REVIEW

Bacterial translocation: Overview of mechanisms and clinical impact

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Abstract

Bacterial translocation (BT) is a phenomenon in which live bacteria or its products cross the intestinal barrier. Gut translocation of bacteria has been shown in both animal and human studies. BT and its complications have been shown clearly to occur in animal models, but its existence and importance in humans has been difficult to ascertain. We review the mechanisms of BT and its clinical impact based on the current literature.

Introduction

The presence of bacterial concentration in the order of 10^{12} per milliliter in an estimated 200 m^2 intestinal lumen surface,[1,2] and the fact that only a unicellular epithelial layer is the barrier between this hostile environment and the sterile bloodstream, has instigated research by scientists for centuries.

In the late 19th century, investigators defended a theory in which the gut was the origin of sepsis and that peritonitis could result from viable bacteria passing through the intact intestinal wall.[3,4] A series of experimental studies were performed supporting the translocation hypothesis. Viable bacteria were detected in the peritoneal cavity of dogs subjected to hemorrhagic shock and these microbes were the same as those identified in normal intestinal microflora.[5,6] Other studies supported the notion that intestinal microflora could be responsible for sepsis. Nosocomial infections were correlated with indigenous gut bacteria isolated in blood cultures and surgical wounds[7,8] and enteric microorganisms were identified in the blood and ascites of cirrhotic patients with spontaneous bacterial peritonitis.[9]

All these facts, associated with evidence that Gram-negative and Gram-positive bacteria, fungi and endotoxins could cross the mucosal barrier of the intestines,[3] made the hypothesis of bacterial translocation (BT) a convincing theory. No doubt resided that the gut bacteria was responsible for sepsis, but the mechanisms of translocation still remained unclear.

Therefore, BT was defined as the invasion of indigenous intestinal bacteria through the gut mucosa into normal sterile tissue, causing disease.[10] New evidence showed that bacteria itself might not need to transpose the epithelial intestinal barrier. Translocation of inflammatory compounds produced at the intestinal wall or toxic products from the gut might be responsible for the systemic injuries (symptoms). This thought broadened the definition of BT in relation to intestinal permeability, including not only the passage of viable bacteria but also endotoxins or antigens from the intestinal lumen into the circulation causing systemic inflammation and distant organ injury.

Normal gut flora and normal gut barrier mechanisms

The human intestinal microflora contains 300 to 500 different species of bacteria. The upper gastrointestinal tract contains only a few species of bacteria due to the composition of the luminal environment, hostile for bacterial growth, and because of the phasic propulsive motor activity, which difficult a stable colonization. In contrast, the colon contains a very high intraluminal concentration of living bacteria. In fact, a great proportion of the fecal mass consists of bacteria (around 60% of fecal solids).[1,11,12]

Some of these bacteria are potential pathogens and can be a source of infection and sepsis under some circumstances. Nevertheless, interaction between the host and its microbial guests determines important health benefits to human organisms.[13,14]

Evidence obtained through studies using animals bred under germ-free conditions suggests that microflora have important physiological functions.[15] The most important are fermentation of non-digestible dietary residue and endogenous mucus by the colonic microflora, production of short-chain fatty acids by the anaerobic metabolism of peptides and proteins, participation in the synthesis of K vitamin, and the absorption of calcium, magnesium and iron. Also, epithelial cell proliferation and differentiation in the bowel are affected by interactions with resident microorganisms. The intestinal mucosa is the main interface between the

immune system and the intraluminal environment and the development of a competent immune system depends partially on intestinal bacteria. Another major function of intestinal microflora is protection against exogenous microorganisms; adherent non-pathogenic bacteria can prevent attachment and subsequent entrance of pathogen enteroinvasive bacteria in the epithelial cells, and normal flora can also inhibit the growth of pathogenic bacteria through the synthesis of antimicrobial substances or by nutrient competition. Nevertheless, under special conditions, even saprophytic bacteria can translocate.[12,16,17]

Knowledge of the structural organization of the intestinal mucosal barrier and the mechanisms of permeability of compounds through it is essential for understanding translocation. Electron microscopy studies documented the components of the epithelial barrier that include, from the intestinal lumen to the outermost surface, an internal water lining, followed by an epithelial surface layer composed of phospholipids and mucous gel coat, the epithelial cells, subepithelial connective tissue and the capillary endothelium.[11]

Between the epithelial cells, holding them together, are the so-called tight junctions.[11] These allow for selective paracellular permeability, normally excluding passive movement of large hydrophilic non-charged compounds, such as bacteria and macromolecules (e.g. lipopolysaccharides and peptidoglycans).

The function of the barrier depends on the normal intestinal flora (ecologic barrier), mucous epithelia (mechanical barrier) and secreting IgA and immune cells (immune barrier). Thus the integrity of the mucosa and the mucus layer and the defensive factors, such as epithelial secretions, immunocompetent cells and an adequate mucosal blood flow, play a role in the barrier function of the gut.[12] The intestinal mucosal barrier against luminal macromolecules and microorganisms consists of both non-immunological and immunological defense mechanisms. The epithelial barrier selectively restricts micromolecular permeation and almost completely restricts macromolecular permeation, while the endothelial barrier has a very limited restriction to micromolecules and only partly to macromolecules. Maintenance of the barrier depends on the integrity of cellular plasma membranes and tight junctions, as well as the elaboration of endothelial and epithelial secretory products.[11–15]

Mechanisms of injury to the gut barrier

Epithelial cell hypoxic injury and subsequent reperfusion have been postulated as major mechanisms involved in BT occurring in several conditions, such as trauma, shock of any origin and thermal injury. Oxygen tension at the tip of the intestinal villus is lower than it is in arterial blood even under normal conditions. Thus, any reduction in blood flow can decrease tissue oxygenation, leading to mucosal acidosis, and consequently epithelial cell injury. Acidosis results in increased mucosal permeability mediated by the production of oxygen free radicals. These substances disarrange the mucosa cytoskeleton, thus increasing epithelial permeability.[12,15] The mechanisms involved during ischemia/reperfusion injury are complex and seem to be mediated by reactive oxygen metabolites followed by activation of polymorphonuclear neutrophils. Ischemia prevents aerobic energetic metabolism and determines the depletion of intracellular levels of adenosine triphosphate (ATP). Large amounts of xanthine dehydrogenase are

converted to xanthine oxidase during ischemia by a calcium-dependent proteolytic process. Oxygen free radicals are formed and cause mucosal injury by direct action and by secondary activation of polymorphonuclear neutrophils, and consequently increase intestinal permeability. When reperfusion is achieved before irreversible alterations and oxygen is reintroduced to the tissues, tissue injury can be exacerbated leading to microvascular injury, cellular necrosis and apoptosis. With the return of blood perfusion, the influx of calcium into the intracellular medium increases, followed by an increase in phospholipase A2 activity and consequent release of arachidonic acid. Metabolism of arachidonic acid generates prostaglandins, thromboxane, prostacyclins and leukotrienes. These substances can cause vasoconstriction, vasodilatation, increased vascular permeability, stimulate platelet aggregation and chemotaxia in the polymorphonuclear neutrophils. Thus, ischemia and reperfusion can provoke the rupture of the mucosa barrier, BT and the activation of inflammatory responses.[12,13,15,17]

However, under normal conditions, even if bacteria run through the intestinal epithelia they should be destroyed by phagocytes before reaching the blood circulation. Gut-associated lymphoid tissue (GALT), considered the largest immunological organ of the body, is organized very similarly to lymph nodes and plays a key role in controlling BT. Thus, immune dysfunction is another major factor involved in BT.[15]

Other factors may affect the mucosal barrier and increase permeability, such as nitric oxide (NO) overproduction,[18,19] interleukin-6 (IL-6),[20] certain commensal bacteria such as *E. coli* and *Klebsiella pneumoniae*,[21] alcohol and non-steroidal anti-inflammatory drugs. NO may be important for intestinal permeability and motility and it has potent antimicrobial properties; thus it may be protective in normal amounts. However, its sustained upregulation may be detrimental, because it may lead to decreased endothelial viability. Hypoxia and acidosis by itself per se, associated with endotoxins, is also related to hyperpermeability.[22]

From all these related studies it can be concluded that gut translocation might be mediated by a three-hit model as proposed by Deitch.[23] The first gut insult might be hypoperfusion and ischemia. Restoration of the intestinal blood flow is the second hit, with migration of neutrophils to the intestinal microcirculation, release of cytokines by leukocytes and GALT and enterocyte damage through an ischemia-reperfusion mechanism. The third hit is the loss of integrity of the gut barrier function, providing translocation of intestinal endotoxins and bacteria and exposure to immune cells. The majority of these bacteria are phagocytosed and contribute to the intestinal inflammatory response. However, some of translocated bacteria and toxic compounds are drained by the mesenteric lymph system and are trapped in the intestinal lymph nodes, causing an inflammatory reaction.

Mechanisms and routes of bacterial translocation

Current data suggest two major pathways of gastrointestinal permeability that might cause translocation: transcellular through the enterocytes and paracellular using the tight junctions.[2] Transcellular permeability is under the control of specific enterocyte channels and membrane pumps.[24] There is experimental evidence showing viable bacteria, including *E. coli* and *Proteus mirabilis*,

within intact enterocytes of rats, providing evidence of transcellular passage through enterocytepinocytosis and active bacteria invasion of the mucosa barrier.[25] Tight junctions translocation is affected by luminal osmolality and direct damage to the enterocyte cytoskeleton and its protein support structures composed of actin filaments and microtubules. An example is cytotoxic chemotherapy that causes hyperpermeability through tight junction damage.[26,27] Macromolecules, as endotoxins, may reach the subepithelial mucosal layer and subsequently the bloodstream due to the unbending of the tight junctions. However, translocation generally occurs transcellularly and directly, even through morphologically intact enterocytes.

In the same way, there are two major routes that bacterial compounds might gain access to the systemic circulation: through the enteric venous system to the portal vein or following lymphatic enteric drainage. To answer this question, investigations were conducted worldwide. The first study assumed that the BT route pathway was the one that suggested that bacterial compounds would drain from intestinal subepithelial capillaries, following enteric venous drainage to the portal vein. But when portal vein blood cultures were analyzed in trauma patients only eight were positive out of 212 and the presence of bacteria was not a predictor of occurrence of multiple organ dysfunction syndrome (MODS).[28] A search for endotoxins in portal vein blood was also performed and did not correlate with MODS.[28] The lack of association between isolation of bacteria and endotoxins in portal blood and the development of systemic inflammatory response system (SIRS) and MODS suggested that another route could be responsible for translocation.

The lymphatic route was investigated and convincing evidence suggested that it might be the principal pathway of translocation.[23] Experimental and clinical studies detected viable bacteria in mesenteric lymph nodes (MLN). Animal studies demonstrated the MLN as the first or the single site presenting indigenous and non-indigenous bacteria.[23] In patients requiring surgery for the treatment of abdominal infection, an important clinical study demonstrated that septic complications were significantly more prevalent in patients with bacteria in their MLN, and that the organisms responsible for the septic condition were correlated with those identified in the MLN.[29]

Measures of bacterial translocation

Several methods have been used to identify BT, including direct and indirect methods. The identification of intestinal bacteria in normally sterile MLN is considered direct evidence of BT.[29–34] Thus, sampling of MLN is a method broadly used in experimental and clinical studies, even if it is recognized that this technique probably underestimates the real incidence of BT. Data using radioactively labeled bacteria, another direct method to measure BT, indicate that BT can occur even if culture of MLN failed to identify any microbe, because most bacteria which breach the epithelial barrier are killed by the GALT.[35,36]

As an indirect marker, any detection of intestinal bacteria in cultures of the portal or peripheral blood may suggest BT, as may the detection of endotoxins in peripheral blood.[37–39] Recent methods involving polymerase chain reaction (PCR) have been introduced for detecting microbial DNA in blood; these methods have a higher sensitivity than blood cultures for assessing BT from the intestine.

Intestinal permeability can be assessed by a variety of techniques. Most commonly used is the assessment of the differential urinary excretion of orally administered non-metabolizable sugars, such as lactulose and mannitol, which are known to pass paracellularly or transcellularly through the epithelium, providing a specific index of intestinal permeability.[40–42]

Permeability tests are performed by the measurement of its urine excretion ratio concentration after oral administration of inert sugars (lactulose and mannitol). It is known that the passage of lactulose through the intestinal mucosa barrier is paracellular because of its large molecule composition.[2,43] Mannitol has a smaller molecule that causes transcellular enterocyte absortion.[2,43] It was then assumed that an increased urine dose of mannitol and lactulose, after oral administration, indicates lost of integrity of the mucosal barrier, consequently increasing the risk of BT. In fact, some authors consider the increased permeability of these tracers as an indirect demonstration of BT.[43,44] Nevertheless, increased intestinal permeability is only a permissive factor for BT, because BT does not always occur in hyperpermeability states. Thus, an elevated index of intestinal permeability does not prove the occurrence of BT.

Bacterial translocation in health and disease

BT may be a phenomenon that occurs in healthy individuals and may be a normal physiologic event without deleterious consequences.[45] Translocation of endotoxins from viable or dead bacteria in very small amounts probably constitutes a physiologically important boost to the reticuloendothelial system, especially to the Kupffer cells in the liver. The baseline rate of translocation in human studies is 5-10%. Berg[10] stated that there is a normal rate in animals of approximately 10–20%. It seems that the frequency of translocation in humans is much lower than that observed in animal models. However, in several disorders such as MODS and intestinal ischemia, rates of positive culture are much higher (16–40%).

An increased permeability to lactulose and mannitol was observed in patients with severe trauma,[46] in burns patients with infection,[40,47] and in Child C cirrhotic patients presenting with bacteremia and spontaneous bacterial peritonitis.[41] Moreover, intestinal hyperpermeability was the only variable predictor of MODS in a clinical study[48] and death was correlated with the degree of hyperpermeability.[48]

BT in humans was postulated to occur in several clinical conditions, especially when a known predisposing factor for BT was present, for example, bacterial overgrowth in small bowel (secondary to alterations in motility, use of antibiotics, absence of intestinal bile etc.), damage to the gut barrier (secondary to alterations of the intestinal microvasculature in situations such as shock, systemic inflammatory response syndrome, or direct injury etc.) and states of systemic immunossuppression.[13,16] In this way, publications have identified BT in a wide group of diseases, such as hemorrhagic shock,[19] acute pancreatitis, cirrhosis, obstructive jaundice, abdominal surgery,[49,50] malignancy, heart failure, aortic aneurysm repair, cardiopulmonary bypass, and bowel transplant.[51–54] However, BT was more convincingly associated with a poor outcome or infectious complications in a few situa-
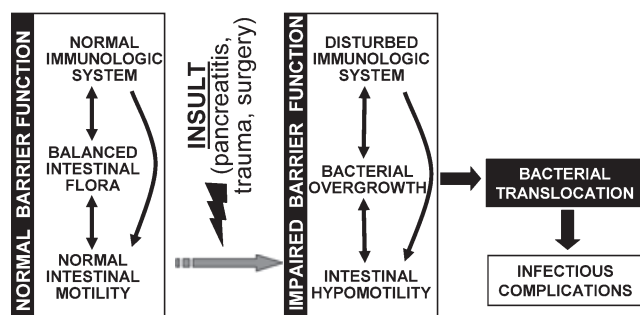
Figure 1 Normal intestinal barrier is sustained by a balance among the immunologic system, intestinal flora and intestinal motility. Insults allowing a disruption of this balance cause damage to barrier function and consequently permit bacterial translocation and its infectious complications.

tions, such as acute pancreatitis, cirrhosis, intestinal obstruction and conditions with an intense inflammatory response or hypotension (hemorrhagic shock, trauma and major burn injury) (Fig. 1).

Evidence and clinical impact of bacterial translocation

Some studies have demonstrated that BT from the gut to MLN is not a rare event, occurring in 4-59% of patients having various clinical conditions, especially when intestinal obstruction or Crohn's disease is present. O'Boyle *et al.*[29] observed this phenomena in 15% of a large series of patients undergoing laparotomy. They also found a significant increase in postoperative sepsis in patients with evidence of BT (45%) compared with those with negative MLN cultures (19%). Furthermore, the organisms responsible for clinical infections were similar to those isolated in the MLN. Conversely, most of the patients with evidence of BT to MLN had no clinical infectious complications, supporting the hypothesis that it could be a natural event in some situations and not clinically significant in the presence of a fully functional immune system.

In systemic infection, isolation of the bacteria responsible for the disease is sometimes not possible in spite of routine bacterial cultures.[43] The knowledge that inflammatory compounds are responsible for clinical symptoms, and not necessarily the bacteria itself, advanced the understanding of SIRS. When the pathogenic bacteria is isolated the patient is considered to have sepsis, when it cannot be identified the diagnosis is of SIRS and antibiotic treatment is administrated either way. This concept that inflammation causes clinical symptoms was transposed to the translocation theory. It was assumed that intestinal injury caused by ischemia secondary to hemorrhagic shock, trauma, burns, intestinal obstruction, sepsis or gastrointestinal injury might result in the gut becoming a cytokine generating organ.[23]

An interesting association is that of lung injury observed in the adult respiratory distress syndrome (ARDS) occurring in septic patients and its correlation to translocation. The anatomic explanation for this association is that the mesenteric lymph flows through the thoracic duct, reaches the systemic circulation through the subclavian vein draining to superior vena cava, then to left atrium and finally to the pulmonary artery and pulmonary vascu-

lature. Thus, the lungs are the first organ to receive the lymph drainage from the gut. To evaluate that translocation might be responsible for lung injury, an animal trauma-hemorrhagic shock model was performed.[30,31]

It was observed that lung injury was prevented by the interruption of the main lymph duct exiting the gut and that factors in the mesenteric lymph, and not in the portal blood, were capable of activating neutrophils, injuring endothelial cells and increasing endothelial permeability.[30,31] The mesenteric lymph was sterile and the exact factors that caused neutrophil activation and endothelial injury and hyperpermeability were not identified.[30,31] A study of the thoracic duct lymph of patients in an intensive care unit (ICU) identified that cytokine and cytokine-receptor-antagonist levels were higher in those with MODS, bacteria were not isolated and endotoxin levels were low.[31]

Bacterial translocation in some important disease states: Systemic inflammatory response syndrome and multiple organ dysfunction syndrome

The human response to severe stress, SIRS, is characterized by massive cytokine release (such as tumor necrosis factor α and IL-1), endothelial cell damage, tissue edema, increased tissue permeability, activation of the coagulation system, platelet aggregation, local tissue hypoxia with shunting, and a hypermetabolic state.[55] The degree of the SIRS response seems to be critical to the clinical outcome. In severe SIRS, a state of immunosuppression may develop, which may then lead to more severe infections. A key event in the pathogenesis of SIRS and multi system organ dysfunction may be intestinal hypoperfusion with reperfusion.[55–57]

BT could indeed be a critical component in the development of SIRS, but human studies addressing this question are plagued by methodological problems because serial cultures of the MLN are not possible in humans. More frequent permeability studies and the use of more reliable and specific markers of BT are urgently needed.

MODS is a syndrome that has reached epidemic proportion in most ICUs and is the most common cause of death in the surgical ICU. MODS is responsible for 50–80% of all ICU deaths and its treatment is mainly supportive, because of a failure to fully understand the pathophysiology of this syndrome. The hypothesis of gut-induced sepsis in critically ill patients was initially that during shock or stress there was a decreased blood flow to the intestines, which would lead to gut injury and loss of normal gut barrier function.[58] This gut barrier failure would allow bacteria and their toxic products, such as endotoxins, to escape from the gut and enter the systemic circulation,[59] thereby causing systemic sepsis and MODS.[3,14,60,61] Several human studies have showed a correlation between loss of gut barrier function and the development of systemic infection and MODS.[34] Other studies established a relationship between the route of nutrient administration, infection and gut barrier function. The physiopathology of this hypothesis has not been completely elucidated.[3] Experimental studies showed that hemorrhagic shock, trauma, or a major burn injury induce the gut to release proinflammatory and tissue injurious factors carried to the MLN,[34,59] suggesting that BT and production of biologically active mediators from the gut could be responsible for the MODS

observed in these disease states, even if no bacteria is recovered in portal or systemic circulations.

Bacterial translocation and acute pancreatitis

The overall mortality rate of patients with acute pancreatitis is 10–15%[62] and in patients with severe disease, the mortality rate is approximately 30–40%.[63] In the first week after the onset of acute pancreatitis, MODS is the main cause of death in these patients. Late mortality and morbidity are particularly due to sepsis.[64] Infectious complications are the most frequent and severe complication of acute necrotizing pancreatitis,[64] with a mortality rate of up to 80%.[65,66] Enteric bacteria are responsible for most pancreatic and peripancreatic infections associated with acute pancreatitis.[67,68] The pathogenesis of this pancreatic infection still remains unclear, but some there is some evidence of translocation of bacteria from the gut to the necrosed tissue.[63]

The route of bacteria migration has not yet been clarified. It could be a direct transmural migration to the peritoneal cavity or retroperitoneum and then to the pancreas; or secondary to lymphatic or hematogenous dissemination to the pancreas.[69] Although the route of dissemination is not clearly identified, the pathogenesis of BT in acute pancreatitis comprise some known morphological and functional alterations, such as small bowel hypomotility, overgrowth of intestinal bacterial, rupture of the gut barrier and systemic immunossuppression.[62,70]

Intestinal dismotility and bacterial overgrowth

Small bowel motility is important in regulating the enteric bacterial population. The relationship between interdigestive myoenteric activity and motility has been shown in animal experiments and there is accumulated evidence that acute pancreatitis resulted in a significant delay in small-intestinal transit time.[62,70] A postulated mechanism by which acute pancreatitis alters the motility of the gut is that the secretion of some gastrointestinal peptides during acute pancreatitis is disturbed. Consequently, the delayed transit time results in bacterial overgrowth, especially in the small bowel, which is a known predisposing factor to BT.[62] Also, the use of morphine (a known inhibitor of coordinated myoenteric activity) causes a marked reduction in propulsion and excessive bacterial overgrowth.[69]

Mucosal intestinal damage

The integrity of the gut mucosa is one of the principal factors in gut protective mechanisms and it is necessary for an adequate delivery of oxygen and nutrients by a normal blood flow to preserve this integrity. It is known that experimental pancreatitis is associated with gross distortion of the local and systemic microvasculature, resulting in reduced oxygen delivery and damage to the tight junctions and the epithelium of the enteric villi.[63,71] Because of these microcirculatory disturbances, an increase in oxygen radicals from macrophages and leukocytes may occur,[72] which could lead to increased mucosal permeability.[73] Some studies in experimentally induced acute pancreatitis demonstrate an impairment of the small bowel mucosa, evident by an increased mucosal permeability to fluorescent latex microspheres, associated with damage to the apical portion of the villi and an alteration in the mucosal microvasculature.[71] The enteric origin of microorganisms translocating to MLN and to the pancreas was evident using labeled bacteria.[74] The mechanism of mucosal damage would be ischemic injury, resulting in alteration of the microvasculature.

Immunosuppression

Immunosuppression is associated with severe acute pancreatitis and the immune-mediated immunosuppression may play an important role in the development of secondary infections in the later course of acute pancreatitis.[75] Larvin *et al.*[75] showed an impaired clearance of circulating macromolecular enzyme inhibitor complexes during severe acute pancreatitis. Recently, Mentula *et al.*[76] demonstrated a low HLA-DR (a method to monitor immunosuppression) in patients with acute pancreatitis and correlated immunosuppression with the development of organ failure in acute pancreatitis. When BT occurs in patients with immunocompetent cells, the bacteria migrating from the gut would be destroyed.[77] However, if there is impairment of the immune system, such as in acute pancreatitis, viable bacteria could reach the pancreatic necrosis and develop infectious complications.

In summary, patients with severe acute pancreatitis present functional and morphological disorders that could be associated with pathological BT and pancreatic contamination, that is, disruption of the gut barrier (morphological mucosal alterations), intestinal bacterial overgrowth (secondary to intestinal hypomotility) and immunosuppression. Therefore, BT in acute pancreatitis appears to play a key role in the occurrence of infectious complications in this disease.

Bacterial translocation in cirrhosis

Patients with cirrhosis have increased susceptibility to severe infections such as spontaneous bacterial peritonitis (SBP), pneumonia, urinary tract infections and bacteremia.[78] Several alterations in the defensive mechanisms could explain the high incidence of these complications.[79] It is known that cirrhotic patients have a decreased small bowel motility, hypochloridria and a reduced secretion of IgA into the intestinal lumen.[80] These factors could be responsible for the occurrence of intestinal bacterial overgrowth.[81]

About one-third of cirrhotic patients have intestinal hypomotility, which is more important in patients with more severe hepatic dysfunction.[82] In this way, Pardo *et al.*[83] showed that patients with cirrhosis had small bowel bacterial overgrowth, which was improved by cisapride. They speculated that cisapride may lower the incidence of BT in humans with cirrhosis and may thereby reduce the number of episodes of sepsis and bacterial peritonitis. Furthermore, some evidence suggests an increased intestinal mucosal permeability when portal hypertension is present.[41] A cohort of 73 cirrhotic patients[84] showed a reduced risk of post-surgical infections with the use of propranolol preoperatively. This reduced risk was probably due to a reduction in portal hypertension, increasing bowel motility and then indirectly decreasing BT.

Intestinal bacterial overgrowth, intestinal hypomotility and increased mucosal permeability are mechanisms suggested to increase BT. In addition, cirrhotic patients have impaired host immune defenses, which is also a major mechanism implicated in BT.[12,78,85] Cirera *et al.*[86] evaluated the incidence of BT in 101 cirrhotic patients undergoing surgery (liver transplantation or hepatectomy). They found an incidence of BT, defined as the isolation of enteric organisms from MLN, of 9% in cirrhotic patients. This incidence was similar in a control group of non-cirrhotic patients (9%). However, BT of enteric organisms was more frequent in Child C patients (31%) compared to Child B patients (8%) and Child A patients (3%). These findings were probably related to an impaired immune function in patients with more severe liver dysfunction. Lin *et al.*[87] also showed that endotoxemia occurred frequently in humans with a variety of chronic liver diseases and that the severity of liver disease correlated with the degree of endotoxemia. Guarner *et al.*[88] showed that patients with cirrhosis had increased serum endotoxin concentrations and increased NO levels compared with control participants. They hypothesized that NO could be the cause of the hyperdynamic state seen in humans with cirrhosis.

Thus, although BT is not the only source of sepsis in cirrhosis it appears to be an important route of entry of bacteria into the cirrhotic host.[41,80,89] BT becomes clinically significant when it produces infectious complications and contributes to the morbidity and mortality in cirrhosis, probably by exacerbating the deterioration of the circulatory disturbance present in these patients.[41,78]

In summary, translocation of bacteria and their products is an undeniable phenomenon that occurs naturally in healthy humans and its occurrence is increased in a certain number of clinical pathological conditions. In this way, BT is certainly involved in the physiopathological mechanisms of many diseases. However, it is probably not the most important factor in most cases. Progress in understanding the mechanism involved in the gut barrier function, BT and host response to this phenomenon will allow future clinical studies to provide answers about the actual impact of BT in various human diseases.

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