-associated hypotension, which further exacerbates the impairment of splanchnic blood flow (40). Furthermore, sepsis patients who are on antithrombotic therapy that comprises antiplatelets and anticoagulants for other comorbid conditions are at increased risk of exhibiting GIB (15).

It is important to identify severe sepsis patients who are at increased risk of GIB. However, it is worth noting that procedures such as gastrointestinal endoscopy increase the risk of infections, either by introducing external microorganisms through the scope itself, or by translocation of the gut

http://dx.doi.org/10.52533/JOHS.2025.51216

microbiota (37). Prophylactic strategies are recommended for stress ulcer in sepsis and septic shock patients at high risk of GIB. Proton pump inhibitors and histamine-2 receptor antagonists (H2Ras) are the most common prophylactic agents (12). They have the potential to lower GIB in high-risk patients. However, their effect on reducing mortality rates is not supported, and they increase the risk of pneumonia (41). Effective prophylaxis and management of GIB in septic patients are still understudied, despite the high association between GIB and severe sepsis (34).

Sepsis-induced acute liver injury

The liver is highly susceptible to sepsis-associated inflammation due to its role in immunoregulation, as well as receiving blood supply from the gastrointestinal tract via the portal vein (42). Sepsis-induced liver injury is a serious gastrointestinal complication in severe sepsis. Impaired intestinal microcirculation and sepsis-related inflammatory response lead to increased vascular permeability and coagulation dysfunction in the liver. This results in a reduction in hepatic blood perfusion and impairment of hepatic microcirculation and blood flow. Moreover, hepatic oxidative stress, cell death, bacterial translocation, and intestinal inflammation play a role in the development of acute liver injury (43).

Incidence of sepsis-induced acute liver injury ranges from 40% to 46% in patients with severe sepsis. The mean incidence of liver dysfunction in sepsis patients is considered lower than the incidences of respiratory, renal, and neurological dysfunction. However, sepsis-induced liver dysfunction and failure are associated with poor outcomes, as well as higher mortality rates than the rates encountered with other organ dysfunction (44, 45). This is attributed to the liver's resilience and its high regenerative capacity and further highlights its role in patient recovery and survival following severe sepsis (16).

Reducing liver injury and restoring liver function are considered fundamental for lowering morbidity and mortality rates in severe sepsis patients (16). Several biomarkers are used to assess liver damage and the extent of injury. These biomarkers include traditional biomarkers, namely albumin, bilirubin, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase. Other emerging biomarkers are used for the detection of liver injury, such as arginase-1, malate dehydrogenase-1, α-glutathione S-transferase, 5'-nucleotidase, and sorbitol dehydrogenase (42).

Management of sepsis-induced liver injury involves early initiation of antibiotic therapy, in addition to initial fluid resuscitation and hemodynamic support to achieve circulatory stability for adequate blood perfusion and oxygenation to the liver (46). Liver function support is also an option. It involves blood purification techniques to eliminate toxins from the body and alleviate the metabolic burden on the liver (47). Moreover, nutritional support in the form of enriched enteral nutrition can support beneficial gut microbiota and alleviate sepsis-associated acute liver injury (48).

Future directions

The bidirectional interactions between the gastrointestinal tract, the liver, and the sepsis-associated inflammation offer key steps that can be taken as novel therapeutic targets. Supporting gastrointestinal barrier function and integrity is an important approach that has the potential to prevent and alleviate several sepsis-associated gastrointestinal complications. A recent study reported the effectiveness of Radix Sanguisorbae, which is the dried roots of the Sanguisorba officinalis plant, in improving intestinal barrier function through inhibiting ferroptosis in septic animal models, resulting in decreased intestinal permeability and restoration of tight junction protein expression (49).

As a central organ in immunoregulation of sepsis-associated inflammation and a prognostic factor for sepsis outcomes, liver injuries should be targeted early in sepsis. Novel approaches for the treatment of sepsis-induced liver injury are under research. These approaches include the use of nanodrug delivery systems for targeted drug delivery to damaged liver tissues using different platforms such as liposomes, solid lipid nanoparticles, polymer

http://dx.doi.org/10.52533/JOHS.2025.51216

micelles, and extracellular vesicles (43), in addition to immunomodulation therapy that involves the use of monoclonal antibodies for reducing key inflammatory mediators to mitigate the sepsis-associated inflammation. Bevacizumab, which is a neutralizing monoclonal antibody that targets vascular endothelial growth factor (VEGF), has been reported to reduce the levels of proinflammatory cytokines and exhibit antiapoptotic effects in sepsis-induced liver injury in mouse models (50).

Moreover, antioxidative stress therapies aim to inhibit oxidative stress pathways to protect the liver. Recent studies investigated the hepatoprotective effects of metformin and melatonin in liver injury in animal models (51, 52). Furthermore, inhibiting hepatocyte cell death has the potential to mitigate sepsis-related liver injury. A recent study reported the effectiveness of clemastine to inhibit apoptosis and pyroptosis in sepsis-induced liver injury in mice through downregulation of Bax, NF-kB, and caspase 3 pro-apoptotic genes and suppressing the production of NLRP-3, caspase-1, and GSDMD c-NT proteins involved in pyroptosis (53).

Conclusion

Sepsis causes serious gastrointestinal complications, which further exacerbate the severity of sepsis, with each amplifying the other's effects. Sepsis-associated gastrointestinal complications are strongly associated with poor prognosis and higher mortality rates among severe sepsis patients. Management of these complications has the potential to decrease sepsis morbidity and mortality rates.

Disclosure

Conflict of interest

There is no conflict of interest.

Funding

No funding.

Ethical consideration

Non applicable.

Data availability

All data is available within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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