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Chapter

Intestinal Barrier Dysfunction, Bacterial Translocation and Inflammation: Deathly Triad in Sepsis

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Abstract

Sepsis, as a complex entity, comprises multiple pathophysiological mechanisms which bring about high morbidity and mortality. The previous studies showed that the gastrointestinal tract is damaged during sepsis, and its main symptoms include increased permeability, bacterial translocation (BT), and malabsorption. BT is the invasion of indigenous intestinal bacteria via the gut mucosa to other tissues. It occurs in pathological conditions such as disruption of the intestine's ecological balance and mucosal barrier permeability, immunosuppression, and oxidative stress through transcellular/paracellular pathways and initiate an excessive systemic inflammatory response. Thereby, recent clinical and preclinical studies focus on the association between sepsis and intestinal barrier dysfunction. This chapter overviews the current knowledge about the molecular basis of BT of the intestine, its role in the progress of sepsis, detection of BT, and actual therapeutic approaches.

Keywords: bacterial translocation, intestinal barrier, inflammation, sepsis, multiple organ failure

1. Introduction

Sepsis has been announced to be a global health priority by the World Health Organization as in 2017, 48.9 million sepsis cases and 11 million sepsis-related deaths were reported worldwide [1, 2]. However, although significant progress has been made regarding the mechanism of sepsis, treatment modalities still have not gone beyond fluid resuscitation, vasopressors, antibiotics, and palliative care, after all [1, 3].

Sepsis is a perilous condition caused by the dysregulated and hyperactive host response to the pathogen. This response leads to an inflammation out of control and eventually multiple organ dysfunction syndrome (MODS), which is the primary cause of sepsis-related deaths. The propulsive force of the severe consequences of sepsis, such as MODS, is the intestines due to its potential to provoke systemic immune response via the injured intestinal epithelia losing its barrier function, and cannot prevent the pathogens and toxins to confined intraluminally and secreting and releasing the pro-inflammatory cytokines into the circulation [1, 3–9]. In this chapter, we aimed to cover the fate of the intestinal barrier (IB) and bacterial translocation (BT) during sepsis along with diagnostic methods and potential therapeutic options for IB dysfunction in the light of this information.

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2. Structure and functions of the IB

The mammalian IB is responsible for fulfilling two primary tasks: to absorb the ingested nutrients and to prevent the microorganisms, toxins, allergens, as well as luminal pro-inflammatory factors from passing through the luminal surface of the intestines into the circulatory system [6, 10–13].

The gastrointestinal tract, which consists of the mouth, esophagus, stomach, small and large intestines, calls for a single layer epithelial lining with its partners in crime, such as cells of innate and adaptive immune system, forming a multifunctional system to fulfill its barrier function [11].

In the name of intestinal homeostasis, "some" (capital S should be replaced with lowercase "s". ome of the complex functions should be performed alongside the absorption of the nutrients like to prevent the trespassing of the pathogens, toxins, or allergens limiting the pathogenic bacterial growth to maintain the balance of the luminal microbiota, detoxification of the endotoxins, and immune response on demand as it is the largest lymphoid organ of the body by a multilayer morpho-functional barrier [9, 14] (for a recent review, *see* reference [13]).

2.1 First line of defense: commensal microbiota as the biological barrier

Human beings are in a symbiotic relationship with millions of bacteria, fungi, and viruses colonized in our gastrointestinal tract [12, 15, 16]. This host-commensal relationship, which starts at birth, even in-utero [17–19], maintains the intestinal homeostasis as a biological barrier and responsible for the differentiation, growth, and integrity of the intestinal epithelium [12, 15, 16]. Most of the species of commensal bacteria are obligate anaerobes, and the rest are facultative anaerobes and aerobic bacteria (**Table 1**) [16, 20]. The majority of the anaerobic bacteria are found in the colon as the oxygen tension is relatively low, whereas the aerobic bacteria are prone to reside in the small intestines [21]. The bacterial population in the proximal small intestines and the colon are around 10^4 ml^{-1} and $\sim 10^7$ ml^{-1}, respectively [22].

These coexisting symbiotic bacteria demonstrate immunologic and metabolic functions and protect the intestines from pathogenic bacteria growth via alimentary competition and colonization suppression. They help ferment and digest carbohydrates and synthesize vitamin B and K, along with short-chain fatty acids, which will then become the energy source for the intestinal epithelium. They are also responsible for the deconjugation of bile acids which will then reenter the enterohepatic circulation [12, 16].

Obligate anaerobes	Facultative anaerobes
Bifidobacterium	*Lactobacillus*
Clostridium	*Bacillus*
Eubacterium	*Streptococcus*
Bacteroides	*Staphylococcus*
Fusobacterium	*Escherichia coli*
Peptococcus	*Klebsiella*
Peptostreptococcus	*Pseudomonas aeruginosa*

Table 1.
The intestinal microbiota: Most common commensal anaerobic bacteria species in the human intestines (95% of them are obligate and 5% are facultative anaerobes) [16].

The intestinal immune system is modulated via the collaboration between the gut microbiota with the adaptive and innate immune systems, which is carried out by interacting pathogen-associated molecular patterns (PAMPs) with the specific receptors in the intestinal immune cells [12, 16].

2.2 Second line of defense: intestinal alkaline phosphatase (IAP)

IAP, one of four of the human alkaline phosphatase family, is an intestinal epithelial cell-derived enzyme constantly staying active intraluminally and in the mucosal lining to ease the gut's inflammatory response triggered by PAMPs. This way, it regulates the pH balance of the duodenal surface via bicarbonate secretion, helps the absorption of the long-chain fatty acids, defends the brush border membrane against the members of the intestinal microbiota. IAP also dephosphorylates bacterial endotoxin lipopolysaccharide (LPS) and pro-inflammatory nucleotides. Hence, it prevents the inhibition of the commensal microorganisms, as they are affected by the excessive luminal ATP by removing the phosphate groups from adenosine di- and triphosphate. LPS, which causes a systemic immune response and septic shock, is located on the wall of gram-negative bacteria and shows these effects by binding to toll-like receptor 4 (TLR4) thanks to its Lipid A moiety. TLR4 is expressed both in myeloid-borne immune cells (dendritic cells (DCs), macrophages, and monocytes) and in non-immune cells (i.e., endothelial cells) [23]. When dephosphorylated Lipid A moiety binds to TLR4, LPS shifts to a TLR4 antagonist, diminishes the pro-inflammatory cytokines, and activates nuclear factor-kappa-B (NF-κB), thereby minimizing the inflammatory response. It was previously shown that even being exposed to a lethal dose of E.coli, 80% of the mice survived with the help of IAP treatment. Thus, it was concluded that microbiota dysbiosis, intestinal inflammatory response, and transmigration of bacteria are inevitable in the absence of IAP [5, 14, 24, 25].

2.3 Third line of defense: the mucous layer

The first layer of the mechanical barrier is the mucosal layer which comprises water (95%), soluble glycoproteins (1–10%), nucleic acids, electrolytes, and antibodies. Mucin, a highly glycated protein, is secreted by goblet cells (specialized epithelial cells located in the villi), and with the help of other secreted proteins, they organize into a coherent mucus layer [11, 14].

Bacteria are responsible for the degradation of the mucus, and the balance between the secretion and the erosion of this layer determines the functionality of the IB. It was previously shown that this highly glycated structure of mucin feeds commensal bacteria, such as *Akkermansia muciniphila*, which is a gram-negative bacteria and gets protection from the potential pathogenic growth in return [26]. A previous study, in which bacterial adherence was coherently found to be elevated in the intestinal epithelia of the Mucin 2−/− mice leading to mucosal barrier dysfunction [14].

The outer intestinal mucosal layer is much looser and thicker in comparison with the inner layer. Therefore, the inner layer restrains the transmigration of the bacteria as it is tightly attached to intestinal epithelia to block the direct contact between epithelial cells and the bacteria. Contrarily, the outer layer retains the commensal microbiota elements to eliminate the opportunistic activity of pathogenic bacteria. For that reason, consistent usage of pro- and prebiotic preparations is reported to boost the number of commensal microbiota in order to promote mucosal barrier function [14].

Besides, the anionic residues like sialic acid or sulfate groups at the N-terminal of the mucin glycoprotein promote convergence of the cationic immune molecules, which serve as a chemical defense mechanism [27].

2.4 Fourth line of defense: physical barrier composed of the intestinal epithelial layer and submucosal capillary endothelial cells

The second mechanical barrier is the polarized single layer of gut epithelial cells (enterocytes-responsible for the absorption, goblet-specialized in mucus production, enteroendocrine cells-responsible for the secretion of the intestinal hormones, Paneth cells-responsible for expressing the microbicidal proteins and peptides among other properties, and microfold cells (M cells)) besides submucosal capillary endothelial cells [21, 28, 29], which act as a selectively permeable interface allowing the transmigration of the essential nutrients, water, electrolytes, and immune factors, and preventing the transfer of luminal pathogenic microorganisms, antigens, and toxins to the circulatory system [4, 12–14, 30]. This feature of selectivity is coordinated by the paracellular pathway regulated by desmosomes, adherens junctions, and tight junctions (TJs), located at the apicolateral membrane junction, lateral membrane, and basolateral membrane, respectively, and the transepithelial pathway, which is maintained mainly by the selective transporters allowing the uptake of the nutrients [13, 14, 28, 31] (for a recent review about mechanobiology of TJs, see reference [32]).

2.5 Fifth line of defense: antibacterial peptides

Hence their vast Golgi and endoplasmic reticulum system Paneth cells known for their cytoplasmic eosinophilic granules, [33], which are exclusively found in the crypts of the small intestine and they the secretory cells of the intestinal mucosa specialized in the secretion of the antimicrobial peptides, which are crucial modulators of innate immunity, as well as with neuropeptides and hormones [14, 34].

α-defensin, a ubiquitous antimicrobial peptide found in the intestine, along with β-defensin, has bactericidal activity, particularly against both the gram-negative and gram-positive bacteria, and any disturbance in the existence of these peptides is shown to increase predisposition to inflammatory bowel disease [14, 34].

Apart from defensins, other antimicrobial proteins such as phospholipase A_2 and lysozyme are also secreted from Paneth cells in case of an interaction with bacteria or bacterial antigen [34].

Besides these Paneth cell-driven antimicrobial activities, immunoglobulin A (IgA), which is secreted by plasma immune cells through lamina propria (transcytosis) [5, 14, 35–37], also contribute to the fifth line of defense in the IB. IgA either binds directly to the potential pathogenic microorganism and toxins to counter the unwanted colonization or epithelial injury or binds and interacts with immune complexes within the lamina propria to clear out these complexes to soothe the systemic inflammatory responses [14]. It also pumps the already translocated bacteria and antigens in the lamina propria back into the lumen [38].

The previous experimental studies on the B cell-deficient mice (as the IgA secreting plasma cells are differentiated from B cells) and the polymeric immunoglobulin receptor (pIgR) knockout mice (as the transcytosis of IgA to the intestinal lumen is conducted by pIgR) noted intestinal inflammation due to faded IgA-operated adaptive immune response is seen in both mice groups [14, 39].

2.6 Sixth line of defense: immune barrier as "the largest lymphoid organ"

As the largest immunological organ [40], the gut's innate and adaptive immune system is in continuous interaction with the biological barrier to prevent the conversion of intestinal microbiota into pathobiota. The immune barrier consists of different types of cells, which are members of the gut-associated lymphoid tissue (GALT) like intraepithelial lymphocytes (IELs), natural killer cells (NK cells), innate lymphoid cells (ILCs), mast cells, and M cells (**Table 2**) [9, 12, 41, 42].

Cell type	Location	Structure and functions
IELs	Within the intestinal epithelium (between intestinal lumen and lamina propria)	T cells specialized in destroying the transformed, damaged, necrotic, or infected intestinal epithelial cells with their cytotoxic activities regulate the growth and proliferation of the enterocytes. They directly contact the antigens, microbiota, and potential pathogens, and during this interaction, interleukin-15 (IL-15) activates IELs and causes them to express cytokines like IL-2, IL-4, IL-1 and interferon-gamma (IFNγ) excessively. Although IELs are mostly T cells, they possess unconventional properties compared to other T cells due to their unique location and tasks. These functions are usually in favor of the intestine as they react immediately to the pathogenic microorganism or antigen, block the initial attempt of trespassing and invasion, and inhibit unnecessary inflammatory reactions against innocuous antigens. Nevertheless, they may mistaken self-antigens from the pathogenic antigens in a chaotic inflammatory milieu and trigger a pathological autoimmune response. There are two types of IELs: "type a" (induced IELs) and "type b" (natural IELs). Type a (induced) IELs are either CD8αβ heterodimer (Major-Histocompatibility-Complex (MHC) class I-restricted) or CD4+ (MHC class II-restricted) T cells, which express an αβ T cell receptor (αβTCR). They arise from the naive T cells and are activated postthymically (in secondary lymph nodes). After contact with the peripheral antigen as a tissue-resident memory, T cells accumulate in the gut. Type b (natural) IELs are CD8αα homodimer-T cells (do not express CD8β), expressing either a γδTCR or an αβTCR, which are thymically derived and activated by the self-antigens (they can be detected in-utero) and migrate to intestinal epithelium for further differentiation. The adult human jejunum predominantly contains type a IELs expressing CD8αβ along with αβTCR, while the ileal and colonic IELs mainly express αβTCR without CD4 and CD8 expression. Also, IELs are recruited in the small intestines via interacting with E-cadherin through their hallmark marker CD103 (αE integrin).
M cells	Peyer's patches	M cells contact the luminal antigens via their irregular short microvilli located on the apical surface and translocate the pathogens to the lymphocytes, or the antigen-presenting cells (APCs) are carried out by the intraepithelial pockets under the basolateral surface, which provides acquired immunity via interaction between the CD4+ T cells and the presented peptide epitopes of the pathogens.
ILCs	Scattered both in the epithelium and the stroma	ILCs are the coordinators of mucosal immunity as they regulate other functions of the other cells that are part of innate and adaptive immunity, and they also secrete certain effector cytokines. These functions together serve to orchestrate the innate immune response during infection, tissue damage, and inflammation in order, so the gut homeostasis is maintained. Based on their cytokine production, they are classified into three groups: Type 1 ILCs (ILC1s): NK cells. They exclusively express IFNγ and no other Th-17 cell-associated cytokines. NK cells are widely in contact with the microorganisms or the microbial components due to their location, and they also interact with immune cells such as DCs, T cells, macrophages, and fibroblasts, and epithelial cells. Intestinal NK cells recruit peripheral NK cells via IFNγ production. Type 2 ILCs (ILC2s): Cells located in the lower respiratory system along with the gut and mesentery. They produce TH2-associated cytokines. Type 3 ILCs (ILC3s): Cells that produce Th-17 cytokines (IL-17 and IL-22; cytokines associated with gut inflammation and immunity to extracellular bacteria). Besides, DCs, modulated by the resident commensal bacteria, stimulate secretion of the antibacterial peptides from induced intestinal epithelial cells by activating ILC3s.

Table 2.
Intestinal immune cells: Different types of the cells of "the largest lymphoid organ" contribute to IB function [9, 12, 21, 41–46].

These cells reside in the intestinal mucosal lymphoid structures of GALT, including the intestinal epithelium, isolated lymphoid follicles (responsible for the local IgA response), and mesenteric lymph nodes the lamina propria and Peyer's patches (5–10% of the follicle-associated epithelial cells) [21, 43, 44, 47] (for a recent review, *see* reference [48]).

ILCs, innate lymphoid cells; ILEs, intraepithelial lymphocytes; M cells, microfold cells; NK, natural killer; Th-17 cell, T helper-17 cell.

3. Mechanism of IB dysfunction in sepsis

All of the aforementioned layers of the IB are the sole protectors of the body, acting as a barrier between 40 trillion luminal microorganisms [49] and the body. Thus they carry a heavy burden in terms of maintaining intestinal homeostasis. Therefore, luminal content should be deliberately compartmentalized, and filtered selectively via preserving intestinal integrity, otherwise increased gut permeability provokes the activation of mucosal immunity via promoting BT along with translocating endotoxins and other pro-inflammatory antigens from lumen to the circulation [3, 5, 9, 14]. This catastrophic cascade can be seen during any infection or any incident triggering local and systemic inflammatory response generating impairment of IB integrity such as sepsis, shock, trauma, abdominothoracic vascular surgery, transplantation, severe burn, and intestinal/mesenteric ischemia and reperfusion [50–52].

3.1 BT

The concept of BT was first described in 1966 [53] and further expanded in 1979 [54] as the transportation of indigenous bacteria through the intestinal wall into the mesenteric lymph nodes and other sterile organs. Translocation of PAMPs, which are small molecular motifs (i.e., LPS, peptidoglycan, and bacterial DNA) located in the microorganism, are added to this definition later on [12]. The mechanism behind the BT are diverse.

3.1.1 Imbalance of the intestinal flora

Intestinal microbiota can be affected by diverse factors, including gastrointestinal secretions, antibiotics, secreted IgA (sIgA), bile salts, and peristalsis of the intestines. Overgrowth of the microbiota upsets the protective features of the beneficial intestinal bacteria and disrupts the first line of defense of the IB resulting in BT.

3.1.2 Dysfunction of mucosal immune function

Under physiological conditions, IgA secreted by the plasma cells has a feature of encapsulation of bacteria to prevent their trespassing and encapsulation of viruses invading the cells. It also has features enhancing the effects of lysozyme and complements. However, pathological processes inhibit the functionality of IgA, including encapsulation ability, as well as their concentration via a declined number of plasma cells secreting the IgA. This will eventually cause BT.

3.1.3 Increased intestinal permeability

Pathological processes such as conditions causing immunocompromisation or immunosuppression, MODS, severe burn injury generate BT via overgrowth of

intestinal microbiota, immune dysfunction of the body together with the physical intestinal injury, particularly in the mucosal barrier. Oxygen depletion (caused by shock, mesenteric ischemia, cardiovascular surgery, transplant surgery) [50], acidosis, nitric oxide (NO), as exaggerated NO production by inducible NO synthase (iNOS) disturbs mitochondrial functions and cellular respiration, resulting in decreased ATP synthesis and accelerated apoptosis which causes mucosal injury, inflammatory mediators (IFN-γ, IL-4, tumor necrosis factor-α (TNF-α), platelet-activating factor (PAF), reactive oxygen species (ROS)) and endotoxins (causes edema in the submucosa, decreases the intestinal blood flow, villi necrosis) are primary factors in charge of the injured intestinal mucosal barrier and increase the intestinal permeability and BT consequently [38].

3.2 Who is the victim? Who is the criminal?

Sepsis is a hazardous organ dysfunction with high mortality and morbidity rate. The main characteristic of sepsis is "dysregulated host response to infection" [55], which will eventually bring about microvascular injury, problematic perfusion, cellular hypoxia, and finally, shock [2–5, 15].

Intestines are usually referred to as the "star of the show" during sepsis as they are accused of causing MODS [4, 7, 9, 12], yet sepsis (and septic shock) also disrupts the intestines by impairing the perfusion of the intestinal mucosa, epithelial edema, initiation of excessive apoptosis and necrosis of the gut epithelia [56], coagulation-associated local dysregulation, and cause hyperpermeability, microbiota transformation into pathobiota, BT and loss of absorptive functions [3].

3.2.1 Systemic inflammatory response

As an exaggerated inflammatory response is implicated in the pathophysiology of sepsis, involvement of inflammatory cells along with pro-inflammatory cytokines in this process is inevitable [2–5, 15, 55].

Upregulation of the adhesion molecules in the endothelial layer of the gut, induced by damage-associated molecular patterns (DAMPs) and PAMPs, leads to migration of the neutrophils, monocytes, and macrophages to the intestinal tissue. Pro-inflammatory cytokines released from these recruited cells initiate local and systemic inflammation [5, 14]. In addition, escalated activated macrophage infiltration into the artery walls inaugurates atherogenesis [14].

Besides, pattern recognition receptors (PRR) of PAMPs (including TLRs and NLRs) recognize the cell wall components of the bacteria via TLRs. TLR4 recognizes gram-negative bacteria, whereas TLR2 recognizes gram-positive bacteria. At this point, LPS-induced TLR4 activates signaling pathways either by activation of mitogen-activated protein kinase (MAPK) and NF-κB via MyD88-dependent signaling pathways or the TIR-domain-containing adapter-inducing IFN-β (TRIF)-dependent (MyD88-independent) by TLR4 endocytosis [23]. In the MyD88-dependent pathway, nuclear translocation of NF-κB encourages the transcription of pro-inflammatory genes such as IL-1 α/β, IL-6, IL-18, and TNF-α, whereas, in the TRIF-dependent pathway, nuclear translocation of IFN regulatory factor 3 (IRF3) promotes IFN-inducible genes and the type I IFNs [14, 23, 57].

TLR4 cannot bind LPS per se, needs a cofactor, CD14, which hands the LPS to TLR4 [14], and controls the LPS-induced endocytosis of TLR4 apart from the signaling pathways mentioned above [23, 58].

Although these reactions initially manifest as local inflammation, the process ultimately transforms into a "cytokine storm" [5, 14]. On the contrary, both the MyD88-dependent and TRIF-dependent signaling pathways produce pro- and

anti-inflammatory mediators (IL-10) synchronously [23]. Thus, although it has been presumed that extinguishing the hyperinflammation is beneficial in septic patients, an overbalance of anti-inflammatory activity causes an inadequate response to primary infection and makes the patient prone to secondary infections [5, 59, 60].

Additionally, TLR4 manages intestinal cell turnover. During sepsis, elevated cytokine levels shift the balance between proliferation and apoptosis of the crypt and villus in favor of apoptosis and necrosis of the intestinal mucosa, which increases the intestinal permeability as a consequence of decreased villus height, increased release of DAMPs which feed the inflammatory process and brings about ulcer development along with hemorrhage and acceleration in intestinal impairment [4, 5, 56]. The elevated levels of pro-inflammatory cytokines are also shown to reduce the thickness of the mucus layer, the adherence of the mucus layer, and the luminal coverage [4, 52].

Besides, several studies reported that M cells located in the villi provide antigens a channel to mucosal lymphoid tissue, which is a trap where they encounter antigen-presenting cells (APCs). APCs present them with the help of MHC class II to CD4+T-cells [61]. In addition to that, DCs interact with T cells and B cells and selectively generate pro- and anti-inflammatory immune responses mostly through LPS-induced TLR-associated pathways (for a recent review, *see* reference [23]).

Inflammatory host response during sepsis may alter the layers of the IB and cause intestinal hyperpermeability and BT, and these alterations modulate the changes in the expression of the proteins of the TJs such as transmembrane proteins (occludin, junctional adhesion molecules, claudins) and peripheral proteins like zonula occludens-1 (ZO-1), which is in a relationship with actin-myosin complex of the cytoskeleton [11]. Furthermore, TNF-α, IL-6, and IL-1β levels can be elevated via activation of myosin light chain kinase (MLCK), an enzyme phosphorylating the myosin regulatory light chain and leading to hyperpermeability and create a positive feedback mechanism of MLCK activation through ZO-1 and occludin alterations. Aggravated systemic inflammation because of the increased permeability leads to a futile cycle [4].

3.2.2 Sepsis-induced self-digestion of the gut

Pancreatic enzymes are shown to cause multiple organ failure via autophagy [62]. Sepsis-induced ischemia of the gut exacerbates self-digestion and causes mucosal barrier damage leading to the release of DAMPs and pro-inflammatory cytokines from intestinal epithelial cells [5, 63].

Proteases, including pancreatic enzymes in the intestines, also activate the pro-metalloproteinases (MMPs) under ischemic conditions. Enzymatic activity of MMPs destructs intercellular junctions via proteolytic cleavage of junctional proteins' ectodomain, therefore increasing the intestinal permeability. Additionally, MMPs can digest the endothelial basal membrane [64].

Besides, LPS can induce expression of MMP7, and Paneth cells' degranulation, which promotes gut hyperpermeability, while MMP7 itself enhances local intestinal inflammation and intestinal damage via activation of α-defensin, subsequently stimulating the release of IL-6 from ileal epithelia and macrophages. Furthermore, it was previously confirmed that MMP7 and MMP13 are correlated with loss of intestinal integrity, inflated BT, and the development of multiple organ dysfunction [5].

After all, it has been reported in several studies that the inhibition of pancreatic enzymes protects the sepsis-induced intestinal autophagy and improves the overall progress [64, 65].

3.2.3 Intestinal circulatory problems during sepsis

25% of the total cardiac output (up to 35% during digestion) is normally diverted to splanchnic vasculature [5]. Intestinal hypoperfusion can be caused by various reasons like mesenteric ischemia, abdominothoracic vascular surgery, shock, severe burns, transplantation surgery, necrotizing enterocolitis, sepsis, and septic shock [50], because of the redistribution of blood to protect the vital organs [38]. Intestines are highly sensitive to hypoperfusion as the enterocytes have the highest turnover rate among other fixed-cell populations in the body, with a lifespan of 2–6 days [3, 66]. Thus, hypoperfusion causes damage to the intestinal mucosal barrier [5]; moreover, the inflammation as a response to hypoperfusion caused by the ischemia/reperfusion further injures the intestines [3], resulting in loss of IB integrity, BT accompanied by systemic inflammatory response via release of pro-inflammatory cytokines [5, 50, 67].

In addition to that, vasodilation emerges as the pro-inflammatory cytokines (IFN-γ, TNF-α, IL-4, platelet-activating factor) affect vascular smooth musculature and endothelium, as well as capillary leakage, venous stasis, and ultimately diminished cardiac output, and hypoperfusion is seen [38, 68, 69]. Furthermore, compensatory mechanisms, such as the renin-angiotensin-aldosterone system, provokes the release of vasoconstriction and contribute to hypoperfusion. Also, regulatory features of the microvasculature (arterioles, venules, and capillaries) related to perfusion and oxygen distribution are lost due to sepsis-induced hyperinflammation and its inevitable outcome, ROS [38, 69–71].

3.2.4 Coagulopathy

Disseminated intravascular coagulation (DIC) is still an up-to-date challenge as of the significant lethal problems of sepsis. It is suggested that both intravascular and extravascular fibrin formation are seen in sepsis-associated DIC due to coagulation activation combined with fibrinolysis inhibition [72].

In sepsis, activation of coagulation is driven mainly by the tissue factor (TF) pathway, in which TF is derived from endothelial cells, monocytes, neutrophils, and liver, whereas suppression of fibrinolysis is coordinated by plasminogen activator inhibitor-1 (PAI-1) [5]. "Activation of coagulation": Neutrophil activation, caused either by direct contact with the pathogen or damaged cell- or bacteria-originated small molecules cause neutrophils initially to release a significant amount of TF [73, 74]. Later on, elastase is released from the neutrophils as well. Elastase has the ability to inhibit plasminogen together with the TF pathway, which is a crucial coagulation suppressor system [75, 76]. Neutrophil extracellular traps (NETs), which are released from neutrophils in order to trap and eliminate the microbes, also contribute to alterations in the coagulation via activation of Factor XII due to their negatively charged surfaces, fibrin formation, and competitively blocking the binding sites of tissue plasminogen activator (tPA) for clot degradation by fibrin cleavage [77–80] This explains the persevere on-going of the post-sepsis micro- and macrothrombosis events [81]. "Inhibition of fibrinolysis": Sepsis-associated DIC differs from malignancy-associated one, since it is characterized by intensive suppression of fibrinolysis via overproduction of PAI-1, instead of the consumption of coagulation factors, od and differs from fibrinolytic phenotype DIC, as the consequential effects of this suppression in sepsis-associated DIC lead to tissue hypoperfusion resulted in organ dysfunction. Hence, the fibrin-related markers are not safe to use to assess the severity of sepsis as hypofibrinogenemia is uncommon [81, 82].

Besides, antibody-mediated action in the presence of pathogens can activate the complement system during sepsis. Coagulation system is also affected by the

activated complement factors via generating an epithelial surface to facilitate clot formation. Activated C3 also activates platelets through the alternative pathway for stimulating aggregation, while activated C5 stimulates endothelial and inflammatory cells, inducing TF expression [83, 84]. In reverse, activated coagulation system can also impact the complement system. TCC production via activation of C5 is achieved by thrombin. Additionally, plasmin can also activate C3 and C5, forby other proteases of the coagulation cascade activate several complement factors like IXa, Xa, XIa, and XIIA [85]. These factors collectively disturb intestinal microcirculation and intestinal physiology and recruit the immune cells throughout the incidence of sepsis-associated DIC [5].

4. Diagnostic techniques

It is pretty challenging to diagnose or assess the IB function directly due to the invasiveness of intestinal tissue sampling. However, there are some methods or biomarkers that indirectly assess IB function. The measurement of biomarkers in urine, blood, or feces generally needs simple, non-invasive test methods.

4.1 Tissue culture methods

The tissue culture methods are based on the direct detection of intestinal bacteria in extraintestinal tissues. The mesenteric lymph nodes (MLN), extraintestinal tissues, swabs of the intestinal wall serosa or abdominal cavity, blood, and lymph are subjected to bacterial culture. Living bacteria are isolated, counted, and detected using microscopy. Direct detection has tremendous importance; however, many factors may interfere with the measurement [38]. For the culture of MLN, lymph nodes are suggested to be excised and be homogenized in saline. The homogenate can be inoculated onto Columbia blood agar and cysteine lactose electrolyte deficient media.

BT can also be measured by identifying intestinal bacteria from MLN, which is normally sterile [86]. For the culture of MLN, a lymph node from the mesentery of the terminal ileum is suggested to be excised at laparotomy and be homogenized in saline. Then, the homogenate can be inoculated onto Columbia blood agar and cysteine lactose electrolyte-free media.

4.2 Use of labeled bacteria

Radioactive tracers or plasmids are used to label bacteria for their in vivo detection. This method can detect the bacteria which is attached to intestinal mucosa-associated lymphoid tissue. However, this method can be used primarily in scientific research labs due to its cost and technical requirements.

Fluorescence and isotopes labeling methods are recently in use. PUC19 plasmid was constructed in the 1980s and was used extensively in molecular cloning and discrimination of gene recombination [87]. In this method, the plasmid vector carries the ampicillin resistance gene; the plasmid contains polyclonal restriction endonuclease sites, which discriminates against the positive bacteria. Thus, the PUC19 plasmid is introduced as an ideal tracer for demonstrating BT.

4.3 PCR techniques

Intestinal BT can be demonstrated by isolating bacterial DNA in patients' blood or body fluids and then amplifying and sequencing them. The PCR detection method is more sensitive, has a higher positive rate, and can specifically detect

certain bacteria when compared to blood culture methods. PCR technic is also a valuable tool for detecting BT in patients with undetected infectious focus. The disadvantage of this method is that only the presence of bacterial debris can be detected, the viability and quantity of the bacteria cannot be determined, and drug sensitivity tests cannot be performed. The quantification of total bacterial 16S rDNA in plasma is used to assess human and animal systemic microbial translocation *in vivo* and thus is a great tool to study the role of systemic microbial products in disease pathogenesis and mucosal barrier function. The bacterial 16S rDNA assay can analyze 90% of bacterial strains, including Gram-positive and Gram-negative bacteria. However, the use of this assay is highly challenging because of its high technical demands and the risk of contamination [88].

4.4 Detection of endotoxin

Lipopolysaccharide (LPS), the integral component of the outer membrane of all gram-negative bacteria are shown to lead to BT. Since sepsis leads to intestinal submucosal edema and impairs the integrity of the mucosal barrier resulting in an imbalance of gut microflora and increased bacterial endotoxin-induced mucosal injury, endotoxin detection in the blood is a good marker of BT [38, 89].

Endotoxins can be detected in biological fluids by the Limulus amoebocyte lysate assay. Methods using fluorescence phage recombinant technology are also introduced [90].

4.5 Measurement of IB function

Several methods are used for the measurement and the evaluation of intestinal permeability and barrier function, such as the measurements of transepithelial resistance and assessment of macromolecular flux across isolated segments of GI tissue or colonic biopsies in Ussing chambers, measurement of permeability using fluorescein isothiocyanate (FITC)-dextran permeability in cell lines, morphological measurements of the TJ components, measurement of dilution potentials, and polyethylene glycol (PEG) profiling to assess the pore pathways [91, 92].

4.6 Intestinal permeability

Methods used to measure intestinal permeability are based on detecting the passage of the molecules across the intestinal epithelium. Several markers can be used alone or in combination to assess intestinal fluxes. Large molecules, lipophilic compounds, and nutrients generally prefer the transcellular route by passing through the intestinal epithelial cells by endocytosis, passive diffusion, or membrane transporters. On the other hand, ions and small hydrophilic molecules prefer the paracellular transport pathway. Thus, molecular size and structure are significant determinants of intestinal permeability [93].

Cell culture-based models using Caco-2 or HT-29 cell lines assess electrical resistance and intestinal flux in vivo. In contrast, differential urinary excretion tests with the use of chromium-labeled EDTA (51Cr-EDTA), polyethylene glycols (PEG), or non-metabolizable sugars such as lactulose and mannitol are frequently used to measure in vivo intestinal permeability [94]. Lactulose can cross the membrane via the paracellular pathway, while mannitol can easily cross the intestinal epithelium through transcellular and paracellular routes. Multi-sugar tests are offered to assess intestinal permeability simultaneously [28, 95]. Ovalbumin, horseradish peroxidase, dextrans, and fluorescently labeled microorganisms are used to measure the intestinal permeability in the blood [96]. Claudin protein levels can be measured in

urine samples for intestinal TJ loss since claudins play a critical role in regulating the paracellular barrier pathway [97].

4.7 Urinary biomarkers

Markers of microbial translocation, inflammation (IL-6), and intestinal damage as well as fatty acid-binding proteins (FABP) and glutathione S-transferases (GSTs), which can be determined using ELISA technics, are suggested as significant biomarkers demonstrating intestinal epithelial cell damage. Fatty acid-binding proteins (FABPs) are small intracellularly or membrane-localized proteins released in the extracellular space in their soluble extracellularly from early after a cell or tissue damage. There are three main types of FABP. Liver-type FABP, intestinal-type FABP, and ileal FABP. During intestinal cell damage, intestinal-type FABP (I-FABP) is released from the enterocytes in the systemic circulation and excreted through the kidney [98]. Therefore, it has been suggested that I-FABP is an early biomarker to detect impairment of IB and injury in sepsis [99–101].

GSTs are cytosolic enzymes released when the cell membrane is damaged and play a crucial role in the detoxification of xenobiotics. Hence, α-GSTs are introduced as intestinal biomarkers [95].

4.8 Fecal biomarkers

Inflammatory molecules such as calprotectin in feces are proposed as a fecal biomarker reflecting the impaired IB function [102]. Calprotectin is a small protein in the leukocytes and is released in the lumen upon neutrophilic infiltration of the gut mucosa during inflammation and can be detected using ELISA technics.

5. Therapeutic options for the improvement of the IB dysfunction in sepsis

Although it has been known that BT is strongly associated with the progress of sepsis and septic morbidity, no decisive clinical therapy is proposed for the repair of the impaired IB and the treatment of sepsis [14]. However, some strategies such as modulation of the IB, inhibiting immoderate bacterial growth, regulating the effects of immune mediators, endotoxins, and NO, preventing oxidative stress, and improving intestinal ischemia and reperfusion injury were reported the severity of sepsis-associated BT [38].

5.1 Selective elimination of pathogenic bacteria

Removal of pathogenic bacteria, including gram-negative bacilli and symbiotic anaerobic bacteria, by the treatment with non-absorbed oral antibiotics such as polymyxin E, polymyxin B, amphotericin B, and tobramycin were suggested to reduce mortality [103, 104]. Although the treatment with non-absorbable antibiotics was believed to reduce the incidence of infection by pathogenic gram-negative bacteria and improve mortality rates, antibiotic resistance appeared as a limiting factor [105]. Since sepsis is an acute disease with high morbidity and mortality in intensive care units leads to intestinal flora disturbance, induces IB impairment, causes BT, systemic inflammation, and MODS; broad-spectrum antibiotics are frequently used in severe sepsis treatment [106]. Antibiotics are reported to affect the inflammatory process and ameliorate intestinal microcirculation in sepsis [107].

It was recently demonstrated that broad-spectrum antibiotics prevent BT to distant organs such as the liver and lungs in septic rats [108]. There is, however, evidence that broad-spectrum antibiotics can lead to an imbalance in the intestinal micro ecological environment, promote BT in sepsis, and cause drug resistance and pathogenicity, especially when MODS develops [109]. High-dose antibiotic therapy is also suggested to promote the translocation of native symbiotic bacteria and induce an inflammatory response, leading to late-onset sepsis [110]. It was concluded that metronidazole, an antibacterial and antiprotozoal drug used to treat giardiasis, anaerobic infections, and inflammatory bowel disease, reduces colonic bacterial counts and improves intestinal inflammation by suppressing cellular immunity [111]. Erythromycin was shown to increase gastric motility by affecting the motilin receptors in smooth muscle cells of the stomach, facilitating gastric emptying and decreasing the acidity and residual gastric fluid volume [112]. Treatment with antibiotic combinations (vancomycin, neomycin, and polymyxin b) prevented the translocation of intestinal bacteria to the pancreas by inhibiting the pancreatic NLRP3 pathway and inhibiting intestinal-pancreatic inflammatory responses [113].

5.2 Modulation of immune function and oxidative stress

During the attack of pathogenic bacteria, which destroys the IB or at decreased IAP conditions and increased LPS levels, the TJs are disintegrated. Macrophages are activated to produce pro-inflammatory cytokines, which also activate macrophages in circulation and cause the transportation of bacteria and LPS into the blood circulation [14, 114]. As previously mentioned, both the quantity and the functions of the secreted IgA diminish during pathological conditions [38]. Oral sIgA supplementation was shown to increase local sIgA levels in the intestine. Epithelial growth factor is suggested to promote the regeneration of intestinal mucosal epithelial cells, maintain the normal structure of intestinal mucosa, protect the intestinal mucosal immune barrier, and prevent BT [115]. Studies indicated that glutamine and growth hormone supplementations reduce intestinal BT and regulate inflammatory pathways [38].

Exogenous IAP administration was suggested to improve the IB function, while oral or enteral administration of IAP ameliorated the disintegrated IB [116, 117]. It was recently reported that high fat, Western-type diet-induced IB dysfunction, improved glucose intolerance, and orally administered IAP improved severe ulcerative colitis patients [118]. Since it was reported that anti-TNFα antibodies and inhibition of myosin light chain kinase (MLCK) prevented the impaired barrier function, treatment with these antibodies and inhibitors was suggested to reduce the severity of inflammatory bowel diseases. As IL-13 induces the disruption of barrier function by upregulation of claudin-2 expression, inhibition of IL-13 or claudin-2 seems to be proper targets for the treatment of BT [14]. The antimicrobial peptide cathelicidin-BF (C-BF) inhibited small IB dysfunction in the LPS-induced septic model in rodents [119].

Curcumin reduces the LPS/IL-1β-induced impairment of TJs [120], while berberine decreases the effects of LPS-mediated signaling through the Wnt/beta-catenin pathway to restore intestinal permeability in a rat model of sepsis [121]. It was suggested that cortisol reduces the expression of TJ proteins by alleviating the glucocorticoid receptor (GR) binding to the occludin and increases paracellular permeability and lubiprostone prevents stress-induced IB dysfunction [122]. A new GR agonist, 16α-hydroxytrametenolic acid (from edible mushrooms), is suggested to ameliorate the barrier dysfunction through PI3K/Akt/NF-κB signaling pathway [123]. Metformin is introduced to be beneficial for the protection of IB dysfunction by the inhibition of JNK activation through the AMPKα1-dependent signaling pathway [124]. Treatment with resveratrol increased the expression of sirtuin-1 in obese septic mice

and decreased the inflammatory response. Sirtuins also play a significant role during the late onset of septic "hypo-inflammation"; SIRT-2 inhibition in obese septic mice preserved a decreased microvascular inflammation and protected against thrombotic events [125]. Tezosentan, a non-selective ETA and ETB receptor antagonist, improved intestinal microcirculation in intestinal ischemia–reperfusion injury by reversing the BT and cellular disintegrate of the intestinal mucosa [50]. Allopurinol, vitamin C, coenzyme A, Quercetin, *Ginkgo biloba* extract, and N-acetyl cysteine are suggested to inhibit ROS production, protect the cell membrane, and intestinal mucosa against ROS-related damage [38]. Rhubarb, the edible petioles of species and hybrids (culinary rhubarb) of Rheum in the family Polygonaceae, was shown to reduce intestinal BT and intestinal mucosal permeability through ROS scavenging and protection of the intestinal mucosa integrity [126]. Huoxue Jiedu Ling, a mixture of wormwood, *salvia miltiorrhiza*, white-headed weng, rhubarb, and licorice, is suggested to inhibit intestinal BT and reduces the oversecretion of cytokines by macrophages [127]. Shen-Fu Decoction (SFD), a traditional Chinese herb formulation, has been widely used to treat sepsis in China. A recent study showed that SFD significantly prevented intestine and liver damage, relieved sepsis-induced intestinal permeability and inflammation, ameliorated sepsis-induced impaired intestinal permeability by regulating the expression of ZO-1, Occludin, Claudin-1, and p-VASP [128].

5.3 Probiotics

The World Health Organization (WHO) describes *probiotics* as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [129]. The most known microorganisms used as probiotics are the Lactobacillus, Bifidobacterium genera, Enterococcus, Streptococcus, and Escherichia, which have been suggested to benefit some gastrointestinal disorders by ameliorating the gut microbiota ecosystem [130]. *Prebiotics* are non-digestible food component fibers selectively inducing the growth and activity of probiotic bacteria, and *synbiotics* are described as the mixtures of probiotics and prebiotics, which are expected to be more beneficial in many pathological conditions. These microecological regulators promote the intestinal flora by inhibiting the colonization of exogenous bacteria and excessive growth of endogenous pathogenic bacteria, maintaining the ecological balance in the intestine, and reducing BT [131]. In addition, it is believed that probiotics produce bacteriocins to kill pathogens, synthesize IgA and reduce inflammation by stimulating regulatory lymphocytes through interleukin (IL)-10 and transforming growth factor signaling [132]. It was reported that *Lactobacillus rhamnosus* GG pretreatment in a septic mouse model effectively reduced mortality, possibly by improving intestinal permeability and modulating microbiota dysbiosis [133]. Studies showed that supplementation of Bifidobacterium breve strain Yakult and *Lactobacillus casei* strain Shirota as probiotics and galactooligosaccharides as prebiotics reduced the incidence of infectious complications such as enteritis, pneumonia, and bacteremia in patients with severe SIRS compared to those who did not receive synbiotics [134]. Synbiotics are a potential treatment option for sepsis patients since the complications of enteritis, and ventilation-associated pneumonia was significantly decreased in the patients treated with synbiotics [135]. However, the application of probiotics on sepsis has been limited due to the theoretical risk of aggravating bacteremia in patients with critical illnesses [136].

5.4 Fecal microbiota transplantation

Clinical studies showed that sepsis is influenced by gut microbiota disruption [137]. Fecal microbiota transplantation (FMT) is the administration of fecal material

from a healthy donor into a patient's intestinal tract with an altered gut microbiota to restore its functions. Randomized controlled trials showed that FMT is successfully applied in treating recurrent *C. difficile* infections. In addition, it helped restore bacterial communities in cecal crypts crucial in protecting intestinal stem cells, preserving immunological pathways by enhancing the expression of toll-like receptors and introduce the short-chain fatty acids, bile acids, eukaryotic, and prokaryotic viruses to the intestinal ecosystem [138, 139]. It has been postulated that if the symbiosis between the commensal bacteria and the human host becomes imbalanced, the innate and adaptive immune systems are disturbed [140]. Protective anaerobes are lost in fecal specimens with severe sepsis, indicating that pathobiota may dysregulate the immune system during sepsis [137]. Thus, FMT provides the restoration of intensive care unit-associated dysbiosis and intestinal decolonization of multidrug-resistant (MDR) organisms.

Furthermore, the introduction of symbiotic bacteria may decrease the antibiotic resistance genes present in the microbiome [139]. Treatment with FMT provides a complete reversal of dysbiosis, decreases the levels of inflammatory mediators, and normalizes T helper-(Th-)1/Th2 and Th1/Th17 ratios. However, since MDR is a leading cause of sepsis complications in intensive care unit patients, FMT has been evaluated in different case series. Results cannot be easily analyzed because of the high risk of bias in smaller studies, results of different studies cannot be conclusive because of different patient populations (with the most common organisms are carbapenem-resistant Enterobacteriaceae, vancomycin-resistant Enterococci, and extended-spectrum β-lactamase-producing bacteria, and Pseudomonas, methicillin-resistant *S. aureus*, and Acinetobacter [141].

6. Conclusion

Sepsis is a severe life-threatening organ dysfunction resulting from a systemic inflammatory response to infection. BT occurs more frequently in patients with intestinal obstruction, endogenous infections, endotoxemia, and impaired immune system, which is the cause of subsequent sepsis and ultimately leads to multiple organ dysfunction. The present chapter focused on sepsis-induced dysfunction of the IB leading to BT and multiple organ dysfunction. In addition, the underlying molecular mechanisms of BT in sepsis, diagnosis, and assessment of BT and therapeutic approaches were also discussed. Elucidating the factors affecting BT may lead to implementing interventions that contribute to improved patient outcomes. Unfortunately, there are no proven beneficial therapeutic options to prevent sepsis-induced BT yet; however, attempts at selective gut decontamination, the use of pre-or probiotics, new regimes for antibiotic prophylaxis, and fecal microbiota transplantation, to patient care will provide significant improvement for the treatment of sepsis.

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