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Current progress of research on intestinal bacterial translocation

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ABSTRACT

Under normal conditions, the intestinal flora and the body are in dynamic equilibrium. When the barrier function of the intestinal tract is damaged due to various reasons, changes in the number and proportion of bacteria or spatial displacement result in bacterial translocation (BT), which ultimately leads to multiple organ dysfunction syndrome (MODS). Endogenous infections and endotoxemia caused by intestinal flora and endotoxin translocation are the origins of inflammatory responses, and the intestinal tract is the organ in which MODS both initiates and targets. Only by ensuring the integrity of the intestinal mucosal barrier can intestinal BT be effectively prevented. Elimination of the primary disease and maintaining blood and oxygen supply to the intestine is the most basic treatment. Early initiation of the intestinal tract, establishment of enteral nutrition, and selective digestive decontamination are also highly effective treatments. Early diagnosis, intervention, or prevention of BT may be a new avenue or important connection in the treatment of various diseases. The mechanism of BT, detection techniques, prevention and treatment, and its interaction with parenteral diseases were reviewed.

1. Introduction

The intestinal tracts of animals contain large numbers of bacteria. Under normal conditions, bacteria in the body and intestines coexist peacefully through the synergy of various intestinal defense mechanisms to form a mutually beneficial symbiotic relationship [1]. The intestinal flora affects the health of humans and animals in many aspects such as digestion, nutrient absorption, energy supply, fat metabolism, immune regulation, and drug metabolism and toxicity [2–6]. In pathological conditions, this dynamic balance is disrupted, causing bacterial translocation (BT), which plays a key role in the development and progression of many diseases. The clinical significance of bacterial translocation depends on the physiological and immune status of the host. Although bacterial translocation can be promoted only by the damage of intestinal defense system, the host can eventually remove the bacteria and survive. When multiple defenses are compromised, the translocated bacteria can spread to multiple organs via mesenteric lymph nodes and cause lethal enterogenous infections. An in-depth understanding and additional studies of bacterial translocation will further elucidate mechanisms of BT and promote the development and clinical applications of novel drug. This article reviews the mechanism of BT, detection techniques, prevention and treatment, and its interaction with parenteral diseases.

1.1. Development of the concept of intestinal BT

The concept of BT can be traced back to the 1960s. In 1966, Wolochow first proposed the term “bacterial translocation”, which was defined as the phenomenon by which resident bacteria of the intestinal tract enter the lamina propria through the mucosal epithelium, subsequently entering the mesenteric lymph nodes and even distant organs [7]. In 1979, Berg et al. extended the definition of BT to include all phenomena by which microorganisms or their products pass through the intestinal mucosal barrier [8]. Since then, researchers have continued to expand and enrich this concept. It is now believed that the normal flora and their endotoxins or peptidoglycans and metabolites that originally colonized the intestine penetrate large numbers of tissues and organs outside the intestine through the intestinal mucosal barrier [9]. BT includes both lateral and vertical translocation. The former refers to the translocation of intestinal flora from the site of initial colonization to the periphery, such as the translocation of coliform bacteria to the small intestine and excessive colonization in blind loops and multiple diverticula of the small intestine, leading to small intestine infection syndrome. The latter refers to the translocation of normal flora from the site of initial colonization to the deep intestinal mucosa, such as bacteria entering the blood through the mucosal barrier [10]. Intestinal BT exists in a variety of pathological conditions and plays an important role in the development and prognosis of many diseases. Its diagnosis, prevention,

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and early treatment are key to reducing the incidence of BT and are also the focus of critical care for medical and surgical treatment.

2. Possible mechanism underlying BT

In recent years, intestinal infection caused by intestinal BT has gained increasing attention as an important pathological phenomenon. Although considerable advancement has been made in understanding the pathological mechanism, it has still not been completely elucidated. Deitch et al. [11] proposed that there are three main factors in intestinal BT and/or endotoxin translocation: (1) overgrowth of intestinal bacteria and dysregulation of intestinal flora; (2) reduced host immune function; and (3) disruption of the intestinal mucosal barrier. Among these three factors, intestinal bacterial overgrowth provides a prerequisite for BT, disruption of the intestinal mucosal barrier provides an opportunity for BT, and reduced immune function provides the conditions for intestinal translocation.

2.1. Disorder of the microecological balance in the intestinal tract

Dysregulation of intestinal flora is also one of the important causes of BT. Overgrowth of the dominant intestinal flora disrupts the resistance of beneficial bacteria in the intestine. Imbalance of the intestinal microecological environment is an important predisposing factor for intestinal bacteria to penetrate the intestinal mucosal barrier. Such bacteria that are translocated to extraintestinal organs (such as *Salmonella*) are generally tolerant to phagocytosis by macrophages and belong to specific types of intracellular pathogens [12]. Intestinal flora is affected by various factors such as diet, stomach acid, gastrointestinal secretions, bile salts, lysozymes, secreted IgA antibodies, antibacterial drugs, interactions among bacteria, and intestinal peristalsis.

2.2. Impaired immune function of the intestinal mucosa

Impaired immune function may be one of the most important factors in BT [13]. IgA is the immunoglobulin secreted in the largest amounts in the body, and sIgA exists primarily as a dimer in the intestinal tract. sIgA is secreted primarily by plasma cells in the lamina propria of the mucosa, and its main function is to prevent bacterial adhesion to the surface of intestinal epithelial cells by encapsulating the bacteria. Notably, sIgA also has an encapsulating effect on viruses that have invaded cells during the penetration process [14]. In addition, sIgA has synergistic effects with complement and lysozyme [14]. When the body is in a pathological state, the function of sIgA is significantly inhibited, sIgA content is reduced, the number of plasma cells synthesizing sIgA decreases, and the ability of sIgA to encapsulate bacteria is reduced [15]. Reduced sIgA in intestinal mucus is an important cause of BT [16].

2.3. Change in intestinal mucosal barrier permeability

The mucosa of the digestive tract is an important barrier that prevents intestinal bacteria from invading the circulatory system and other tissues of the body. However, in certain pathological states, such as chemotherapy, bone marrow transplantation, burn injury, and multiple organ failure, inhibition of the immune function of the body, overgrowth of intestinal bacteria, and physical damage to the intestinal mucosal barrier takes place, and this may cause intestinal BT to occur. The mucosa secreted by the intestinal epithelial cells is the first line of defense against bacterial invasion, preventing the adhesion of intestinal bacteria to the intestinal epithelium. In addition, the intestinal mucosa is also rich in IgA antibodies, which can bind to overgrowing bacteria and the antigenic substances they produce, prevent their translocation through immune clearance, and pump bacteria and their antigens that have translocated to lamina propria back into the intestinal lumen. Toll-like receptors located on the intestinal surface can recognize invading microorganisms and activate host defense mechanisms. Immediately as the pathogen passes through the mucosal and epithelial barriers, it is engulfed by submucosal macrophages. However, the most important barrier of the intestinal mucosa is the mucosal epithelial cells themselves, which selectively prevent pathogens and their harmful products from being translocated to other tissues. Intestinal mucosal hypoxia and acidosis, inflammation, endotoxin, and nitric oxide (NO) are important mediators of intestinal mucosal barrier damage.

2.3.1. Mucosal hypoxia and acidosis

Under normal conditions, the intestinal villi are the most susceptible to ischemic damage. When various types of trauma, hemorrhage, or cardiogenic or septic shock occur, the body protects important organs such as the heart and brain, redistributes the blood, increases vascular tension of the internal organs, and reduces intestinal mucosal and submucosal blood flow. Necrosis of mucosal epithelial cells reduces mucosal repair capacity and creates conditions for BT [16]. In contrast, towing to the reduced perfusion in the intestinal mucosa, the partial pressure of oxygen in intestinal epithelial cells is reduced, increasing anaerobic metabolism in the cells. A large number of acidic metabolites is produced, resulting in mucosal acidosis and increased intestinal mucosal permeability. The mechanism of increased intestinal permeability due to acidosis may be attributed to the inhibition of glutathione reductase and glutathione peroxidase to promote lipid peroxide- and oxidizer-mediated cell damage [12].

2.3.2. Inflammatory mediators

Numerous animal studies have found that a variety of cytokines such as interferon-γ (IFN-γ), interleukin-4 (IL-4), tumor necrosis factor-α (TNF-α), platelet activating factor (PAF), and oxygen free radicals can increase the permeability of intestinal epithelial cells in experimental animals [17]. Further studies of PAF have shown that it plays a key role in the pathological changes in intestinal ischemia-reperfusion, mucosal barrier damage, and BT, and promotes the release of key mediators in the development of systemic inflammatory response syndrome (SIRS) [17]. TNF-α affects intestinal mucosa permeability by altering the morphology and function of intestinal epithelial cells. IFN-γ stimulates the production of large amounts of NO, which has the effect of damaging the intestinal epithelium and increasing its permeability [18]. Oxygen free radicals act primarily on the intestinal epithelial cell membrane, causing damage from lipid peroxidation [19].

2.3.3. Endotoxins

Endotoxin is a lipopolysaccharide component of the cell wall in gram-negative bacteria that can cause submucosal edema, decreased mucosal blood flow, necrosis of the apex of the intestinal villi, and increased intestinal permeability, which are conducive to BT [14]. In addition, endotoxin can also cause disorders of glutamine metabolism, thereby affecting intestinal mucosa repair [19].

2.3.4. NO

Damage to the human body causes overexpression of inducible nitric oxide synthase, which generates excessive NO. These high concentrations of NO cause deposition of peroxynitrite and nitrogen dioxide on the mitochondrial membrane, disrupting mitochondrial membrane potential or permeability and reducing ATP synthesis. NO also disrupts cellular respiration and accelerates apoptosis, leading to persistent destruction of the mucosal epithelium and loss of part of the mucosal epithelium, and BT occurs at sites of epithelial loss [20]. Several studies [6] have shown that endotoxin can increase excessive NO production in intestinal barrier damage.

3. Detection of BT

With respect to the incidence of BT, animal studies have found that the incidence of intestinal BT can reach 100% [21] and clinical studies have found that the incidence of BT was 14.0% [22]. The reason for the

difference in the incidence of BT in animal and clinical studies is attributed to differences between species, underlying diseases, and genetics among individuals, and differences in sampling. Currently, methods for detecting intestinal BT generally use tissue bacterial culture methods such as collecting mesenteric lymph node tissue for bacterial culture. In human studies, the number of mesenteric lymph nodes sampled is fewer than that in animal experiments because of ethical considerations, which results in differences in research results. To summarize the existing research, BT detection includes both *in vivo* and *in vitro* detection methods. The former includes both direct and indirect detection methods, and *in vivo* detection methods are more commonly used.

3.1. Direct detection

3.1.1. Tissue culture methods

The tissue culture method is the most commonly used method for direct detection of intestinal bacteria in extraintestinal tissues. The mesenteric lymph nodes, extraintestinal tissues, swabs of the intestinal wall serosa or abdominal cavity, blood, and lymph are subjected to bacterial culture. Live bacteria are isolated, counted, and classified using light or electron microscopy. Direct detection has the greatest significance but is susceptible to interference from various factors.

3.1.2. Use of labeled bacteria

The use of labeled bacteria is a technique that involves applying radioactive tracers or plasmids to label bacteria for *in vivo* detection. The advantage of this method is that when bacteria pass through the intestinal epithelial barrier, they can still be localized even if they are engulfed in intestinal mucosa-associated lymphoid tissue. This method is limited to scientific research laboratories because of its cost and technical requirements.

3.2. Indirect detection methods for BT

3.2.1. PCR

The presence or absence of intestinal BT can be determined by isolating the DNA fragments of specific bacteria in the peripheral blood or body fluids of patients and then amplifying and sequencing them [23]. Compared to blood culture, the PCR detection method is more sensitive, has a higher positive rate, and can specifically detect certain bacteria. 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.

3.2.2. Metagenomics, also known as environmental genomics and proteogenomics

A metagenomics library can be constructed by extracting the DNA of all microorganisms directly from environmental samples, and their genetic composition and community functions can be studied using genomics research strategies. Such methods can overcome the shortcomings of traditional culture for the detection of bacteria, and not only serve as an indicator of BT development but also as a prognostic indicator for early diagnosis of BT [24–27].

3.2.3. Endotoxin detection

Endotoxin is specific to the structure of the outer cell wall of all gram-negative bacteria. Detection of endotoxin in the blood is also a method for indirect detection of BT.

3.2.4. Detection of non-metabolizable sugars and diamine oxidase (DAO)

Increased urinary excretion rates of lactulose and mannitol and increased blood DAO levels in patients suggest disruption of the integrity of the intestinal mucosal barrier and increased risk of BT [28–31].

3.3. Prevention and treatment of intestinal BT

Currently, prevention and treatment of intestinal BT focuses primarily on inhibiting excessive bacterial growth, regulating intestinal flora to maintain intestinal microecological balance, and regulating and protecting intestinal mucosal barrier function and the immune function of the body. Intestinal BT can only be effectively prevented by eliminating the damaging effects of inflammatory mediators, endotoxin, NO, and other substances that are harmful to the intestinal mucosa and correcting intestinal mucosal ischemia and hypoxia. In addition to treatment of the primary disease, local treatment of the intestine is also very important.

3.4. Rational selection of nutrients

Food in the intestinal lumen stimulates the growth of the intestinal mucosa, maintains its stability, promotes the secretion of gastrointestinal hormones, which are beneficial to the structure and function of the intestinal mucosa, and reduces BT. Oral feeding can promote intestinal motility and reduce intestinal ischemia. Enteral nutrition, as soon as possible, is preferred for patients that can tolerate it. It is believed that in the early stages of trauma, gastrointestinal paralysis occurs primarily in the stomach and colon, and the small intestine still retains its absorptive function. Therefore, enteral nutrition helps to improve blood supply to the small intestine and protect the intestinal mucosal barrier. While advocating the use of enteral nutrition, the composition of nutrient solutions should also be continuously optimized. Glutamine can promote cell DNA synthesis, increase protein content, thicken the intestinal mucosa, normalize IgA secretion, enhance immune function, promote wound healing, and reduce the incidence of BT. The addition of arginine to the diet can increase the synthesis of ornithine and polyamines in intestinal cells to stabilize the intestinal mucosa [32]. ω-3 polyunsaturated fatty acid (PUFA), the principal component of the cell membrane [33], can maintain membrane fluidity and participates in the biological processes of most cells. ω-3 PUFA supplementation can competitively reduce PGE2 product synthesis and reduce TNF, IL-1, IL-2, and IL-6 secretion. Addition of nucleotides to the diet (especially uracil) can selectively inhibit helper T cell activity and IL-2 production and improve the survival rate of animals with bacterial infections. Currently, enteral nutrition preparations containing these components and soluble fibers to enhance immune function have been developed [34], and clinical observations have shown that as the number of T and B lymphocytes is increased, T-cell function is improved, and Th1 cells are increased.

3.5. Selective digestive decontamination (SDD)

SDD refers to selective elimination of pathogenic bacteria in the intestine, including gram-negative *Enterobacter* and symbiotic anaerobic bacteria, using non-absorbed oral antibiotics. In critically ill patients, oral cavity flora and aerobic intestinal bacteria may cause BT and inflammation, including pneumonia, bacteremia, and urinary tract inflammation. In actual clinical work, selective digestive decontamination is primarily focused on *Enterococcus*, *Pseudomonas*, *Acetobacter*, and yeast-like fungi. Common non-absorbed oral antibiotics include polymyxin E, amphotericin B, and tobramycin [35]. Patient outcome was better for those in the ICU with SDD, with a relative risk reduction of hospital mortality of 3–22% and a shortened length of stay in ICU [36, 37].

SDD must be thorough, otherwise BT will persist. If the patient has already developed MODS, applying SDD is not only ineffective but also harmful. Conversely, SDD is an effective preventive treatment for those with high-risk factors. Untimely application of SDD may affect or disrupt the microecological balance of the intestine and weaken the intestinal mucosal barrier. Therefore, more studies still need to be performed [38].

3.6. Protective effects of gastric acid

Reduced gastric acid production decreases bactericidal effects in the stomach and duodenum, leading to overgrowth of intestinal bacteria and endogenous infection due to BT, which in particular makes patients in the intensive care unit prone to gastrointestinal decompression and mechanical ventilation [35]. Therefore, the application of drugs that can protect the gastrointestinal mucosa without reducing gastric acid production, such as aluminum hydroxide and prostaglandin E, can prevent stress damage to the gastrointestinal mucosa. The use of anti-reflux drugs such as cisapride can prevent the reflux of digestive fluids and retrograde colonization of bacteria, resulting in the maintenance normal pH in the gastrointestinal tract [39].

3.7. Inhibition of oxygen free radicals

Allopurinol can effectively inhibit the production of oxygen free radicals. Large doses of vitamin C have significant protective effects on the intestinal mucosa. Vitamin C is a cost-effective oxygen free radical scavenger. Substances such as glucocorticoids and coenzyme A exert good protective effects on the cell membrane and can effectively reduce oxygen free radical damage to the cell membrane [16].

3.8. Enhancement of immune function

Based on the mechanism underlying BT, oral sIgA supplementation increases local sIgA levels in the intestine in order to resist intestinal BT, and it is an important measure for preventing intestinal infection. Epithelial growth factor can promote the regeneration of intestinal mucosal epithelial cells, maintain the normal structure of intestinal mucosa, protect the intestinal mucosal immune barrier, and reduce the occurrence of BT [20]. Studies have shown that glutamine not only can reduce intestinal mucosal permeability, intestinal BT, and endotoxin levels, but can also regulate inflammatory mediators and cytokines, thereby increasing intestinal and systemic immunity [40].

The role of growth hormone (GH) in the repair of internal organ damage is a popular topic of research worldwide in the field of tissue repair. GH can promote growth and differentiation of gastrointestinal mucosal cells, improve intestinal ischemia and hypoxia, promote the uptake of glutamine by intestinal mucosal cells, and improve intestinal mucosal permeability, thus reducing intestinal BT [41]. Rational use of GH is also a measure conducive to protecting the gastrointestinal barrier. Histamine and neurotensin are hormones widely distributed in the gastrointestinal tract. They function to provide nutrients to intestinal mucosal cells, enhance local immunity, and regulate intestinal movement. Existing experiments have shown that both have a protective effect on the intestinal barrier under stress conditions [42].

3.9. Microecological treatments

Microecological regulators include probiotics, prebiotics, and symbiotics. They can directly supplement the normal flora in the human intestinal tract or selectively stimulate growth and reproduction of the normal flora, thereby competitively inhibiting the colonization of exogenous bacteria and excessive growth of endogenous pathogenic bacteria. This effectively corrects dysregulation of intestinal flora, maintains the ecological balance between various bacterial species in the intestine, and reduces the development of BT [43–45]. Probiotics were associated with a significant reduction in infections (risk ratio 0.80, 95% confidence interval (CI) 0.68, 0.95, $P = 0.009$; heterogeneity $I(2) = 36\%$, $P = 0.09$). Further, a significant reduction in the incidence of ventilator-associated pneumonia was found (risk ratio 0.74, 95% CI 0.61, 0.90, $P = 0.002$; $I(2) = 19\%$). No effect on mortality [46]. Prebiotics and probiotics are often used in combination. However, for patients with concomitant organ failure, supplementation with probiotics has the opposite effect, increasing BT and intestinal mucosal damage [46,47]. Therefore, supplementation with probiotics should be limited to patients who do not have concomitant organ failure.

3.10. Promotion of intestinal tract motility

Normal intestinal peristalsis prevents excessive proliferation and adhesion of pathogenic intestinal bacteria. Inhibited intestinal motility can lead to intestinal barrier dysfunction [12] and increase the development of BT. Drugs can be used to improve intestinal blood supply and promote intestinal peristalsis, and the traditional Chinese medicine theory of Zusanli acupoint stimulation can also be used to stimulate intestinal motility.

3.11. Treatment with traditional Chinese medicine

In addition to the preventive measures discussed above, Currently, animal experiments and clinical observations have shown that many Chinese medicine has unique effects on the prevention and treatment of BT by inhibiting the absorption of toxins, protecting the microecology of intestinal flora, and promoting intestinal mucosal repair.

3.11.1. rhubarb

In rats with hypovolemic shock and endotoxemia, the researchers found that rhubarb had a significant protective effect on the mucosal barrier, reduced intestinal bacterial translocation, intestinal mucosal permeability and plasma endotoxin levels, and improved the survival rate of rats (30%). Rhubarb can also maintain the average arterial pressure, reduce the permeability of intestinal wall vessels, improve the pathological damage of intestinal wall, and inhibit obvious intestinal bacterial translocation. The possible mechanisms of rhubarb in prevention and treatment of BT include: scavenging oxygen free radicals; increase tissue irrigation flow and improve microcirculation; decrease vascular permeability; protect the intestinal mucosa and epithelial cells and maintain the integrity of the intestinal mucosa; maintain a balance of intestinal flora [48].

3.11.2. Huoxue Jiedu Ling

Huoxue Jiedu Ling is composed of wormwood, salvia miltiorrhiza, White-headed weng, rhubarb and licorice, with the functions of clearing away heat and detoxifying poison, promoting blood circulation and relieving diarrhea.Using the isotope-labeled *Escherichia coli* as tracers, the portal venous blood, peripheral blood, liver, lung and spleen were detected to observe the intestinal BT in rats with acute biliary tract infection and the effect of Huoxue Jiedu Ling on the intestinal BT. The results showed that the treatment of bile duct decompression or bile duct decompression with ampicillin cannot prevent the occurrence of BT, but aggravates the degree of BT. The traditional Chinese medicine Huoxue Jiedu Ling can effectively inhibit intestinal BT and the over-activation and secretion of cytokines by macrophages [49].

3.11.3. Qingyi decoction

This prescription is an effective prescription for the treatment of acute necrosis pancreatitis (ANP). It is composed of rhubarb, Bupleurum, White peony, Baicalin, Rhizoma Coptidis, Yuanhu, Woody incense and Glauber's salt. It has the functions of clearing away heat and detoxification, disperse the liver depression, promoting blood circulation and removing blood stasis. Qingyi Decoction can alleviate the pathological changes of various organs during ANP, especially pancreas and intestine tissues.Significantly inhibit the proliferation of enterobacteriaceae and opportunistic pathogens, protect bifidobacteria and lactobacillus, and balance the intestinal microecology; significantly reduce the plasma endotoxin level. It decreased serum pancreatic amylase levels and reduces the total translocation rate of intestinal bacteria and the number of translocated bacteria. The results suggest that Qingyi Decoction can comprehensively alleviate various pathophysiological changes caused by ANP, has a protective effect on

intestinal mucosal barrier, and can significantly reduce the incidence of BT and infection. The mechanism of preventing ANP posterior enteral bacterial translocation may be as follows: promoting intestinal peristalsis, relieving toxic enteroparalysis, promoting intestinal endotoxin excretion, and reducing endotoxin damage to the body; inhibit the reproduction of bacteria and maintain the microecological balance of intestinal flora; improve the blood flow perfusion of the gastrointestinal mucosa, relieve its ischemia and hypoxia state, which is conducive to the repair of gastrointestinal mucosal injury; it may also be involved in the immunity function of the modulation body [50].

Traditional Chinese medicine has significant effects on preventing intestinal mucosal damage and inhibiting BT, but the current research on its mechanisms is superficial and more in-depth investigations are needed. Currently, there are many different protocols for the prevention and treatment of BT. However, because of the heterogeneity of individual patients and different interpretations of various research results, there is no consensus regarding the appropriate prevention and treatment of BT. Only through deeper clinical studies can the clinical value of these interventional measures be further evaluated.

4. Interrelationship between BT and extraintestinal diseases

BT can occur randomly in healthy individuals, and has little or no adverse consequences by itself. This may also reflect the "outpost" effect of regional draining lymph nodes. However, BT does have the potential to cause severe infection. It causes bacteria and endotoxins in the intestine to enter the systemic circulation through the lymphatic vessels, gaps between intestinal epithelial cells, and the portal system, resulting in a series of complications [51,52].

4.1. BT and acute pancreatitis

Severe acute pancreatitis (SAP) has a high risk of mortality due to SIRS, MODS, and sepsis, with a mortality rate between 10% and 20% [53]. Intestinal dysfunction is a common complication of SAP and can exacerbate MODS and affect the progression of SAP [54]. Pancreatic infection and necrosis are important prognostic indicators in SAP patients [55], and enterogenous bacteria are the main bacterial source of pancreatic and peripancreatic infections in SAP [56]. Intestinal flora, bacteria, and endotoxin (ET) are translocated into other tissues and organs through the intestinal lumen and activate the release of various inflammatory mediators to trigger an inflammatory cascade, thereby constituting a “second strike” to the body. Tissues and organs are injured by inflammation mediated by ET,TNF-α, interleukin-6 (IL-6), and other inflammatory mediators in the intestinal lymph, and dysfunctional intestinal immunity results in imbalances in intestinal lymphocytes, thereby aggravating pancreatic injury [56]. At the same time, the cascade release of inflammatory factors such as TNF-α during SAP leads to intestinal mucosal ischemia-reperfusion injury, which causes severe oxidative stress and severe apoptosis of the intestinal mucosa [57]. In addition, activation of autophagy in the intestinal epithelial cells of SAP patients can reduce the occurrence of intestinal BT. The mechanism for this may be to regulate intestinal permeability by regulating the expression of tight junction proteins in intestinal epithelial cells and maintaining intestinal mucosal barrier function [58]. Antibiotics are not recommended for mild non-biliary pancreatitis. But mild biliary pancreatitis or severe pancreatitis with infection should be treated with antibiotics.

4.2. BT and liver disease

Under normal conditions, the liver relies on its powerful innate immune system to quickly and effectively resist intestinal bacterial products transported through the normal intestinal circulation, environmental toxins, food antigens, and other potentially toxic substances without causing harmful immune responses [59]. When the intestinal barrier function is impaired by various causes, bacteria and their endotoxins enter the portal system in large quantities from the intestine, activate Kupffer cells in the liver, release inflammatory factors, and cause liver damage.

In mice with impaired intestinal barrier function, the intestinal flora significantly down regulates the transcription of ribosomal protein L29 through the intestinal-hepatic axis, which is associated with hepatic steatosis and insulin resistance (IR) [60]. BT often causes spontaneous bacterial peritonitis as a complication in patients with cirrhosis [61]. BT is also extremely important in the compensatory and non-cirrhotic stages of liver disease, and is closely associated with progression of liver disease such as fibrosis and possible cancerous transformation. In the decompensated stage of cirrhosis, the increased permeability of the intestinal wall allows a large number of intestinal bacteria to enter the intestinal lamina propria and interact with the intestinal mucosal immune system, and a large number of bacteria eventually cause damage to the intestinal mucosal immune system, causing damage to the immune cells in the intestinal lamina propria in cirrhosis. The intestinal immune system is unable to completely kill the invading intestinal bacteria, leading to the development of BT and translocation of intestinal bacteria into the liver and other extraintestinal organs. Bacteria in the liver provoke immune reactions and also lead to immune changes in the liver during cirrhosis. BT and impaired integrity of the intestinal mucosal immune system are interdependent. Recent studies have shown that the proportion of T reg cells increases in the livers of rats with cirrhosis induced by CCl_4, the proportion of Th1 cells in the cecum and blood decreases, and the incidence of BT increases significantly. BT causes the proportion of T regs cells in the proximal small intestine of cirrhotic rats to increase, and the proportion of Th17 cells in the intestine and blood decreases. BT also exacerbates the decrease in Th1 cells in the small intestine and liver of rats with cirrhosis, the increase of Th17 cells in the liver, and the increase of T regs cells in the distal small intestine and colon. The interaction of BT with $CD4^+$ T cells exacerbates liver damage and diminishes liver function. In conclusion, the distribution and change in proportion of intestinal immune cells in cirrhosis lead to the development of BT, which in turn aggravates this immune disorder and forms a vicious cycle [62]. SDD in patients with advanced cirrhosis can effectively reduce the occurrence of bacterial translocation.

Translocation of bacteria and bacterial products into circulation is an important factor leading to the development and progression of alcoholic liver cirrhosis (ALC) in mice, and overgrowth of intestinal bacteria is common in ALC mice [63]. During treatment of non-alcoholic fatty liver disease (NAFLD), the clinical symptoms of NAFLD and IR can be greatly improved by controlling imbalances in the intestinal flora [64–66].

4.3. BT and cancer

Studies in animals and humans have demonstrated that many diseases are associated with infections caused by bacteria originating from the gut [67–72]. Intestinal barrier injury and BT also have important connections with colon cancer [73]. In addition, BT is one of the causes of rapid disease progression in patients with advanced gastric cancer [74]. Gastric cancer patients have dysregulated intestinal flora, intestinal mucosal barrier dysfunction, and decreased immunity. Because of the reduced immunity in gastric cancer patients, the translocated bacteria cannot be completely eliminated, and surviving bacteria may multiply and release endotoxins outside the intestinal tract, causing an increase in cytokine concentrations. BT causes inflammatory reactions and increased cytokine concentrations in the body. High cytokine concentrations play an important role in the development of gastric cancer cachexia and affect the clinical outcomes of gastric cancer patients. Current studies have found that the BT rate was significantly higher in patients with gastric cancer cachexia than in patients without cachexia. The two-year survival rate of patients with BT-positive cachexia was significantly lower than that of patients with BT-negative cachexia. The

outcome of patients with cachexia is also related to other factors, and BT is not the only factor affecting outcomes [75]. A recent study has shown that the translocated bacteria in the intestinal mucus layer are associated with lower levels of T-cell subsets and NK cells in the intestinal epithelium in BT-positive patients ($P < 0.05$). Endotoxin was detected within the small intestinal wall, and the concentration of endotoxin decreased from the mucosal to serosal side gradually in these patients. These were associated with an altered composition of the tight junctions. The tight junction could be a possible pathway of BT [76].

Proteoglycan (pSK), a regulator of biological response, is a substance extracted from the mycelium of a fungus. It can induce the production of various cytokines and exerts a therapeutic effect on bacterial infection. pSK is widely used in Japan as an adjunct to chemotherapy for malignant cancer and can enhance the immune function of cancer patients. Studies have shown that it can reduce intestinal BT during parenteral nutrition and protect intestinal immune function. Using a Wistar rat parenteral nutrition model, the authors studied the effect of PSK on intestinal BT and found that PSK could inhibit overgrowth of intestinal bacteria during parenteral nutrition and alleviate intestinal atrophy caused by parenteral nutrition. Concurrenly, it increases the number of lymph nodes in the small intestine and prevents the decrease of immunocompetent cells in the intestinal mucosa and intestine-associated lymphoid tissues, such as sIgA- and IL-2-secreting cells, and has a protective effect on intestinal immune function [77].

4.4. BT and arteriosclerosis

Whether pathogenic microorganisms are involved in the development and progression of chronic non-communicable diseases such as arteriosclerosis has been one of the major medical questions that has garnered considerable attention in recent decades. Lower levels of bacterial components can be detected in the circulation of many patients with chronic metabolic diseases such as obesity, type 2 diabetes, and arteriosclerosis. Bacterial endotoxicity may be involved in the process through which metabolic syndrome develops, namely, "metabolic endotoxemia". Intestinal bacteria are the major initiating factor in metabolic endotoxemia [78,79]. Numerous studies have found that the genetic components of intestinal bacteria are present in the blood and arteriosclerotic plaques of patients with coronary heart disease, suggesting that the bacterial components in arteriosclerotic plaques originate from the intestine. Thus, chronic infection serves as a novel risk factor for arteriosclerosis.

The mechanism by which chronic bacterial infections increase the risk of arteriosclerosis is very complex, and one type is a mechanism by which bacteria indirectly cause arteriosclerosis. After entering the blood, bacteria and endotoxin can affect the reverse transport of cholesterol through immune activation and inflammatory factor release, which in turn leads to insulin resistance, hyperlipidemia, and vasculitis. Bacteria can also participate in the development and progression of arteriosclerosis by participating in the reverse transport of cholesterol, activation of inflammation, and platelet activation in the body through the production of small molecule active substances, such as trimethylamine, during the metabolism of phosphatidylcholine and L-carnitine [80–82]. In addition, in coronary heart disease, some bacteria are present in the blood and plaques. Evidence suggests the involvement of intestinal bacteria in the development of arteriosclerosis, but the specific mechanism is currently unclear. Bacteria play an important role in the development and progression of arteriosclerosis, but it may be a "hit-and-run" role, that is, they only play a role in the injury of endothelial cells in the early stages of arteriosclerosis development, but do not exert significant effects in lipid deposition and foaming during the later stages of arteriosclerosis progression. Because several large-scale randomized controlled clinical trials have shown that antibiotic treatment against *Chlamydia pneumoniae* in patients with arteriosclerosis does not delay arteriosclerosis progression or improve clinical outcomes [83,84], in addition to typical drug treatments (antiplatelet therapy, lipid-lowering drug, and heart rhythm control), timely improvement of the intestinal flora (such as probiotic treatment and fecal transplantation) may play some role in improving arteriosclerosis progression in patients with coronary heart disease [85].

5. BT and common surgical diseases

In recent years, the important role played by BT in the series of pathophysiological changes after severe trauma has garnered much attention in the field of surgery. These common diseases are described below.

5.1. Hemorrhagic shock

Infections often become the leading cause of death in hemorrhagic shock. Moreover, among patients who died of infected wounds, 30% had bacteremia with no noticeable infected lesion [86]. Sori et al. [87] showed that bacteria migrate rapidly from the intestine to the bloodstream after hemorrhagic shock and can cause sepsis. Two hours after hemorrhagic shock, a variety of intestinal bacteria dominated by gram-negative bacilli can be found in circulation [88]. Eight hours after shock, the mortality rate of blood culture-positive animals was 100%, whereas the survival rate of blood culture-negative animals was as high as 83%. Hemorrhagic shock experiments in mice confirmed the presence of *Escherichia coli* and *Enterococcus* in the mesenteric lymph nodes, liver, spleen, and blood [89]. Studies have found that during hemorrhagic shock, intestinal mucosal blood flow is reduced, peroxidase permeability is increased, cell membrane connections are disrupted, and the intestinal villi are damaged to the point that the intestinal mucosa is ruptured, bleeding, necrotic, and ulcerated. The release of free radicals can exacerbate mucosal damage. In the end, the intestinal mucosa is damaged, its barrier function is lost, and bacterial displacement develops. However, BT did not necessarily occur in some hemorrhagic shock experiments. In addition, the current models for shock have not considered the effects of internal bleeding on BT, as blood products are key adjuvants in other infection processes [90].

5.2. Burns

Infections in burn patients have always been a significant problem, and sepsis is the primary complication of burn patients. In rats, burns can cause *Pseudomonas aeruginosa* in the intestine to invade the body, causing a systemic infection of intestine-derived *P. aeruginosa* after a burn. Animals did not develop BT when subjected to 20% body surface area burns. When the burn area reaches 40% body surface area, bacteria could translocate to the mesenteric lymph nodes, and a distant translocation phenomenon could be observed after the effects of antibiotics diminished [91,92]. Increased intestinal mucosal permeability and severe physical injury after burns are the main causes of BT. In addition, immune function is reduced after a burn, and during the low-blood flow and nutrient deficiency state, the use of broad-spectrum antibiotics destroys the microecology of the intestine, and the dysregulation of intestinal flora can promote BT [93].

5.3. Intestinal obstruction

It is known that the motility, absorption, and secretion of the intestine all change after intestinal obstruction. Bacteria can be cultured from the blood and organs at 4 h after intestinal obstruction. As the time of obstruction increases, not only does the incidence of BT increase, but the number of bacteria invading the internal organs of mice and the mortality rate of the mice also increase. This is primarily due to the intestinal mucosa being susceptible to damage by intestinal bacteria and its products at the time of intestinal obstruction [94].

5.4. Obstructive jaundice

Infection and endotoxemia remain one of the leading causes of death in patients with obstructive jaundice. Obstruction of the common bile duct for one week could cause BT in 30% of animals [95]. Biliary obstruction increases the permeability of the intestinal mucosa to bacteria and endotoxin. The endotoxin in circulation promotes a further increase in the permeability of the intestinal mucosa and causes BT. In the case of biliary obstruction, lack of bile salts in the intestinal tract causes disturbances in intestinal flora, overgrowth of gram-negative bacteria, and reduced IgA levels, which promote BT.

6. Conclusions

Intestinal barrier can effectively prevent intestinal bacteria and their toxins from translocating out of the intestinal cavity. Therefore, understanding the mechanism underlying BT to identify a treatment method to protect intestinal barrier function and reduce BT is an urgent clinical problem that needs to be solved. As are mentioned above, factors such as ischemia, hypoxia, acidosis, inflammatory mediators, and NO collectively induce necrosis of epithelial cells, impair the intestinal mucosal barrier, increase intestinal permeability, and cause bacterial and endotoxin translocation, leading to endogenous infection and initiation of uncontrolled SIRS that progresses into MODS. Conversely, MODS can increase intestinal mucosal necrosis and BT, resulting in a vicious cycle.

BT exists in a variety of pathological conditions and is notably related to the development of extraintestinal diseases. Recently. Andersen et al. found intestinal dysbiosis, barrier dysfunction, and bacterial translocation account for CKD–related systemic inflammation [96], and Carron et al. reported the evolution of BT after kidney transplantation [97]. Clinically, severe patients should try to minimize the adverse effects of BT. BT is a focus of many current studies and is attracting attention from an increasing number of investigators. Thorough investigation of the phenomenon of BT has greatly developed the theory of intestinal infection. For example, Kobayashi et al. reported Aeromonas sobria serine protease decreases epithelial barrier function in T84 cells and accelerates bacterial translocation across the T84 monolayer *in vitro* [98]. However, it is clear that there is no consensus regarding the mechanisms associated with BT and its early diagnosis and treatment, and further studies are required. Currently, there are many different options for the prevention and treatment of BT, such as early enteral nutrition, selective digestive decontamination (or oral decontamination), probiotic supplementation, immune nutrition (primarily glutamine), increasing blood flow to the internal organs. Parenteral nutrition is an indispensable procedure in surgical treatment of complex gastrointestinal diseases, but long-term parenteral nutrition can lead to significant atrophy of gut-associated lymphoid tissue, a local decrease in local intestinal immune function, and intestinal BT. So guidelines need to be formulated to guide their use in clinical applications. Thus, when SDD's clinical efficacy, microbiological safety, and value for money benefits are proven, it will be readily embraced by icu physicians and promoted as a treatment that saves the lives of critically ill patients.

In addition, traditional chinese medicine has a long history of empirical usage of herbal for medical purposes, representing an extensive, practice-based and information-rich foundation of regimens and medical knowledge. The traditional Chinese medicine exerts marked effects on preventing intestinal mucosal damage and inhibiting BT. The benefits derived from prescriptions of multiple components can be from mutually enhancing or synergetic effects of the ingredients targeting multiple events in BT pathology. Thus a combination of multiple natural compounds may be a better remedy achieving synergic effects. The natural compounds and their derivatives may be as effective novel therapeutic reagents against BT. However the mechanisms of their protective properties require further clarification as do issues with regard to quality control, mechanisms of interactions with different components and toxicity. Up to now only limited studies on its underlying mechanisms of action have been conducted. More in-depth and extensive clinical research is needed in the future to further evaluate the clinical value of these prevention measures. Thus, the continued study of traditional Chinese medicine will promote new breakthroughs in the prevention and treatment of intestinal BT in the near future.

Declaration of competing interest

The authors declare no conflict of interest.

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