Bacterial Translocation

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Received for publication, December 20, 2004

This lecture first highlights the methods available to detect bacterial translocation (BT) as well as shortcomings related to those. Secondly, mechanisms involved in the process of BT with special focus on intestinal flora, gut barrier dysfunction and the role of immune defence mechanisms are discussed. Thirdly, the potentially huge clinical relevance of BT is reviewed. BT is the key to our understanding of spontaneous bacterial peritonitis in liver cirrhosis, the multiorgan failure syndrom induced by hemorrhagic shock, burns or sepsis and is involved in a multitude of diverse gastrointestinal lesions. Therefore, BT may represent a common and so far inadequately recognized trigger for a multitude of complications known for long in various clinical entities. Finally, the focus will be to discuss advances in therapeutic approaches in preventing BT and associated potential complications. There is much evidence linking diet with the maintenance of intestinal integrity and multiple enteral manoeuvres have been tested. Particularly promising is the avenue of using probiotics known to exert many effects and to protect the gut from BT. Various other therapeutic approaches include binding/neutralizing of endotoxins, hyperbaric oxygen, prostaglandins, antioxidants etc. A more general attempt to reduce the presumed risk of BT is selective gut decontamination (SGD). In summary, the concept of BT contributing to morbidity is of extraordinary importance and its detailed investigation will eventually open an avenue for preventive measures against infectious complications.

Key words: bacterial translocation; mechanisms; immunity; therapy

INTRODUCTION

The passage of large particles through the intestinal barrier, initially called perseption, was recognized as early as 1844 by Herbst (131). Volkheimer and Schulz reported 1968 that intact starch particles could be transported across the intestine of healthy normal human subjects (297). The term bacterial translocation (BT) has been coined by Berg and Garlington describing “the passage of viable enteric bacteria from the intestinal lumen through the epithelial mucosa into the lamina propria and then into mesenteric lymph nodes (MLN’s) and possibly other organs” (26). This definition has later been refined by including all microbial translocation, defined as the passage of both viable and non-viable microbes and microbial products such as endotoxin across an even anatomically intact intestinal barrier.

MATERIALS AND METHODS

The endpoint most commonly used to prove and quantitate BT is by enumerating culturable organisms in the MLN’s. However, data using radioactively labelled bacteria indicate that this technique vastly underestimates the extend of translocation since, most

microbes breaching the epithelial barrier are killed. In fact, less than 0.1% of radioactive labeled *Escherichia coli* localizing in MLN’s was associated with viable bacteria (6). This indicates that increases in BT demonstrated by increases in colony forming units (CFU’s) in MLN’s are predominantly due to a decrease in killing rather than an increase in transepithelial penetration. As indirect marker any detection of intestinal bacteria in culture of portal or peripheral blood also evidences BT. Similarly, the discovery of endotoxin in peripheral blood suggests BT. However, in animal studies bacteria are rarely cultured from peripheral blood a finding most likely due to the defense mechanisms provided by liver and lungs eliminating microorganisms by tissue macrophages.

Recently, PCR-methods have been introduced for detection of microbial DNA in blood demonstrating a higher sensitivity than blood cultures for assessment of BT from the intestine (145). Over the last couple of years thus, several approaches have been published for the PCR-based detection of bacterial DNA (bactDNA) used as sort of surrogate marker for BT also in humans. However, some critical notes have to be considered when interpreting such data. It should be noted that the often used term “universal PCR” is misleading somehow since no sections within the 16S rDNA sequences of eubacteria are perfectly conserved among all known species. Primer design is always conducted by best compromises,

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and the fact that some species may escape from efficient amplification and are therefore underrepresented in the final PCR reaction mixture, is reflected by the more common term “broad-range PCR” (65). Broad-range eubacterial PCR however, is highly sensitive, and even minor contamination with DNA of any other bacterial species may result in false-positive results. In fact, a well-known problem in detecting small amounts of bactDNA is the possibility of exogenous bactDNA contamination events in the course of obtaining and/or processing the corresponding sample material as well as endogenous contamination due to the presence of residual bactDNA in the various reaction components. Most importantly, analytical sensitivity of the current technology is heavily restricted by bactDNA contamination of PCR reagents and DNA extraction kits. For example, in an earlier study on blood samples from patients with bacteremia, the superior sensitivity of eubacterial PCR assays was instantly called into question because the rate of false-positive PCR findings was as high as 40% (272). In principle, reliable detection of very small numbers of bactDNA in clinical samples requires the elimination of any contaminating DNA to avoid false-positive results and to achieve an adequate signal to noise ratio of the respective assay concept (151). In routine practice, however, these promising options are consistently vitiated by the fact that all of the various decontamination protocols are reducing the overall analytical sensitivity of the PCR assay to a certain extent (61). Nonetheless, applying an eubacterial PCR assay and taking efficient precautions to prevent exogenous contamination also in healthy volunteers or patients with chronic fatigue syndrome a variety of bacterial species could be identified in plasma samples (130, 204, 296). Since no independent method of detecting low amounts of bactDNA in culture-negative samples is available, it is not possible to tell with absolute certainty whether positive PCR results in the presence of negative culture results are true- or false-positives. As in many other fields of molecular microbiology the qualitative or quantitative determination of bactDNA by PCR or comparable methodology for nucleic acid amplification is an promising and fascinating tool for the detection of traces of bactDNA in normally sterile body fluids or biopsies. The degree of analytical sensitivity, however, which is at least theoretically required for investigating and tracing BT events approaches the intrinsic limitations of current PCR technology. It is simply not possible to distinguish between low copy numbers of bactDNA in clinical specimens and the bactDNA that contaminates the

reagents used for specimen processing and PCR amplification. With the use of culture-independent and highly-sensitive molecular methods for the detection of bacterial DNA, there is growing evidence of “microbial contamination” within anatomically privileged compartments of the human body that have previously been considered sterile most of the time. Since a number of reliable studies have clearly demonstrated the circulation of bactDNA in the blood of healthy individuals (130, 204, 296) the solely detection of bactDNA should no longer be considered as a diagnostic marker for infection or disease. As a consequence, aspects of target DNA quantitation and the use of species-specific assays are of increasing importance to establish etiologic diagnoses by investigating the relationships between circulating bactDNA and disease.

Moreover, intestinal permeability can be assessed by a variety of techniques (for review see (34)). Initially, single test substances (various polymers of polyethylene glycol [PEG] or nondegraded radiolabeled chelates such as Cr^{51} -labeled ethylenediaminetetraacetic acid [Cr^{51} -EDTA] or $^{99\text{m}}\text{Tc}$ -deitehyleneetriaminopentaacetate [$^{99\text{m}}\text{Tc}$ -DTPA]) and calculation of plasma-to-intestinal luminal clearance of these tracer molecules was used. However, results were influenced by a change in any of the premucosal or postmucosal factors apart from intestinal permeability itself. This led to the principle of differential urinary excretion of two different orally administered nonmetabolizable sugars, which provides a specific index of intestinal permeability. One probe typically consists of a relatively small molecule, which permeates moderately well through even normal mucosa. A second probe consists of a larger molecule, which minimally permeates a normal mucosa. By measuring the concentration of both probes in urine and thus, monitoring differential absorption, confounding effects are somewhat factored out. Ideally such permeability probes have to be nontoxic, nondegradable, should exhibit first-order-kinetics of permeation and lack natural presence in urine. Finally urinary excretion at best should be complete following instillation and measurement of the probe has to be sensitive and accurate as well as easy. Most commonly used are a monosaccharide and a disaccharide together, such as mannitol and lactulose, known to pass transcellularly or paracellularly, respectively, through the epithelium. Unfortunately, a multitude of various factors affect urinary excretion of orally administered test substances such as gastric/intestinal dilution, intestinal transit time, bacterial degradation (e.g. in case of bacterial overgrowth), alterations in intestinal blood flow, renal

function and even timing and completeness of urinary collection. Moreover, attention has to be paid on osmolality of the test solution potentially affecting paracellular permeability as well as on water-/ lipid-solubility influencing the predominant anatomic pathway the probe is using for transepithelial passage. All these shortcomings need to be considered when interpreting any results obtained particularly in disease processes known to affect any of the stated parameters.

Due to the inherent limitations of in-vivo studies other approaches to delineate BT in more detail have been developed in experimental settings using either pure enterocyte cell culture grown to confluence on semipermeable membranes or segments of intestine being stripped from seromuscular coat leaving the mucosal layer. Transepithelial electrical resistance (TEER) can be assessed in such preparations (usually using an ohmmeter) reflecting permeability and correlating with the tightness of epithelial cell-occluding junctions. Another way to estimate permeability is to determine by fluorescent or radioactive probes being applied to the apical compartment of those preparations and calculated as flux of per unit membrane/mucosal layer. Finally, a new modality to investigate mechanisms of BT uses green-fluorescence-(GFP)-marked bacteria (119, 176, 277). GFP was first isolated from the jellyfish *Aequorea aequorea* being responsible for autofluorescence in presence of oxygen. Due to its small size, formidable stability and ease to use it is utilized increasingly to visualize bacteria. GFP-marked bacteria can easily be sensed and detected by fluorescence microscopy. Moreover, bacteria expressing plasmid-encoded GFP have been shown to do so without selective pressure for a substantial time and for up to 100 doublings and even after the cell has become non-proliferative (19). Using GFP-transfected E.coli Samel et al. could visualize the process of BT across the gut wall into the submucosa and muscularis propria in a model of small bowel obstruction by intravital microscopy (256). Moreover, intestinal ischemia induced by selective clamping of the supplying mesenteric vessel drastically accelerated this translocation of GFP-marked E.coli and two hours after intraluminal administration GFP-E.coli were also visible in frozen sections of mesentery, liver and spleen demonstrating bacterial spreading. This promising tool will also ease investigations to unravel the major site of BT as well as the exact anatomic route of translocation.

RESULTS AND REVIEWS

Mechanisms of BT

The gastrointestinal tract is unique as it represents the largest surface area of the body and on top is constantly exposed to microorganisms. Therefore, it is unlikely that this microbial ecosystem evolved by chance and likewise unlikely that the mutual co-operation with the host is achieved without clearly defined lines of communication. In general proposed mechanisms promoting BT include a) changes in intestinal microflora, b) mucosal barrier failure and c) defects in host immunity (Fig. 1). These determinants of BT should not be viewed as individual separate etiopathological factors but rather as interrelated aspects influencing each other. In fact, a concerted synergistic interplay of multiple defense mechanisms has been developed during coevolution of humans and bacteria ensuring an adaptive commensal relationship where neither partner is harmed.

Intestinal microflora

This review does not intend to summarize microbiological aspects however, important facts related to the issue of BT are as follows. It has been commented that > 90% of the total cells of a healthy human are actually bacterial cells. Overall bacteria account for up to 50% of the volume the human colon contains and the total weight of microflora in the human gut has been estimated to be about 1 kg. Most of these are commensals that coexist peacefully with their host and remain harmless provided that they do not stray beyond the gut lumen. Composition of the microbial flora differs widely along the gastrointestinal tract and from the lumen to the mucosa as well as between individuals. Though whereas the upper GI tract is usually sparsely populated microbial density increases towards the ileum and reaches 10^{12-14} / gram in the colon. It is important to stress the qualitative and quantitative differences between luminal bacteria and bacteria attached to the mucosal surface since, only the latter are prone to translocate. As for individual heterogeneity twin studies clearly demonstrated a large diversity in microorganisms populating homozygotic twins (326, 327). Host environment factors regulate not only the composition of the intestinal microflora but also bacterial virulence factors (121).

The bacteria that seem to translocate most readily are those usually classified as facultative intracellular pathogens - i.e. those that are able to survive outside the white blood cell but are also able to resist phagocytic killing. Classic examples are *Salmonella* species and

Fig. 1. Mechanisms of BT. Factors involved in the process of BT include changes in the intestinal microflora, alterations in mechanisms preventing attachment and penetration of bacteria and finally, local and systemic immune responses aiming to kill bacteria that have translocated.

Listeria monocytogenes which translocate readily after oral inoculation into experimental animals that have previously undergone intestinal antibiotic decontamination and subsequent intestinal overgrowth of an antibiotic-resistant translocating organism. In contrast, normal enteric species are easily killed after phagocytosis, surviving only under circumstances that impair host defenses. Of the more than 500 species of normal intestinal bacteria relatively few have been shown to translocate with any frequency. Steffen et al. investigated whether the various organisms in the indigenous gastrointestinal flora translocate at the same rate or whether certain species are especially adept in translocating from the gut (282). Particularly aerobic and facultative anaerobic gram-negative bacteria were found to translocate in high numbers to the MLN's of monoassociated gnotobiotic mice. In detail, the few intestinal bacteria that most frequently translocate include *E. coli*, *K. pneumoniae*, other *Enterobacteraceae*,

P. aeruginosa, Enterococci and other Streptococci (307). Curiously, these species are those most frequently associated with complicating infections in severely ill, hospitalized and particularly cirrhotic patients.

Recently, it has been evidenced that also the strain of bacteria is important for its capacity to translocate. For instance, special strains of *E. coli* have been reported to be more efficient translocators as compared to others (146, 164, 198). One explanation could be that several strains of *E. coli* show better adherence and attachment to the mucus-epithelium layer than non-pathogenic bacteria (23). In general, adhesins have been shown to be associated with fimbriae of enteric bacilli. This fimbriated surface structure (so called colonization factor) of e.g. *E. coli* has been evidenced in volunteers to be required for intestinal multiplication, clinical illness and humoral antibody production (258). Moreover, differences in virulence among strains has been suggested in respect to resistance against host defence

mechanisms allowing survival and spreading of those bacteria more efficiently than others (8, 87).

Although intestinal anaerobic bacteria outnumber aerobic bacteria by 100:1 to 1000:1 anaerobes can very rarely be induced to translocate (282). The reason for this is still unclear. Translocation of anaerobic bacteria has been reported only in extreme circumstances such as athymic (213), lethally irradiated (41) or severely burned rodents (307). In nearly all these conditions, breaks in enteric integrity are found, and anaerobic bacteria appear to translocate in direct proportion to the degree of tissue damage. Thus, in contrast to aerobic gram-negative bacilli that translocate easily and even across a histologically intact intestinal epithelium (282, 304, 306, 307) anaerobic bacteria seem to translocate in situations in which the intestinal tract is mechanically damaged. Moreover, it is well-known that anaerobic bacteria as a carpet on the mucosal surface limit colonization and overgrowth of other potentially invasive microbes. Thereby, anaerobic bacteria rather help to confine potential pathogenic bacteria to the intestinal lumen and support maintaining the stability of the intestinal flora than to promote BT (304). In fact, selective elimination of anaerobic bacteria facilitates intestinal overgrowth and translocation of facultative bacteria (304). In deed, most evidence linking translocation of normal enteric flora and intestinal overgrowth has been derived from models of gnotobiotic animals or selective-decontaminated animals given a corresponding antibiotic-resistant organism. In these animals extremely high intestinal population levels are achieved associated with translocation to extraintestinal sites. This has lead to the conclusion of bacterial overgrowth being one of the main factors promoting BT. In fact, a direct relationship between the numbers of a bacterial strain populating a segment of the intestine and the numbers of viable bacteria of this strain present in MLN has been demonstrated in mice (283). In this context, it is important to differentiate two distinct intestinal microfloras. The first, is found within the lumen of the gut, and the second is associated with the mucosal surface. Although the levels of luminal bacteria clearly are important in the development of infections in situations of bowel injury or perforation, the levels of mucosally adherent bacteria are most likely to be more important in the development of BT (37). Bacterial overgrowth in general is defined as a bacterial count $> 10^5$ colony forming units/ml in fluid obtained from the intestine during duodenal intubation. Factors promoting bacterial overgrowth include reduced gastric acidity (e.g. due to use of antiacids) but predominantly

gastrointestinal dysmotility. In fact, disruption of the migration motor complex by morphine results in an increase of bacterial growth and associates with BT to MLN (203). Interestingly, bacterial overgrowth per se has been proposed to result in selective loss of brush border alkaline phosphatase activity (20) and to modulate systemic cytokine response to e.g. hemorrhagic shock leading to marked increases in plasma TNF and IL-6 (122, 123).

Mucosal barrier dysfunction and site of translocation

Secretory mucosal barrier: Preventive measures against attachment of microbes to the epithelial surface known to be the first important step in epithelial penetration include mucus, chloride, gastric acid, pancreatic enzymes, bile and a diversity of antimicrobial peptides. Mucins, secreted by epithelial goblet cells in copious amounts (3 L/day), create a layer of membrane-anchored negatively charged glycoproteins forming the so-called filamentous brush border glycocalyx (17). This thick (400–500 nm) layer serves 1) as a diffusion barrier that prevents direct contact of most macromolecules, particles and bacteria with the microvillus membrane but is easily accessible to digested nutrients 2) acts as a lubricant to reduce physical abrasion of the mucosa and participates in the protection of the mucosa from damage induced by acid and other luminal toxins and 3) serves as a highly degradative microenvironment owing to the entrapped pancreatic enzymes and membrane-bound hydrolytic enzymes. Additional trefoil factors concomitantly secreted by mucin secreting epithelial cells participate in stabilisation of the mucous gel protection from deleterious agents and promote mucosal repair at sites of mucosal injury (316). Active chloride transport by epithelial cells promotes intraluminal fluid flux that washes away harmful agents. Mucosal secretions are rich in IgA antibodies that effectively bind and aggregate bacteria preventing mucosal adherence and colonization (so called immune exclusion) (279). In fact, IgA accounts for more than 70% of total body immunoglobulin production (> 5 g/day and $> \text{IgG}$ and IgM combined). However, one has to distinguish serum and secretory IgA since mucosal surfaces are neither source nor destination of serum IgA. Secretory mucosal IgA serves not only as guardian from microbial entry but also neutralizes toxins and infectious organisms and even may actively transport IgA-bound antigens/microbes as a sort of “sump pump” from the lamina propria back to the lumen. IgA is secreted by plasma cells derived from B cells that “home” to the lamina propria where they mature. IgA is transported across the epithelial border by

receptor-mediated endocytosis initiated by a secretory component, which is the extracellular domain of a 110000 molecular weight transmembrane glycoprotein. Bile inhibits bacterial overgrowth, has a trophic effect on the intestinal mucosa (162) decreases epithelial internalization of enteric bacteria (302), exerts detergent actions with anti-adherence effects and binds and neutralizes endotoxins (33, 293). Moreover, the absence of bile in the intestinal tract has been shown to affect homing and distribution of T lymphocytes in the GALT decreasing the numbers of CD4+ and CD8+ T lymphocytes and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressing cells in the lamina propria (257). Finally, bilirubin has been shown to impair bactericidal activity of neutrophils attenuating bacterial clearance mechanisms (16).

Several antimicrobial peptides and proteins have been identified and thought to function as natural antibiotics due to their ability to kill a variety of microbes under laboratory conditions (323). α -defensins are released by a cluster of cells located at the bottom of each intestinal crypt, so called Paneth cells, in response to bacteria and lipopolysaccharides (18, 209). Paneth cells are normally restricted to the small intestine and are found most abundantly in jejunum and ileum, where they may play an important role in maintaining the relative sterility of the lumen. In contrast to enteric α -defensins, human β -defensin 1 (HBD1) appears to be expressed by most epithelial cells of the small and large intestine (205). Evidence for the functional importance of defensins comes from studies in mice lacking matrilysin, an enzyme that activates several mouse intestinal defensins, presenting with impaired resistance to intestinal infections, e.g. defect in clearance of orogastrically administered gram-negative bacteria (312). Human Paneth cells code for two α -defensins, HD-5 and -6. Genetic transplant of human defensin 5 (HD-5) into mice is associated with greater antibacterial activity against *E. coli* as well as improved resistance to intestinal infections with e.g. *Salmonella typhimurium* (254). The peptide also remains active even after partial proteolysis, an indication of its potential to function within the environment of the intestinal lumen (228). Other larger proteins such as lysozyme (181) and secretory phospholipase A2 (126) are likewise released by Paneth cells and may also be involved in local defense against commensal bacteria. Thus strategically located just below the stem cell zone, Paneth cells detect bacteria that occupy the crypt lumen and secrete defensins in order to kill them and inhibit colonization of the crypt lumen. By this the microenvironment is protected from bacterial

overgrowth and bacterial infection and stem cell replication can proceed continuously to maintain mucosal integrity. In chronic inflammatory bowel disease HD-5 and -6 occurs also in the colonic epithelium (64) and has been speculated to assist in the killing of luminal microbes to prevent invasion across the damaged mucosal surface. As for HBD1, in vitro testing evidenced antimicrobial activities against gram-negative bacteria including *E. coli* and *Pseudomonas aeruginosa* but limited activity against gram-positive bacteria (63). A variety of stimuli have been observed to induce β -defensin genes which contain recognition sites for NFkB including bacteria, LPS, TNF, IL-1 and IL-6 (63, 205, 288). Moreover, commensal bacteria itself have been shown to stimulate epithelial surfaces to express antimicrobial peptides at levels that kill pathogen microbes (38). Therefore, intestinal epithelial cells actively participate in host defense and do not simply constitute an inert barrier for this purpose. Defensins are also stored in granules of polymorph mononuclear cells facilitating killing of ingested microorganisms (85). Interestingly, several neutrophil defensins kill gram-positive bacteria at concentrations as low as 1 μ g/ml, whereas higher concentrations are required to kill gram-negative bacteria (267). In contrast, the converse is true for enteric defensins indicating the divergent functional evolution in dependency on the natural environment (209). Since, several defensins have been shown to exhibit chemoattractant properties and particularly to attract both immature dendritic cells (DC) and memory T cells (86, 319) it is tempting to speculate that in inflamed mucosa this may contribute to shape innate immune host response as well as sets the stage for the adaptive phase of immune response. Moreover, chemokines itself have been shown to exert potent antimicrobial activity, e.g. against *E. coli* but also *Staphylococcus aureus*, *Candida albicans* and others (60, 86).

Physical mucosal barrier

The most critical barrier between the host and the external environment preventing absorption of intraluminal microbes and microbial products however, is the epithelium per se. Four different types of epithelial cells absorptive enterocytes, goblet cells, enteroendocrine cells and Paneth cells exist. Although consisting of only a single layer of cells arranged into villus and crypt components, the intestinal epithelium must control the access of potential antigens and pathogens. For this purpose epithelial cells are well equipped to face such a pathogen-rich foreign environment. Specialized cell-cell junctional complexes

allow for selective paracellular permeability (tight junctions: TJ), maintain intercellular adhesion (intermediated junctions and desmosomes) and permit intercellular communication (gap junctions). Paracellular permeability is regulated by the so-called apical junctional complex (AJC) consisting of TJs and subjacent adherens junction (AJ). Major constituents of TJs are three transmembrane proteins, occludin, claudin and junction adhesion molecule that are associated with intracytoplasmic proteins (zonula occludens ZO-1,-2,-3) as well as E-cadherin and catenins. At the apicolateral epithelial surface these TJs maintain a permeability seal restricting paracellular movement of even very small (2 kDA)-molecules/ or a molecular size > 11.5 Å preventing therefore e.g. transepithelial movement of bacteria, macromolecules but also LPS, peptidoglycan-polysaccharides etc. Even histological intact rat intestine has been shown to exhibit increased paracellular flux of H-mannitol and/or CrEDTA during stress mediated at least in part via modifications and redistributions of occludin and ZO-1 (184, 259).

Major factors known to disrupt mucosal barrier are mucosal acidosis, hypoxia, oxidative stress and ATP-depletion. These conditions are interrelated in most circumstances but, e.g. mucosal acidosis induced deliberately by increasing arterial carbon dioxide tension leads to substantial increases in epithelial permeability even in the presence of unchanged perfusion and oxygen tension (253). This clearly indicates that acidosis per se promotes barrier dysfunction. Moreover, oxidants such as hydrogen peroxide and superoxide radicals have been shown to disrupt the cytoskeleton and to increase intestinal permeability (309). As for hypoxia the intestinal villus is particularly dependent on sufficient oxygen delivery since the oxygen tension per se is much lower than in arterial blood even under physiological conditions explaining the increased susceptibility for hypoxic injury. Any decrease in intestinal blood flow ultimately aggravates this condition as soon as oxygen consumption becomes supply dependent concomitantly leading also to mucosal acidosis and ATP-depletion. In thermal injury, trauma, hemorrhagic/ cardiogenic or septic shock there is diminished blood flow to the intestinal mucosa. Therefore, ischemia-induced mucosal injury represents a common pathway to different disease processes leading to dysfunction of the gut barrier.

Mucosal atrophy, particularly as consequence of luminal nutrient deprivation has been suggested as well as predisposing factor for BT (308). However, several experimental models of BT could not convincingly demonstrate morphological changes as cause of

intestinal hyperpermeability and/or BT (55). Moreover, Sedman et al. also failed to demonstrate a significant difference in villus height of small bowel biopsies between patients with and without BT (265). Finally, in a mixed population of gastroenterological patients the index of villus atrophy was found not to correlate with intestinal permeability (206). Nonetheless, increased intestinal permeability has been demonstrated in patients with burns (163), following cardiopulmonary bypass (241), elective or emergency major vascular surgery (248), hemorrhagic shock (247), jaundice (217), indomethacin (67), parenteral endotoxin (208) as well as in intensive care patients (125). Gut permeability was also found increased in trauma patients however, presenting no difference between patients with or without infection (216, 247). Likewise, O'Boyle et al. did not find any significant differences in the incidence of BT in gastroenterologic patients with normal permeability as compared to patients with increased permeability (206). Finally, BT may not occur even in the presence of gross intestinal mucosal permeability abnormalities (91). Therefore, it appears that increased intestinal permeability is a permissive factor for BT but does not prove that BT has occurred. The failure of evidencing a causative direct link between gut barrier dysfunction and infectious complications in humans suggests that increased intestinal permeability and subsequently infective complications are, at least partly, independent phenomena.

Site of translocation

In the small intestine amplification of surface area is an adaptation to improve digestion and absorption of nutrients however, at first appearance this seems concomitantly to increase the risk of mucosal colonization by potential pathogens and commensals. Nevertheless, the bacterial load of the small intestine remains very low due to predominant secretion of digestive juices and mucus as well as antibiotic peptides at this site. In contrast to the upper gastrointestinal tract towards the ileocecal junction the number of bacteria increases and species of microflora resemble those found in the colon. It has been suggested that the lower part of the gut because of containing a large number of microbes, has a more efficient capacity for the killing of translocating bacteria. Moreover, the colon presents with different permeability characteristics than the small bowel, including higher electrical resistance and less permeability to the passive movement of ions (229). In fact, under the same bacterial concentrations of *E. coli* loading significantly higher rates of BT from small

bowel than from large bowel have been observed indicating that the threshold to the onset of BT is markedly lower in the small intestine (153). Therefore, it appears that bacterial overgrowth and alterations in intestinal permeability in the small bowel have greater potential danger to promote BT.

Noteworthy, in endotoxemia gut mucosal injury has been reported to be greater in the ileum and cecum than in the jejunum (74). During intravenous total parenteral nutrition loss of gut barrier function is observed throughout the small bowel and cecum (but not the colon) whereas oral elemental diet increased intestinal permeability only at the ileum (193). In burn injury models isolated gut loops from the jejunum, ileum and proximal colon showed equivalent rates of translocation of ^{14}C -marked *E. coli* (radionuclide counts) (103). However, higher numbers of viable bacteria in MLN were detected (microbiological culture) when *E. coli* organisms were inoculated into the jejunal loop as compared to the ileal or colonic loop. In accordance with this concept, particularly proximal gut colonization has been evidenced to be associated with increased BT and septic morbidity in surgical intensive care patients (168, 177). In experimental cirrhosis however, histological changes were found to be most marked in the cecum (106). In this context, species known to translocate frequently including *E. coli* and enterococci achieve particularly high densities and metabolic activity in the cecum, since 50% of total bacterial ribosomal RNA in cecal contents corresponds to these species (178). By contrast, these species account for only 7% of bacterial ribosomal RNA in faecal samples. Moreover, In the cecum (and right colon) fermentation is very intense leading to high production of short-chain fatty acids, an acidic pH (5–6) and rapid bacterial growth. Finally, the total anaerobe counts are 100 times less in the cecal content as compared to fecal samples (178) what may well contribute to increases in BT at this site.

Host immunity

BT into the underlying tissue can normally be detected in animals and humans without harm to most healthy individuals (207), since organisms are usually efficiently removed by phagocytes. For this purpose the mucosal system is shaped by, and specifically responds to, the commensal flora. Moreover, commensal bacteria exert profound immunomodulatory activity on the surrounding intestinal tissue. However, a major key question relates to defence mechanisms integrated to restrict the penetration and spread of commensal bacteria. Essential among the armamentarium of defence mechanisms is the

mucosal immune system.

Gut-associated-lymphatic-tissue (GALT): The intestinal tract is an active immune organ, containing essentially every type of leucocyte involved in immune response. The antigen-specific local immune system, termed gut-associated lymphatic tissue (GALT) is the largest immunological organ of the body making up 25% of mucosal cell mass. This may reflect the constant exposure to the vast and diverse bacterial microflora at the mucosal site. In fact, microbial colonisation of the GI tract affects the composition of the GALT. Exposure to luminal microbes expands the number of intraepithelial lymphocytes, germinal centres with Ig-producing cells arise rapidly within follicles and lamina propria and serum concentrations of Ig's increase substantially. In contrast, germ-free animals have reduced numbers of lamina propria or intra-epithelial T cells (124) and these are increased following the restoration of a normal microflora (137). Moreover, exclusion of microbes from the gut results in decreased macrophage chemotaxis, reduced intracellular killing of pathogens. The GALT comprises more than half of the lymphoid cells in the body and hosts numerous plasma cells, macrophages, neutrophils, Paneth cells and specialized M-cells playing a key role in controlling BT. It consists of three distinct populations: Peyer's patches, immunocytes within the lamina propria and interepithelial lymphocytes. However, the precise role of each cell in the different steps of translocation has not been delineated in detail so far.

Macrophages and dendritic cells (DC) located just below the epithelial dome are well positioned to detect microbial entry. DC are present in peyer patches, MLN and cryptopatches, isolated lymphoid follicles and lymphocyte filled villi as well as in the lamina propria and possibly in the epithelium (200). Proposed mechanisms of bacterial sampling by DC are as follows (281): Firstly, DC may open TJ between epithelial cells sending processes into the lumen directly phagocytosing microbes. This has been evidenced to occur without compromising the epithelial barrier function due to expression of major TJ proteins by these DC (238, 239). Secondly, following transport of antigens by M cells, being only present in epithelium overlying organized lymphatic tissue, which sample and deliver luminal antigens to the underlying lymphoid tissue (201). Thirdly, more indirect via up-take of antigen-bearing exosomes shed from epithelial cells. Finally, antigenic material interacts with DC in underlying tissue which may occur particularly when epithelial integrity is

Fig. 2. BT in relation to the pathophysiology of Multiple Organ Failure (MOF). Gut hypoperfusion often leads to bacterial overgrowth via different mechanisms including ileus, standard therapies such as antacids, total parenteral nutrition, antibiotics, morphine etc. Ischemic damage to the epithelium increases mucosal permeability via inadequate intracellular PO₂, acidosis and ATP-depletion due to hypoperfusion, anemia, arterial hypoxaemia and/or hypermetabolism secondary to critical illness limiting mitochondrial respiration. Pathophysiological hallmark in the pathogenesis of the SIRS and subsequent MOF is the activation of the endothelium. This may occur via local translocation of bacteria, endo- or exotoxins (that can be limited to the intestinal wall) as well as by subsequent production of oxidants and pro-inflammatory cytokines (e.g. TNF, IL-1). Activation of the endothelium results in attraction, rolling, adherence and transmigration of *neutrophils*. Adherent neutrophils are primed to produce oxidants, proteases and cytokines resulting in tissue injury. During reperfusion additional oxidants are produced via xanthin oxidase (in endothelial cells and neutrophils). Activation and stimulation of macrophages results in further cytokine release. Thereby, the gut becomes a “cytokine-releasing organ” delivering tissue injury to remote organs. Shock has been shown to depress lymphocytic and macrophage-mediated functional capacities leading to immunosuppression: BT/ endotoxins per se suppress non- and specific immune function: via GALT (stimulation of suppressor T-cells migrating to systemic lymphoid organs), via portal circulation (Kupffer cells: antigen processing and initiation of the specific immune response and tolerance/ insufficiency of non-specific phagocytosis due to overwhelming of the defense capacity), and via systemic circulation (endotoxin-macrophage-lymphocyte interactions causing systemic immunosuppression). Moreover, many anaesthetics can cause immune dysfunction. This immunosuppression contributes essentially to the spreading of bacteria/toxic products and sets the stage for SIRS and MOF to occur.

compromised. Those mechanisms most likely are responsible for the observed engulfment of labeled latex beads or *E. coli* after oral or direct intestinal application and recovery from MLN (303, 305). In fact, GALT-macrophages and DC transport the bacteria to MLN initiating an adaptive immune response and if the bactericidal activity is impaired to release the microbial products. Mature DC thereby, determine the class of

immune response by instructing naïve Th-cells to develop into either effector Th1-, Th2-cells or a mixed phenotype by the selective expression of polarizing molecules (144). Interestingly, gram-negative bacteria have been reported to induce expression of Th1-polarizing signals in human DC whereas gram-positive bacteria did prime for neither Th1- nor Th-2 development (274).

The MLN is a central organ in the BT process as well as a major organ in the intestinal immune system. The MLN complex as series of lymph nodes drains lymph from different anatomic regions of the intestine (48). Factors determining trafficking and migration of DC to MLN depend on the state of maturation and source of DC (25). Key regulators of DC migration however, are chemokine-chemokine receptor combinations, especially CCL20/CCR6 for unstimulated lymph DC and CCL21/CCR7 for mature DC (152). Traffic of DC follows afferent lymph vessels and is directed towards MLN. Indeed intragastrically applied marked *Enterobacteriae* could be isolated from MLN and were shown to reside in DC (170). Several lines of evidence indicate that MLN confine live commensals within DC to the mucosal immune system and avoid systemic spread and priming by these organisms (169, 170). In mice, after surgical removal of MLN and enteral bacterial challenge live bacteria could be cultured from the spleen, whereas bacteria did not penetrate beyond MLN in wild-type mice. (170). Moreover, usually enteric bacteria induced to translocate by oral antibiotics remain confined to the MLN and do not appear to establish a persistent infection in the MLN since, the MLN returns to sterile state when the antibiotic therapy is discontinued and the cecal population of enteric organisms returns to normal levels (27, 30). Immunosuppression however, allowed the translocating bacteria to spread systemically and ultimately resulted in lethal sepsis (28). Therefore, it becomes apparent that for BT to become clinically significant a failure of local and/or systemic immune defense must occur.

Mechanisms and immunological aspects

The reader should not be left with the impression that BT has to be considered always as negative aspect of biology and being linked intellectually to systemic disease unequivocally. BT occurs in the normal host, as evidenced by recovery of viable intestinal bacteria from MLN of a small proportion of healthy animals and humans (29, 42, 265). Moreover, it is likely that also dead bacteria translocate as a normal biological process. After being sensitized antigen-presenting cells and immature immune cells of the GALT not only leave the intestinal tract (as stated migrating through the thoracic duct and participating in systemic immunity) but also preferentially seed back to the intestinal mucosa as mature T and B cells. In fact, a tissue- and region-specific homing might be more precise, rather than simple traffic to the entire gut. For instance, CCR 9 has been identified as a gut-homing chemokine receptor that marks,

essentially, all CD4⁺ and CD8⁺ memory or effector T lymphocytes in the small intestine, whereas in the colon only a few cells express CCR 9 (322). Thus, it is conceivable to consider BT as a probably normal and essential process regulating local and systemic immunity and tolerance to the innumerable antigens that contact the intestinal epithelium.

The acquired immune response appears to play a significant role in limiting BT. Owens and Berg noted spontaneous BT of certain indigenous bacteria, such as *E. coli*, to MLN, spleen and liver in athymic (nu/nu) mice, whereas no translocation was noted in heterozygous (nu/+) or nude mice grafted with thymus (213). Moreover, T-cell depletion not only caused accumulation of bacteria in MLN in healthy rats but also increased bacterial numbers observed in MLN of alcohol- and burn-injured rats and did cause spreading of bacteria to extraintestinal sites (55). Therefore, it appears that appropriate activation of intestinal T cells is critical in maintaining immunity against the translocation of enteric bacteria (108). Additional studies showed the ability of adoptively transferred T cells to confer protection against a number of bacterial infections including *E. coli* (109). Mechanisms by which T cells help maintaining humoral immunity may include T-cell dependent antibody production and production of chemokines/cytokines by which macrophages and neutrophils are recruited and activated. T-cell depletion (Th- and Ts-compartment) is also observed in patients with advanced cirrhosis (5) but its exact contribution to increases in BT is unknown.

Despite increased BT in IgA-deficient mice (169) commensal-related sepsis is not observed in IgA-deficient animals or humans. Interestingly, DC are also involved in direct IgA induction against commensal bacteria in the lamina propria. This has been demonstrated by repeated intragastrical conditioning of mice with *Enterobacter cloacae* leading to a selective IgA response in-vivo (170). Moreover, *in vitro* B cells developed an IgA response only when co-cultured with DC that have been pulsed prior by *E. cloacae*. This anti-commensal intestinal secretory IgA-response was induced similarly by LPS, is T-cell-independent and is antigen-driven or in other words does not simply reflect the presence of "natural antibody" but is specifically induced by antigenic changes. Such specific IgA functions to coat commensal bacteria that have escaped DC and then being emenable for rapid up-take by Fcα/μ-bearing phagocytic cells (270). However, the inability of IgA to fix complement efficiently or to act as an opsonin avoids initiation of an inflammatory response (see

below).

Innate immunity represents the most ancestral and ubiquitous system of defence against microbes/-products. Innate immune function is determined by sensing of bacteria/-products, release of chemokines and cytokines leading ultimately to killing of the invader by mononuclear cells. The really crucial importance of phagocytic function of the monocyte/macrophage lineage in the host response when bacteria have penetrated the mucosa and hence, for limiting BT is underscored by several lines of evidence. Since, commensals are usually not pathogenic they have obviously found there “evolutionary niche” without subverting the phagocytic process, presumably because else it would cause inflammation and thereby disrupt the biofilms and filamentous brush border glycocalyx on the epithelium. Therefore, the normally highly functional macrophage bactericidal activity ensures true symbiosis, keeping the commensals right on the edge of the immune system and rapidly eliminating those that have translocated.

Surprisingly, commensal bacteria share abundant molecular patterns used for innate immune recognition of pathogenic bacteria. These highly conserved microbial signature molecules called pathogen-associated molecular patterns (PAMPs) are recognized by most mononuclear cells by so-called pattern recognition receptors (PRRs) (for review see (4)). These include the family of toll-like-receptors (TLRs) of which TLR2, 4 and 9 amongst its 11 members are the most relevant ones. The local cellular components of defence against BT (epithelium and GALT-MNC) all express TLR's but do so tightly controlled and predominantly intracellularly/compartementalized (290) in order to avoid unintended stimulation and mucosal inflammation. In fact, in contrast to pathogenic bacteria commensals normally do not trigger acute inflammation at the epithelium due to its hypo-responsiveness to PAMPs such as LPS. Moreover, efficient killing of commensals penetrating the mucosa normally prevents an inflammatory response. In addition, binding of non-pathogenic bacteria to the epithelium suppresses NFkB-activation by blocking IkB degradation explaining why neutrophils are rarely seen in healthy intestinal mucosa (174). In other words, the intestinal epithelium sets the anti-inflammatory tone of the GALT. However, as soon as inflammation occurs or mucosal LPS load becomes overwhelming DC and other monocytes and neutrophils are recruited the process of BT may become perpetuated (143, 271). For instance, migration of neutrophils across epithelial surfaces increase TJ permeability as do pro-inflammatory

cytokines, particularly TNF and $\text{INF}\gamma$ (58).

Genetic aspects/polymorphisms

Whether susceptibility genes for increased BT exist are not yet known. However, several new insights into genetic aspects of mucosal immunity may well point to a “genetic component” in the pathophysiology of BT. For instance, a newly discovered family of proteins, the NBS-LRR proteins (for nucleotide-binding site and leucine-rich repeat) are involved in intracellular recognition of microbes and their products. One such candidate gene mediating increases in microbial invasion and associated inflammation may be the caspase-activating and recruitment domain-15 (CARD15)/NOD2 gene. The CARD15/NOD2 protein has been described as an intracellular sensor to muramyl dipeptide, a component of the bacterial cell wall, mediating consecutive NF-kB activation (138). Functional studies have shown that NOD2 confers responsiveness to LPS and peptidoglycan and enables sensing of gram-positive and -negative bacteria (49, 138). Multiple mutations in CARD15/NOD2 have thus been associated with an impaired activation of NFkB in intestinal epithelial cells but also monocytes and macrophages in response to intestinal bacteria (49). Insufficient activation of NFkB has been suggested then to result in deficient elimination of translocated bacteria. In fact, transfection of epithelial cells with CARD15/NOD2 has been shown to strongly accelerate bacterial clearance (132). Interestingly NOD proteins confer LPS responsiveness independently of TLR4/MD88 suggesting that they form a new intracellular LPS signaling axis (114). Moreover, TNF up-regulates NOD2-expression in intestinal epithelial cells via the transcription factor NFkB increasing LPS susceptibility (245). Overall CARD15/NOD2 may initiate a gene program aimed at eliminating invasive intracellular bacteria. In deed, polymorphisms in CARD15/NOD2 gene expression have been implicated in the pathogenesis of morbus crohn (136, 210) as well as gastrointestinal GvHD and mortality after allogeneic stem cell transplantation (134) all conditions known to be associated with increased BT.

In summary, immunological host defence against BT is subject to regulation at many levels including sensing of microbes/-ial products by PRRs, release of chemokines and cytokines, induction of an adaptive immune response and biosynthetic pathways mediating synthesis and release of antimicrobial peptides and mediators. Moreover, all these pathways are not acting separately but in a most likely concerted synergistic manner. This complexity however, blurs the view on alterations of

Table 1. Human studies on BT (modified after Wiest et al. (311)).

Clinical Condition	Method testing BT	References
Intestinal obstruction/ Ileus	MLN, serosa	(76, 265)
Crohn's disease	MLN	(11, 159)
Organ donors	MLN, BC, endotoxin	(294)
Elective surgery	MLN	(265)
Aortic aneurysm repair	BC	(317)
Cardiac surgery	Endotoxin, L/M ratio	(14, 179)
Burn injury	BC, L/M ratio	(72, 163, 313)
Trauma / Hemorrhagic shock	BC, MLN, endotoxin	(93, 133, 191, 192, 219, 247, 249)
Obstructive jaundice	MLN	(158, 217)
Heart failure	Endotoxin	(44, 45, 161, 202, 227)
(Hemorrhagic) Pancreatitis	MLN, BC	(13, 24, 142, 167, 197)
Bowel transplant	BC, stool, liver culture	(56)
Liver cirrhosis	MLN, endotoxin, BC	(57, 100, 120)
Malnutrition	L/M ratio	(308)
Alcohol	PEG400, endotoxin	(218)
Drugs, Chemotherapy	BC, EM	(10, 97, 148, 189)
Neutropenia	BC	(62, 286)
Malignancy	BC	(286)

specific pathways and particularly the sequence of events leading to increases in BT. Thus, what seems to be a peaceful coexistence between the host and its beneficial microbial flora in reality reflects a permanent struggle, illustrating the extraordinary effectiveness of the mucosal immune system. Thus, we still need to obtain much better direct data on the mechanisms that each of these stated defence arms is using to contain the commensals largely within the intestinal lumen.

Clinical relevance of bacterial translocation

The economic burden of BT can be substantial. In the U.S. up to 10% of hospitalized patients develop nosocomial infections costing more than 4.5 billion \$ annually. Although many of these infections are acquired exogenously there is increasing evidence that many infections are caused by translocating enteric bacteria. The incidence of gram-negative bacteremia varies from 70.000 to 330.000 cases per year in the U.S. with an associated persistently high mortality of 20–40% despite intense efforts in improving therapy.

The first evidence that translocation can occur in humans comes in form of a report by Krause et al. who documented that oral ingestion of a suspension of viable *Candida albicans* resulted in transient fungaemia and funguria in a normal volunteer (156). Increased BT has been shown to occur in various patient populations ranging from mildly to the critically ill (Table 1). Deitch et al. could isolate viable enteric bacteria from MLN's obtained at laparotomy from patients with small bowel obstruction (76). Similar results were observed by

Ambrose et al. investigating patients undergoing abdominal surgery for Crohn's disease (11). In general, gastrointestinal dysmotility or at its extreme ileus due to functional and/or mechanical intestinal obstruction promotes BT via intestinal dilatation, increased luminal pressure and bacterial overgrowth (171, 203). In brain-dead organ donors with anatomically intact gastrointestinal tract intestinal bacteria could be isolated in > 50% of cases (294). Sedman et al. studied 267 consecutive general surgery patients and found evidence of BT to MLN's in 10.3% of patients (265). A comparable rate of BT of 16% was found in 114 patients in whom operation afforded access of the peritoneal cavity for various reasons (42). Increased incidences of BT were observed again in patients with distal intestinal obstruction (38.5%) and in patients with inflammatory bowel disease (15.8%). Without these two subgroups overall rate of positive cultures of MLN's was 5%. Woodcock et al. investigated 51 patients undergoing open abdominal aortic aneurysm repair and found enteric bacteria isolated from MLN's in 5/51 patients (10%). Septic complications occurred significantly more frequent in patients with BT. In fact, one patient in whom *E.coli* was grown from MLN developed an aortoenteric fistula, with a coliform bacteria isolated from the graft (317). Also cardiac surgery has been evidenced to be accompanied by increases in intestinal permeability and systemic endotoxemia (14, 179, 241). One of the most established causes of increased BT not only in experimental models but also in humans is thermal injury. Burn patients with $39 \pm 12\%$ of surface

area affected were found to present uniformly increased L/M ratio indicating increased intestinal permeability (163). Moreover, in burn patients that died more than 50% had intestinal lesions and more than 80% were septic mostly with intestinal organisms (79). Finally, after thermal injury increased plasma levels of endotoxin are detectable within 24 hours of the burn with the degree of endotoxemia being closely correlated to the magnitude of injury (313).

In severely injured trauma patients Moore et al. failed to demonstrate bacteria or endotoxin in the portal or systemic blood obtained over the first 5 days of hospitalization even though 60% of the patients were in shock at the time of presentation (191). Also Peitzman et al. did find only sterile cultures of MLN's obtained at the time of coeliotomy from trauma patients (219). However, Rush et al. as well as Moore et al. found a high incidence of positive blood cultures in severely injured patients with shock in the early phase after trauma as compared to those patients without shock. Nonetheless, an exceptionally high proportion of gram-positive organisms was observed (192, 249) and most notably, these gram-positive microbes appeared to be of no clinical significance. In contrast, typical enteric bacteremia was detected in few cases, mostly in cases of severe shock and with fatal outcome. Finally, Endo et al. obtained serial blood samples (0.5 to 168 hours after arrival) in severely injured patients who arrived in shock and detected elevated LPS levels in only 2% of specimen (93). Therefore, it appears that BT can be demonstrated only in a small number of trauma patients who are moribund at arrival rendering the clinical importance of BT in this situation at least doubtful.

However, a number of studies have documented increases in gut permeability and BT in humans challenged with low doses of endotoxin (208) or patients with critical illness of various reasons (125, 246, 248). It has been claimed that BT may represent a significant source of sepsis in the critically ill patient via intestinally derived bacteria/endotoxin and subsequently induced production and release of pro-inflammatory cytokines (as well as eicosanoids and degranulation products) (71, 276). The hypothesis that the gut can become a cytokine-releasing organ is attractive because it might explain why signs and symptoms of sepsis frequently are present in critically ill patients even in the absence of a well-defined focus of infection. Thus, the gut may compromise a reservoir of triggering compounds that initiate, perpetuate or intensify the systemic inflammatory response, ultimately leading to the development of multi-organ dysfunction/ failure (MOF) (Fig. 2). An increased

incidence of septic complications in those patients who had evidence of BT at surgical operation compared with those who did not has been observed first by Brooks et al. and was confirmed by Sedmann et al. and other groups (42, 265, 317). However, occurrence of BT was not affecting mortality. In addition, it is important to note that in the study by Sedman et al. overall most cases of sepsis occurred in patients without BT. This also brings about attention to the method of detecting BT since, Sedman et al. like most studies evaluating BT in humans did culture only one lymph node at one location. Perhaps if multiple cultures of MLN's had been performed more positive MLN's would have been found in patients in whom sepsis later developed. The mesenteric lymph has been suggested to be an important channel for delivery of a variety of inflammatory mediators from the gut to remote organs (172, 173). Toxic products in mesenteric lymph has been demonstrated when none could be identified in the portal or systemic circulation. This route of spreading gut-derived cytokines has been demonstrated to play a key role for development of shock-induced lung injury. Division or ligation of lymphatics in the gut mesentery before induction of shock prevented increases in lung permeability and limited shock-induced pulmonary neutrophil recruitment and lung injury (70, 255). Likewise, prevention of gram-negative translocation has been reported to reduce the severity of hepatopulmonary syndrome in chronic-bile-duct-ligated rats (233).

Due to the stated effects of bile obstructive jaundice and the associated lack of endoluminal bile in the intestine has been shown to facilitate BT (59, 217, 240, 273) and to enhance susceptibility for further translocation in response to endotoxins (240). In contrast to animal models evidencing increased BT in obstructive jaundice O'Boyle et al. and Sedman et al. however, failed to observe an increase in positive cultures of MLN's in such patients (207, 265). Parks et al. nonetheless, demonstrated increased intestinal permeability in patients with obstructive jaundice being normalized after internal biliary drainage (217). Moreover, Kuzu et al. detected BT in 5/21 patients (24%) undergoing laparotomy for obstructive jaundice versus 1/30 (3.5%) electively operated control patients ($p < 0.05$) (158). Since, positive lymph node culture was not associated with systemic infection in either group the clinical importance and associated risk remains to be defined.

Poor cardiac function has also been linked to BT. Patients with severe acute heart failure displayed elevated serum endotoxin levels being significantly higher in the hepatic vein as compared to the left

ventricle indicating translocation from the bowel into the blood stream (227). Also chronic heart failure and recent-onset peripheral edema has been reported to present with significantly elevated serum endotoxin and cytokine concentrations in absence of any signs of active infection (202). Short-term intensive diuretic treatment significantly decreased and almost normalized endotoxin levels indicating that mesenteric venous congestion due to congestive heart failure at least partly may be responsible for the observed increase in translocation of endotoxins. Moreover, in children with congenital heart disease undergoing surgical repair pre-operative endotoxemia was observed in 40% of cases being associated with more severe hemodynamic disturbances and elevated mortality postoperatively (161).

The bacterial contamination of pancreatic necrosis in acute pancreatitis has been indicated to occur through translocation of intestinal bacteria (139). However, few studies have evaluated the issue of BT in pancreatitis. Nettelbladt et al. report a patient suffering from hemorrhagic pancreatitis, developing MOF with fatal outcome, in whom the same strain of *E. coli* was found in feces, blood, MLN's and intraperitoneal fluid suggesting that BT was the pathway of infection (197). Beger et al. already 1986 tested bacteriologically necrotic material obtained at surgery from patients with acute necrotizing pancreatitis. Intestinal microorganisms were cultured in almost 40% of cases and was associated with more widespread necrosis and significantly elevated mortality (24). A collective latest review of organisms associated with secondary pancreatic infection in patients with acute pancreatitis confirmed that most of them are intestinal flora strongly indicating BT from the gut as source of contaminating bacteria (230). This may well be due to increased intestinal permeability that has been demonstrated in patients with acute pancreatitis being significantly more pronounced in patients with severe pancreatitis (142). However, despite evidencing endotoxemia Ammori et al. failed to detect microbial DNA by PCR-methods in any patient with severe acute pancreatitis suggesting a discrepancy between the significant increase in intestinal permeability and BT (12). Nonetheless, several experimental studies revealed that acute pancreatitis promotes BT, in turn leading to infection of the pancreas and septic complications (129, 140). Interestingly, it has been demonstrated that when pancreatic infection occurs interstitial pancreatitis progresses to necrotizing pancreatitis with the action of nonpancreatic proteolytic enzymes, including amidase, produced by bacteria (150).

In small bowel transplantation very traumatic surgery,

ischemia/reperfusion injury, prolonged postoperative ileus or rejection predispose to BT. In rats, BT, endotoxemia and bacteremia have been reported to occur within hours of transplantation (43, 231). Since, inclusion of the colon to the graft increased fecal bacterial counts, rate of BT and infectious complications the colon is suspected to be the predominant source of translocating organisms (56, 278). Few human data are available, but BT has been reported to occur in 44% of pediatric patients undergoing small bowel transplantation with prolongation of cold ischemia time strongly influencing the rate of BT (56). Unfortunately, no statement on the effect on outcome is made.

In liver cirrhosis BT is thought to be causative for the development of spontaneous infections such as spontaneous bacterial peritonitis (165) but also to be linked to other severe complications such as the hyperdynamic circulatory syndrome (107) a key factor in the growth of varices and in the development of ascites and hepatorenal syndrome. Increased BT in cirrhosis has been attributed to intestinal bacterial overgrowth (21, 22), increased intestinal permeability (47) as well as a defect in host immunity (128, 318). Intestinal bacterial overgrowth has been indicated to be due to small intestinal dysmotility and prolonged intestinal transit time (51) related at least partly to enhanced adrenergic sympathetic nerve activity in cirrhosis (226). As for mucosal barrier dysfunction oxidative damage (237) as well as increased serum levels of nitric oxide and endotoxins (120) both known to disrupt the epithelial barrier may contribute. Moreover, decreased secretory IgA levels have been observed (250) easing bacterial attachment to the mucosa and hence penetration. Finally, host immune response is impaired in liver cirrhosis by decreased reticuloendothelial phagocytic activity, deficiencies in serum immunoglobulins, complement and qualitative neutrophil function (99, 234, 243, 318). For instance, cirrhotic patients with lower serum complement (C3 and C4) levels have been considered prone to develop SBP (284). Moreover, impaired tuftsin activity, known to modulate biological activities of phagocytic cells, is reduced in cirrhotic patients and is associated with a higher incidence of bacterial infections (287).

In animal models, starvation and malnutrition as well as total parenteral nutrition (TPN) promotes bacterial overgrowth, diminishes intestinal mucin production, decreases global gut IgA levels, causes mucosal atrophy increasing intestinal permeability, attenuates the T and B lymphocyte cell number and function in Peyer Patches and lamina propria and accelerates oxidative stress (9, 75, 199). Therefore, it appears that lack of enteral

feeding profoundly affects the cellular and immunological status designed to protect the host from BT. In fact, also in malnourished patients significant increases in intestinal permeability in association with a heightened acute phase response has been evidenced (308). In this context of nutrition, alcohol intake has been associated with deterioration of humoral and cellular components of GALT-function, namely decreased phagocytic function of macrophages (194), decreased natural killer activity (186), reduction in numbers of polymorphnuclear leukocytes, T cells and B cells (301) and attenuation of mitochondrial antioxidant glutathion (147) as well as decreases in mucosal IgA transcytosis (82). Therefore, not surprisingly alcohol consumption has been shown to increase intestinal permeability resulting in increased portal levels of endotoxins in animal models and patients with alcoholic liver disease (35, 180, 218). This indeed may explain why selective gut decontamination almost completely protects animals from liver injury due to alcohol exposure/intake (268).

The association of hematological malignancies with bacterial infections is well-known and is represented by > 50% of febrile episodes most likely being caused by common enteric residential organisms (36). Moreover, a strong correlation seems to exist between granulocytopenia and bacteraemia caused by *Enterobacteriaceae* and *Pseudomonas*. Indeed, characterization of those bacteria by antibiotypic, biotypic and serotypic parameters evidenced concordance with strain isolates from faeces indicating that the blood-borne strains originate from the patients gastrointestinal tract (286). Accordingly, an increase in bowel permeability has been observed after bone-marrow transplantation peaking at 1-2 weeks after transplantation and normalizing by 4 weeks (97). Moreover, divers drugs (e.g. colchicine, cyclosporine) may alter intestinal permeability (10, 189). In this respect, particularly chemotherapeutic agents have been shown to impair mucosal barrier not only in patients with hematological malignancies and bone marrow transplantation but also solid tumors (97, 148). In summary, BT may represent a common and so far inadequately recognized trigger for a multitude of complications known for long in various clinical entities.

THERAPY

Three broad approaches are used to prevent or treat BT which are directed against the three main mechanisms promoting BT and hence are manipulations of the intestinal microflora, protection of the gut mucosa

barriere and immunomodulatory efforts.

As for the first, the most attractive and consequent therapy aiming at prevention of BT is selective gut decontamination (SDD). Major targets of SDD performed typically with tobramycin, polymyxin E, amphotericin or cefotaxim are *Enterobacter*, *Pseudomonas*, *Acetobacter* and yeast. The whole issue in respect to its use in the intensive care unit (ICU) treating critical ill patients is still under review. Although several previous large-scale clinical trials failed to demonstrate a significant survival benefit, current meta-analyses challenged that conclusion. An unusual and provocative review of 53 randomized trials and 6 meta-analysis involving more than 8500 ICU patients clearly evidenced significant reductions in the rate of pneumonia and also mortality (66, 196, 295). In addition a most recent prospective controlled (but unblinded) trial randomized 934 ICU patients to either oral and enteral polymyxin E, tobramycin and amphotericin B combined with an initial 4 day intravenous cefotaxime (as SDD) or to standard therapy. The use of SDD led to a significant reduction in ICU and hospital mortality (68). Particularly colonization with gram-negative bacteria was reduced in SDD patients. Despite these encouraging and valid evidences SDD is used only rarely, in the UK in only 4% of ICU's. Most likely this reflects the frequently practiced basis of treatment that opinion prevails over evidence, driven additionally by pharmaceutical industry pressure to promote expensive systemic antibiotic use at the time of infection rather than using cheap and effective but difficult to administer prophylactic SDD. Nonetheless, in special entities systemic and/or topical antibiotics are used more frequently such as acute-necrotizing pancreatitis or liver cirrhosis. SDD has been shown to reduce the incidence of secondary pancreatic infection and, in those with a high expected mortality, to improve survival (167). A recent meta-analysis of three randomized-controlled trials comparing antibiotic prophylaxis with no prophylaxis in patients with acute-necrotizing pancreatitis revealed that antibiotic prophylaxis significantly reduced the rate of sepsis and mortality as compared to controls (196, 269). Moreover, SDD has been used in patients undergoing liver transplantation and is routinely used in patients undergoing intestine and bone marrow transplantation (92). This is based on the well-known high incidence of serious postoperative bacterial infections and the intensive immunosuppression in those patients. Furthermore, prophylactic usefulness of SDD has been evidenced to decrease the rate of SBP and to improve

Table 2. Examples of therapeutic approaches in prevention of BT (modified after Wiest et al. (311)).

Therapy	Disease/ Model	References
Enteral nutrition	Surgical patients	(190)
Immunonutrition/ fiber	Severly injured patients	(157, 280)
Immunoglobulin A	Formula-fed neonatal rabbits/ low-birth-weight infants	(81, 83, 89)
Fish-oil	TPN/ Low endotoxin	(232)
Prostacyclin/ prostaglandin E	Low-dose endotoxin in cat Burn injury in mice	(78) (102)
Ornithine- α ketoglutarate	Endotoxin / Small bowel transplant in rat	(69, 263)
Lactulose	Obstructive jaundice, portal hypertension, surgery	(94, 214, 215)
Lactobacillus/ probiotics	Liver injury, short bowel, enterocolitis in rat	(1, 90, 175)
Hyperbaric oxygen	Intestinal obstruction, obstructive jaundice, LPS in rat	(2, 3)
Polymyxin /anti-endotoxin	Septic/ burned patients	(15, 195325)
BPI	Endotoxemia/ hemorrhagic shock in rats Meningococcal sepsis/ trauma patients	(154, 321) (77, 116)
Neutrophil depletion	Thermal injury in rats	(96)
Anti-L-selectin	Hemorrhagic shock in baboons	(262)
Xanthine oxidase inhibition	Hemorrhagic/ portal hypertensive rats	(260)
C1-inhibitor	Thermal injury in pigs	(236)
IL-6	Hemorrhagic shock in mice	(244)
IL-11	Burn injury mice, leukemia-chemotherapy patients	(91, 261)
ACE-inhibition (enalapril)	Thermal injury mice	(110)
Angiotensin-II-inhibitor DuP753	Thermal injury / endotoxin in minipigs	(285)
Preferential iNOS-inhibition	Thermal injury/ endotoxemia in rat	(54, 289)
NOX (NO-scavenger)	Endotoxemia in rat	(80)
Cholylsarcosine (conj. bile acid)	Liver cirrhosis, in rat	(166)
Glucagon-like peptide 2	Acute necrot. Pancreatitis in rat	(155)
Growth hormone, IGF-1	Acute necrotizing pancreatitis, TPN, sepsis, irradiation, burn injury, etc.	(7, 104, 135, 264, 299)
SDD	Critical ill, pancreatitis, liver-,bone marrow transplant-, cirrhotic patients	(31, 92, 149, 167, 242, 266)

Note: We apologize that, due to limitation of references being allowed to be cited only examples are given and the list of references is far from being complete.

survival in cirrhotic patients with gastrointestinal hemorrhage known to be at high risk of developing severe bacterial infections (31). Finally, due to the excessive risk of recurrence of SBP secondary prophylaxis is recommended in any cirrhotic patient recovering from an episode of SBP (242). The recommended first choice antibiotics in cirrhotics are quinolones, usually norfloxacin due to its simple administration and low cost.

Another approach to manipulate intestinal microflora is by using probiotics such as lactobacilli. Lactobacilli constitute an integral part of the normal gastrointestinal microecology and may play an important role in the preservation of the natural biological equilibrium of the intestinal tract and the growth modulation of other groups of bacteria (98). The oral administration of lactobacilli induces changes in intestinal environmental factors including increased formation of short chain fatty acids and reduction of colonic pH which promotes the growth of gram positive and anaerobic bacteria, thereby

inhibiting the growth of gram-negative bacteria (105, 141, 252). However, Lactobacilli show many other additional nutritional and protective benefits such as: induction of growth factors (118), maintenance of gastrointestinal epithelial proliferation and function (117), removal of toxins, inhibition of adherence and invasion of enterovirulent bacteria to human intestinal cell lines (32), enhancement of intestinal IgA secretion and host resistance against infection through an increase in global phagocytic activity, as well as the induction of interferon and cytokine production and an increase in killer cells and T lymphocytes (220–225, 275). This battery of effects have been shown to inhibit translocation of *E. coli* in an in-vitro human colonic cell culture and to attenuate BT in experimental models of acute liver injury, enterocolitis, short bowel syndrome and others (1, 90, 175, 182). In humans, probiotics have been tested in a number of gastrointestinal diseases and beneficial effects have been evidenced in inflammatory bowel disease, chronic pouchitis and diarrheal diseases,

particularly in children, postantibiotic as well as clostridial or rotaviral enterocolitis (for review (101)). However, direct evidence for probiotics lowering BT in patients suffering from any of these conditions is lacking.

As for measures to protect the gut mucosa barrier multiple enteral manoeuvres have been tested. Oral supplementation with IgA completely abrogated BT in formula-fed neonatal rabbits by enhancing the gut mucosal barrier (81). Similar results as well as a decrease in translocation to liver and spleen in neonatal gut-derived sepsis has been observed after enteral IgA-supplementation by Maxson et al. (183). Moreover, feeding a combination of IgA and IgG prevented necrotizing enterocolitis in low-birth-weight infants (89). One of the suggested mechanisms by which IgA is mediating these benefits are oligosaccharide receptors for *E. coli* type 1 fimbrial lectin. IgA possesses high mannose type N-linked side chains effectively agglutinating and binding *E. coli* inhibiting its epithelial adherence (314, 315). Addition of fiber or glutamine to enteral or parenteral diet, both supposed to be trophic for the mucosa of ileum and colon, has been shown to ameliorate alterations in gut barrier function (280). Results of therapeutic use of glutamine in humans at nonphysiological doses however, indicate limited efficacy and although it is generally recognized to be safe side effects have been reported. Thus, its use in clinical practice is controversial (46). The administration of ornithin- α -ketoglutarate (OKG) has also been shown to exert beneficial effects on intestinal structure and to function as well as on cellular immunity. OKG is a salt formed from two molecules of ketoglutarate and one ornithin which are absorbed in the jejunum and after dissociation release glutamate, arginine and proline. OKG-supplemented diet has been demonstrated to limit bacterial dissemination after endotoxin challenge and to reduce BT after small-bowel transplantation in rats (69, 263). Modulation of the fatty-acid composition by fish-oil-enriched diets has been shown to preserve intestinal blood flow and to enhance host's ability to kill translocated bacteria in various experimental models (113, 232). Fish-oil contains precursors of the less inflammatory leukotrienes of the 5-series and favors formation of prostaglandins of the 3-series which have been reported to reverse endotoxin-induced intestinal vasoconstriction, enhance mucus secretion and down-regulate TNF-synthesis (78). Moreover, it has been demonstrated that prostaglandin E analogues reduce the number of translocating bacteria being associated with improved survival in experimental thermal injury (102).

Several growth-factors (GF) have been shown to be

effective in preventing mucosal damage to divers injurious events. Growth hormone is known to exert multiple effects including increases in intestinal absorption of amino acids, promotion of protein synthesis causing hyperplasia of intestinal epithelial cells and to increase the thickness of the mucosal membrane as well as secretory IgA release. In a combined sepsis/TPN-animal model as well as in irradiated rats prophylactic treatment with growth hormone has been shown to alleviate damage to intestinal barrier function and to reduce BT (84, 292). In a rat model of acute necrotizing pancreatitis growth hormone reduced the severity of injury in the ileum, improved intestinal mucosal barrier function, decreased endotoxin levels and lowered the incidence of BT and improving survival (299). It has been suggested that growth hormone mediated effects may depend largely on the associated hepatic and gastrointestinal production of insulin-like-growth-factor-1 (IGF-1). In fact, for instance in radiation enteritis even small doses of IGF-1 could reproduce the effects of growth hormone and in some parameters the effects were more pronounced (7). Similar beneficial effects for growth hormone as well as IGF-1 have been reported in animal models of obstructive jaundice (264), severe burn injury (104, 135) and small intestinal transplantation (324). Whether the same holds true in human patients needs to be answered. Other agents awaiting further assessment after individual reports on lowering BT include glucagon-like peptide-2 (GLP-2) (50, 155), granulocyte-macrophage colony-stimulating factor (GM-CSF) (88, 111), epidermal growth factor (EGF) (52, 185), bombesin (53, 127), neurotensin (291) or peptide YY.

IL-11 is a multifactorial bone marrow stromal-derived GF whose major effect is proliferation of megakaryocyte progenitor cells, preventing chemotherapy-induced thrombocytopenia. Recombinant IL-11 also protects enterocytes from toxic injury. In an experimental *P. aeruginosa* model, rhIL-11 supported intestinal mucosal integrity, reduced bacteraemia/endotoxemia and increased survival (211). In a recent double-blind placebo-controlled randomised trial in human leukaemia subjects undergoing chemotherapy rhIL-11 reduced significantly the frequency and load of bacteraemia of gastrointestinal origin and preserved enterocyte integrity (91). RhIL-11, administered orally as enteric-coated multiparticulate pellets, providing local release, is also effective (212). IL-6 orally has likewise been demonstrated to reduce the number of translocating bacteria to MLN, liver and spleen during hemorrhagic shock in mice and to prevent histological changes in the

intestine induced by hemorrhagic shock (244). In contrast, IL-6 has been suggested by others to play an essential role in mediating gut mucosal permeability and BT as a consequence of haemorrhagic shock and resuscitation as demonstrated in IL-6 knock out mice (320). Therefore, its role remains controversial.

Increased infiltration of neutrophils promotes BT and hence, interference with neutrophil function or adhesion decreases mucosal injury. Neutrophil depletion has been shown to reduce BT in a model of thermal injury in rats (96) and to improve survival time in a hemorrhagic-traumatic shock model (262). A recent randomized prospective double-blind and placebo-controlled trial showed that inhibition of leukocyte adherence by administration of monoclonal antibody directed against ICAM-1 improves wound healing without increasing infectious complications indicating the potential use of such an approach (187, 188). Moreover, the role of reactive oxygen species derived, for instance from activated neutrophils, is supported by the utility of free-oxygen radical scavengers or inhibitors of xanthine oxidase which increase cellular energy stores, decrease mucosal injury and reduce the incidence of BT in various animal models (72, 73, 298). In this context, *NOX*, a NO scavenger, also significantly reduced transmucosal passage of bacteria and hence, the incidence of BT and bacteremia after high dose endotoxin challenge in rats (80). This has been attributed to a reduction in peroxynitrite formation known to induce DNA strand breaks, activating the poly(ADP)-ribose synthetase system and causing ATP-depletion.

Finally, approaches aiming at enhancing immunological defense mechanisms against BT have been multiple. Hyperbaric delivery of hyperoxia (HBO2) has been reported to reduce BT in experimental models of intestinal obstruction, burn injury, endotoxemia systemic inflammation and obstructive jaundice (2, 3, 112, 235, 251). HBO2 has multiple biochemical and physiological tissue and antibacterial effects including enhancing tissue repair, angiogenesis, optimizing tissue oxygenation, bacteriostasis and enhancing host defenses. For instance, HBO2 exerts bacteriostatic effects on some strains of *E.coli*, preventing bacterial overgrowth. Moreover, it increases killing capacity of phagocytes and neutrophils - which require molecular oxygen as a substrate for microbial killing. Finally, it has been demonstrated to attenuate mucosal nuclear factor- κ B activation and thus, lowering iNOS-derived NO overproduction as well myeloperoxidase activity (251). This dramatic benefit of HBO2 has been reported to be synergistic with that of IgA in reducing BT (83). HBO2 has been used

successfully in individual cases of haemorrhagic shock in patients who refused blood on religious grounds (160). However, randomized-controlled trials and hence, clinical evidence for its use in critical illness are yet absent.

The therapeutic use of anti-endotoxin antibodies has been reported to reduce mortality in patients with gram-negative sepsis (325) but these results have been criticized and could not be confirmed (310). However, the use of monoclonal antibody to endotoxin was evidenced to result in greater resolution of organ failure and prevention of adult respiratory distress syndrome in patients with gram-negative sepsis (39). Moreover, the use of endotoxin neutralizing peptides such as polymyxin has been shown to reduce endotoxin levels in burn patients without effect on mortality (195). This lack of effect has been attributed to the fact that although the antibodies bound to endotoxin they did not neutralize its toxic effect completely (40, 300). In addition, "immunoparalysis" as compensatory anti-inflammatory response to the systemic appearance of inflammatory mediators may be excessive in some patients causing immunosuppression that hinders the effect of antibodies against endotoxin. A physiological protein with potent anti-endotoxin properties is bactericidal/permeability increasing protein (BPI), found in granulas of neutrophils. BPI binds to, neutralizes and accelerates clearance of LPS, suppresses endotoxin-mediated cellular activation and also exhibits antibacterial properties specifically against gram-negative bacteria. rBPI has been shown to protect against endogenous bacteria or endotoxin-related disorders in experimental models of severe hemorrhagic shock or thermal injury improving survival (95, 321). It has likewise been used safely and efficiently in children with meningococemia (115, 116) and has demonstrated a favourable trend in reducing mortality or serious complications in patients with hemorrhage due to trauma (77). These promising results need further validation and confirmation by larger randomized controlled trials.

In summary, despite promising results for treatment and prevention of BT in experimental studies the heterogenous nature of human patients, diversity of clinical endpoints and result interpretation, wide range of perceptions and priorities has hindered the clarity of expert opinion in this arena. The only way to battle these shortcomings is to perform corresponding randomized controlled clinical trials in well-defined patient cohorts evaluating such treatment strategies.

The authors regret that, due to space limitations, it was not possible to cite all of the many contributions by

investigators who have advanced understanding in this area. Parts of the following manuscript have been published previously in Baillieres Best Clinical Practice North America (311).

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