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A review of gut failure as a cause and consequence of critical illness

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Abstract

In critical illness, all elements of gut function are perturbed. Dysbiosis develops as the gut microbial community loses taxonomic diversity and new virulence factors appear. Intestinal permeability increases, allowing for translocation of bacteria and/or bacterial products. Epithelial function is altered at a cellular level and homeostasis of the epithelial monolayer is compromised by increased intestinal epithelial cell death and decreased proliferation. Gut immunity is impaired with simultaneous activation of maladaptive pro- and anti-inflammatory signals leading to both tissue damage and susceptibility to infections. Additionally, splanchnic vasoconstriction leads to decreased blood flow with local ischemic changes. Together, these interrelated elements of gastrointestinal dysfunction drive and then perpetuate multi-organ dysfunction syndrome. Despite the clear importance of maintaining gut homeostasis, there are very few reliable measures of gut function in critical illness. Further, while multiple therapeutic strategies have been proposed, most have not been shown to conclusively demonstrate benefit, and care is still largely supportive. The key role of the gut in critical illness was the subject of the tenth Perioperative Quality Initiative meeting, a conference to summarize the current state of the literature and identify key knowledge gaps for future study. This review is the product of that conference.

Key points

- The healthy gut maintains an epithelial barrier that simultaneously cooperates with and contains gut microbes.
- In critical illness, blood is diverted away from the gut, gut integrity is compromised by intestinal epithelial cell death and failure of intercellular junctions, and the microbial community undergoes taxonomic and functional remodeling.
- Gut barrier failure leads to translocation of live microbes, microbial components, or microbial products into host tissues where they elicit local and systemic inflammatory and immune responses.
- Diagnosing gastrointestinal (GI) failure is challenging due to a lack of gut specific diagnostic tests.
- Therapeutic interventions are in development for nearly all aspects of GI failure, but none have yet shown efficacy in large clinical trials.

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- Ultimately, there is an urgent need to identify key molecular mechanisms that lead to gut barrier failure, develop diagnostics to detect their activation, and create therapeutic strategies to counteract them.

Introduction

The gastrointestinal (GI) tract plays an essential role in both health and critical illness. Crosstalk occurs between the gut and every major organ system. Consequently, GI failure is often the first in a cascade of events leading to multi-organ dysfunction syndrome (MODS). To summarize what is known and establish future research directions related to the gut in critical illness, the Perioperative Quality Initiative Group convened in Cleveland, Ohio, on June 24th, 2023. Faculty performed a comprehensive literature review, summarized the literature, and identified key knowledge gaps [1].

The healthy gut

Gastrointestinal tissue

The gastrointestinal tract is composed of the mouth, esophagus, stomach, small intestine (duodenum, jejunum, and ileum), colon (right, transverse, left, and sigmoid), and rectum. Each of these components has specialized functions, and contributes to the overall digestive, absorptive, secretory, motility, and barrier functions of the gut. Intestinal epithelial cells (IEC) lining the gut perform absorptive, secretory, and barrier functions while extensive neuromuscular systems are responsible for motility. Additionally, innate and adaptive immune cells in the lamina propria support barrier function and rapidly address any microbial incursions into host tissues. Together, these systems move nutrients and waste through the GI tract and maintain the gut microbiota in a commensal state [2].

Microbiota

The normal gastrointestinal tract is home to a large and diverse microbial community, the gut microbiota. The gut microbiota is often interchangably referred to as the gut microbiome, although this second term has several definitions and is frequently used in the context of gut microbial ecology [3]. The gut microbiota consists of trillions of bacteria, fungi, archaea, unicellular eukaryotes, and viruses (primarily bacteriophages infecting bacteria) that reside within the gut lumen [4]. The focus of this manuscript is on bacteria due to the wealth of evidence from patients and pre-clinical models implicating bacteria in gut failure and efforts to target gut bacteria in treatment of critical illness.

The density and complexity of the bacterial community increases along the GI tract, with the highest absolute numbers and taxonomic diversity occurring within the colon [2]. The gut bacteria are highly bioactive and perform molecular exchanges among themselves and with host cells. In healthy states, gut bacteria are critical partners in energy extraction from ingested food, provide or regulate molecules used in communication between the gut and other organs, and act as a bulwark against incursions by pathogens [5].

The gut mucosal barrier

In the small and large intestine, a single cell layer of epithelium separates the approximately 40 trillion microbes residing in the gut lumen from the human host (Fig. 1A) [6]. Multipotent Lgr-5 expressing stem cells reside near the base of the intestinal crypt and give rise to daughter cells that migrate up the crypt. As cells move up the crypt, they lose the capacity to proliferate and differentiate into absorptive enterocytes (which make up 85% of the IEC) or secretory cells. The secretory cells then further differentiate into (a) hormone-producing enteroendocrine cells that function in metabolic regulation, appetite control, intestinal motility and mucosal immunity, (b) mucus-producing goblet cells, or (c) tuft cells which act as chemosensors and employ taste receptors to monitor the intestinal lumen [7]. When cells reach the apex of the crypt/villus, they either die by apoptosis or are exfoliated whole into the gut lumen. The entire journey from cell birth through migration and differentiation to death/exfoliation takes 3–5 days. A fourth type of secretory cell, the Paneth cell, is also present in the small intestine. These defensin-producing cells are generated from stem cells like the other IEC but migrate downward and reside at the crypt base [8].

On the luminal side of the epithelium, an acellular mucus layer provides physical defense and acts as a habitat for bacteria, providing binding sites and an energy source to the microbiota [9, 10]. The properties and thickness of the mucus layer vary along the gut, dependent upon the function of each geographic location and environmental factors such as diet and signals from the microbiota [11–13].

Under the mucus layer, the cellular intestinal barrier is precisely regulated to allow paracellular movement of water, solutes and immune modulating factors, while simultaneously preventing microbes and microbial components from leaving the intestinal lumen and injuring the host [14]. Permeability can occur via the transcellular route (movement through cells, mediated

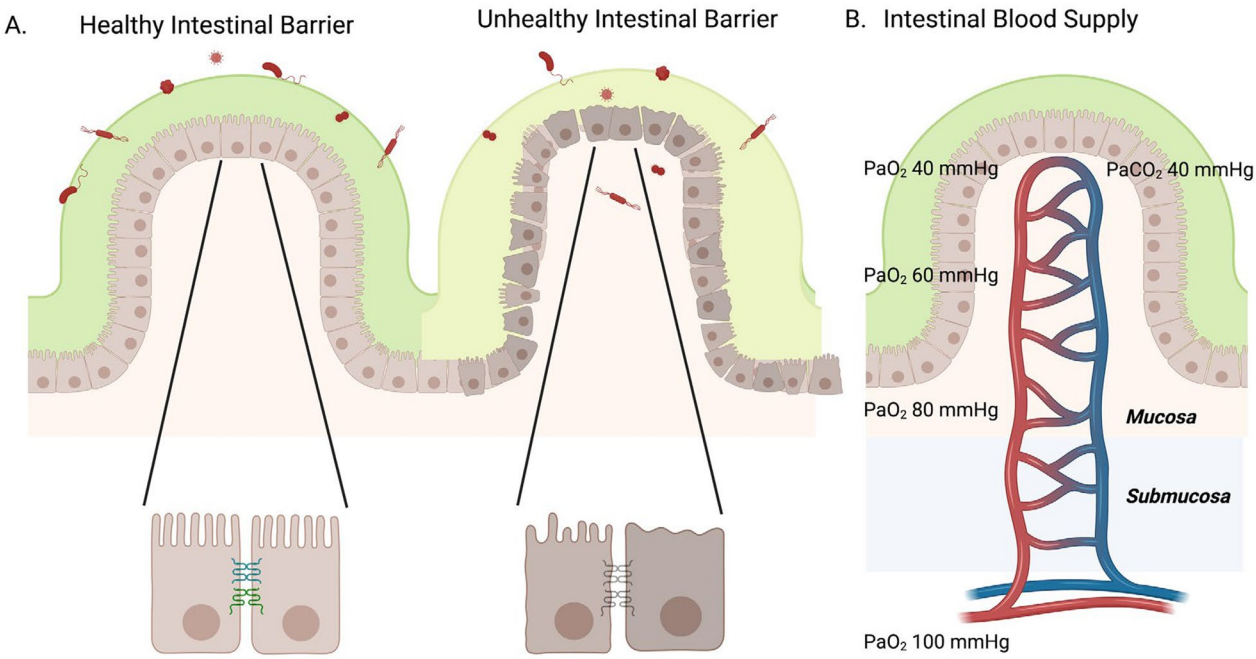

Fig. 1 The gastrointestinal epithelium in health and disease. **A** A healthy intestinal barrier consists of intestinal epithelial cells that are constantly renewed through maturation and migration of multipotent crypt progenitors, and intact junctions that hold epithelial cells in tight apposition. In contrast, epithelial cell damage, decreased proliferation, and apoptosis combine with failed intercellular junctions to compromise intestinal barrier integrity and allow bacterial translocation. **B** The submucosal plexis supplies blood to the gut mucosa. The arrangement of the arterioles and venules allows for countercurrent exchange of oxygen. Created with BioRender.com

by transmembrane transporters with exquisite substrate specificity) or the paracellular route (between cells). Paracellular permeability is mediated by the apical tight junction (TJ). Two distinct pathways mediate TJ permeability [15]. The pore pathway is high-capacity, size, and charge-selective, and only molecules smaller than 8 angstroms (Å) in diameter can pass through. The claudin family of TJs modulate the pore pathway. The leak pathway is low-capacity and nonselective, and larger molecules < 100 Å diameter can pass through. Numerous TJs and TJ-associated proteins such as occludin, zonula occludens (ZO)-1, and junctional adhesion molecule (JAM)-A mediate the leak pathway. In addition, the TJ is structurally and functionally linked to the peri-junctional actin-myosin ring which is mediated by myosin light chain kinase (MLCK). A third TJ-independent pathway, the unrestricted pathway, occurs at sites of epithelial damage and does not have a size limit [16]. The unrestricted pathway is the only way in which intact bacteria can cross the intact epithelial layer other than direct cellular invasion and transcytosis. In addition to their role in mediating permeability, certain tight junction proteins such as occludin and ZO-1 also regulate proliferation and apoptosis in the gut epithelium [17].

Blood supply and lymphatics

The fore-, mid- and hindgut (roughly the lower third of the esophagus to the colon) receives its blood supply from the mesenteric vessels [18]. This is important for understanding the pathophysiology of gut perfusion disturbances because the areas supplied by mesenteric vessels are compromised early in stress or shock states to preserve heart–lung-brain circulation.

The main arteries involved in gut blood supply include the celiac artery, the superior mesenteric artery, and the inferior mesenteric artery. The celiac artery supplies blood to the stomach, spleen, liver, and parts of the esophagus and duodenum. The superior mesenteric artery supplies blood to the small intestine (jejunum and ileum), cecum, ascending colon, and part of the transverse colon. The inferior mesenteric artery supplies blood to the descending colon, sigmoid colon, and rectum.

The majority of the blood supply to the gut mucosa comes from the superior mesenteric artery [19]. This artery gives rise to smaller branches known as intestinal arteries, which further divide into arterioles and capillaries that supply the mucosa (Fig. 1B). Within the connective tissue beneath the mucosa, these arterioles and capillaries are organized into a specialized network of blood vessels called the submucosal plexus. Both the

mucosa and the microvilli, tiny finger-like projections on the surface of the intestinal epithelial cells, receive their blood supply from the submucosal plexus. The capillaries and venules in the submucosal plexis are in a looped counter-current arrangement, similar to that seen in the kidney. This configuration allows for efficient absorption of nutrients and exchange of water and electrolytes but is susceptible to reduced perfusion states. The tip of the microvilli is always relatively hypoxic compared to the base, and in reduced perfusion states, oxygen will tend to move down a gradient from arteriole to venule closer to the base, thus exacerbating hypoxia at the tip and potentially switching apoptosis to necrosis in epithelial cells. The capillaries within the mucosa eventually give rise to small vessels called venules, which join together to form larger veins. The venous blood from the gut mucosa drains into the superior mesenteric vein, which then joins with the splenic vein to form the portal vein. The portal vein carries nutrient-rich blood from the gut to the liver for processing and detoxification.

The gut lymphatic system also provides a conduit between the gut and the rest of the body. In contrast to the blood circulatory system, the gut lymphatics operate unidirectionally to transport dietary lipids out of the gut, return fluid to the bloodstream, and facilitate immune surveillance of the gut [20]. In the intestine, the lymphatic system consists of two non-communicating networks, (1) the lymphatics that drain the muscular layer of the intestine and (2) the lacteals and submucosal lymphatics [21]. The lacteals are located in the intestinal vili and act as lymphatic capillaries that drain into collecting lymphatics in the intestinal mesentery [20].

The gut in critical illness

The initial triggers of gut failure in critical illness are often difficult to definitively identify. Damage can originate in the gut lumen or from sites outside of the gut and it may result from more than one source. For example, heart failure leads to decreased blood flow to the gut with subsequent mucosal barrier damage and changes in the gut microbiota [22]. In addition, many of the drugs used to treat cardiac disease can directly damage the gut microbiota and impair gut functions [23, 24]. Regardless of the initial trigger, common causes of gut failure in critical illness include compromised GI blood supply, lymphatic dysfunction, epithelial damage, and alterations in the gut microbiota.

Blood supply

Splanchnic vasoconstriction is a physiologic response that occurs to redirect blood flow from the splanchnic or abdominal organs to other areas of the body, such as the heart and brain. The splanchnic organs receive 25–30% of the overall cardiac output and oxygen delivery at rest, and this increases considerably after a meal [25, 26]. However, blood flow is diverted away from the splanchnic organs by vasoconstriction in stressed states (Fig. 2).

Splanchnic vasoconstriction is primarily regulated by the sympathetic nervous system. When the body is under stress, the sympathetic nerves release norepinephrine which binds to alpha-adrenergic receptors on the smooth muscle cells of the splanchnic blood vessels. Activation of the alpha-adrenergic receptors causes the smooth muscle to contract, leading to vasoconstriction and a decrease in blood flow to the abdominal organs. This is highly effective since splanchnic blood vessels are many-fold more responsive to vasoconstrictors than other, non-splanchnic vessels [27, 28].

During hypovolemia or stress, the body initiates a compensatory response to maintain blood pressure and perfusion to vital organs. Splanchnic vasoconstriction is part of this response, as it helps shunt blood away from the abdominal organs, including the GI tract, and towards the heart and brain. While splanchnic vasoconstriction is a normal physiological response, prolonged or excessive vasoconstriction can have negative effects on the abdominal organs. Reduced blood flow to the intestines, for example, can lead to ischemia and damage to the intestinal mucosa.

Hemorrhage or hypovolemia from other medical causes (i.e. diarrhea, burns, emesis, prolonged poor oral

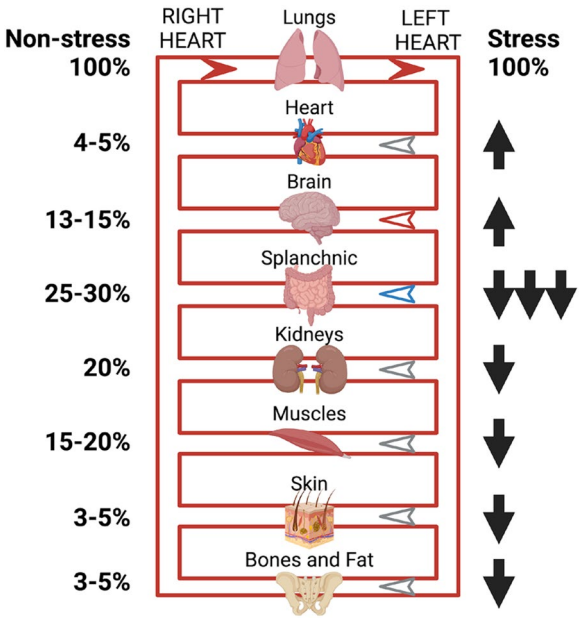

Fig. 2 Distribution of blood flow in critical illness. During stress states, such as those found in critical illness, blood flow is redistributed away from the gut to favor perfusion of the heart, brain, and lungs. Created with BioRender.com

intake, or insensible losses due to "third spacing") can also decrease blood flow to the gut. As little as 5% blood loss (approximately 250 ml in a 70 kg person; the equivalent of donating one unit of blood) can result in gut mucosal hypoperfusion [29]. Even smaller amounts of blood loss could also lead to hypoperfusion since changes in gut mucosal perfusion are detectable in animal models following as little as 3% blood loss (approximately 150 ml in a 70 kg subject) using microscopic imaging of the small bowel mucosa [30]. Monitoring for gut hypoperfusion can be difficult since hemorrhage is only detected by changes in blood pressure, stroke volume, and cardiac output when 10–15% of blood volume is lost (covert compensated shock), even when patients are under general anesthesia and closely monitored.

Gut epithelium

Epithelial cells

Multiple elements of gut epithelial integrity are perturbed in critical illness. Epithelial cell apoptosis is increased in septic patients and pre-clinical models of sepsis, and is exacerbated by aging, alcohol, and cancer in pre-clinical models [31–34]. Epithelial cell replacement is also compromised in animal models of critical illness since proliferation is decreased and migration slowed [35, 36]. Notably, prevention of gut epithelial apoptosis prevents sepsis-associated hyperpermeability in pre-clinical studies [37, 38]. Targeted anti-apoptotic therapy also improves survival in pre-clinical models of both *Pseudomonas* pneumonia and intra-abdominal sepsis, although the former benefit was lost in septic hosts with pre-existing cancer [37–41].

Junctions between epithelial cells

Epithelial barrier integrity is also compromised by changes in the junctions between epithelial cells during critical illness. Permeability is increased in all interepithelial pathways following critical illness, although this is best studied in the leak pathway [42–46]. A pilot study in 21 mechanically ventilated patients demonstrated that measuring small intestine and whole-gut permeability using a multisugar test is feasible in the nonfasted state, although gastroduodenal permeability cannot be measured reliably [47, 48]. Manipulating intestinal permeability by targeting TJs or the perijunctional actin-myosin ring has been proposed as a method to improve survival in critical illness. Claudin 2 is upregulated in the intestine in septic patients compared to those who undergo elective surgical resection. Additionally, mice with genetic alterations in claudin 2 have improved survival after polymicrobial sepsis, associated with preservation of pore pathway integrity [49]. MLCK and myosin II regulatory light chain regulate the perijunctional actomyosin ring [50, 51]. Mice that are genetically deficient in MLCK have improved survival after intraabdominal sepsis, although survival is worsened after *Pseudomonas* pneumonia [52–54]. Furthermore, membrane permeant inhibitor of MLCK (PIK), which reverses MLC phosphorylation, mitigates tumor necrosis factor alpha (TNFα)-induced decreases in transepithelial resistance in cell culture and protects against gut damage in a model of binge ethanol exposure and burn injury [55, 56]. Paradoxically, PIK increased mortality in a murine model of polymicrobial sepsis [57].

Microbiota

Microbes within the gastrointestinal tract can be a primary cause of gut failure and critical illness or can act to perpetuate or exacerbate disease after the gut fails. However, establishing a definitive sequence of events or pinpointing a specific microbial culprit(s) is often difficult. This is in part because microbes damaging the GI tract can originate in or out of the gut and cause disease through both shared and strain-specific virulence mechanisms.

Microbial virulence

Gastrointestinal infections with true pathogens can compromise gut functions, including mucosal barrier integrity [58]. By definition, true pathogens are acquired microbes and are likely to cause disease if they obtain access to the GI tract. These include both bacteria that initially infect the gastrointestinal tract and those that infiltrate the body at other sites and migrate to the gastrointestinal tract.

Virulence mechanisms can also be activated in normally commensal gut microbes during critical illness. Bacteria are exquisitely sensitive to environmental cues and can initiate new genetic programs within minutes of detecting changes in resource availability (i.e., iron, phosphate, nitrogen, carbohydrates, or oxygen,), signals from other stressed or damaged bacteria (i.e., acyl-homoserine lactones or autoinducing peptides), or host signals of damage or inflammation (i.e., temperature, products of host cell damage, cytokines, or neurotransmitters) [59–66]. These new genetic programs often lead to expression of virulence factors, traits that allow bacteria to adapt and survive in the altered environment, but that also damage host tissues, trigger inflammation, and activate innate and adaptive immunity [67]. Common phenotypic changes associated with virulence include production of appendages for adhesion and motility, altered metabolism and production of new metabolites, including toxins, and modifications to the cell surface that make bacteria resistant to environmental stress [68, 69].

Many of the therapeutic interventions used to treat patients with critical illness also directly or indirectly trigger virulence factor expression in bacteria. Morphine acts as a chemoattractant for *Pseudomonas aeruginosa* and these bacteria increase PA-I lectin expression in response to the drug [70]. In addition, colonizing *Pseudomonas aeruginosa* respond to stress by increasing expression of both the PA-I lectin (an adhesin) and endotoxin A [71]. Further, surgical stress in pre-clinical models activates virulence mechanisms in resident *E. coli* that allow these bacteria to adhere to intestinal epithelium [72, 73]. While these elegant studies demonstrated stress-activated virulence in single bacterial strains, there is increasing appreciation that the entire microbial community reacts to these same stimuli.

Microbial dysbiosis

Microbial dysbiosis, changes in density, taxonomic composition, and/or behavior of microbial communities, is a consistent feature of critical illness. Overall bacterial density in rectal swabs at the time of critical care admission has been shown to be in independent predictor of extra-intestinal infections [74]. Changes in bacterial community composition with critical illness were recognized as early as 1969 when it was reported that the prevalence of Gram-negative bacilli in the oropharynx increased in proportion to the clinical severity of illness in hospitalized patients [75]. A number of studies have since demonstrated that critically ill patients have dramatic changes in the taxonomy of their gut bacterial communities (as well as microbiota in lung, skin, and other body sites), and that these changes are associated with increased risk of adverse outcomes [76–80].

Gastrointestinal dysbiosis is of particular interest in critical illness since the gut harbors the largest, most diverse, and most biologically active of the resident bacterial communities. However, diagnosing dysbiosis in the gut microbiota is challenging. Technical challenges in this field include identification of the optimal sample method, sample site, sample processing, data acquisition, and data analysis methods [81]. Methods often vary widely across studies, which has proven to be a challenge for meta-analysis. Diagnosis based on taxonomy has proved difficult since there is enormous taxonomic diversity across healthy humans and taxonomic signatures of disease have varied across studies [82]. Measures of bacterial density are often absent in studies of the gut microbiota, so it is unclear whether changes in overall bacterial numbers or numbers of specific bacterial taxa are most important for patient outcomes. It has also been difficult to define dysbiosis based on functional changes in the microbiota since the majority of the genes carried by gut bacteria have not been annotated. The most consistent features of gut microbial dysbiosis across studies have been collapse of taxonomic diversity and loss of short chain fatty acid production [83]. Dysbiotic communities are commonly dominated by *Enterobacteriaceae*, especially *Proteobacteria* [77] However, some studies have reported dramatic increases in *Enterococcus* Spp. in critical illness [84]. In either case, taxa thought to produce short chain fatty acids are dramatically decreased in the dysbiotic community.

The causes of gut dysbiosis are complex and multifactorial. Underlying disease processes both within and without the gut can influence the gut bacterial community. Patients with critical illness also receive many different types of interventions that directly and indirectly influence bacteria [85]. In particular, antibiotics and changes in the type, amount, or delivery method of nutrition can have profound influences on gut bacteria. Additionally, bacteria introduced into the gut due to decreased colonization resistance or interventions can cause dysbiosis, as can changes in innate or adaptive host defenses that occur in critical illness. For these reasons, it is often impossible to distinguish which aspects of dysbiosis are the cause versus the consequence of disease in the gut.

Consequences of GI tract failure

Microbial translocation

Microbial translocation refers to passage of live microbes, dead microbes, microbial components, or microbial products across the gut barrier into host tissues (Fig. 1) [86]. Translocation can occur due to active virulence mechanisms that allow bacteria to cross the barrier or may be passive when barrier failure has already occurred. For example, production of specialized pili or flagella allows live bacteria to become motile and move close to epithelial cells for adhesion or to cross into host tissues in areas where the mucosal barrier has already failed. Conversely, areas of severe epithelial damage can allow bacteria to essentially drift across the barrier. With live bacteria, adhesion is an early and critical event in translocation since it anchors bacteria in place, leads to physical damage to host cells, concentrates toxins at cell surfaces, and activates cellular microbe-associated molecular pattern (MAMP) sensors [87, 88]. After adhesion, bacteria are able to invade into host cells, translocate across the epithelial barrier into deeper tissues, or remain in privileged niches that provide access to high levels of nutrients needed for replication [89, 90].

Local response to gut barrier failure

The intestinal barrier consists of physical, biochemical, and immunological components. When the barrier is breached, microbes can interact with deeper host tissues including cells of the innate and adaptive immune

systems. Host defenses are activated by microbial and host signals and work to contain threats and repair the intestinal barrier (Fig. 3).

Release of extracellular vesicles

Intestinal epithelial and immune cells utilize chemical messages and extracellular vesicles (EV) for cell–cell communication during health and disease states. The EVs mediate cross-regulation between different cell types and can have immunostimulatory or immunoregulatory functions. When the gut mucosal barrier fails, intestinal epithelial cells release EVs containing molecules that are typically present in antigen-presenting cells [91]. Intestinal epithelial cell-derived EVs facilitate dendritic cell activation which in turn, leads to T-cell activation in the intestinal microenvironment [92]. EVs released by neutrophils are rich in matrix metalloprotein 9, which has been implicated in membrane breakdown. Neutrophil-derived EVs can also be engulfed by macrophages, where they trigger Ca^{++} influx and release of TGF-β, suggesting an immunomodulatory role for these EVs [93].

Innate immune response

Epithelial cell injury and barrier disruption leads to activation of neutrophils and macrophages in the intestinal lamina propria [94]. Neutrophils, the first responders in any injury, accumulate quickly in the face of epithelial damage. Their migration across the endothelial and epithelial barriers is facilitated by selectins, including CD11b/CD18, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM) [95, 96]. Once they reach the intestine, neutrophils disrupt the apical junctional complex, further compromising the intestinal barrier [97]. Neutrophils contain an extensive antimicrobial arsenal that includes a) Pentraxin 3 contained in specific granules and neutrophil extracellular traps, b) elastase (a component of azurophil granules), and c) nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase.

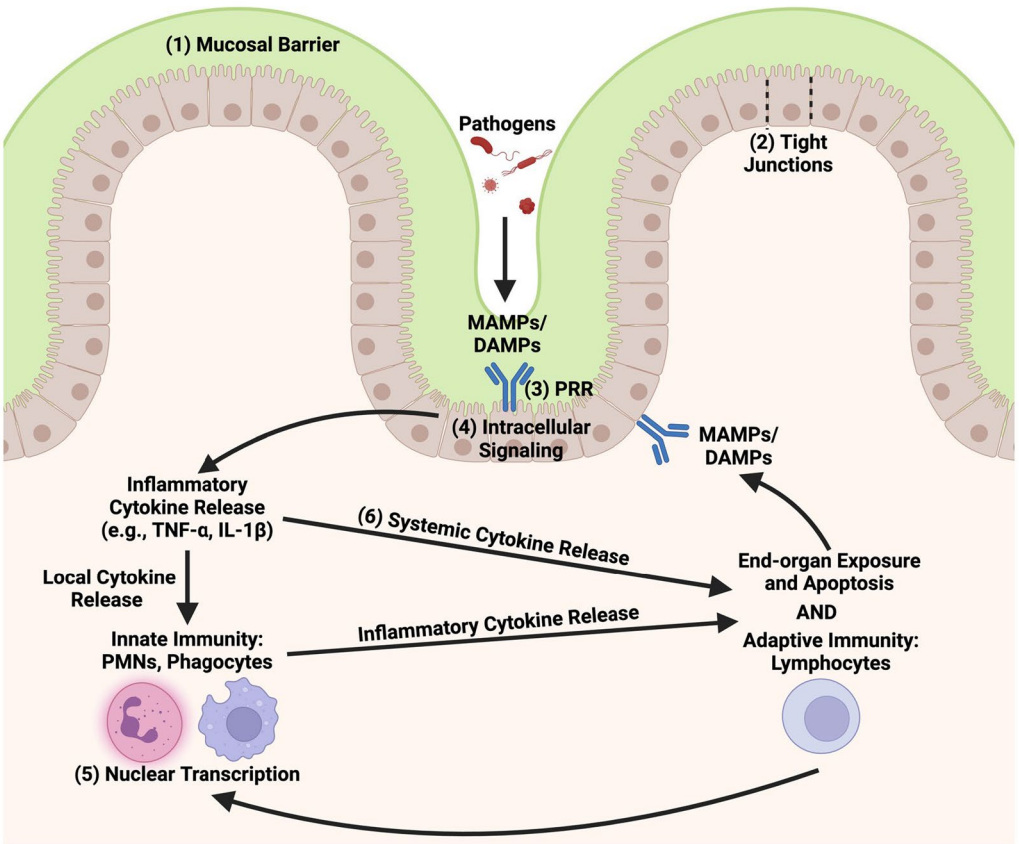

Fig. 3 Consequences of GI barrier failure. Injury to the GI tract can occur from intraluminal and extraluminal sources. Regardless of the source of injury, intestinal epithelial cells and innate and adaptive immune cells in the lamina propria release chemical messages (cytokines, chemokines, and DAMPs) that act locally and travel through the blood and lymph, resulting in inflammation throughout the GI system and the entire body. The numbers in this figure correspond to the potential therapeutic targets, found in Table 2. DAMP, damage-associated molecular pattern; MAMP, microbe-associated molecular pattern; PMN, polymorphonuclear leukocytes; PRR, pattern recognition receptor. Created with BioRender.com

Although intended to kill microbes, if dysregulated, these antimicrobials can exacerbate the pro-inflammatory response and further damage the intestinal epithelium. Thus, neutrophil accumulation is a double-edged weapon [94, 98].

Innate lymphoid cells (ILC) also react to barrier failure. These cells originate from common lymphoid progenitor cells but belong to the innate immune system. Described as the naïve T-cell counterparts of the innate immune system, ILCs lack T-cell receptors. These cells are bona fide tissue-resident cells, as they are produced locally, and are not constantly replenished by circulating cells [99]. Three types of ILCs exist, ILC1, ILC2, and ILC3 and all are crucial for microbe sensing, cytokine production, and regulating innate and adaptive immune functions to maintain homeostasis in the intestinal microenvironment [100]. ILCs respond to cytokines secreted by other immune cells and secrete cytokines themselves. For example, ILC and dendritic cells secrete IL-23 in response to epithelial injury. IL-23 in turn leads to the secretion of IL-17A with subsequent transcription of G-CSF in the bone marrow. Further cascading events culminate in the release of additional neutrophils into circulation [96].

Macrophages are distributed throughout the gut lamina propria, submucosa, and the muscularis externa where they perform location and context-specific tasks and restrain inflammatory responses to allow peaceful co-existence with gut microbes [101–104]. Intestinal macrophages are conventionally subdivided into three subtypes (1) monocyte-derived mature macrophages, (2) monocyte-derived inflammatory macrophages, and (3) self-maintaining macrophages. Subtypes 1 and 2 mainly reside in the lamina propria and are regularly replenished by circulating monocytes. Subtype 3 macrophages mainly reside in muscularis externa. The monocyte derived subtype 1 macrophages provide signals to intestinal stem cells and help give rise to Paneth cells and goblet cells [105, 106]. During inflammation and intestinal barrier dysfunction, monocytes differentiate into pro-inflammatory macrophages or subtype 2 macrophages to fight invading pathogens and modulate T-cell responses [107]. Recent evidence suggests that intestinal macrophage activation during sepsis is dependent upon intestinal epithelial barrier function [49]. Subtype 3 macrophages reside predominantly in muscularis externa, and derive either from embryonic precursors or are monocyte derived [104, 108]. With their proximity to the muscularis layer, subtype 3 macrophages show functional similarity to microglia and communicate with the enteric nervous system, form synapses with myenteric neurons and influence gut motility [104, 109, 110]. Ultimately, all three macrophage subtypes may influence gut dysbiosis and epithelial dysfunction.

Adaptive immune response

Under steady-state conditions, the gut contains very few CD4 + T cells (T helper or Th cells). However, when the mucosal barrier fails, the number of CD4 + T cells increases dramatically [111–113]. This increase is primarily due to rapid recruitment of naïve T cells into the area of the breach followed by expansion and differentiation into mature Th subsets [111]. These subsets are defined by the specific transcriptional programs that generate them, cytokines they secrete, and their functions. At least five different types of Th cells have been described including Th1, Th2, Th17, T follicular helper cells, and T regulatory cells [114]. Th1 and Th17, in particular, play important roles in the setting of mucosal barrier failure. Th1 cells secrete interferon gamma (IFN-γ) and interleukin 2 (IL-2) which then stimulate cytotoxic CD8 + T cells to neutralize intracellular pathogens including bacteria and viruses. In addition to preventing pathogen invasion, Th1 cells secrete IL-2 and IL-10, promoting T-regulatory (T-reg) differentiation to counter intestinal inflammation. Th1 cells also stimulate intestinal stem cell proliferation and facilitate epithelial restoration [111]. Th17 cells influence the mucosal inflammatory milieu by secreting cytokines such as IL-17, IL-22, and IL-26 [115]. IL-17 promotes the proliferation of intestinal epithelial cells and Immunoglobulin A (IgA) secretion to encourage healing in intestinal injury [115, 116]. IL-17 also counters intestinal inflammation by downregulating chemokines involved in CD8 + cytotoxic T cell recruitment and upregulating immunoregulatory M2 macrophages [115, 117]. Th17 cells express chemokine receptor CCR6, which allows them to migrate to intestinal tissue presenting chemokine CC ligand 20 [115]. Evidence suggests that the differentiation of Th17 cells is regulated by intestinal microbes and cytokines secreted by other immune cells.

Dissemination of translocated material

Gut lymphatics

The gut-associated lymphoid tissue (GALT) is a significant component of the immune system that plays a pivotal role in immune surveillance and tolerance to commensal microorganisms (microbiota) [118]. In sepsis, the gut lymphatic vessels play a dual role, they act as a conduit for the transfer of pathogens from the gut to distant organs, and they contribute to the systemic inflammatory response through dissemination of pro-inflammatory cytokines to other parts of the body [119]. The significance of the gut lymphatics in MODS and shock pathophysiology has been elegantly reviewed by Deitch [120].

Blood circulation

Once pathogens and their products breach the gut barrier, they may be carried in the bloodstream to distant organs. One of the defining features of sepsis is microvascular dysfunction [121]. The endothelial cells lining blood vessels become activated and compromised, leading to increased permeability of the blood vessel walls. This increased permeability can lead to leakage of fluid and proteins into the tissues, causing edema and impairing organ function. Additionally, the dysfunctional endothelial cells can themselves promote formation of microthrombi within blood vessels, further compromising blood flow and oxygen delivery to organs [122]. Further discussion of tissue/vascular leak pathophysiology in sepsis and septic shock may be found in McMullan et al. and Dargent et al. [123, 124].

Interplay between gut lymphatics and blood circulation

The relationship between the gut lymphatic system and the blood circulation in sepsis is both intricate and bidirectional. As gut-derived pathogens and their products enter the bloodstream, they can interact with circulating immune cells, triggering an immune response that can affect both local and distant organs. The systemic inflammatory response initiated by gut-derived factors can, in turn, impact gut lymphatic integrity and function [125]. Inflammation alters the permeability of the lymphatic vessels, affecting the flow of lymph and potentially leading to lymphatic dysfunction. This dysfunction can impair clearance of inflammatory mediators and immune cells, further perpetuating the vicious cycle of inflammation.

Systemic response to gut barrier failure

Systemic inflammation

Gastrointestinal barrier failure may result in dissemination of bacteria, bacterial products, soluble molecules, and non-microbial immunogenic proteins, such as gluten and casein, from the intestinal lumen into the systemic circulation. This systemic dissemination of intestinal content can lead to widespread inflammation and bacteremia, both of which may cause or perpetuate MODS [126]. Bacterial translocation releases MAMPs from the gut into host tissues. These include lipopolysaccharide (LPS, also called endotoxin), lipopeptides, and nucleic acids.

Gut failure can also lead to release of damage-associated molecular patterns (DAMPs) from stressed or dead host cells. DAMPs serve as signals of "danger" and heighten proinflammatory immune responses. MAMPs and DAMPs trigger pattern recognition receptors (PRR) on or within host cells (Table 1). The PRR consist of TLRs, nucleotide-binding and leucine-rich repeat receptors/nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and C-type lectin receptors (CLRs) [127]. PRR activation triggers intracellular signaling cascades that lead to release of cytokines, chemokines, and hormones that initiate inflammation, activate adaptive immunity, and activate coagulation [128–131]. Note that MAMPs and DAMPs can activate multiple PRRs, leading to multiple activation sites and amplification of MAMP and DAMP signals [127, 132]

Table 1 Innate immune activation in gut barrier failure

PRR target	Activated by
TLR2	**MAMPs**
	Gram-positive bacteria lipoteichoic acid
	Fungal β-Glucan
	Fungal zymosan
	DAMPs
	Histones
	HMBG1
	HSPs
TLR4	**MAMPs**
	Gram-negative bacteria LPS
	Fungal β-Glucan
	DAMPs
	DNA
	Mitochondrial DNA
	Histones
	High mobility group box 1 (HMGB1)
	Heat shock proteins (HSPs)
Other TLR groups	**MAMPs**
	Bacterial filaments
	Mycobacterial lipoarabinomannan
	Bacterial triacyl lipoproteins
	Bacterial and fungal CpG
	Viral ssRNA
	DAMPs
	Host RNA and/or DNA
NOD-like receptors (NLRs)	**MAMPs**
	Viral ssRNA
	Gram negative bacteria cell wall
	Bacterial cell wall muramyl dipeptide
RIG-I-like receptors (RLRs)	**MAMPs**
	Viral nucleic acids
C-type lectin receptors (CLRs)	**MAMPs**
	Fungal carbohydrates

DAMP, damage associated molecular proteins; LPS, lipopolysaccharide; MAMP, microbe-associated molecular protein; NOD, nucleotide oligomerization domain; PRR, pattern recognition receptor; RIG, retinoic acid-inducible gene I; TLR, toll-like receptor

TLR signaling, the best characterized of the PRR, is mediated via two main pathways: The myeloid differentiation factor 88 (MyD88) pathway and the TIR domain-containing adaptor inducing IFN-β–mediated transcription factor (Trif) pathway. (Fig. 4) The MyD88-dependent pathway is activated by all TLRs, with the exception of TLR3, and leads to activation of the transcription factor nuclear factor kappa B (NF-κB). NF-κB activation triggers its translocation to the cell nucleus, resulting in the upregulation of leukocyte adhesion molecules and cytokines that mediate leukocyte activation and recruitment [133]. The Trif-dependent signaling pathway is employed by TLR3 and TLR4 and triggers upregulation of type I interferon and inflammatory cytokines through the transcription factor interferon regulatory factor 3 (IRF3) [133]

In parallel to the proinflammatory response, anti-inflammatory responses are also initiated to prevent unbalanced overactivation of the immune system and damage to host tissues. The anti-inflammatory response is mediated by neuroendocrine and parasympathetic pathways that down regulate TNFα and IL-6 [134]. These anti-inflammatory pathways may also be responsible for enhanced susceptibility to secondary infections in the later stage of sepsis. Translocated microbes or their components clearly influence innate and adaptive immune activity throughout the body. However, evidence that bacterial translocation occurs more often in immunocompromised individuals argues that these systems also participate in maintaining the mucosal barrier and the normal composition of the microbiota [135, 136].

Liver dysfunction

The gut and liver engage in extensive molecular crosstalk essential for digestion, nutrient metabolism, and clearance of cell debris and bacterial products [137]. The interaction is bidirectional since liver disease is often associated with dysbiosis and in turn, changes in the composition of the microbiota can negatively affect antitumor mechanisms in the liver [138, 139]. The impact of the microbiota on the liver is also exemplified by the finding that fecal microbial transfer or transplantation (FMT) from septic patients caused more severe liver injury in mice subjected to cecal ligation puncture, compared to mice receiving FMT from healthy individuals [140]. The influence of the liver on the gut was demonstrated by a study showing that hepatic sinusoidal endothelial cells play an important role in the integrity of the gut-liver barrier axis [141].

Both cirrhosis and sepsis are characterized by a hyperdynamic state with low systemic vascular resistance and the release of endogenous vasodilators [142]. In both, changes in intestinal permeability and bacterial translocation promote intra-abdominal hypertension, which in

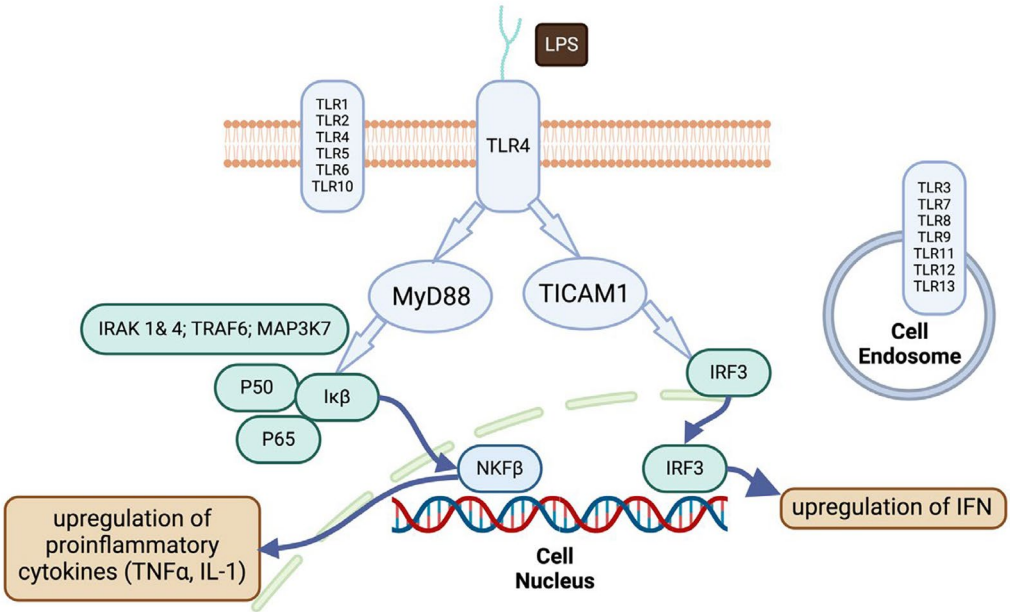

Fig. 4 TLR signaling activated by GI failure. TLR are responsible for detection of microbial components that cross the gut mucosal barrier into host tissues. The best characterized of the TLR is TLR4, which senses LPS from Gram negative bacteria. IL-1, interleukin; IFN, interferon; IRAK, IL-1 receptor associated kinase; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; MAP3K7, mitogen-activated protein kinase kinase 7 (also known as TAK1); TIR, toll/interleukin-1 receptor; TLR, toll like receptor; TNFa, tumor necrosis factor alphal; TICAM1, Toll-IL-1 receptor domain-containing adaptor molecule (also known as TRIF). Created with Biorender.com.

turn, may lower effective perfusion pressure to the gut and promote intestinal edema. This may cause intestinal ischemia as well as increased oxidative stress and inflammation, all of which may further exacerbate intestinal barrier disruption and failure [143].

Neurologic dysfunction

The brain is commonly affected in septic patients. Sepsis-induced encephalopathy is the most common presentation, with signs ranging from mild delirium to coma [144, 145]. As with the liver, communication between the gut and the central nervous system is bidirectional. In normal individuals, the central nervous system (CNS) influences gut-resident immune cells, which in turn, influences the composition of the microbiota [146]. Likewise, the intestinal microbiota influences the CNS via production of metabolites, such as short chain fatty acids, that modulate neuronal inflammation [147]. The microbiota may also affect blood brain barrier permeability and vagal nerve activation [148, 149]. In healthy states, gut microbes produce or metabolize many neurotransmitters or their precursors. For example, *Bifidobacterium* and *Lactobacillus* species normally produce gamma amino butyric acid (GABA), the main inhibitory neurotransmitter in the CNS. During sepsis, changes in the gut microbiota also affect the function of the CNS through alterations in the abundance or functions of microbes that lead to changes in the types or amounts of neurotransmitters delivered from the gut, resulting in altered mental states [150]. Disease-associated gut microbiota also promote neuroinflammation due to decreased short chain fatty acid production [151]. Finally, the immune response to sepsis is constrained by vagal nerve stimulation (also known as the cholinergic anti-inflammatory response) [152]. In this process, stimulation by inflammatory mediators leads to vagal nerve signaling to the spleen, resulting in the release of acetylcholine, which in turn, activates cholinergic receptors on macrophages, causing them to decrease the release of pro-inflammatory cytokines [153].

Cardiovascular dysfunction

Sepsis is associated with glycocalyx disruption and endothelial injury which often results in increased capillary leak and interstitial edema. In addition, sepsis is often characterized by hypovolemia and hypotension, as well as decreased vascular tone, which is mainly attributed to increased levels of nitric oxide and peroxynitrites [154]. These factors combine to decrease organ perfusion, resulting in inadequate cellular oxygen delivery and lactic acidosis [126]. This may be further exacerbated by microcirculatory failure, due to direct effects of inflammatory mediators, vasodilation, interstitial edema, and microthrombi formation [155]. Sepsis also leads to myocardial dysfunction due to direct myocardial toxicity caused by inflammatory mediators [156].

LPS release from the compromised gut

Detection of LPS in host tissues

Over a century of work has defined LPS as a microbe-derived mediator of critical illness [157]. LPS is a major component of the Gram-negative bacterial cell wall that is composed of an oligosaccharide inner and outer core, a lipid A moiety, and sometimes a polysaccharide O antigen facing external space. LPS is shed into the environment as aggregates and can be strongly immunostimulatory in mammals, triggering endotoxic shock on its own and contributing to severe infection pathogenesis [158, 159]. It is such an important indicator of infection that mammals have evolved at least three LPS detecting pathways that rely on cellular reception (TLR4/LY96, BAI1, human CASP 4/5/, and mouse CASP 11/12), and at least another five based on serum factors that either bind and neutralize LPS (complement, acyloxyacyl hydrolase, lactoferrin) or bind and deliver it to TLR4/LY96 complexes (high density lipoprotein binding protein, bactericidal permeability increasing protein) [160].

A common myth of immunology is that LPS is highly conserved across large swaths of bacterial species and, therefore, stimulates LPS detecting pathways to the same degree regardless of source bacteria. In truth, lipid A and O antigen configurations are highly variable and fluid, not just between bacteria species but within them. For example, *Escherichia coli* O55:B5, a pathogenic bacterium, maintains a highly immunostimulatory lipid A with 6-acyl chains, and a short O antigen, whereas *E. coli* K12, a non-pathogenic bacterium, has no O antigen [161, 162]. Mammals have evolved to readily detect lipid A with five or more acyl chains, a configuration of lipid A that is very common in commensal gut bacteria found in humans and other mammals [163]. O antigen, which can be detected by complement, and receptors such as CD14 and C-type lectin-2, has far less immunostimulatory potential. Both components fulfill important functions including biofilm formation, protection from environmental insults such as antibiotics and host antimicrobial peptides, interactions with other bacteria, and stimulation/manipulation or escape from host responses and immune factors [164–169]. Modification of both O antigens and lipid A are common bacterial responses to environment changes such as temperature, sheer, and immunological or chemical stress [170–174]. Thus, while the effects of LPS and Gram-negative bacterial leakage from the gut may contribute to broadly similar clinical pathologies, immunologically the host pathways and cells engaged are at least partially dependent on LPS structure.

LPS sensitivity and tolerance

Mammals have evolved strongly differing sensitivities to LPS, and the mechanisms governing these differing responses are far from clear. (Fig. 5A) Humans are exquisitely sensitive to very small doses of LPS (2–4 ng/kg, intravenously) [175]. In contrast, close monkey relatives (baboons and macaques) and mice require at least 100 µg/kg to exhibit similar symptoms [160]. Stimulating shock with LPS from commensal *E. coli* in these species requires a biologically unlikely 6–25 mg/kg dose, compared to a 2–15 µg/kg dose incidentally established in humans [160]

Physiological and transcriptional responses to LPS are highly dependent on the location/route of administration, type of LPS, and other bacterial signals delivered with LPS. However, these inter-experimental variations do not explain the stark differences in LPS sensitivity observed between humans and other species [159, 175]. Importantly, the pattern of LPS sensitivity in mammals departs from species evolutionary relationships. The only animals approaching human sensitivity to LPS are rabbits, mounting symptoms at roughly tenfold the symptomatic dose for humans [176, 177]. Examination of LPS detection and response mechanisms in humans, monkeys, and mice has provided ample evidence of differences in LPS sensitivity between humans and their most common biomedical models [160, 178–183]. This is a profound problem for development of interventions aiming to sequester or degrade LPS since indicators of LPS bioactivity are substantially blunted in pre-clinical animal models compared to humans. For example, scaling LPS doses from minimal symptoms to severe infection in monkeys and mice causes them to bypass hyperdynamic phases of sepsis unless the doses are continuously infused, leading to endotoxic intoxication, as opposed to severe infection complicated by LPS translocation [159, 184].

Systemic effects of LPS

Systemic effects of LPS include deleterious effects on the cardiac, pulmonary, hepatic, renal, vascular, and neurological systems as well as the metabolome (Fig. 5B) [185–197] Crosstalk between organs or cascades of organ involvement can also influence the severity of disease. This last concept was illustrated in a piglet model of acute lung injury in which the investigators perfused only the ventilated lung or both the lung and liver with LPS. Interestingly, when both the lung and liver were perfused, lung injury was much worse than when the lung alone was perfused [188].

Diagnosing GI failure

Clinical assessment of GI function

Diagnosing GI failure in critical illness is challenging due to the large number of functions that the GI tract performs and the lack of clinically measurable indicators of GI function. Signs of GI failure are also frequently nonspecific. For example, one of the most common signs of

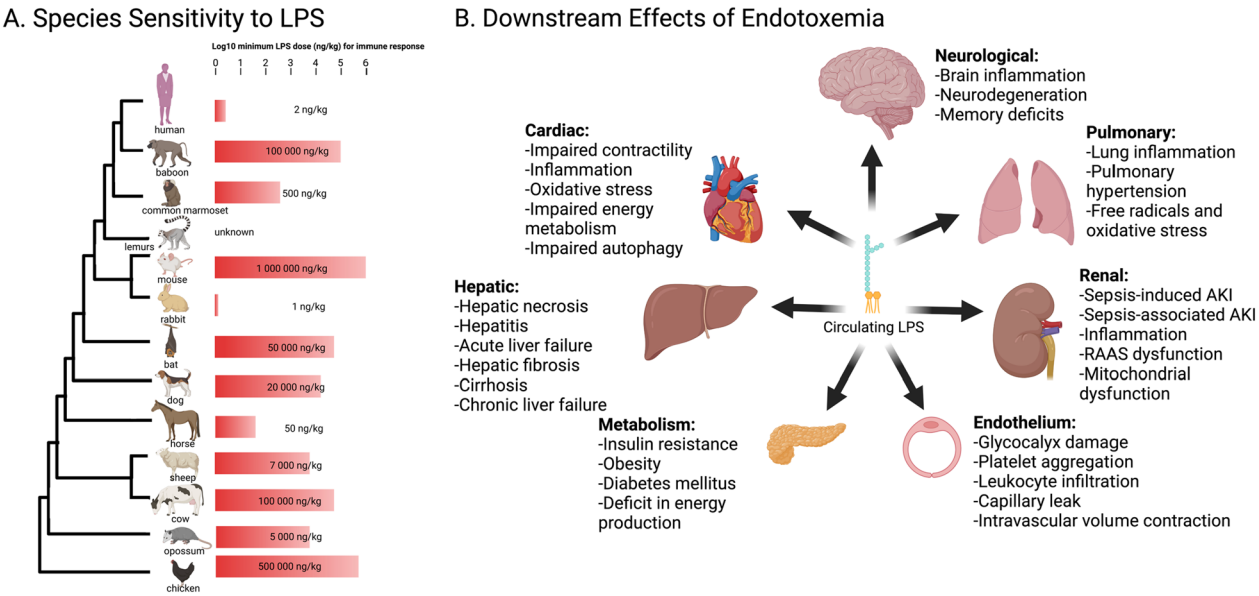

Fig. 5 Susceptibility to endotoxemia and downstream systemic effects. **A** Humans are much more sensitive to LPS than most other species. **B** Endotoxemia results in systemic sequelae, impacting numerous organ systems and may result in multi-organ dysfunction. LPS, lipopolysaccharide. Created with BioRender.com

GI failure is abdominal distention. Abdominal distention can be secondary to dilation of intestinal loops caused by obstruction or paralytic ileus. However, it can also be caused by peritoneal fluid collection (ascites) or solid organ tumors.

A number of different techniques have been developed to assess GI function, although few enjoy widespread use. Imaging techniques including X-radiography, computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) can differentiate among structural causes of disease, but they provide no information about other aspects of GI function such as gut barrier integrity. Gastric residual volume measurement is commonly used in conjunction with enteral feeding and is thought to be an indirect assessment of GI peristalsis [198]. However, studies have not shown a clear correlation between gastric residual volume and outcomes [199]. Gastric tonometry uses a gastric balloon to measure partial pressure of CO_2 (PCO_2) and pH in the stomach mucosa [200]. This technique has largely been abandoned due to complications associated with the invasive nature and difficulty of the procedure, the failure of tonometry data to change outcomes in critically ill patients on meta-analysis, and the advent of superior tools to assess splanchnic blood flow [201].

Since no standardized method for daily monitoring of GI function exists in the ICU, a large international effort recently proposed a core outcome set for daily monitoring of GI function in all critically ill patients. This involved a modified Delphi consensus as well as a systematic review of existing parameters in a two stage process that involved 181 participants. Out of a toal of 77 potential outcomes, a total of 13 essential outcomes was proposed for daily monitoring of GI function in future studies, with a specifically described definition for each outcome. The effort proposed assessment of the following outcomes: abdominal distension, bowel dilatation, intra-abdominal pressure, abdominal pain, stool passage, vomiting, GI bleeding (upper and lower), use of parenteral nutrition due to intolerance of enteral nutrition, prokinetics, postpyloric feeding due to gastroparesis, lower GI paralysis, gastroparesis, and intolerance to enteral nutrition. Ideally, this core outcome set and associated definitions will provide a framework to guide future research in GI dysfunction in all critically ill patients [202].

Assessing the gut microbial barrier

Enterocyte-related biomarkers

Two enterocyte-related biomarkers have been proposed as measures of gut barrier integrity (1) plasma citrulline, a marker of functional enterocyte mass, and (2) plasma or urinary intestinal fatty acid-binding protein (I-FABP), a marker of enterocyte injury [203, 204]. Citrulline is an amino acid that is primarily synthesized by enterocytes, but not incorporated into proteins [205, 206]. After synthesis, citrulline is released into the portal circulation, passes through the liver, and then enters systemic circulation. In the kidneys citrulline is converted into arginine, which is released back into circulation [207]. Therefore, plasma citrulline concentration reflects the equilibrium between enterocyte synthesis/release and renal conversion to arginine. In individuals with normal kidney function, a decrease in plasma citrulline usually reflects a reduction in intestinal synthesis due to loss of functional enterocytes [208, 209]. Clinical trials have demonstrated that decreased plasma citrulline is associated with sepsis, bacterial translocation (although not with LPS concentration), acute gastrointestinal injury, and higher 28-day mortality [210–214]. Intestinal fatty acid-binding protein (I-FABP) is a 14-kD protein that has a role in lipid absorption in the small intestine [215]. Under normal conditions, I-FABP is present only within the enterocyte cytosol, and detection of it in the plasma or urine is indicative of intestinal injury [216–219]. I-FABP may be an early marker for intestinal or mesenteric ischemia and has been shown to correlate with mortality [220–223].

Both citrulline and I-FABP have shown promise as biomarkers of intestinal barrier dysfunction in small clinical trials [214, 224]. However, the largest prospective trial to date (540 critically ill patients) failed to demonstrate a correlation between citrulline or I-FABP levels and higher GI dysfunction score or survival [225]. Furthermore, additional challenges limit use of citrulline and I-FABP in clinical practice. First, neither plasma citrulline nor I-FABP measurements are available in real time for clinical use. Current assays are time consuming and not widely clinically available [203]. Second, interpretation of plasma citrulline levels needs to be considered in the context of kidney function. Kidney dysfunction can result in normalization of citrulline concentrations secondary to decreased conversion to arginine, even if enterocyte functional mass is low [226]. Alternatively, citrulline level may be low in glutamine deficiency even with normal intestinal activity. Lastly, normal threshold levels for both citrulline and I-FABP have not been determined [227–229].

Other biomarkers of gut barrier failure

Zonulin is a human protein that was originally identified in the intestine and shares significant structural similarities with a *Vibrio cholera* toxin called zonula occludins toxin (Zot) [230]. Zot acts on tight junctions to increase epithelial permeability and zonulin has a similar effect on the intestinal epithelium [231]. Zonulin was initially thought to be specific to the intestine, but was later discovered to be identical to pre-haptoglobin-2, which

is synthesized in the liver as part of the acute phase response [232]. Zonulin dysregulation has been reported in a wide range of diseases associated with mucosal barrier failure, including sepsis [233–236]. However, data regarding performance of zonulin as a biomarker in critical illness remains scarce, and technical problems have been reported with commercially available zonulin ELISA kits [237–240]. Furthermore, increased serum zonulin has been reported in many conditions associated with chronic, low grade mucosal barrier damage, including autoimmune diseases, diabetes, obesity, neurological and cognitive impairments, ageing, and cancer [240–250].

CD14 is a receptor molecule produced primarily by macrophages and hepatocytes as part of the innate immune surveillance for LPS and endotoxemia [251, 252]. Microbial translocation and LPS release from the gut into deeper tissues leads to activation of the TLR4 complex, which includes CD14 [253, 254]. CD14 is anchored to myeloid cell membranes and released as a soluble form (sCD14) when the cells are activated by LPS [255]. These characteristics have led to the use of sCD14 as a surrogate marker for bacterial translocation and gut barrier dysfunction, and even as a potential target for developing monoclonal antibodies to treat sepsis [256, 257]. However, similar to zonulin, elevation of sCD14 is not specific to gut barrier dysfunction and has been reported in numerous other conditions including autoimmune diseases, consumption of a "western diet" (higher intake of red meats, sugars, and processed grains), high alcohol intake, atherosclerosis and metabolic syndrome, neuropsychiatric disorders, cancer, and HIV infection [258–269].

Therapeutic interventions

Supportive GI care

Nutrition

Enteral nutrition (EN) is important for recovery of the damaged gut. However, EN in patients on vasopressors, a major subset of critically ill patients, remains a topic of debate. Evidence of this debate permeates the literature as evidenced by publications entitled "Enteral Nutrition Can Be Given to Patients on Vasopressors" and "Enteral Nutrition Should Not Be Given to Patients on Vasopressor Agents" [270–276]. The reality of providing enteral nutrition to patients on vasopressors is likely rather nuanced, with a number of factors to consider including degree of instability, vasopressor dose, vasopressor agent(s), route of administration of enteral nutrition (gastric vs. post-pyloric), formulation of enteral nutrition, amount of enteral nutrition (trophic vs. full feeds), and likely the underlying disease process.

GI perfusion

Gastrointestinal perfusion is vital for delivery of oxygen and nutrients and removal of toxic metabolic byproducts from the gut mucosa. As with all organs, oxygen delivery depends upon arterial oxygen saturation (SaO_2) and hemoglobin levels in the blood, although the gut is far more tolerant of anemia than many other organs [277]. GI perfusion is dependent on cardiac output, intravascular volume and vascular tone. Ensuring euvolemia can be clinically challenging since it can be masked by compensatory mechanisms that normalize most commonly measured hemodynamic variables, including measures of venous pressure or estimates of capacitance [278]. This difficulty can be at least partially overcome by fluid challenge with assessment of dynamic responses, such as the change in stroke volume. Fluid challenge has been shown to reduce the incidence of gut mucosal hypoperfusion in patients undergoing some forms of surgery, although it does carry a risk of rendering patients moderately net fluid positive [279]. The gut is much more sensitive to hypovolemia than other organs such as the heart or brain. However, excessive fluid administration or fluid overload can also impair gut mucosal perfusion. This demonstrates the importance of careful monitoring and individualized fluid management to prevent fluid overload and its negative effects on gut mucosal perfusion.

Vasopressors are often used to maintain blood pressure and central blood volume in critically ill patients. Prior to vasopressor administration, it is important to ensure adequate fluid volume since mild fluid restriction has been shown to cause worse outcomes than moderately liberal fluid balance in adult patients after major intracavity surgery [280]. Balancing this are the facts that a) a fairly robust body of literature suggests that there is no difference in conservative vs. liberal fluid administration strategies in critical illness and b) there are many who believe (with some physiological rationale) that earlier pressor administration is beneficial. The fluid vs vasopressor debate is far from settled – for example in a large retrospective cohort analysis of adults undergoing major noncardiac surgery, the exclusive use of intraoperative phenylephrine was associated with increased risk of acute kidney injury [281]. The balance between fluid administration and use of vasoactive agents is more complicated in sepsis and established critically ill patients [28, 282]. However, it is reasonable to assume that restoring intravascular blood volume should precede the use of moderate to high dose vasopressors.

Inflammation and immune activation

Local and systemic inflammation and immunity activated in response to gut barrier failure can in turn perpetuate

intestinal damage and impair healing. These processes also impact the gut microbiota and contribute to dysbiosis and microbial mechanisms of disease. Thus, treating inflammation and immunity in critical illnesses can be an important component of therapy to restore gut homeostasis. However, these types of therapies are not selective for the gut and should be used with caution in the face of potential translocation of live microorganisms across the gut barrier.

Pattern recognition receptor (PRR) blockade

The goal of PRR-targeted therapies is to inhibit PRR activation or intracellular signaling pathways and limit inflammatory cytokine release (Table 2). One target for this type of therapy is triggering receptors expressed on myeloid cells (TREM-1), a PRR expressed on the surface of circulating neutrophils and monocytes. Many DAMPs bind to TREM-1, including nuclear proteins of leukocytes, Hsp70, and actin. Potential TREM-1 related diagnostics and therapeutics include a) soluble TREM-1, a cleaved form of TREM-1 that is increased during sepsis and thought to be a prognostic indicator of sepsis severity, b) LP17 which is a direct competitive inhibitor to the TREM-1 receptor, and c) a decoy receptor for TREM-1 [283]. Among the most interesting anti-TREM-1 therapeutics is nangibotide (also known as LR12), which has undergone both phase 2a and phase 2b (ASTONISH) trials for use in patients with septic shock [284–286]. Nangibotide is a 12 amino acid peptide that acts as a decoy receptor and binds the TREM-1 ligand [287]. Preclinical results with nangibotide were very promising and early trials suggested that it was safe in patients [284, 285, 287]. However, a recent phase 2b trial failed to achieve the primary outcome of improvement in Sequential Organ Failure Assessment (SOFA) score across all patients, although there was clinically relevant improvement in SOFA score of patients with higher soluble TREM-1 levels [286]

Decreasing cytokine production or blocking function

Cytokines are small proteins (mostly < 40 kDa) that are passed between host cells to coordinate responses to cell damage or infection. They are a subject of great interest in sepsis and other systemic inflammatory diseases since they regulate inflammatory and immune responses and are often dysregulated in critically ill patients. In fact, the term "cytokine storm" is used to refer to the massive increase in proinflammatory cytokine levels commonly seen in critically ill patients [288].

Cytokine production and release can be suppressed using drugs that somewhat non-specifically affect the cellular cytokine production pathways, such as corticosteroids [289]. Another drug in this group is recombinant human activated protein C, which inhibits the release of cytokines including IL-1β and IL-6 and is anti-apoptotic [290]. These have had different efficacy in clinical trials. The majority of studies on human activated protein C failed to show an improvement in survival [290–292].

Table 2 Potential therapeutic targets for the gut-sepsis "motor" [corresponds to the numbers found in Fig. 4]

Location	Specific target	Examples
1. Mucosal Barrier	Commensal microbiota	Probiotics, FMT, Nutrition
	Mucins, defensins, antimicrobial peptides	Brilacidin [343, 344]
2. Tight Junctions	Extracellular occludins, claudins and junctional adhesive molecules	Cholecystokinin Myosin light chain kinase
	Intracellular zonula occludens	Growth arrest-specific protein 6 Emodin
3. Pattern Recognition Receptors	Toll-Like Receptors	Berberine
	Triggering receptors expressed on myeloid cells	Nangibotide Soluble TREM-1
4. Intracellular Signaling	NF-κB signaling pathway	Corticosteroids
5. Nuclear Transcription	NET	Ethyl pyruvate
	JAK	Jakinibs
	STAT	STAT3 inibitors
	GPCR	SPMs
6. Blood	MAMPs, LPS Cytokines	Blood Purification: Polymethylmethacrylate Polymyxin B
	Complement	C5a receptor antagonist
	Coagulation cascade	Recombinant activated protein C

GPCR, G-protein coupled receptors; JAK, Janus kinase; LPS, lipopolysaccharide; MAMP, microbe-associated molecular pattern; NET, neutrophil extracellular trap; SPM, specialized pro-resolving mediators; STAT, signal transducer and activator of transcription; TREM, Triggering receptors expressed on myeloid cells

In contrast, corticosteroids have been shown to improve survival in both randomized controlled studies and meta-analyses in septic shock (and more recently community acquired pneumonia), and are recommend by international consensus guidelines [293–299]. Janus kinases (JAK) are involved in intracellular signaling pathways that touch more than 50 cytokines and growth factors [300]. Drugs targeting JAKs decrease the expression of cytokines implicated in sepsis including TNF-α and IL-6, so they may be useful in sepsis [301]. However, rebound release can occur once JAK inhibitors are discontinued and chronic use is associated with increased risk of infection [300]. Finally, several monoclonal antibodies that directly target cytokines have been tested in septic patients [302]. Tumor necrosis factor alpha is among the most thoroughly studied of the sepsis-associated cytokines and has been implicated in many of the systemic signs of sepsis [303]. For this reason anti-TNF agents have been tested in septic patients over at least 15 clinical trials [304, 305]. While results from these trials have not been encouraging for anti-TNF efficacy, meta-analysis suggested that further studies may be warranted [305].

Manipulating the cellular components of inflammation and immunity

Innate immune cells such as neutrophils and macrophages as well as adaptive immune cells such as B- and T-cells play many important roles in both resolving and perpetuating critical illness. These cells produce and respond to many of the signals already defined as potential therapeutic targets. However, they also have unique features that are being exploited for therapy. For example, Gi-coupled G-protein coupled receptors (GPCRs) are a family of cell surface receptors on phagocytes and lymphocytes that mediate directional migration. Blocking these GPCRs can prevent accumulation and activation of leukocytes, reducing inflammation and cell damage [306]. Conversely, stimulating phagocytes with cytokines such as IFN-γ, IL-7, and IL-15 can increase phagocytosis and killing capacity of these cells. Finally, increased leukocyte recruitment and bacterial clearance have been reported with use of the SIRT1 inhibitor, EX-527, in a model of abdominal sepsis [307].

Gut mucosal barrier

Treatments that restore the gut barrier and prevent bacterial translocation have the potential to remove underlying causes of infection, inflammation, and immune activation in critical illness [308]. The majority of therapies in this space are related to restoring or reinforcing junctions between epithelial cells. One of the most interesting of the junction-targeting drugs is larazotide acetate (LA; AT-1001), a single-chain eight amino acid (peptide) zonulin antagonist [309]. LA is thought to act via competitive inhibition of zonulin, preventing its binding to target receptors [236, 309, 310]. Additionally, LA appears to promote tight junction assembly via rearrangement of actin myofilaments and stabilization of tight junction structure [311]. One of the most useful aspects of LA is that it is not systemically absorbed, so its effect can be limited to the GI tract, potentially reducing systemic toxicity. LA has been shown to restore intestinal barrier function in patients with celiac disease and in preclinical models of intestinal injury [311, 312]. LA was also tested in a small number of children with multi-system inflammatory syndrome due to *SARS-CoV-2* where it appeared safe and improved time to resolution of GI symptoms [313]. However, a recent large phase 3 clinical trial for this drug in celiac disease was halted due to disappointing results [314].

Microbes or their components

Probiotics

Probiotics are live microorganisms that are introduced into the body with the intent that they provide a health benefit to the host. In contrast, prebiotics are non-digestible nutrients that stimulate commensal bacterial growth, while synbiotics combine probiotics and prebiotics. Of these, probiotics have been studied in significantly more detail in critical illness than prebiotics or synbiotics. The largest study of probiotics examined 2653 patients requiring mechanical ventilation for greater than 72 h in 44 ICUs that were given *Lactobacillus rhamnosus* GG [315]. No difference was noted in the primary outcome of ventilatory associated pneumonia and/or 20 other pre-specified secondary outcomes. Additionally, there were potentially some safety concerns as 15 patients in the experimental group had the probiotic organism present in a sterile site or as the predominant organism in a non-sterile site compared to a single patient in the control group. The largest meta-analysis on probiotics in critical illness included 65 randomized controlled trials with 8,483 patients [316]. The analysis demonstrated that probiotics may reduce the risk of ventilator-associated pneumonia, healthcare-associated pneumonia, ICU length of stay, hospital length of stay and duration of invasive mechanical ventilation (all with low certainty). However, post-hoc sensitivity analyses without high risk of bias studies negated the beneficial effect of probiotics on nearly all outcomes including mortality (moderate certainty). Similar findings were reported in a 2024 meta-analysis of probiotics and synbiotics in critical illness, that found decreased risk of ventilator associated pneumonia and length of mechanical ventilation without a change in hospital mortality [317].

Fecal microbial transplantation (FMT)

FMT is the transfer of an entire intestinal microbial community from a healthy donor to a diseased recipient. There have been numerous successful uses of FMT, most notably for recurrent *Clostridia difficile* colitis, for which the FDA recently approved its first fecal microbiota product [318–320]. There are, however, many barriers to using FMT in the ICU. The majority of critically ill patients receive antibiotics, and initiation or continuation of antibiotics will almost certainly alter the microbiome after FMT. As such, there must be a commitment to stopping antibiotics prior to FMT, which is frequently difficult to do in the ICU setting. In addition, the impact of giving bacteria to a patient with an already altered microbiome or damaged mucosal barrier is unknown, especially considering that many patients in the ICU are immunosuppressed. Further, rare reports of drug resistant bacteremia have been described following FMT, raising safety concerns [321]. Despite these well-deserved cautionary tales, FMT has proven to be successful in the ICU in select cases, although its use should be considered experimental [322, 323].

Selective digestive tract decontamination

In contrast to probiotics and FMT which are intended to increase the "good" bacteria in the host (understanding that bacteria are not inherently good or bad), selective decontamination of the digestive tract (SDD) aims to prevent or eradicate oropharyngeal and intestinal carriage of pathogens without adversely impacting the remaining microbiome of the patient or the entire ICU. Despite its relatively low usage worldwide, the data supporting SDD are compelling. A 2021 meta-analysis of 41 trials with over 11,000 patients on mechanical ventilation demonstrated decreased mortality with an odds ratio of 0.84 (95% CI 0.73 to 0.96), translating to 48 fewer deaths per 1000 patients. SDD also drastically reduced respiratory tract infections with an odds ratio of 0.43 (95% CI − 0.35 to 0.53), translating to 238 fewer infections per 1000 patients [324]. Although this sounds quite impressive, nearly all studies were performed in a single country with low baseline antimicrobial resistance. Two subsequent trials have partially clarified the role of SDD. A study of 8,665 patients receiving mechanical ventilation in ICUs with moderate to high risk of antimicrobial resistance demonstrated no difference between SDD, oral decontamination, or chlorhexidine mouthwash for either ICU-acquired bacteremia with resistant Gram-negative infections (primary outcome) or mortality (secondary outcome) [325]. Further, a study randomizing 5,982 patients on mechanical ventilation to SDD or standard of care demonstrated no difference in mortality (primary outcome) or the proportion of antibiotic resistant organisms [326]. While an updated meta-analysis of 32 randomized trials including 24,389 patients showed SDD was associated with lower mortality, it should be noted that the vast majority of positive trials were published well over a decade ago and are in settings with low antimicrobial resistance [327].

Extracorporeal blood purification

Extracorporeal blood purification (EBP) therapies can be used to clear microbes or microbial components from the bloodstream [193]. While EBP therapies are often utilized in-line with kidney replacement therapy, these modalities can also be used on their own, although they do require vascular access. EBP can be performed via hemadsorption or plasmadsorption, depending on the modality and is selected based on the patient's clinical need. Adsorptive extracorporeal therapies impact immune dysfunction via non-selective removal of cytokines, pathogens, endotoxin, and inflammatory factors. While adsorptive EBP therapies are neither commonly used, nor approved, in the United States, they are more widely used in Europe and Asia. EBP for LPS removal has been used clinically in Asia for several decades and has also recently been used successfully in neonates [328–330]. The EUPHRATES randomized control trial did not demonstrate improvement in 28-day survival from hemadsorption EBP in patients with septic shock and elevated LPS levels [331]. However, a post hoc analysis evaluating the efficacy in patients without extremely high serum levels of LPS did demonstrate benefit in survival and mean arterial blood pressure in treated patients compared to sham controls [332].

Antibiotics, vaccines, immunoglobulin, and monoclonal antibodies

Antimicrobial therapies may be of use in gut failure to manipulate dysbiosis or address translocation of live microbes out of the gut and into host tissues where they cause local or systemic infections. While early treatment with antibiotics remains the mainstay of treatment for bacterial infection, the growing problem of antibiotic resistance, and the paucity of new, effective antimicrobial agents, has led researchers to look for additional therapies [333]. Targets for bacterial vaccine development have generally been those that are surface accessible and crucial for disease, such as LPS [334]. Polyvalent vaccines have also been used to generate hyperimmune plasma enriched in antibodies against specific bacterial serotypes contained in the vaccines [335]. Monoclonal antibodies, especially recombinant monoclonal antibodies, are a more modern version of vaccination and hyperimmune serum [336]. Monoclonal antibodies against virulence factors such as adhesins, bacterial outer membrane

proteins or biofilms, and antibodies that enhance bacterial killing via complement activation or phagocytic opsonization are currently in development [89, 337–341]. Monoclonal antibodies can also be conjugated to drugs, including antibiotics, to facilitate targeted delivery and minimize side effects [342].

Critical research needs

In the course of the POQI conference and literature review, three critical questions were identified that must be answered in order to effectively treat patients with gut failure and critical illness.

How does the gut drive multiple organ dysfunction?

GI failure is thought to allow microbial contents of the gut to leak into host tissues, resulting in tissue damage, inflammation, and immune activation. While this is undoubtedly true, it has become clear that the specific nature of the gut content influences both the risk of failure and how disease develops after the barrier fails. It is also clear that the precise nature of barrier failure and its potential for repair depend on host factors that we do not yet understand. Mechanisms underlying loss of microbial diversity, induction of virulence factors, crosstalk among microbes and between microbes and host cells, as well as host responses to altered or uncontained microbiota are but a few of the knowledge gaps that require future research. Identifying which tight junctions mediate pore and leak permeability in critical illness and mechanisms responsible for their upregulation and downregulation is also a high priority. Finally, delineating mechanisms responsible for both gut epithelial and immune dysregulation is vital to understanding how the gut is dysregulated in critical illness [345].

How can we monitor the gut in critical illness?

In critical care, monitoring the gut currently involves measures of pain, abdominal distention, stool output, gastric residual volume, intraabdominal pressure, and organ integrity. Unfortunately, many of these measures are non-specific and their correlation to patient outcome is unclear. The GI dysfunction score has been proposed as a method of improving prognostication over the SOFA score but this needs validation [225, 346]. Further, new technologies that allow for real-time assessment of gut dysfunction and mucosal barrier failure are needed for development and application of therapeutic interventions that change patient outcomes. Future efforts should also prioritize rapid assessment of the microbiome, in addition to determining which components of the gut lumen to measure and where to measure them.

How do we target the gut to restore vital functions and reverse multiple organ dysfunction?

Novel strategies for preventing or treating gut failure in critical illness should consider both the host and microbial components of the gut. While multiple methods of targeting the microbiome are currently used, none has been convincingly shown to improve outcomes in a generalizable manner. Future research requires a move towards precision medicine where specific alterations in a patient's microbiome can be targeted with the best approach at the best time as opposed to a "one size fits all." For example, instead of giving a standing dose of probiotics, independent of patient-specific factors including whether the microbes given are even altered in a given host, targeting specific microbes that are altered specifically when they are altered may yield improved outcomes. Similarly, rather than giving an entire new microbiota via FMT, a more targeted approach may be beneficial. However, this would require both assessment of the microbiome in patients and clinical trials to determine best approaches. New therapeutics should also be developed to improve barrier function, decrease intestinal epithelial cell apoptosis, restore mucus, and control inflammation. Further, large randomized controlled trials are needed to investigate the use of enteral nutrition in patients on vasopressors and to determine which pressors are most likely to preserve intestinal blood flow in a clinically significant manner. Finally and most importantly, it is crucial that future studies determine the impact of targeting the gut on patient-centric outcomes including (but not limited to) survival, length of mechanical ventilation, and long-term quality of life. While there are published data on some of these outcomes on specific interventions (such as SDD), there is an overall paucity of evidence on the majority of these. While studies examining physiology and biochemical outcomes are assuredly important, clinical practice will only be changed by demonstrating changes in outcomes that are important to patients.

Summary

In critical illness, GI dysfunction is often the first event in a cascade that culminates in MODS and death. In addition, once MODS develops, the gut is continuously injured by a combination of factors intrinsic to critical illness (dysbiosis, ischemia, etc.) and unintended consequences of interventions not aimed at the gut but that injure components of the gut (proton pump inhibitors, antibiotics, opioids, etc.). Methods to detect gut failure and interventions that restore its functions and/or protect other organs from metabolic and microbial consequences of failure are urgently needed and represent an attractive future state in critical illness.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors approved the final manuscript and consented to publication.

Competing interests
MM is now an employee of Edwards Lifesciences.

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References

1. Kellum JA, Palevsky P, Mehta R, Bellomo R, Ronco C. Acute dialysis quality initiative: methodology. Curr Opin Crit Care. 2002;8:500–1. https://doi.org/10.1097/00075198-200212000-00002.
2. Kim HJ, Li H, Collins JJ, Ingber DE. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. Proc Natl Acad Sci USA. 2016;113:E7-15. https://doi.org/10.1073/pnas.1522193112.
3. Berg G, et al. Microbiome definition re-visited: old concepts and new challenges. Microbiome. 2020;8:103. https://doi.org/10.1186/s40168-020-00875-0.
4. Selber-Hnatiw S, et al. Human gut microbiota: toward an ecology of disease. Front Microbiol. 2017;8:1265. https://doi.org/10.3389/fmicb.2017.01265.
5. Hou K, et al. Microbiota in health and diseases. Signal Transduct Target Ther. 2022;7:135. https://doi.org/10.1038/s41392-022-00974-4.
6. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell. 2016;164:337–40. https://doi.org/10.1016/j.cell.2016.01.013.
7. Kolev HM, Kaestner KH. Mammalian intestinal development and differentiation-the state of the art. Cell Mol Gastroenterol Hepatol. 2023;16:809–21. https://doi.org/10.1016/j.jcmgh.2023.07.011.
8. Lueschow SR, McElroy SJ. The paneth cell: the curator and defender of the immature small intestine. Front Immunol. 2020;11:587. https://doi.org/10.3389/fimmu.2020.00587.
9. Hansson GC. Mucins and the microbiome. Annu Rev Biochem. 2020;89:769–93. https://doi.org/10.1146/annurev-biochem-011520-105053.
10. Suriano F, Nyström EEL, Sergi D, Gustafsson JK. Diet, microbiota, and the mucus layer: the guardians of our health. Front Immunol. 2022;13:953196. https://doi.org/10.3389/fimmu.2022.953196.
11. Ermund A, Schütte A, Johansson ME, Gustafsson JK, Hansson GC. Studies of mucus in mouse stomach, small intestine, and colon. I. Gastrointestinal mucus layers have different properties depending on location as well as over the Peyer's patches. Am J Physiol Gastrointest Liver Physiol. 2013;305:G341–7. https://doi.org/10.1152/ajpgi.00046.2013.
12. Johansson ME, et al. Normalization of host intestinal mucus layers requires long-term microbial colonization. Cell Host Microbe. 2015;18:582–92. https://doi.org/10.1016/j.chom.2015.10.007.
13. Volk JK, et al. The Nlrp6 inflammasome is not required for baseline colonic inner mucus layer formation or function. J Exp Med. 2019;216:2602–18. https://doi.org/10.1084/jem.20190679.
14. Horowitz A, Chanez-Paredes SD, Haest X, Turner JR. Paracellular permeability and tight junction regulation in gut health and disease. Nat Rev Gastroenterol Hepatol. 2023;20:417–32. https://doi.org/10.1038/s41575-023-00766-3.
15. Zuo L, Kuo WT, Turner JR. Tight junctions as targets and effectors of mucosal immune homeostasis. Cell Mol Gastroenterol Hepatol. 2020;10:327–40. https://doi.org/10.1016/j.jcmgh.2020.04.001.
16. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target? Nat Rev Gastroenterol Hepatol. 2017;14:9–21. https://doi.org/10.1038/nrgastro.2016.169.
17. Kuo WT, Odenwald MA, Turner JR, Zuo L. Tight junction proteins occludin and ZO-1 as regulators of epithelial proliferation and survival. Ann N Y Acad Sci. 2022;1514:21–33. https://doi.org/10.1111/nyas.14798.
18. Bhatia A, Shatanof RA, Bordoni B. In: StatPearls (StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., 2024).
19. Singhal R, Shah YM. Oxygen battle in the gut: hypoxia and hypoxia-inducible factors in metabolic and inflammatory responses in the intestine. J Biol Chem. 2020;295:10493–505. https://doi.org/10.1074/jbc.REV120.011188.
20. Cifarelli V, Eichmann A. The intestinal lymphatic system: functions and metabolic implications. Cell Mol Gastroenterol Hepatol. 2019;7:503–13. https://doi.org/10.1016/j.jcmgh.2018.12.002.
21. Miller MJ, McDole JR, Newberry RD. Microanatomy of the intestinal lymphatic system. Ann N Y Acad Sci. 2010;1207(Suppl 1):E21-28. https://doi.org/10.1111/j.1749-6632.2010.05708.x.
22. Gallo A, et al. The gut in heart failure: current knowledge and novel frontiers. Med Princ Pract. 2022;31:203–14. https://doi.org/10.1159/000522284.
23. Paraskevaidis I, Briasoulis A, Tsougos E. Oral Cardiac Drug-gut microbiota interaction in chronic heart failure patients: an emerging association. Int J Mol Sci. 2024. https://doi.org/10.3390/ijms25031716.
24. Amjad W, et al. Gastrointestinal side effects of antiarrhythmic medications: a review of current literature. Cureus. 2017;9: e1646. https://doi.org/10.7759/cureus.1646.
25. Asfar P, De Backer D, Meier-Hellmann A, Radermacher P, Sakka SG. Clinical review: influence of vasoactive and other therapies on intestinal and hepatic circulations in patients with septic shock. Crit Care. 2004;8:170–9. https://doi.org/10.1186/cc2418.
26. Takala J. Determinants of splanchnic blood flow. Br J Anaesth. 1996;77:50–8. https://doi.org/10.1093/bja/77.1.50.
27. Jozwiak M, et al. Vasopressors and risk of acute mesenteric ischemia: a worldwide pharmacovigilance analysis and comprehensive literature review. Front Med (Lausanne). 2022;9:826446. https://doi.org/10.3389/fmed.2022.826446.
28. Woolsey CA, Coopersmith CM. Vasoactive drugs and the gut: is there anything new? Curr Opin Crit Care. 2006;12:155–9. https://doi.org/10.1097/01.ccx.0000216584.72427.e4.

29. Hamilton-Davies C, et al. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med. 1997;23:276–81. https://doi.org/10.1007/s001340050328.
30. Davies SJ, Mythen M. Hemodynamic and intestinal microcirculatory changes in a phenylephrine corrected porcine model of hemorrhage. Anesth Analg. 2021;133:1060–9. https://doi.org/10.1213/ane.0000000000005388.
31. Hotchkiss RS, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med. 1999;27:1230–51. https://doi.org/10.1097/00003246-199907000-00002.
32. Turnbull IR, et al. Age disproportionately increases sepsis-induced apoptosis in the spleen and gut epithelium. Shock. 2004;22:364–8. https://doi.org/10.1097/01.shk.0000142552.77473.7d.
33. Yoseph BP, et al. Chronic alcohol ingestion increases mortality and organ injury in a murine model of septic peritonitis. PLoS ONE. 2013;8:e62792. https://doi.org/10.1371/journal.pone.0062792.
34. Morris NL, Cannon AR, Li X, Choudhry MA. Protective effects of PX478 on gut barrier in a mouse model of ethanol and burn injury. J Leukoc Biol. 2021;109:1121–30. https://doi.org/10.1002/jlb.3a0820-323rr.
35. Meng M, et al. Regulators of intestinal epithelial migration in sepsis. Shock. 2019;51:88–96. https://doi.org/10.1097/shk.0000000000001117.
36. Husain KD, et al. Mechanisms of decreased intestinal epithelial proliferation and increased apoptosis in murine acute lung injury. Crit Care Med. 2005;33:2350–7. https://doi.org/10.1097/01.ccm.0000182797.89252.a3.
37. Chen WY, et al. Acrolein disrupts tight junction proteins and causes endoplasmic reticulum stress-mediated epithelial cell death leading to intestinal barrier dysfunction and permeability. Am J Pathol. 2017;187:2686–97. https://doi.org/10.1016/j.ajpath.2017.08.015.
38. Otani S, et al. Overexpression of BCL-2 in the intestinal epithelium prevents sepsis-induced gut barrier dysfunction via altering tight junction protein expression. Shock. 2020;54:330–6. https://doi.org/10.1097/shk.0000000000001463.
39. Coopersmith CM, et al. Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. JAMA. 2002;287:1716–21. https://doi.org/10.1001/jama.287.13.1716.
40. Coopersmith CM, et al. Overexpression of Bcl-2 in the intestinal epithelium improves survival in septic mice. Crit Care Med. 2002;30:195–201. https://doi.org/10.1097/00003246-200201000-00028.
41. Fox AC, et al. Prevention of lymphocyte apoptosis in septic mice with cancer increases mortality. J Immunol. 2011;187:1950–6. https://doi.org/10.4049/jimmunol.1003391.
42. Oami T, et al. Chronic ethanol use worsens gut permeability and alters tight junction expression in a murine sepsis model. Shock. 2023;60:280–90. https://doi.org/10.1097/shk.0000000000002162.
43. Yoseph BP, et al. Mechanisms of intestinal barrier dysfunction in sepsis. Shock. 2016;46:52–9. https://doi.org/10.1097/shk.0000000000000565.
44. Li Q, et al. Disruption of tight junctions during polymicrobial sepsis in vivo. J Pathol. 2009;218:210–21. https://doi.org/10.1002/path.2525.
45. Clark JA, et al. Enterocyte-specific epidermal growth factor prevents barrier dysfunction and improves mortality in murine peritonitis. Am J Physiol Gastrointest Liver Physiol. 2009;297:G471-479. https://doi.org/10.1152/ajpgi.00012.2009.
46. Khailova L, Baird CH, Rush AA, Barnes C, Wischmeyer PE. Lactobacillus rhamnosus GG treatment improves intestinal permeability and modulates inflammatory response and homeostasis of spleen and colon in experimental model of Pseudomonas aeruginosa pneumonia. Clin Nutr. 2017;36:1549–57. https://doi.org/10.1016/j.clnu.2016.09.025.
47. Tatucu-Babet OA, et al. Use of a sensitive multisugar test for measuring segmental intestinal permeability in critically ill, mechanically ventilated adults: a pilot study. JPEN J Parenter Enteral Nutr. 2022;46:454–61. https://doi.org/10.1002/jpen.2110.
48. Burgstad CM, et al. Sucrose malabsorption and impaired mucosal integrity in enterally fed critically ill patients: a prospective cohort observational study. Crit Care Med. 2013;41:1221–8. https://doi.org/10.1097/CCM.0b013e31827ca2fa.
49. Oami T, et al. Claudin-2 upregulation enhances intestinal permeability, immune activation, dysbiosis, and mortality in sepsis. Proc Natl Acad Sci USA. 2024;121:e2217877121. https://doi.org/10.1073/pnas.2217877121.
50. Clayburgh DR, et al. Epithelial myosin light chain kinase-dependent barrier dysfunction mediates T cell activation-induced diarrhea in vivo. J Clin Invest. 2005;115:2702–15. https://doi.org/10.1172/jci24970.
51. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol. 2009;9:799–809. https://doi.org/10.1038/nri2653.
52. Ralay-Ranaivo H, et al. Protection against endotoxic shock as a consequence of reduced nitrosative stress in MLCK210-null mice. Am J Pathol. 2007;170:439–46. https://doi.org/10.2353/ajpath.2007.060219.
53. Lorentz CA, et al. Myosin light chain kinase knockout improves gut barrier function and confers a survival advantage in polymicrobial sepsis. Mol Med. 2017;23:155–65. https://doi.org/10.2119/molmed.2016.00256.
54. Chihade DB, et al. Myosin light chain kinase deletion worsens lung permeability and increases mortality in pneumonia-induced sepsis. Shock. 2023;59:612–20. https://doi.org/10.1097/shk.0000000000002081.
55. Zahs A, et al. Inhibition of long myosin light-chain kinase activation alleviates intestinal damage after binge ethanol exposure and burn injury. Am J Physiol Gastrointest Liver Physiol. 2012;303:G705-712. https://doi.org/10.1152/ajpgi.00157.2012.
56. Zolotarevsky Y, et al. A membrane-permeant peptide that inhibits MLC kinase restores barrier function in in vitro models of intestinal disease. Gastroenterology. 2002;123:163–72. https://doi.org/10.1053/gast.2002.34235.
57. Sun Y, et al. Membrane permeant inhibitor of myosin light chain kinase worsens survival in murine polymicrobial sepsis. Shock. 2021;56:621–8. https://doi.org/10.1097/shk.0000000000001759.
58. Rogers AP, Mileto SJ, Lyras D. Impact of enteric bacterial infections at and beyond the epithelial barrier. Nat Rev Microbiol. 2023;21:260–74. https://doi.org/10.1038/s41579-022-00794-x.
59. Kitamoto S, Nagao-Kitamoto H, Kuffa P, Kamada N. Regulation of virulence: the rise and fall of gastrointestinal pathogens. J Gastroenterol. 2016;51:195–205. https://doi.org/10.1007/s00535-015-1141-5.
60. Mekalanos JJ. Environmental signals controlling expression of virulence determinants in bacteria. J Bacteriol. 1992;174:1–7. https://doi.org/10.1128/jb.174.1.1-7.1992.
61. Green J, Rolfe MD, Smith LJ. Transcriptional regulation of bacterial virulence gene expression by molecular oxygen and nitric oxide. Virulence. 2014;5:794–809. https://doi.org/10.4161/viru.27794.
62. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med. 2012. https://doi.org/10.1101/cshperspect.a012427.
63. Azimi S, Klementiev AD, Whiteley M, Diggle SP. Bacterial quorum sensing during infection. Annu Rev Microbiol. 2020;74:201–19. https://doi.org/10.1146/annurev-micro-032020-093845.
64. Shogan BD, et al. Intestinal anastomotic injury alters spatially defined microbiome composition and function. Microbiome. 2014;2:35. https://doi.org/10.1186/2049-2618-2-35.
65. Högbom M, Ihalin R. Functional and structural characteristics of bacterial proteins that bind host cytokines. Virulence. 2017;8:1592–601. https://doi.org/10.1080/21505594.2017.1363140.
66. Kumar A, et al. The serotonin neurotransmitter modulates virulence of enteric pathogens. Cell Host Microbe. 2020;28:41-53.e48. https://doi.org/10.1016/j.chom.2020.05.004.
67. Diard M, Hardt WD. Evolution of bacterial virulence. FEMS Microbiol Rev. 2017;41:679–97. https://doi.org/10.1093/femsre/fux023.
68. Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. Nat Rev Drug Discov. 2010;9:117–28. https://doi.org/10.1038/nrd3013.
69. Zhou J, Ma H, Zhang L. Mechanisms of virulence reprogramming in bacterial pathogens. Annu Rev Microbiol. 2023;77:561–81. https://doi.org/10.1146/annurev-micro-032521-025954.
70. Babrowski T, et al. Pseudomonas aeruginosa virulence expression is directly activated by morphine and is capable of causing lethal gut-derived sepsis in mice during chronic morphine administration. Ann Surg. 2012;255:386–93. https://doi.org/10.1097/SLA.0b013e3182331870.
71. Wu LR, et al. Surgical injury and metabolic stress enhance the virulence of the human opportunistic pathogen Pseudomonas aeruginosa. Surg Infect (Larchmt). 2005;6:185–95. https://doi.org/10.1089/sur.2005.6.185.
72. Rocha F, et al. Surgical stress shifts the intestinal *Escherichia coli* population to that of a more adherent phenotype: role in barrier regulation. Surgery. 2001;130:65–73. https://doi.org/10.1067/msy.2001.115360.
73. Thomas S, Kang G, Balasubramanian KA. Surgical manipulation of the intestine results in quantitative and qualitative alterations in luminal

Escherichia coli. Ann Surg. 2004;240:248–54. https://doi.org/10.1097/01.sla.0000133119.38175.97.
74. Chanderraj R, et al. The bacterial density of clinical rectal swabs is highly variable, correlates with sequencing contamination, and predicts patient risk of extraintestinal infection. Microbiome. 2022;10:2. https://doi.org/10.1186/s40168-021-01190-y.
75. Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. N Engl J Med. 1969;281:1137–40. https://doi.org/10.1056/nejm196911202812101.
76. Akrami K, Sweeney DA. The microbiome of the critically ill patient. Curr Opin Crit Care. 2018;24:49–54. https://doi.org/10.1097/mcc.0000000000000469.
77. McDonald D, et al. Extreme dysbiosis of the microbiome in critical illness. mSphere. 2016;1:15. https://doi.org/10.1128/mSphere.00199-16.
78. Yeh A, et al. Dysbiosis across multiple body sites in critically Ill adult surgical patients. Shock. 2016;46:649–54. https://doi.org/10.1097/shk.0000000000000691.
79. Schlechte J, et al. Dysbiosis of a microbiota-immune metasystem in critical illness is associated with nosocomial infections. Nat Med. 2023;29:1017–27. https://doi.org/10.1038/s41591-023-02243-5.
80. Dickson RP. The microbiome and critical illness. Lancet Respir Med. 2016;4:59–72. https://doi.org/10.1016/s2213-2600(15)00427-0.
81. Bharti R, Grimm DG. Current challenges and best-practice protocols for microbiome analysis. Brief Bioinform. 2021;22:178–93. https://doi.org/10.1093/bib/bbz155.
82. Brüssow H. Problems with the concept of gut microbiota dysbiosis. Microb Biotechnol. 2020;13:423–34. https://doi.org/10.1111/1751-7915.13479.
83. Miniet AA, Grunwell JR, Coopersmith CM. The microbiome and the immune system in critical illness. Curr Opin Crit Care. 2021;27:157–63. https://doi.org/10.1097/mcc.0000000000000800.
84. Liu W, et al. Classification of the gut microbiota of patients in intensive care units during development of sepsis and septic shock. Genomics Proteomics Bioinformatics. 2020;18:696–707. https://doi.org/10.1016/j.gpb.2020.06.011.
85. Otani S, Chihade DB, Coopersmith CM. Critical illness and the role of the microbiome. Acute Med Surg. 2019;6:91–4. https://doi.org/10.1002/ams2.383.
86. Assimakopoulos SF, et al. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection. 2018;46:751–60. https://doi.org/10.1007/s15010-018-1178-5.
87. Drolia R, Tenguria S, Durkes AC, Turner JR, Bhunia AK. Listeria adhesion protein induces intestinal epithelial barrier dysfunction for bacterial translocation. Cell Host Microbe. 2018;23:470-484.e477. https://doi.org/10.1016/j.chom.2018.03.004.
88. Pizarro-Cerdá J, Cossart P. Bacterial adhesion and entry into host cells. Cell. 2006;124:715–27. https://doi.org/10.1016/j.cell.2006.02.012.
89. Asadi A, Razavi S, Talebi M, Gholami M. A review on anti-adhesion therapies of bacterial diseases. Infection. 2019;47:13–23. https://doi.org/10.1007/s15010-018-1222-5.
90. Stones DH, Krachler AM. Against the tide: the role of bacterial adhesion in host colonization. Biochem Soc Trans. 2016;44:1571–80. https://doi.org/10.1042/bst20160186.
91. Lin XP, Almqvist N, Telemo E. Human small intestinal epithelial cells constitutively express the key elements for antigen processing and the production of exosomes. Blood Cells Mol Dis. 2005;35:122–8. https://doi.org/10.1016/j.bcmd.2005.05.011.
92. Mallegol J, et al. T84-intestinal epithelial exosomes bear MHC class II/peptide complexes potentiating antigen presentation by dendritic cells. Gastroenterology. 2007;132:1866–76. https://doi.org/10.1053/j.gastro.2007.02.043.
93. Eken C, Sadallah S, Martin PJ, Treves S, Schifferli JA. Ectosomes of polymorphonuclear neutrophils activate multiple signaling pathways in macrophages. Immunobiology. 2013;218:382–92. https://doi.org/10.1016/j.imbio.2012.05.021.
94. Zhou GX, Liu ZJ. Potential roles of neutrophils in regulating intestinal mucosal inflammation of inflammatory bowel disease. J Dig Dis. 2017;18:495–503. https://doi.org/10.1111/1751-2980.12540.
95. Brazil JC, Louis NA, Parkos CA. The role of polymorphonuclear leukocyte trafficking in the perpetuation of inflammation during inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:1556–65. https://doi.org/10.1097/MIB.0b013e318281f54e.
96. Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol. 2010;10:479–89. https://doi.org/10.1038/nri2800.
97. Kucharzik T, Walsh SV, Chen J, Parkos CA, Nusrat A. Neutrophil transmigration in inflammatory bowel disease is associated with differential expression of epithelial intercellular junction proteins. Am J Pathol. 2001;159:2001–9. https://doi.org/10.1016/s0002-9440(10)63051-9.
98. Fournier BM, Parkos CA. The role of neutrophils during intestinal inflammation. Mucosal Immunol. 2012;5:354–66. https://doi.org/10.1038/mi.2012.24.
99. Gasteiger G, Fan X, Dikiy S, Lee SY, Rudensky AY. Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. Science. 2015;350:981–5. https://doi.org/10.1126/science.aac9593.
100. Saez A, et al. Innate lymphoid cells in intestinal homeostasis and inflammatory bowel disease. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22147618.
101. Delfini M, Stakenborg N, Viola MF, Boeckxstaens G. Macrophages in the gut: masters in multitasking. Immunity. 2022;55:1530–48. https://doi.org/10.1016/j.immuni.2022.08.005.
102. Saez A, Herrero-Fernandez B, Gomez-Bris R, Sánchez-Martinez H, Gonzalez-Granado JM. Pathophysiology of inflammatory bowel disease: innate immune system. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24021526.
103. Smythies LE, et al. Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. J Clin Invest. 2005;115:66–75. https://doi.org/10.1172/jci19229.
104. Yip JLK, Balasuriya GK, Spencer SJ, Hill-Yardin EL. The role of intestinal macrophages in gastrointestinal homeostasis: heterogeneity and implications in disease. Cell Mol Gastroenterol Hepatol. 2021;12:1701–18. https://doi.org/10.1016/j.jcmgh.2021.08.021.
105. Sehgal A, et al. The role of CSF1R-dependent macrophages in control of the intestinal stem-cell niche. Nat Commun. 2018;9:1272. https://doi.org/10.1038/s41467-018-03638-6.
106. Hadis U, et al. Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria. Immunity. 2011;34:237–46. https://doi.org/10.1016/j.immuni.2011.01.016.
107. Shaw MH, Kamada N, Kim YG, Núñez G. Microbiota-induced IL-1β, but not IL-6, is critical for the development of steady-state TH17 cells in the intestine. J Exp Med. 2012;209:251–8. https://doi.org/10.1084/jem.20111703.
108. De Schepper S, et al. Self-maintaining gut macrophages are essential for intestinal homeostasis. Cell. 2019;176:676. https://doi.org/10.1016/j.cell.2019.01.010.
109. Phillips RJ, Powley TL. Macrophages associated with the intrinsic and extrinsic autonomic innervation of the rat gastrointestinal tract. Auton Neurosci. 2012;169:12–27. https://doi.org/10.1016/j.autneu.2012.02.004.
110. Ji S, et al. Muscularis macrophages establish cell-to-cell contacts with telocytes/PDGFRα-positive cells and smooth muscle cells in the human and mouse gastrointestinal tract. Neurogastroenterol Motil. 2021;33:e13993. https://doi.org/10.1111/nmo.13993.
111. Gomez-Bris R, et al. CD4 T-cell subsets and the pathophysiology of inflammatory bowel disease. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24032696.
112. Basso L, et al. Mobilization of CD4+ T lymphocytes in inflamed mucosa reduces pain in colitis mice: toward a vaccinal strategy to alleviate inflammatory visceral pain. Pain. 2018;159:331–41. https://doi.org/10.1097/j.pain.0000000000001103.
113. Rabe H, et al. Distinct patterns of naive, activated and memory T and B cells in blood of patients with ulcerative colitis or Crohn's disease. Clin Exp Immunol. 2019;197:111–29. https://doi.org/10.1111/cei.13294.
114. Zhu X, Zhu J. CD4 T Helper Cell Subsets and Related Human Immunological Disorders. Int J Mol Sci. 2020;21:15. https://doi.org/10.3390/ijms21218011.
115. Chen L, et al. The role of Th17 cells in inflammatory bowel disease and the research progress. Front Immunol. 2022;13:1055914. https://doi.org/10.3389/fimmu.2022.1055914.
116. Matsunaga Y, et al. Intestinal IL-17R signaling controls secretory IgA and oxidase balance in citrobacter rodentium infection. J Immunol. 2021;206:766–75. https://doi.org/10.4049/jimmunol.2000591.

117. Nishikawa K, et al. Interleukin-17 induces an atypical M2-like macrophage subpopulation that regulates intestinal inflammation. PLoS ONE. 2014;9:e108494. https://doi.org/10.1371/journal.pone.0108494.
118. van der Voort PH. Linking gut-associated lymphoid tissue to multiple organ dysfunction syndrome and infection. Crit Care Med. 2006;34:257–8. https://doi.org/10.1097/01.ccm.0000196087.29912.a0.
119. Tsujimoto H, Ono S, Mochizuki H. Role of translocation of pathogen-associated molecular patterns in sepsis. Dig Surg. 2009;26:100–9. https://doi.org/10.1159/000206143.
120. Deitch EA. Gut lymph and lymphatics: a source of factors leading to organ injury and dysfunction. Ann N Y Acad Sci. 2010;1207(Suppl 1):E103-111. https://doi.org/10.1111/j.1749-6632.2010.05713.x.
121. Pool R, Gomez H, Kellum JA. Mechanisms of organ dysfunction in sepsis. Crit Care Clin. 2018;34:63–80. https://doi.org/10.1016/j.ccc.2017.08.003.
122. Donati A, et al. From macrohemodynamic to the microcirculation. Crit Care Res Pract. 2013;2013: 892710. https://doi.org/10.1155/2013/892710.
123. McMullan RR, McAuley DF, O'Kane CM, Silversides JA. Vascular leak in sepsis: physiological basis and potential therapeutic advances. Crit Care. 2024;28:97. https://doi.org/10.1186/s13054-024-04875-6.
124. Dargent A, et al. Role of the interstitium during septic shock: a key to the understanding of fluid dynamics? J Intensive Care. 2023;11:44. https://doi.org/10.1186/s40560-023-00694-z.
125. Chelazzi C, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. Crit Care. 2015;19:26. https://doi.org/10.1186/s13054-015-0741-z.
126. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol. 2018;14:417–27. https://doi.org/10.1038/s41581-018-0005-7.
127. Li D, Wu M. Pattern recognition receptors in health and diseases. Signal Transduct Target Ther. 2021;6:291. https://doi.org/10.1038/s41392-021-00687-0.
128. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140:805–20. https://doi.org/10.1016/j.cell.2010.01.022.
129. Hotchkiss RS, et al. Sepsis and septic shock. Nat Rev Dis Primers. 2016;2:16045. https://doi.org/10.1038/nrdp.2016.45.
130. Williams B, et al. Toll-like receptors 2 and 7 mediate coagulation activation and coagulopathy in murine sepsis. J Thromb Haemost. 2019;17:1683–93. https://doi.org/10.1111/jth.14543.
131. Chen F, Zou L, Williams B, Chao W. Targeting toll-like receptors in sepsis: from bench to clinical trials. Antioxid Redox Signal. 2021;35:1324–39. https://doi.org/10.1089/ars.2021.0005.
132. Chancharoenthana W, Kamolratanakul S, Schultz MJ, Leelahavanichkul A. The leaky gut and the gut microbiome in sepsis - targets in research and treatment. Clin Sci (Lond). 2023;137:645–62. https://doi.org/10.1042/cs20220777.
133. Burgueño JF, Abreu MT. Epithelial toll-like receptors and their role in gut homeostasis and disease. Nat Rev Gastroenterol Hepatol. 2020;17:263–78. https://doi.org/10.1038/s41575-019-0261-4.
134. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol. 2006;6:318–28. https://doi.org/10.1038/nri1810.
135. Levy M, Thaiss CA, Elinav E. Metagenomic cross-talk: the regulatory interplay between immunogenomics and the microbiome. Genome Med. 2015;7:120. https://doi.org/10.1186/s13073-015-0249-9.
136. Taur Y, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2012;55:905–14. https://doi.org/10.1093/cid/cis580.
137. Wang C, Li Q, Ren J. Microbiota-immune interaction in the pathogenesis of gut-derived infection. Front Immunol. 2019;10:1873. https://doi.org/10.3389/fimmu.2019.01873.
138. Ma C, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science. 2018. https://doi.org/10.1126/science.aan5931.
139. Lobo LA, Benjamim CF, Oliveira AC. The interplay between microbiota and inflammation: lessons from peritonitis and sepsis. Clin Transl Immunology. 2016;5:e90. https://doi.org/10.1038/cti.2016.32.
140. Liu Z, et al. Enteric dysbiosis is associated with sepsis in patients. Faseb j. 2019;33:12299–310. https://doi.org/10.1096/fj.201900398RR.
141. Wang Y, Zhang Y, Liu Y, Xu J, Liu Y. Gut-liver axis: liver sinusoidal endothelial cells function as the hepatic barrier in colitis-induced liver injury. Front Cell Dev Biol. 2021;9:702890. https://doi.org/10.3389/fcell.2021.702890.
142. Vincent JL, Gustot T. Sepsis and cirrhosis: many similarities. Acta Gastroenterol Belg. 2010;73:472–8.
143. Leng Y, et al. Effect of acute, slightly increased intra-abdominal pressure on intestinal permeability and oxidative stress in a rat model. PLoS ONE. 2014;9:e109350. https://doi.org/10.1371/journal.pone.0109350.
144. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA. 1996;275:470–3.
145. Gofton TE, Young GB. Sepsis-associated encephalopathy. Nat Rev Neurol. 2012;8:557–66. https://doi.org/10.1038/nrneurol.2012.183.
146. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28:203–9.
147. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol (Lausanne). 2020;11:25. https://doi.org/10.3389/fendo.2020.00025.
148. Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol. 2020;19:179–94. https://doi.org/10.1016/s1474-4422(19)30356-4.
149. Braniste V, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6:263ra158. https://doi.org/10.1126/scitranslmed.3009759.
150. Barlow B, Ponnaluri S, Barlow A, Roth W. Targeting the gut microbiome in the management of sepsis-associated encephalopathy. Front Neurol. 2022;13:999035. https://doi.org/10.3389/fneur.2022.999035.
151. Chen L, et al. NU9056, a KAT 5 inhibitor, treatment alleviates brain dysfunction by inhibiting NLRP3 inflammasome activation, affecting gut microbiota, and derived metabolites in LPS-treated mice. Front Nutr. 2021;8:701760. https://doi.org/10.3389/fnut.2021.701760.
152. Wang DW, Yin YM, Yao YM. Vagal modulation of the inflammatory response in sepsis. Int Rev Immunol. 2016;35:415–33. https://doi.org/10.3109/08830185.2015.1127369.
153. Kox M, Pickkers P. Modulation of the innate immune response through the vagus nerve. Nephron. 2015;131:79–84. https://doi.org/10.1159/000435843.
154. Levy B, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. Intensive Care Med. 2010;36:2019–29. https://doi.org/10.1007/s00134-010-2045-8.
155. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014;5:73–9. https://doi.org/10.4161/viru.26482.
156. Antonucci E, et al. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. J Crit Care. 2014;29:500–11. https://doi.org/10.1016/j.jcrc.2014.03.028.
157. Guest RL, Rutherford ST, Silhavy TJ. Border control: regulating LPS biogenesis. Trends Microbiol. 2021;29:334–45. https://doi.org/10.1016/j.tim.2020.09.008.
158. Taveira da Silva AM, et al. Brief report: shock and multiple-organ dysfunction after self-administration of Salmonella endotoxin. N Engl J Med. 1993;328:1457–60. https://doi.org/10.1056/nejm199305203282005.
159. Fink MP. Animal models of sepsis. Virulence. 2014;5:143–53. https://doi.org/10.4161/viru.26083.
160. Brinkworth JF, Valizadegan N. Sepsis and the evolution of human increased sensitivity to lipopolysaccharide. Evol Anthropol. 2021;30:141–57. https://doi.org/10.1002/evan.21887.
161. Rodriguez-Loureiro I, Latza VM, Fragneto G, Schneck E. Conformation of single and interacting lipopolysaccharide surfaces bearing O-side chains. Biophys J. 2018;114:1624–35. https://doi.org/10.1016/j.bpj.2018.02.014.
162. Zanoni I, et al. Similarities and differences of innate immune responses elicited by smooth and rough LPS. Immunol Lett. 2012;142:41–7. https://doi.org/10.1016/j.imlet.2011.12.002.
163. Munford RS. Endotoxemia-menace, marker, or mistake? J Leukoc Biol. 2016;100:687–98. https://doi.org/10.1189/jlb.3RU0316-151R.
164. Sperandeo P, Martorana AM, Polissi A. Lipopolysaccharide biosynthesis and transport to the outer membrane of gram-negative

bacteria. Subcell Biochem. 2019;92:9–37. https://doi.org/10.1007/978-3-030-18768-2_2.
165. Simpson BW, Trent MS. Pushing the envelope: LPS modifications and their consequences. Nat Rev Microbiol. 2019;17:403–16. https://doi.org/10.1038/s41579-019-0201-x.
166. Maldonado RF, Sá-Correia I, Valvano MA. Lipopolysaccharide modification in Gram-negative bacteria during chronic infection. FEMS Microbiol Rev. 2016;40:480–93. https://doi.org/10.1093/femsre/fuw007.
167. Homma JY, et al. Structural requirements of lipid A responsible for the functions: a study with chemically synthesized lipid A and its analogues. J Biochem. 1985;98:395–406. https://doi.org/10.1093/oxfordjournals.jbchem.a135294.
168. Grant MA, Wacław B, Allen RJ, Cicuta P. The role of mechanical forces in the planar-to-bulk transition in growing *Escherichia coli* microcolonies. J R Soc Interface. 2014;11:20140400. https://doi.org/10.1098/rsif.2014.0400.
169. Lau PC, Lindhout T, Beveridge TJ, Dutcher JR, Lam JS. Differential lipopolysaccharide core capping leads to quantitative and correlated modifications of mechanical and structural properties in Pseudomonas aeruginosa biofilms. J Bacteriol. 2009;191:6618–31. https://doi.org/10.1128/jb.00698-09.
170. Moffatt JH, et al. Colistin resistance in *Acinetobacter baumannii* is mediated by complete loss of lipopolysaccharide production. Antimicrob Agents Chemother. 2010;54:4971–7. https://doi.org/10.1128/aac.00834-10.
171. van Mourik A, et al. Altered linkage of hydroxyacyl chains in lipid A of Campylobacter jejuni reduces TLR4 activation and antimicrobial resistance. J Biol Chem. 2010;285:15828–36. https://doi.org/10.1074/jbc.M110.102061.
172. Cullen TW, et al. Helicobacter pylori versus the host: remodeling of the bacterial outer membrane is required for survival in the gastric mucosa. PLoS Pathog. 2011;7:e1002454. https://doi.org/10.1371/journal.ppat.1002454.
173. Jefferies D, Shearer J, Khalid S. Role of O-antigen in response to mechanical stress of the *E. coli* outer membrane: insights from coarse-grained MD simulations. J Phys Chem B. 2019;123:3567–75. https://doi.org/10.1021/acs.jpcb.8b12168.
174. Li Y, et al. LPS remodeling is an evolved survival strategy for bacteria. Proc Natl Acad Sci USA. 2012;109:8716–21. https://doi.org/10.1073/pnas.1202908109.
175. Calvano SE, et al. A network-based analysis of systemic inflammation in humans. Nature. 2005;437:1032–7. https://doi.org/10.1038/nature03985.
176. Parbhakar OP, Duke T, Townsend HG, Singh B. Depletion of pulmonary intravascular macrophages partially inhibits lipopolysaccharide-induced lung inflammation in horses. Vet Res. 2005;36:557–69. https://doi.org/10.1051/vetres:2005016.
177. Greisman SE, Hornick RB. Comparative pyrogenic reactivity of rabbit and man to bacterial endotoxin. Proc Soc Exp Biol Med. 1969;131:1154–8. https://doi.org/10.3181/00379727-131-34059.
178. Brinkworth JF, Pechenkina EA, Silver J, Goyert SM. Innate immune responses to TLR2 and TLR4 agonists differ between baboons, chimpanzees and humans. J Med Primatol. 2012;41:388–93. https://doi.org/10.1111/jmp.12002.
179. Barreiro LB, Marioni JC, Blekhman R, Stephens M, Gilad Y. Functional comparison of innate immune signaling pathways in primates. PLoS Genet. 2010;6:e1001249. https://doi.org/10.1371/journal.pgen.1001249.
180. Haudek SB, et al. Lipopolysaccharide dose response in baboons. Shock. 2003;20:431–6. https://doi.org/10.1097/01.shk.0000090843.66556.74.
181. von Bülow GU, Puren AJ, Savage N. Interleukin-1 from baboon peripheral blood monocytes: altered response to endotoxin (lipopolysaccharide) and *Staphylococcus aureus* stimulation compared with human monocytes. Eur J Cell Biol. 1992;59:458–63.
182. Glode LM, Mergenhagen SE, Rosenstreich DL. Significant contribution of spleen cells in mediating the lethal effects of endotoxin in vivo. Infect Immun. 1976;14:626–30. https://doi.org/10.1128/iai.14.3.626-630.1976.
183. Hawash MBF, et al. Primate innate immune responses to bacterial and viral pathogens reveals an evolutionary trade-off between strength and specificity. Proc Natl Acad Sci USA. 2021. https://doi.org/10.1073/pnas.2015855118.
184. Kingsley SM, Bhat BV. Differential paradigms in animal models of sepsis. Curr Infect Dis Rep. 2016;18:26. https://doi.org/10.1007/s11908-016-0535-8.
185. Jakob SM, et al. Effects of cardiac preload reduction and dobutamine on hepatosplanchnic blood flow regulation in porcine endotoxemia. Am J Physiol Gastrointest Liver Physiol. 2012;303:G247-255. https://doi.org/10.1152/ajpgi.00433.2011.
186. Dubey PK, et al. Increased m6A-RNA methylation and FTO suppression is associated with myocardial inflammation and dysfunction during endotoxemia in mice. Mol Cell Biochem. 2022;477:129–41. https://doi.org/10.1007/s11010-021-04267-2.
187. Zhang J, et al. The endotoxemia cardiac dysfunction is attenuated by AMPK/mTOR signaling pathway regulating autophagy. Biochem Biophys Res Commun. 2017;492:520–7. https://doi.org/10.1016/j.bbrc.2017.08.034.
188. Siore AM, et al. Endotoxin-induced acute lung injury requires interaction with the liver. Am J Physiol Lung Cell Mol Physiol. 2005;289:L769-776. https://doi.org/10.1152/ajplung.00137.2005.
189. Brigham KL, Meyrick B. Endotoxin and lung injury. Am Rev Respir Dis. 1986;133:913–27.
190. Abraham E, Carmody A, Shenkar R, Arcaroli J. Neutrophils as early immunologic effectors in hemorrhage- or endotoxemia-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2000;279:L1137-1145. https://doi.org/10.1152/ajplung.2000.279.6.L1137.
191. Han DW. Intestinal endotoxemia as a pathogenetic mechanism in liver failure. World J Gastroenterol. 2002;8:961–5. https://doi.org/10.3748/wjg.v8.i6.961.
192. Nolan JP. Endotoxin, reticuloendothelial function, and liver injury. Hepatology. 1981;1:458–65. https://doi.org/10.1002/hep.1840010516.
193. Zarbock A, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2023;19:401–17. https://doi.org/10.1038/s41581-023-00683-3.
194. Czabanka M, Peter C, Martin E, Walther A. Microcirculatory endothelial dysfunction during endotoxemia–insights into pathophysiology, pathologic mechanisms and clinical relevance. Curr Vasc Pharmacol. 2007;5:266–75. https://doi.org/10.2174/157016107782023389.
195. Goligorsky MS, Sun D. Glycocalyx in endotoxemia and sepsis. Am J Pathol. 2020;190:791–8. https://doi.org/10.1016/j.ajpath.2019.06.017.
196. Brown GC. The endotoxin hypothesis of neurodegeneration. J Neuroinflammation. 2019;16:180. https://doi.org/10.1186/s12974-019-1564-7.
197. Alvarez S, Vico T, Vanasco V. Cardiac dysfunction, mitochondrial architecture, energy production, and inflammatory pathways: interrelated aspects in endotoxemia and sepsis. Int J Biochem Cell Biol. 2016;81:307–14. https://doi.org/10.1016/j.biocel.2016.07.032.
198. Metheny NA, Mills AC, Stewart BJ. Monitoring for intolerance to gastric tube feedings: a national survey. Am J Crit Care. 2012;21:e33-40. https://doi.org/10.4037/ajcc2012647.
199. Lindner M, et al. Current practice of gastric residual volume measurements and related outcomes of critically ill patients: a secondary analysis of the intestinal-specific organ function assessment study. JPEN J Parenter Enteral Nutr. 2023;47:614–23. https://doi.org/10.1002/jpen.2502.
200. Creteur J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: in vitro and in vivo validation studies. Anesthesiology. 1997;87:504–10. https://doi.org/10.1097/00000542-199709000-00008.
201. Zhang X, et al. Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis. Crit Care. 2015;19:22. https://doi.org/10.1186/s13054-015-0739-6.
202. Bachmann KF, et al. Core outcome set of daily monitoring of gastrointestinal function in adult critically ill patients: a modified Delphi consensus process (COSMOGI). Crit Care. 2024;28:420. https://doi.org/10.1186/s13054-024-05192-8.
203. Piton G, Capellier G. Biomarkers of gut barrier failure in the ICU. Curr Opin Crit Care. 2016;22:152–60. https://doi.org/10.1097/mcc.0000000000000283.
204. Blaser A, Padar M, Tang J, Dutton J, Forbes A. Citrulline and intestinal fatty acid-binding protein as biomarkers for gastrointestinal dysfunction in the critically ill. Anaesthesiol Intensive Ther. 2019;51:230–9. https://doi.org/10.5114/ait.2019.86049.

205. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clin Nutr. 2008;27:328–39. https://doi.org/10.1016/j.clnu.2008.02.005.
206. Windmueller HG, Spaeth AE. Source and fate of circulating citrulline. Am J Physiol. 1981;241:E473-480. https://doi.org/10.1152/ajpendo.1981.241.6.E473.
207. Curis E, et al. Almost all about citrulline in mammals. Amino Acids. 2005;29:177–205. https://doi.org/10.1007/s00726-005-0235-4.
208. Herrera OR, Talati AJ, Helms RA. Plasma citrulline concentrations in neonates with or without gastrointestinal disease during periods of parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr. 2019;43:977–85. https://doi.org/10.1002/jpen.1671.
209. Crenn P, et al. Plasma citrulline: a marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology. 2003;124:1210–9. https://doi.org/10.1016/s0016-5085(03)00170-7.
210. Chaignat C, et al. Plasma citrulline concentration and plasma LPS detection among critically ill patients a prospective observational study. J Crit Care. 2024;79:154438. https://doi.org/10.1016/j.jcrc.2023.154438.
211. Kao C, Hsu J, Bandi V, Jahoor F. Alterations in glutamine metabolism and its conversion to citrulline in sepsis. Am J Physiol Endocrinol Metab. 2013;304:E1359-1364. https://doi.org/10.1152/ajpendo.00628.2012.
212. Crenn P, et al. Plasma L-citrulline concentrations and its relationship with inflammation at the onset of septic shock: a pilot study. J Crit Care. 2014;29(315):e311-316. https://doi.org/10.1016/j.jcrc.2013.11.015.
213. Tyszko M, et al. Citrulline, intestinal fatty acid-binding protein and the acute gastrointestinal injury score as predictors of gastrointestinal failure in patients with sepsis and septic shock. Nutrients. 2023. https://doi.org/10.3390/nu15092100.
214. Ajeje ET, et al. Measurements of I-FABP and citrulline in the postoperative period of non-cardiac surgeries with gastrointestinal complications: a prospective cohort observational study. J Crit Care. 2024;81:154530. https://doi.org/10.1016/j.jcrc.2024.154530.
215. Buttet M, et al. From fatty-acid sensing to chylomicron synthesis: role of intestinal lipid-binding proteins. Biochimie. 2014;96:37–47. https://doi.org/10.1016/j.biochi.2013.08.011.
216. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. Surgery. 1993;113:545–51.
217. Piton G, et al. Enterocyte damage in critically ill patients is associated with shock condition and 28-day mortality. Crit Care Med. 2013;41:2169–76. https://doi.org/10.1097/CCM.0b013e31828c26b5.
218. Habes QLM, van Ede L, Gerretsen J, Kox M, Pickkers P. Norepinephrine contributes to enterocyte damage in septic shock patients: a prospective cohort study. Shock. 2018;49:137–43. https://doi.org/10.1097/shk.0000000000000955.
219. Kanda T, et al. Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol. 2011;46:492–500. https://doi.org/10.1007/s00535-011-0373-2.
220. Matsumoto S, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. Br J Surg. 2014;101:232–8. https://doi.org/10.1002/bjs.9331.
221. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Intern Emerg Med. 2017;12:821–36. https://doi.org/10.1007/s11739-017-1668-y.
222. Grimaldi D, et al. Markers of intestinal injury are associated with endotoxemia in successfully resuscitated patients. Resuscitation. 2013;84:60–5. https://doi.org/10.1016/j.resuscitation.2012.06.010.
223. Derikx JP, Poeze M, van Bijnen AA, Buurman WA, Heineman E. Evidence for intestinal and liver epithelial cell injury in the early phase of sepsis. Shock. 2007;28:544–8. https://doi.org/10.1097/shk.0b013e3180644e32.
224. Kosar E, Grill HJ, Norgren R. Gustatory cortex in the rat. I. Physiological properties and cytoarchitecture. Brain Res. 1986;379:329–41. https://doi.org/10.1016/0006-8993(86)90787-0.
225. Reintam Blaser A, et al. Development of the gastrointestinal dysfunction score (GIDS) for critically ill patients—a prospective multicenter observational study (iSOFA study). Clin Nutr. 2021;40:4932–40. https://doi.org/10.1016/j.clnu.2021.07.015.
226. Lau T, et al. Arginine, citrulline, and nitric oxide metabolism in end-stage renal disease patients. J Clin Invest. 2000;105:1217–25. https://doi.org/10.1172/jci7199.
227. Piton G, et al. Plasma citrulline kinetics and prognostic value in critically ill patients. Intensive Care Med. 2010;36:702–6. https://doi.org/10.1007/s00134-010-1751-6.
228. Sekino M, et al. Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: a preliminary study. J Crit Care. 2017;42:92–100. https://doi.org/10.1016/j.jcrc.2017.07.012.
229. Voth M, et al. I-FABP is a novel marker for the detection of intestinal injury in severely injured trauma patients. World J Surg. 2017;41:3120–7. https://doi.org/10.1007/s00268-017-4124-2.
230. Veres-Székely A, et al. Zonulin as a potential therapeutic target in microbiota-gut-brain axis disorders: encouraging results and emerging questions. Int J Mol Sci. 2023;24:15. https://doi.org/10.3390/ijms24087548.
231. Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. Tissue Barriers. 2016;4:e1251384. https://doi.org/10.1080/21688370.2016.1251384.
232. Tripathi A, et al. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2. Proc Natl Acad Sci USA. 2009;106:16799–804. https://doi.org/10.1073/pnas.0906773106.
233. Fasano A, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet. 2000;355:1518–9. https://doi.org/10.1016/s0140-6736(00)02169-3.
234. Fasano A. Zonulin, regulation of tight junctions, and autoimmune diseases. Ann NY Acad Sci. 2012;1258:25–33. https://doi.org/10.1111/j.1749-6632.2012.06538.x.
235. Sapone A, et al. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. Diabetes. 2006;55:1443–9. https://doi.org/10.2337/db05-1593.
236. Klaus DA, et al. Increased plasma zonulin in patients with sepsis. Biochem Med (Zagreb). 2013;23:107–11. https://doi.org/10.11613/bm.2013.013.
237. Martinez EE, Mehta NM, Fasano A. The Zonulin pathway as a potential mediator of gastrointestinal dysfunction in critical illness. Pediatr Crit Care Med. 2022;23:e424–8. https://doi.org/10.1097/pcc.0000000000002985.
238. Yonker LM, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. J Clin Invest. 2021. https://doi.org/10.1172/jci149633.
239. Donmez-Altuntas H, et al. Gut barrier protein levels in serial blood samples from critically ill trauma patients during and after intensive care unit stay. Eur J Trauma Emerg Surg. 2023;49:2203–13. https://doi.org/10.1007/s00068-023-02298-6.
240. Scheffler L, et al. Widely used commercial ELISA does not detect precursor of haptoglobin2, but recognizes properdin as a potential second member of the zonulin family. Front Endocrinol (Lausanne). 2018;9:22. https://doi.org/10.3389/fendo.2018.00022.
241. Ciccia F, et al. Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis. Ann Rheum Dis. 2017;76:1123–32. https://doi.org/10.1136/annrheumdis-2016-210000.
242. Jayashree B, et al. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. Mol Cell Biochem. 2014;388:203–10. https://doi.org/10.1007/s11010-013-1911-4.
243. Zak-Gołąb A, et al. Gut microbiota, microinflammation, metabolic profile, and zonulin concentration in obese and normal weight subjects. Int J Endocrinol. 2013;2013:674106. https://doi.org/10.1155/2013/674106.
244. Esnafoglu E, et al. Increased serum zonulin levels as an intestinal permeability marker in autistic subjects. J Pediatr. 2017;188:240–4. https://doi.org/10.1016/j.jpeds.2017.04.004.
245. Camara-Lemarroy CR, et al. Biomarkers of intestinal barrier function in multiple sclerosis are associated with disease activity. Mult Scler. 2020;26:1340–50. https://doi.org/10.1177/1352458519863133.
246. Maes M, Sirivichayakul S, Kanchanatawan B, Vodjani A. Upregulation of the intestinal paracellular pathway with breakdown of tight

and adherens junctions in deficit schizophrenia. Mol Neurobiol. 2019;56:7056–73. https://doi.org/10.1007/s12035-019-1578-2.
247. Alvarez-Mon MA, et al. Abnormal distribution and function of circulating monocytes and enhanced bacterial translocation in major depressive disorder. Front Psychiatry. 2019;10:812. https://doi.org/10.3389/fpsyt.2019.00812.
248. Qi Y, et al. Intestinal permeability biomarker zonulin is elevated in healthy aging. J Am Med Dir Assoc. 2017;18(810):e811-810.e814. https://doi.org/10.1016/j.jamda.2017.05.018.
249. Skardelly M, Armbruster FP, Meixensberger J, Hilbig H. Expression of zonulin, c-kit, and glial fibrillary acidic protein in human gliomas. Transl Oncol. 2009;2:117–20. https://doi.org/10.1593/tlo.09115.
250. Kushlinskii NE, et al. Blood serum zonulin in colorectal cancer, autoimmune bowel diseases, and irritable bowel syndrome. Bull Exp Biol Med. 2022;173:376–9. https://doi.org/10.1007/s10517-022-05552-w.
251. Landmann R, et al. Human monocyte CD14 is upregulated by lipopolysaccharide. Infect Immun. 1996;64:1762–9. https://doi.org/10.1128/iai.64.5.1762-1769.1996.
252. Meuleman P, et al. Human hepatocytes secrete soluble CD14, a process not directly influenced by HBV and HCV infection. Clin Chim Acta. 2006;366:156–62. https://doi.org/10.1016/j.cca.2005.09.022.
253. Kim SJ, Kim HM. Dynamic lipopolysaccharide transfer cascade to TLR4/MD2 complex via LBP and CD14. BMB Rep. 2017;50:55–7. https://doi.org/10.5483/bmbrep.2017.50.2.011.
254. Marks MA, et al. Markers of microbial translocation and risk of AIDS-related lymphoma. AIDS. 2013;27:469–74. https://doi.org/10.1097/QAD.0b013e32835c1333.
255. Shive CL, Jiang W, Anthony DD, Lederman MM. Soluble CD14 is a nonspecific marker of monocyte activation. AIDS. 2015;29:1263–5. https://doi.org/10.1097/qad.0000000000000735.
256. Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. Eurasian J Med. 2017;49:53–8. https://doi.org/10.5152/eurasianjmed.2017.17062.
257. Gabarin RS, et al. Intracellular and extracellular lipopolysaccharide signaling in sepsis: avenues for novel therapeutic strategies. J Innate Immun. 2021;13:323–32. https://doi.org/10.1159/000515740.
258. Tabung FK, et al. Influence of dietary patterns on plasma soluble CD14, a surrogate marker of gut barrier dysfunction. Curr Dev Nutr. 2017. https://doi.org/10.3945/cdn.117.001396.
259. Reiner AP, et al. Soluble CD14: genomewide association analysis and relationship to cardiovascular risk and mortality in older adults. Arterioscler Thromb Vasc Biol. 2013;33:158–64. https://doi.org/10.1161/atvbaha.112.300421.
260. Cani PD, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56:1761–72. https://doi.org/10.2337/db06-1491.
261. Madison AA, et al. Endotoxemia coupled with heightened inflammation predicts future depressive symptoms. Psychoneuroendocrinology. 2020;122:104864. https://doi.org/10.1016/j.psyneuen.2020.104864.
262. Weber NS, et al. Monocyte activation detected prior to a diagnosis of schizophrenia in the US Military New Onset Psychosis Project (MNOPP). Schizophr Res. 2018;197:465–9. https://doi.org/10.1016/j.schres.2017.12.016.
263. McGill RB, et al. Monocyte CD14 and HLA-DR expression increases with disease duration and severity in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23:430–7. https://doi.org/10.1080/21678421.2021.1964531.
264. Gustafson MP, et al. Intratumoral CD14+ cells and circulating CD14+HLA-DRlo/neg monocytes correlate with decreased survival in patients with clear cell renal cell carcinoma. Clin Cancer Res. 2015;21:4224–33. https://doi.org/10.1158/1078-0432.Ccr-15-0260.
265. Prat M, et al. Circulating CD14(high) CD16(low) intermediate blood monocytes as a biomarker of ascites immune status and ovarian cancer progression. J Immunother Cancer. 2020. https://doi.org/10.1136/jitc-2019-000472.
266. Fuentelsaz-Romero S, et al. The macrophage reprogramming ability of antifolates reveals soluble CD14 as a potential biomarker for methotrexate response in rheumatoid arthritis. Front Immunol. 2021;12:776879. https://doi.org/10.3389/fimmu.2021.776879.
267. Ferreira S, et al. Effect of gluten-free diet on levels of soluble CD14 and lipopolysaccharide-binding protein in adult patients with celiac disease. Cent Eur J Immunol. 2021;46:225–30. https://doi.org/10.5114/ceji.2021.107012.
268. Somsouk M, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. AIDS. 2015;29:43–51. https://doi.org/10.1097/qad.0000000000000511.
269. Hunt PW, et al. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. J Infect Dis. 2014;210:1228–38. https://doi.org/10.1093/infdis/jiu238.
270. Wischmeyer PE. Enteral nutrition can be given to patients on vasopressors. Crit Care Med. 2020;48:122–5. https://doi.org/10.1097/ccm.0000000000003965.
271. Arabi YM, McClave SA. Enteral nutrition should not be given to patients on vasopressor agents. Crit Care Med. 2020;48:119–21. https://doi.org/10.1097/ccm.0000000000003362.
272. Patel JJ, et al. Early trophic enteral nutrition is associated with improved outcomes in mechanically ventilated patients with septic shock: a retrospective review. J Intensive Care Med. 2016;31:471–7. https://doi.org/10.1177/0885066614554887.
273. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: a propensity-matched analysis. Clin Nutr. 2020;39:460–7. https://doi.org/10.1016/j.clnu.2019.02.020.
274. Pardo E, et al. Association between early nutrition support and 28-day mortality in critically ill patients: the FRANS prospective nutrition cohort study. Crit Care. 2023;27:7. https://doi.org/10.1186/s13054-022-04298-1.
275. Reignier J, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309:249–56. https://doi.org/10.1001/jama.2012.196377.
276. McClave SA, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically Ill patient: society of critical care medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40:159–211. https://doi.org/10.1177/0148607115621863.
277. Layland M, Mythen MG, Wang KY, Albaladejo P, Leone BJ. Measurement of gastrointestinal intramucosal pH is a poor guide to tolerable levels of anemia during isovolemic hemodilution in a canine model of coronary stenosis. Arch Surg. 1997;132:547–52. https://doi.org/10.1001/archsurg.1997.01430290093019.
278. Martin GS, et al. Perioperative Quality Initiative (POQI) consensus statement on fundamental concepts in perioperative fluid management: fluid responsiveness and venous capacitance. Perioper Med (Lond). 2020;9:12. https://doi.org/10.1186/s13741-020-00142-8.
279. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg. 1995;130:423–9. https://doi.org/10.1001/archsurg.1995.01430040085019.
280. Myles PS, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378:2263–74. https://doi.org/10.1056/NEJMoa1801601.
281. Khanna AK, Saha AK, Segal S. Association of the exclusive use of intraoperative phenylephrine for treatment of hypotension with the risk of acute kidney injury after noncardiac surgery. Anaesth Crit Care Pain Med. 2023;42:101224. https://doi.org/10.1016/j.accpm.2023.101224.
282. Ackland G, Grocott MP, Mythen MG. Understanding gastrointestinal perfusion in critical care: so near, and yet so far. Crit Care. 2000;4:269–81. https://doi.org/10.1186/cc709.
283. Siskind S, Brenner M, Wang P. TREM-1 modulation strategies for sepsis. Front Immunol. 2022;13:907387. https://doi.org/10.3389/fimmu.2022.907387.
284. Cuvier V, et al. A first-in-man safety and pharmacokinetics study of nangibotide, a new modulator of innate immune response through TREM-1 receptor inhibition. Br J Clin Pharmacol. 2018;84:2270–9. https://doi.org/10.1111/bcp.13668.
285. François B, et al. Nangibotide in patients with septic shock: a Phase 2a randomized controlled clinical trial. Intensive Care Med. 2020;46:1425–37. https://doi.org/10.1007/s00134-020-06109-z.
286. François B, et al. Prospective evaluation of the efficacy, safety, and optimal biomarker enrichment strategy for nangibotide, a TREM-1 inhibitor, in patients with septic shock (ASTONISH): a double-blind, randomised,

controlled, phase 2b trial. Lancet Respir Med. 2023;11:894–904. https://doi.org/10.1016/s2213-2600(23)00158-3.
287. Theobald V, et al. Triggering receptor expressed on myeloid cells-1 in sepsis, and current insights into clinical studies. Crit Care. 2024;28:17. https://doi.org/10.1186/s13054-024-04798-2.
288. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39:517–28. https://doi.org/10.1007/s00281-017-0639-8.
289. Rochwerg B, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis (protocol). BMJ Open. 2017;7:e016847. https://doi.org/10.1136/bmjopen-2017-016847.
290. Ranieri VM, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366:2055–64. https://doi.org/10.1056/NEJMoa1202290.
291. Abraham E, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med. 2005;353:1332–41. https://doi.org/10.1056/NEJMoa050935.
292. Marti-Carvajal AJ, Sola I, Gluud C, Lathyris D, Cardona AF. Human recombinant protein C for severe sepsis and septic shock in adult and paediatric patients. Cochrane Database Syst Rev. 2012;12:CD004388. https://doi.org/10.1002/14651858.CD004388.pub6.
293. Annane D, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862–71. https://doi.org/10.1001/jama.288.7.862.
294. Sprung CL, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–24. https://doi.org/10.1056/NEJMoa071366.
295. Venkatesh B, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018;378:797–808. https://doi.org/10.1056/NEJMoa1705835.
296. Annane D, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018;378:809–18. https://doi.org/10.1056/NEJMoa1705716.
297. Dequin PF, et al. Hydrocortisone in severe community-acquired pneumonia. N Engl J Med. 2023;388:1931–41. https://doi.org/10.1056/NEJMoa2215145.
298. Pirracchio R, et al. Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. NEJM Evid. 2023;2:EVIDoa2300034. https://doi.org/10.1056/EVIDoa2300034.
299. Evans L, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063–143. https://doi.org/10.1097/CCM.0000000000005337.
300. Adas MA, et al. The infection risks of JAK inhibition. Expert Rev Clin Immunol. 2022;18:253–61. https://doi.org/10.1080/1744666x.2022.2014323.
301. Clere-Jehl R, et al. JAK-STAT targeting offers novel therapeutic opportunities in sepsis. Trends Mol Med. 2020;26:987–1002. https://doi.org/10.1016/j.molmed.2020.06.007.
302. Rizvi MS, Gallo De Moraes A. New decade, old debate: blocking the cytokine pathways in infection-induced cytokine cascade. Crit Care Explor. 2021;3:e0364. https://doi.org/10.1097/cce.0000000000000364.
303. Spooner CE, Markowitz NP, Saravolatz LD. The role of tumor necrosis factor in sepsis. Clin Immunol Immunopathol. 1992;62:S11-17. https://doi.org/10.1016/0090-1229(92)90036-n.
304. Evangelatos G, Bamias G, Kitas GD, Kollias G, Sfikakis PP. The second decade of anti-TNF-a therapy in clinical practice: new lessons and future directions in the COVID-19 era. Rheumatol Int. 2022;42:1493–511. https://doi.org/10.1007/s00296-022-05136-x.
305. Qiu P, et al. Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: a meta-analysis. Crit Care Med. 2013;41:2419–29. https://doi.org/10.1097/CCM.0b013e3182982add.
306. Ge YJ, et al. Anti-inflammatory signaling through G protein-coupled receptors. Acta Pharmacol Sin. 2020;41:1531–8. https://doi.org/10.1038/s41401-020-00523-1.
307. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol. 2017;17:407–20. https://doi.org/10.1038/nri.2017.36.
308. Ducarmon QR, et al. Gut microbiota and colonization resistance against bacterial enteric infection. Microbiol Mol Biol Rev. 2019. https://doi.org/10.1128/mmbr.00007-19.
309. Slifer ZM, Krishnan BR, Madan J, Blikslager AT. Larazotide acetate: a pharmacological peptide approach to tight junction regulation. Am J Physiol Gastrointest Liver Physiol. 2021;320:G983-g989. https://doi.org/10.1152/ajpgi.00386.2020.
310. Khaleghi S, Ju JM, Lamba A, Murray JA. The potential utility of tight junction regulation in celiac disease: focus on larazotide acetate. Therap Adv Gastroenterol. 2016;9:37–49. https://doi.org/10.1177/1756283x15616576.
311. Leffler DA, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology. 2015;148:1311-1319.e1316. https://doi.org/10.1053/j.gastro.2015.02.008.
312. Hoilat GJ, et al. Larazotide acetate for treatment of celiac disease: a systematic review and meta-analysis of randomized controlled trials. Clin Res Hepatol Gastroenterol. 2022;46:101782. https://doi.org/10.1016/j.clinre.2021.101782.
313. Yonker LM, et al. Zonulin antagonist, larazotide (AT1001), As an adjuvant treatment for multisystem inflammatory syndrome in children: a case series. Crit Care Explor. 2022;10:e0641. https://doi.org/10.1097/cce.0000000000000641.
314. Machado MV. New developments in celiac disease treatment. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24020945.
315. Johnstone J, et al. Effect of probiotics on incident ventilator-associated pneumonia in critically Ill patients: a Randomized Clinical Trial. JAMA. 2021;326:1024–33. https://doi.org/10.1001/jama.2021.13355.
316. Sharif S, et al. Probiotics in critical illness: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med. 2022;50:1175–86. https://doi.org/10.1097/ccm.0000000000005580.
317. Lou J, et al. Efficacy of probiotics or synbiotics in critically ill patients: a systematic review and meta-analysis. Clin Nutr ESPEN. 2024;59:48–62. https://doi.org/10.1016/j.clnesp.2023.11.003.
318. van Nood E, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407–15. https://doi.org/10.1056/NEJMoa1205037.
319. Quraishi MN, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. 2017;46:479–93. https://doi.org/10.1111/apt.14201.
320. Lee C, et al. Safety of fecal microbiota, live-jslm (REBYOTA(™)) in individuals with recurrent Clostridioides difficile infection: data from five prospective clinical trials. Therap Adv Gastroenterol. 2023. https://doi.org/10.1177/17562848231174277.
321. DeFilipp Z, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. N Engl J Med. 2019;381:2043–50. https://doi.org/10.1056/NEJMoa1910437.
322. McClave SA, Patel J, Bhutiani N. Should fecal microbial transplantation be used in the ICU? Curr Opin Crit Care. 2018;24:105–11. https://doi.org/10.1097/mcc.0000000000000489.
323. Limketkai BN, Hendler S, Ting PS, Parian AM. Fecal microbiota transplantation for the critically Ill patient. Nutr Clin Pract. 2019;34:73–9. https://doi.org/10.1002/ncp.10228.
324. Minozzi S, et al. Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. Cochrane Database Syst Rev. 2021;1:Cd000022. https://doi.org/10.1002/14651858.CD000022.pub4.
325. Wittekamp BH, et al. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a Randomized Clinical Trial. JAMA. 2018;320:2087–98. https://doi.org/10.1001/jama.2018.13765.
326. Myburgh JA, et al. Effect of selective decontamination of the digestive tract on hospital mortality in critically Ill patients receiving mechanical ventilation: a Randomized Clinical Trial. JAMA. 2022;328:1911–21. https://doi.org/10.1001/jama.2022.17927.
327. Hammond NE, et al. Association between selective decontamination of the digestive tract and in-hospital mortality in intensive care unit patients receiving mechanical ventilation: a systematic review and meta-analysis. JAMA. 2022;328:1922–34. https://doi.org/10.1001/jama.2022.19709.
328. Shoji H, Tani T, Hanasawa K, Kodama M. Extracorporeal endotoxin removal by polymyxin B immobilized fiber cartridge: designing and

antiendotoxin efficacy in the clinical application. Ther Apher. 1998;2:3–12. https://doi.org/10.1111/j.1744-9987.1998.tb00066.x.
329. Shoji H. Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). Ther Apher Dial. 2003;7:108–14. https://doi.org/10.1046/j.1526-0968.2003.00005.x.
330. Kim YA, Kim H, Kim YM, Park SE. A successful application of adult polymyxin B-immobilized fiber column hemoperfusion to a neonate with septic shock. Acute Crit Care. 2019;34:284–8. https://doi.org/10.4266/acc.2017.00528.
331. Dellinger RP, et al. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES Randomized Clinical Trial. JAMA. 2018;320:1455–63. https://doi.org/10.1001/jama.2018.14618.
332. Klein DJ, et al. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018;44:2205–12. https://doi.org/10.1007/s00134-018-5463-7.
333. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. N Engl J Med. 2013;368:299–302. https://doi.org/10.1056/NEJMp1215093.
334. Shapiro ED, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325:1453–60. https://doi.org/10.1056/nejm199111213252101.
335. Donta ST, et al. Immunoprophylaxis against klebsiella and pseudomonas aeruginosa infections. The Federal Hyperimmune Immunoglobulin Trial Study Group. J Infect Dis. 1996;174:537–43. https://doi.org/10.1093/infdis/174.3.537.
336. Castelli MS, McGonigle P, Hornby PJ. The pharmacology and therapeutic applications of monoclonal antibodies. Pharmacol Res Perspect. 2019;7:e00535. https://doi.org/10.1002/prp2.535.
337. Nie D, et al. Outer membrane protein A (OmpA) as a potential therapeutic target for *Acinetobacter baumannii* infection. J Biomed Sci. 2020;27:26. https://doi.org/10.1186/s12929-020-0617-7.
338. Lu LL, Suscovich TJ, Fortune SM, Alter G. Beyond binding: antibody effector functions in infectious diseases. Nat Rev Immunol. 2018;18:46–61. https://doi.org/10.1038/nri.2017.106.
339. Jurcisek JA, Hofer LK, Goodman SD, Bakaletz LO. Monoclonal antibodies that target extracellular DNABII proteins or the type IV pilus of nontypeable Haemophilus influenzae (NTHI) worked additively to disrupt 2-genera biofilms. Biofilm. 2022;4:100096. https://doi.org/10.1016/j.bioflm.2022.100096.
340. Fu Y, et al. Blockade of macrophage-associated programmed death 1 inhibits the pyroptosis signalling pathway in sepsis. Inflamm Res. 2021;70:993–1004. https://doi.org/10.1007/s00011-021-01493-8.
341. Varshney AK, et al. A natural human monoclonal antibody targeting Staphylococcus Protein A protects against *Staphylococcus aureus* bacteremia. PLoS ONE. 2018;13:e0190537. https://doi.org/10.1371/journal.pone.0190537.
342. Peck M, et al. A phase 1, randomized, single-ascending-dose study to investigate the safety, tolerability, and pharmacokinetics of DSTA4637S, an anti-staphylococcus aureus thiomab antibody-antibiotic conjugate, in healthy volunteers. Antimicrob Agents Chemother. 2019. https://doi.org/10.1128/aac.02588-18.
343. Kowalski RP, Romanowski EG, Yates KA, Mah FS. An independent evaluation of a novel peptide mimetic, brilacidin (PMX30063), for ocular anti-infective. J Ocul Pharmacol Ther. 2016;32:23–7. https://doi.org/10.1089/jop.2015.0098.
344. Solanki SS, Singh P, Kashyap P, Sansi MS, Ali SA. Promising role of defensins peptides as therapeutics to combat against viral infection. Microb Pathog. 2021;155:104930. https://doi.org/10.1016/j.micpath.2021.104930.
345. Coopersmith CM, et al. Surviving sepsis campaign: research priorities for sepsis and septic shock. Intensive Care Med. 2018;44:1400–26. https://doi.org/10.1007/s00134-018-5175-z.
346. Moreno R, et al. The Sequential Organ Failure Assessment (SOFA) Score: has the time come for an update? Crit Care. 2023;27:15. https://doi.org/10.1186/s13054-022-04290-9.

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