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Bacterial translocation in the gut

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The human gastrointestinal tract is colonized by a dense population of microorganisms, referred to as the bacterial flora. Although the gut provides a functional barrier between these organisms and the host, bacterial translocation is a common event in the healthy person. However, in critically ill patients, with various underlying diseases, this bacterial translocation may lead to infections and consequently to a further reduction in general health status. The mechanism of bacterial translocation is widely, and somehow controversially investigated in vitro and in animal models. In human studies, several diseases have been associated with bacterial translocation. However, methodological shortcomings, insufficient populations and conflicting results leave many open questions. This is also reflected in the various published therapeutic strategies. To overcome this problem more investigations in humans are needed, especially in techniques for detecting bacterial translocation.

Key words: intestinal bacteria; bacterial translocation; bacterial overgrowth; intestinal permeability; barrier dysfunction; nitric oxide; mucosal hypoxia; mucosal acidosis; thermal injury; trauma; liver cirrhosis.

The bacteria which initially colonize the gastrointestinal tract in the newborn come from the mother's intestinal flora, which is present in traces in the birth canal. The development of this flora depends on food supplementation in the first months of life. Eventually, the bacterial flora develops into a large autochthonous part and a small transient part. Environmental factors, such as the composition of the food and the luminal pH, influence the transient part. The autochthonous part, however, is relatively stable throughout life.

The microflora of the large intestine is the best examined, most dense, and most complex part of the gut microflora. There are up to 10^{12} colony-forming units (c.f.u.) per gram of stool (dry weight), with up to 350 different species—almost exclusively autochthonous bacteria. Obligate anaerobes form up to 99% of the viable bacteria. The most common species are those of the genera *Bacteroides*, *Peptostreptococcus*, *Bifidobacterium*, *Clostridium*, *Lactobacillus*, *Eubacterium* and *Fusobacterium*.

The term bacterial translocation (BT) was first coined by Berg and Garlington[1], and was later defined as the passage of both viable and non-viable microbes and microbial products, such as endotoxin, from the intestinal lumen through the epithelial mucosa

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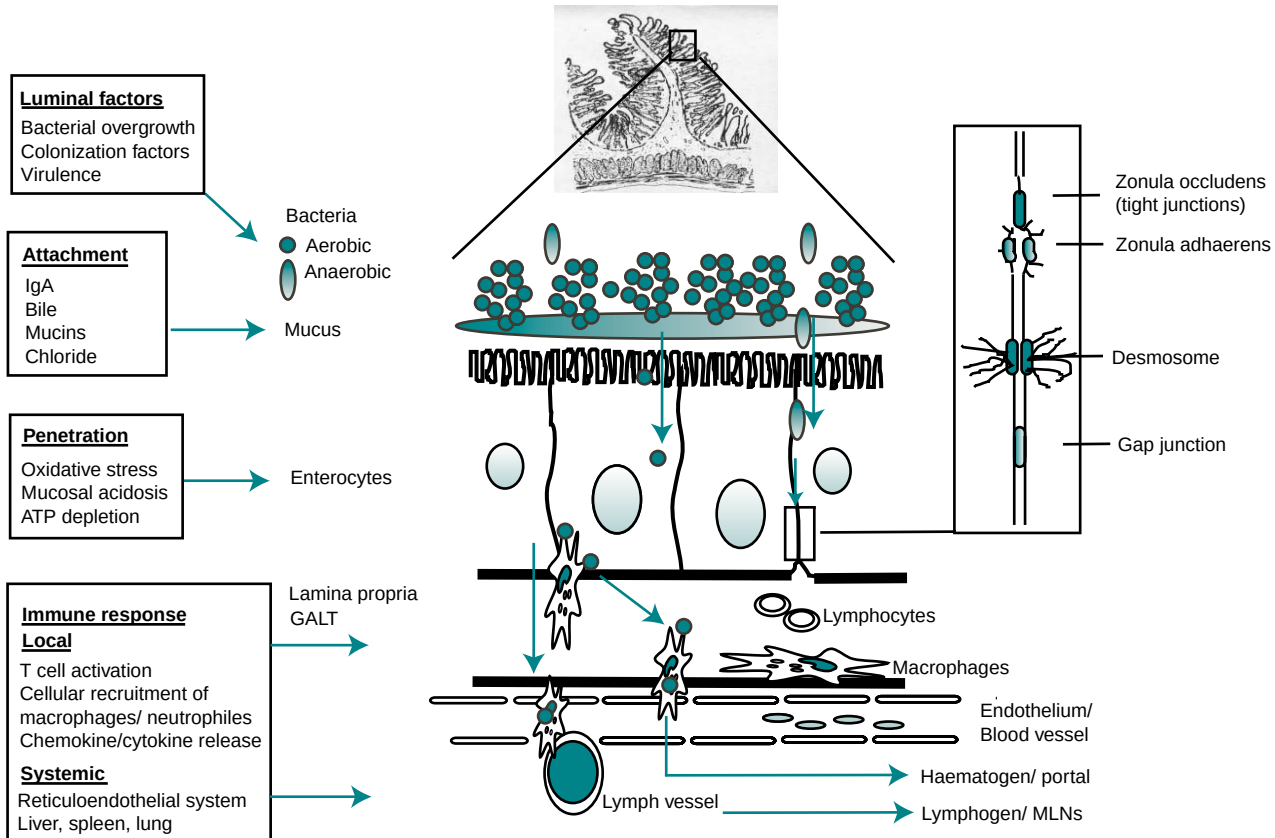

Figure 1. Mechanisms and components involved in the process of BT. Parameters which increase the rate of BT can be divided anatomically and functionally. *Luminal factors* influence the number and grade of virulence of bacteria that translocate easily. Parameters interfering with the *attachment* of bacteria and causing epithelial damage ease the *penetration* of the intestinal mucosa. Finally, the *local and systemic immune response* determines host defence against BT.

into the mesenteric lymph nodes (MLNs) and possibly other organs. Such translocation is the key to our understanding of spontaneous bacterial peritonitis (SBP) in liver cirrhosis, and it may contribute to the development of the multiorgan failure syndrome induced by haemorrhagic shock, burns or sepsis; it is also involved in diverse gastrointestinal disorders such as malnutrition, intestinal obstruction and biliary obstruction, all of which promote BT.

MECHANISMS OF BACTERIAL TRANSLOCATION

The principal mechanisms involved in promoting BT are (a) an alteration in the normal gastrointestinal microflora, resulting in bacterial overgrowth; (b) physical disruption of the gut mucosal barrier, for example, by direct injury to the enterocytes (e.g. by radiation or toxins) or by reduced blood flow to the intestine, and (c) an impaired host defence (Figure 1).

The phenomenon of BT has been studied extensively in animal models (Table 1). The endpoint most commonly used to prove and quantify BT involves enumeration of culturable organisms in the MLNs. However, data using radioactively labelled bacteria indicate that this technique vastly underestimates the extent of translocation because most microbes which breach the epithelial barrier are killed.[2] Increases in BT, demonstrated by increases in colony-forming units in the MLNs, are predominantly due

Table 1. Animal models of BT.

Model	Animal	Reference
Burn injury	Mouse, pig	133,165
Haemorrhagic shock	Rat	157,166
Intestinal ischaemia	Rat	167
Intestinal obstruction	Rat	168
Small bowel bacterial overgrowth	Rat	169
Acute liver injury	Rat	170
Liver cirrhosis	Rat	104,105
Pre-hepatic portal hypertension	Rat	171
Jaundice	Rat	27,94
Hepatopulmonary syndrome	Rat	92
Acute pancreatitis	Rat	172
Total parenteral nutrition	Rat	66,120
Protein malnutrition	Mouse	173
Small-bowel transplantation	Rat	174
Graft-versus-Host-disease	Rat	175
Chemotherapeutic agents	Mouse	37
Oral antibiotics	Mouse	11
Clostridium difficile	Mouse	176
Small bowel syndrome	Rat	177
Lectin-induced diarrhoea	Rat	178
Sleep deprivation	Rat	179
Low-dose endotoxin	Mouse	180

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to a decrease in killing rather than an increase in transepithelial penetration. 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 endotoxin in peripheral blood. However, in animal studies bacteria are rarely cultured from peripheral blood; this finding is most likely due to the defence mechanisms of the liver and lungs—in which microorganisms are eliminated by tissue macrophages. Recently, methods involving the 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.[3] Such methods could possibly improve the accuracy of detecting BT but they have not been used adequately in clinical practice.

Intestinal permeability can be assessed by a variety of techniques.[4] 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; this provides a specific index of intestinal permeability.

Bacterial overgrowth

The intestinal tract is a dynamic milieu of interdependent phenomena, each of which may directly or indirectly influence the translocation of intestinal particles. The bacteria which 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 which are also able to resist phagocytic killing (e.g. *Salmonella* species). In contrast, normal enteric species are easily killed after phagocytosis, surviving only under circumstances in which host defences are impaired. Only a few types of intestinal bacteria are able to translocate into MLNs; these include *Escherichia coli*, *Klebsiella pneumoniae*, other enterobacteraceae, *Pseudomonas aeruginosa*, enterococci and some streptococci.[5] Interestingly, these species are most frequently associated with complicating infections in severely ill, hospitalized patients.

Recently, it has been shown that the capacity for translocation is greater in specific strains; in these strains, such capacity has been attributed to better adherence and facilitated attachment to the mucus–epithelium layer—as compared to non-pathogenic strains.[6] In general, adhesins have been shown to be associated with the fimbriae of enteric bacilli. In volunteers, these fimbriated surface structures (so-called colonization factors)—found, for example, in *E. coli*—have been shown to be needed for intestinal multiplication, clinical illness and the production of antibodies.[7] Moreover, differences in virulence among strains, together with the level of resistance in the host, are factors which determine the survival and spread of the more virulent strains.[8]

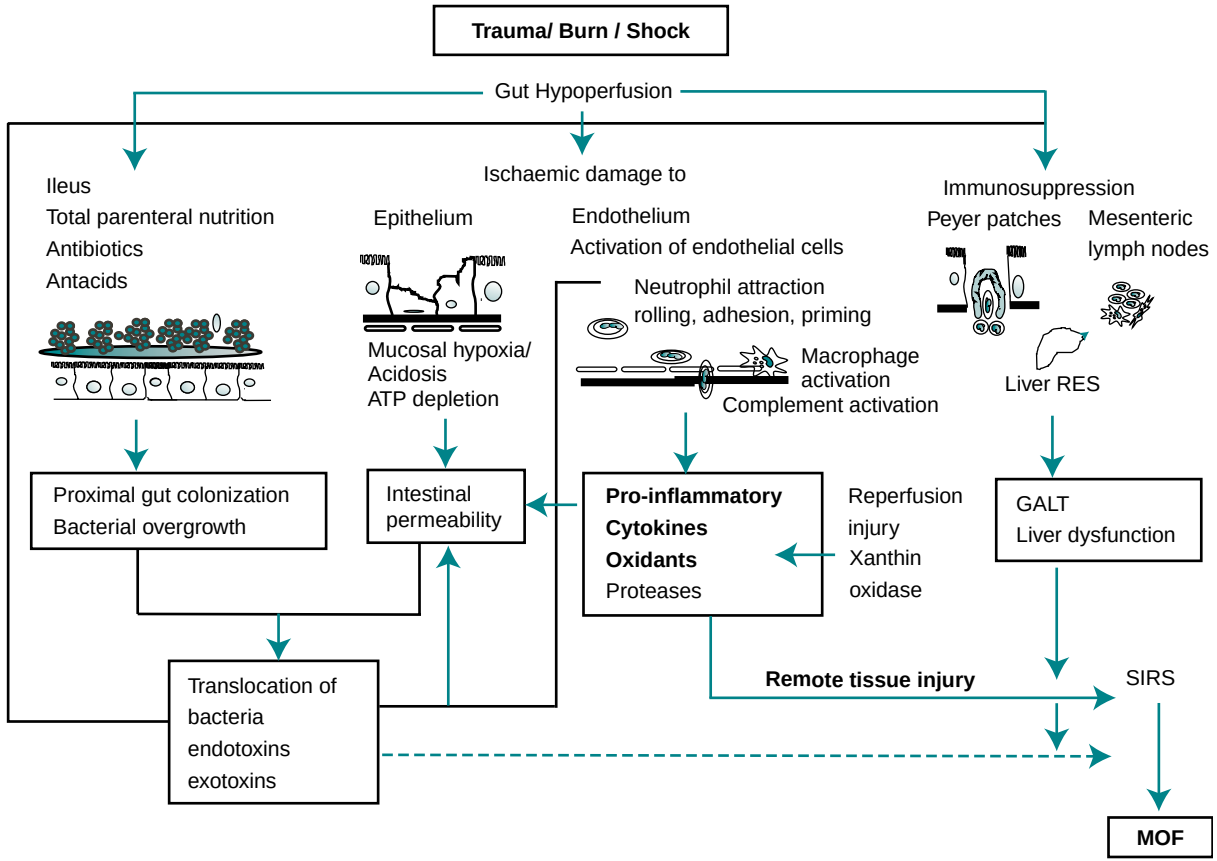
Although intestinal anaerobic bacteria outnumber aerobic bacteria by 100:1 to 1000:1, translocation of anaerobic bacteria has been reported only in extreme circumstances such as athymic[9], lethally irradiated[10] or severely burned rodents.[5] In nearly all of these conditions there are breaks in enteric integrity, and anaerobic bacteria appear to translocate in direct proportion to the degree of tissue damage. Thus, in contrast to the aerobic Gram-negative bacilli that translocate easily—even across histologically intact intestinal epithelium[5,11]—anaerobic bacteria seem to translocate in situations in which the intestinal tract is structurally damaged. Moreover, anaerobic bacteria act as a carpet on the mucosal surface, limiting colonization and overgrowth of other potentially invasive microbes.[11] In fact, selective elimination of anaerobic bacteria facilitates intestinal overgrowth and the translocation of facultative bacteria.[11] This has led to the assumption that bacterial overgrowth is one of the main

factors promoting BT. There is a direct correlation between the density of a given strain of luminal bacteria and the numbers of viable bacteria of this strain which are present in MLNs.[12] In this context, it is important to differentiate between luminal bacteria and bacteria attached to the mucosal surface. Although the levels of luminal bacteria are clearly important in the development of infections in situations of bowel injury or perforation, the levels of mucosally adherent bacteria are likely to be more important in the development of BT.[13] Factors reported to promote bacterial overgrowth are reduced gastric acidity[14], impaired gastrointestinal motility and, consequently, prolonged intestinal transit time.[15]

Barrier dysfunction

The host defence directed against invasion of microbes from the gut consists of numerous local factors, such as mucus, gastric acid, pancreatic enzymes, bile, the epithelial cell barrier with its intracellular junctions, and bowel motility. *Mucins*, secreted by epithelial goblet cells in copious amounts (3 l/day), create a protective viscous gel that hampers bacterial penetration.[16] Mucus also 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. 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).[17] The absence of *bile* in the intestine has been shown to facilitate BT[18], and exposure to bile during bacterial growth decreased epithelial internalization of enteric bacteria.[19] All of these mechanisms help to prevent attachment of bacteria to the epithelium—an event that has been proposed as an important first step in epithelial penetration. The most critical barrier against uptake of intraluminal microbes/microbial products, however, is the *epithelium* per se. Structurally, the intestine comprises a single-layered columnar epithelium arranged into villus and crypt components. Specialized cell–cell junctional complexes allow for selective paracellular permeability (tight junctions), maintain intercellular adhesion (intermediate junctions and desmosomes) and permit intercellular communication (gap junctions). The zonula occludens is a circumferential band of atypical tight junctions that limit paracellular passage of ions and fluid. Normally, tight junctions exclude passive movement of hydrophilic non-charged compounds with a molecular size >11.5 Å, thus preventing for example, transepithelial movement of bacteria and also macromolecules such as lipopolysaccharides (LPS), peptidoglycan–polysaccharides, etc. For the most part, translocation occurs transcellularly and directly, even through morphologically intact enterocytes, rather than paracellularly between enterocytes.[2]

Mucosal atrophy, particularly as a consequence of luminal nutrient deprivation, has been suggested as a predisposing factor for BT. However, several experimental models of BT could not convincingly demonstrate that morphological changes cause intestinal hyperpermeability and/or BT.[20] Moreover, in humans, this parameter is hard to obtain, but Sedman et al failed to demonstrate a significant difference in villus height of small bowel biopsies between patients with and without BT.[21] Finally, in a mixed population of gastroenterological patients, the index of villus atrophy was found not to correlate with intestinal permeability.[22] Nonetheless, increased intestinal permeability has been demonstrated in patients with burns[23], following cardiopulmonary bypass[24], elective or emergency major vascular surgery[25], haemorrhagic shock[26], jaundice[27],


Trauma/ Burn / Shock
Gut Hypoperfusion
Ileus
Total parenteral nutrition
Antibiotics
Antacids
Ischaemic damage to
Epithelium
Endothelium
Activation of endothelial cells
Mucosal hypoxia/
Acidosis
ATP depletion
Neutrophil attraction
rolling, adhesion, priming
Macrophage
activation
Complement activation
Immunosuppression
Peyer patches
Mesenteric
lymph nodes
Liver RES
Proximal gut colonization
Bacterial overgrowth
Intestinal
permeability
Pro-inflammatory
Cytokines
Oxidants
Proteases
Reperfusion
injury
Xanthin
oxidase
GALT
Liver dysfunction
Translocation of
bacteria
endotoxins
exotoxins
Remote tissue injury
SIRS
MOF

indomethacin[28], parenteral endotoxin[29], and malnourishment[30] as well as in trauma and intensive-care patients.[31,32]

Mucosal hypoxia and acidosis

The oxygen tension at the tip of the intestinal villus is much lower than it is in arterial blood, even under normal conditions; consequently, the susceptibility of the epithelium to hypoxic injury is increased. Any reduction in blood flow aggravates these conditions, and epithelial cell injury may readily develop when the oxygenation of tissues is diminished. During intestinal ischaemia a strong correlation between the degree of mucosal acidosis and the degree of ileal mucosal hyperpermeability has been observed.[33] On the other hand, mucosal acidosis induced by deliberately increasing arterial carbon dioxide tension leads to substantial increases in epithelial permeability even in the absence of mucosal ischaemia.[33] This indicates that acidosis *per se* promotes epithelial hyperpermeability, which has been suggested to be due to oxidative stress. Oxidants, such as hydrogen peroxide or superoxide radical, have been shown to disrupt the cytoskeleton and to increase epithelial permeability.[34] Moreover, reactive oxygen metabolites can lead to depletion of ATP, a condition which is well known to increase epithelial permeability.[35] In thermal injury, as well as in trauma/haemorrhagic, cardiogenic or endotoxaemic shock, there is diminished blood flow to the mucosa and submucosa of the jejunum, ileum and colon, whereas flow to other organs is preserved. Moreover, the development of gastrointestinal mucosal acidosis has been demonstrated in these conditions. Therefore, ischaemia-induced epithelial injury in the gut is a pathway common to shock, trauma and thermal injury, and this pathway may lead to dysfunction of the gut barrier and set the stage for BT (Figure 2).

Figure 2. BT in relation to the pathophysiology of multiorgan failure (MOF). Gut hypoperfusion often leads to *bacterial overgrowth* via different mechanisms: ileus is known to promote proximal gut colonization. Standard therapies, such as antacids, total parenteral nutrition, antibiotics, morphine, etc. further promote colonization. Ischaemic damage to the epithelium *increases mucosal permeability*: inadequate intracellular PO_2 can result from hypoperfusion, anaemia, arterial hypoxaemia and/or hypermetabolism secondary to critical illness, limiting mitochondrial respiration. Subsequent mucosal acidosis and ATP depletion cause epithelial damage. Bacterial overgrowth and gut barrier dysfunction both contribute to the process of BT. The pathophysiological hallmark in the pathogenesis of 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 (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 xanthine oxidase (in endothelial cells and neutrophils). Activation and stimulation of macrophages results in further cytokine release. Thereby, the gut becomes a 'cytokine-releasing organ' causing tissue injury in remote organs. Shock has been shown to depress lymphocytic and macrophage-mediated functional capacities, leading to *immunosuppression*: BT/endotoxins per se suppress non-specific and specific immune function via GALT (stimulation of suppressor T-cells migrating to systemic lymphoid organs), via the 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 defence capacity), and via the 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.

Immune status

Because it has been noted that intestinal bacteria cause systemic disease in immuncompromised patients, it has been logical to assume that immune dysfunction is a primary factor promoting BT.[36] The intestinal tract is an active immune organ, containing essentially every type of leukocyte involved in the 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 the mucosal cell mass. 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.

The reader should not be left with the impression that BT always has to be considered as a negative aspect of biology, being linked intellectually and unequivocally to systemic disease. BT occurs in the normal host, as can be shown by recovery of viable intestinal bacteria from MLNs in a small proportion of healthy animals and humans.[21,37,38] Moreover, it is likely that dead bacteria also translocate as a normal biological process. After being sensitized, antigen-presenting cells and immature immune cells of the GALT have been noted to leave the intestinal tract, migrate through the thoracic duct, participate in systemic immunity and preferentially seed the intestinal mucosa as mature T and B cells. 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 make contact with the intestinal epithelium.

Owens and Berg noted spontaneous BT of certain indigenous bacteria, such as *E. coli*, to MLNs, spleen and liver in athymic (nu/nu) mice, whereas no translocation was noted in heterozygous (nu/ +) or nude mice grafted with thymus.[9] Moreover, T-cell depletion not only caused accumulation of bacteria in the MLNs of healthy rats but also increased the bacterial numbers observed in the MLNs of alcohol- and burn-injured rats and caused spreading of bacteria to extra-intestinal sites.[20] Therefore, it appears that appropriate activation of intestinal T cells is critical in maintaining immunity against the translocation of enteric bacteria. Additional studies showed the ability of adoptively transferred T cells to confer protection against a number of bacterial infections, including *E. coli*.[39] Mechanisms by which T cells help to maintain humoral immunity may include T-cell-dependent antibody production and the production of chemokines/cytokines which recruit and activate macrophages and neutrophils.

It has been reported that immunosuppression coupled with intestinal bacterial overgrowth (induced by oral penicillin G) synergistically promoted BT in mice with an intact, histologically normal intestinal tract.[40] Usually, enteric bacteria induced to translocate by oral antibiotics remain confined to the MLNs and do not appear to establish a persistent infection in the MLNs because the MLNs return to a sterile state when the antibiotic is discontinued and the caecal population of enteric organisms returns to normal levels.[41,42] Immunosuppression, however, can allow the translocating bacteria to spread systemically, ultimately resulting in lethal sepsis.[40] Therefore, it becomes apparent that, for BT to become clinically significant, a failure of local and/or systemic immune defence must also occur.

Nitric oxide (NO)

NO is synthesized by three different isoforms of NO synthase (NOS), of which the endothelial (eNOS) and neuronal (nNOS) isoforms constitutively produce low levels of NO. In contrast, the inducible isoform (iNOS) is synthesized de novo only after

stimulation by LPS, endotoxins and pro-inflammatory cytokines, and it releases NO in large amounts. Many types of cells in the gut are potential sources of NO; they include vascular endothelial cells, myenteric neurons, inflammatory cells in the submucosa (macrophages, polymorphonuclear leukocytes) and enterocytes. NO participates in many physiological and pathophysiological processes in the gut (Figure 3).[43] NO increases gastrointestinal mucus secretion, modulates epithelial chloride transport and associated fluid secretion, maintains blood flow, inhibits intestinal muscular motor activity, reduces mast cell reactivity and mediator release, suppresses neutrophil aggregation and sequestration, scavenges reactive oxygen metabolites and is an important modulator of mucosal repair. All of these mechanisms are involved in maintaining gut barrier function. Depending on the experimental system employed, and the local concentrations of NO achieved, NO has been shown to modulate intestinal permeability and BT in different ways and directions.

Non-specific inhibition of NO synthesis resulted in increased ileal epithelial permeability[44], and the administration of an NO donor ameliorated gut mucosal hyperpermeability induced by ischaemia-reperfusion or endotoxin.[45] Conversely, inhibition of NOS has been found to aggravate barrier dysfunction induced acutely by ischaemia/reperfusion, LPS or other noxious stimuli.[46,47] Thus, endogenously and constitutively synthesized NO appears to be a regulator of the normal, intact mucosal barrier, and removal of this protective agent allows injury to occur more easily. In contrast, overproduction of NO has been shown to be deleterious to the integrity of the intestinal epithelium. Infusion of NO donors at high concentrations induces damage to the gastric mucosa in the rat and decreases the viability of rat colonic epithelial cells.[48,49] Moreover, NO at high local concentrations has been shown directly to dilate

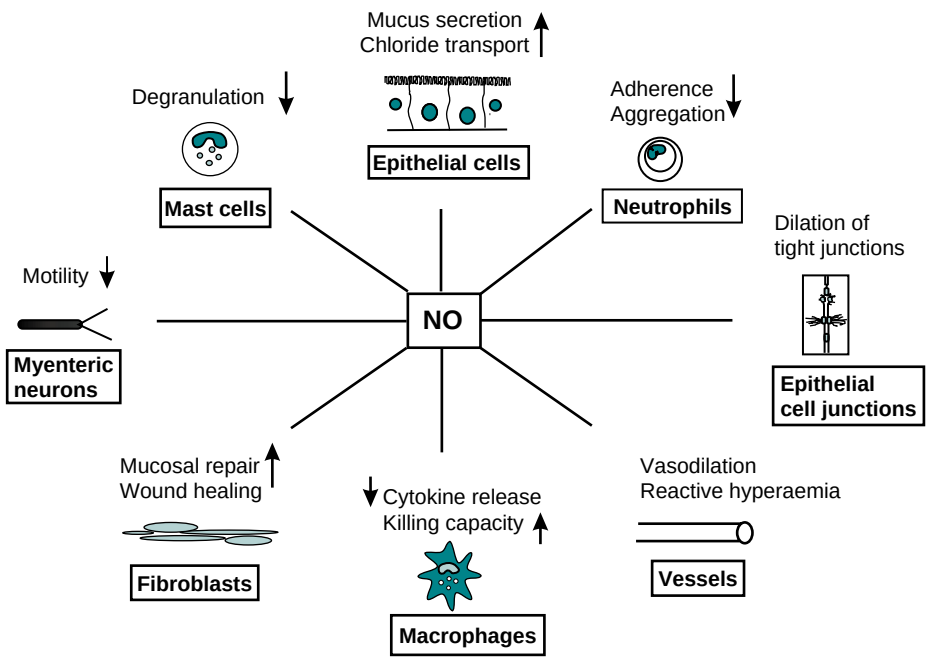


Figure 3. Actions of nitric oxide (NO) in modulating components of mucosal defence. Adapted from Wallace JL and Miller MJ (2000, *Gastroenterology* **119**: 512–520) with permission.

tight junctions in intestinal epithelial monolayers, disrupt the actin cytoskeleton, inhibit ATP formation and hence, increase intestinal permeability.[50,51] Moreover, in the chronic/late phases of inflammation/sepsis—in contrast to the acute phase—inhibition of NO synthesis no longer exacerbated, but significantly reduced, intestinal injury.[52] The cytotoxic effects of NO depend mainly on conversion into much stronger oxidants, such as peroxynitrite. For such reactions to prevail in tissues, however, the high-output isoform iNOS is usually up-regulated. The importance of iNOS-derived NO production in promoting BT has been shown experimentally after insults such as endotoxaemia, haemorrhagic shock, ischaemia-reperfusion or thermal injury.[53,54] This has been confirmed in iNOS knock-out mice exposed to LPS; these mice exhibited decreased physiological response, reduced mortality and no BT at all.[55] The detrimental effects of sustained high levels of NO production in gut inflammation have also been shown in humans. Up-regulation of iNOS and 3-nitrotyrosine immunostaining (footprint of peroxynitrite) are seen in the intestinal mucosa of patients with active ulcerative colitis.[56,57] Moreover, iNOS expression co-localizes with enterocyte apoptosis and accumulation of nitrate proteins in the intestinal villi in necrotizing enterocolitis.[58] These observations suggest that sustained over-expression of NO (via iNOS) and its toxic metabolites may promote mucosal injury and failure of the gut barrier, possibly through the induction of apoptosis in enterocytes. Finally, NO has also been shown to modulate macrophage function, with important implications for mucosal defence. For example, NO reduces cytokine release by macrophages, and the ability of macrophages to kill bacteria depends on the generation of NO.[43]

Route and site of translocation

There are multiple possible routes by which an organism can translocate out of the gut to extra-intestinal sites—retrograde migration to the lungs, direct transmural migration across the intestinal wall, lymphatic migration via Peyer's patches, MLNs, the thoracic duct and the systemic circulation—or via vascular channels to reach the portal system. There is substantial evidence that overgrowth in the upper intestine facilitates aspiration and retrograde migration of intestinal bacteria in severely ill trauma patients, primarily those on mechanical ventilation. Transmural migration has never been shown adequately and appears to be rather unlikely from the standpoint of clinical relevance. As for the lymphatic route, translocation of inert particles suggests that non-viable particles can translocate across the intestinal epithelium, possibly as passive passengers within motile phagocytes rather than as victims within lymph flow.[59] In fact, it has been suggested that the intestinal macrophage may play a key role in the process of BT. Cells of labelled *E. coli* have been shown to translocate into the lamina propria, by direct transit through enterocytes[2], and then to be engulfed by tissue macrophages. These macrophages transport the bacteria to MLNs and release them if the macrophage bactericidal activity is impaired.[60] More recently, direct transport of *Salmonella* from the gastrointestinal tract to the bloodstream via phagocytes has been elegantly demonstrated.[61] Brathwaite et al reported the presence of bacteria in macrophages within MLNs in each of 22 trauma patients studied by means of immunofluorescent staining of *E. coli* β-galactosidase.[62] However, in humans, lymphatic translocation beyond MLNs has rarely been studied. The main physiological impact of translocation beyond MLNs into the thoracic duct would be a bypass of the reticuloendothelial system of the liver, which serves as a scavenger of toxins and microbes. Lemaire et al reported translocation of endotoxin into the thoracic duct of patients with multiple organ failure (MOF) but the amount of endotoxin transported by

the thoracic duct was low and was not different from that in patients without MOF.[63] Predominant translocation via the portal vein has been demonstrated in experimental models of severe inflammatory insult, demonstrating the appearance of viable bacteria in the portal circulation even before their appearance in efferent intestinal lymph and in much greater numbers.[64]

The site of BT has rarely been addressed and may well depend on the experimental model used and the cause of BT. In endotoxaemia, gut mucosal injury has been reported to be greater in the ileum and caecum than in the jejunum.[65] During intravenous total parenteral nutrition, loss of gut barrier function is observed throughout the small bowel and caecum (but not the colon) whereas oral elemental diet increased intestinal permeability only at the ileum.[66] In burn injury models, isolated gut loops from the jejunum, ileum and proximal colon showed equivalent rates of translocation of ^{14}C-labelled *E. coli* (radionuclide counts).[67] However, higher numbers of viable bacteria in MLNs were detected (microbiological culture) when cells of *E. coli* were inoculated into the jejunal loop as compared to the ileal or colonic loop. In contrast to the upper gastrointestinal tract, which is normally relatively clean, towards the ileocoecal junction the number of bacteria increases and the species of microflora resemble those found in the colon. It has been suggested that, because the lower part of the gut contains a large number of microbes, it has a more efficient capacity for killing translocated bacteria. Moreover, the colon has different permeability characteristics compared with the small bowel; it has higher electrical resistance and a lower permeability to the passive movement of ions.[68] In fact, with equivalent concentrations of *E. coli*, significantly higher rates of BT have been observed from the small bowel compared with the large bowel; this indicates that the threshold for the onset of BT is markedly lower in the small intestine.[69] Therefore, it appears that bacterial overgrowth and alterations in intestinal permeability in the small bowel have a greater potential to promote BT.

CLINICAL RELEVANCE OF BACTERIAL TRANSLOCATION

The economic burden of BT can be substantial. In the USA, up to 10% of hospitalized patients develop nosocomial infections which cost more than $4.5 billion annually. Although many of these infections are acquired exogenously there is increasing evidence that many are caused by translocating enteric bacteria. The incidence of Gram-negative bacteraemia varies from 70 000 to 330 000 cases per year in the USA with an associated persistently high mortality of 20–40% despite intense efforts to improve therapy.

The first and most dramatic evidence that translocation can occur in humans came in the 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.[70] Increased BT has been shown to occur in various populations of patients ranging from the mildly ill to the critically ill (Table 2). 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 ± 12% of surface area affected were found uniformly to present an increased lactulose/mannitol ratio, indicating increased intestinal permeability.[23] Moreover, in the burn patients who died, more than 50% had intestinal lesions and more than 80% were septic—mostly with intestinal organisms.[71] Finally, after thermal injury, increased plasma levels of endotoxin are detectable within 24 hours of the burn—with the degree of endotoxaemia being closely correlated to the magnitude of injury.[72]

Table 2. Studies on BT in humans.

Clinical condition	Method for testing BT	References
Burn injury	BC, L/M ratio	23,71,72
Trauma/haemorrhagic shock	BC, MLN, endotoxin, L/M ratio	32,73–79
Endotoxin	L/M ratio	29
Obstructive jaundice	MLN	27,95
Acute pancreatitis	MLN, BC, L/R ratio	97,98
Bowel transplant	BC, stool, liver culture	103
Liver cirrhosis	MLN	106
Intestinal obstruction	MLN, serosa	21,181
Crohn's disease	MLN, serosa	182
Organ donors	MLN, BC, endotoxin	183
Elective surgery	MLN, serosa	21
Aortic aneurysm repair	MLN, serosa	84
Cardiopulmonary bypass	Endotoxin, L/M ratio	24
Heart failure	Serum endotoxin	184
Colchicine overdose	BC	185
Neutropenia	BC	186
Malignancy	BC	187

BC = blood culture. L/M (L/R) ratio = lactose/mannitol or (lactose/rhamnose) ratio. We apologize that, owing to limited space for citation of references in the chapter, only examples are given, and the list of references is far from complete.

Data are more controversial for 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.[73] Also, Peitzman et al found only sterile cultures of MLNs obtained at the time of coeliotomy from trauma patients.[74] In contrast, a high incidence of positive blood cultures was observed in severely injured patients with shock—in the early phase after trauma—as compared to those patients without shock.[75,76] However, an exceptionally high proportion of Gram-positive organisms was observed and, most notably, these Gram-positive microbes appeared to be of no clinical significance. Nonetheless, typical enteric bacteraemia was detected in a few cases, mostly in cases of severe shock and virtually all with fatal outcome (Table 3). Finally, Endo et al obtained

Table 3. Mortality by emergency department, shock and blood culture results.

	Patient groups (total $n = 132$)		Mortality, number	(%)
1	No shock	No bacteraemia	1/72	1
2	No shock	Bacteraemia	0/10	0
3	Shock	No bacteraemia	7/27	26
4	Shock	Plus bacteraemia	8/12	75[a]
5	Shock	Plus enteric bacteraemia	7/7	100

Reproduced from Moore F A et al (1992, *Archives of Surgery* **127**: 893–897) with permission.
[a] $P < 0.05$ versus groups 1–3. Shock was defined as systolic blood pressure <90 mmHg. Bacteraemia = any positive blood culture result (in five patients with shock: *Staphylococcus* or other non-enteric bacteria).

serial blood samples (0.5–168 hours after arrival) in severely injured patients who arrived in shock and detected elevated levels of LPS in only 2% of specimens.[77] Therefore, it appears that BT can be demonstrated only in a small number of severely traumatized patients who are moribund on arrival, rendering the clinical importance of BT in this situation at least doubtful. Nonetheless, gut permeability has been found to be increased in trauma patients.[32,77–79] Therefore, it appears that increased intestinal permeability is a permissive factor for BT but does not prove that BT has occurred.

A number of studies have shown increases in gut permeability and BT in humans challenged with low doses of *endotoxin*[29] and in patients with *critical illness* of various causes.[31,32,79–81] It has been claimed that BT may represent a significant source of sepsis in the critically ill patient. This has been based on the observation that no septic focus could be identified clinically, or at autopsy, in more than 30% of bacteraemic patients, including those dying of MOF.[82] Therefore, Marshall called the gut the 'motor of MOF' in that it comprises a reservoir of triggering compounds which initiate, perpetuate or intensify the systemic inflammatory response syndrome (SIRS),ultimately leading to the development of MOF (for details see Figure 2).[83] In fact, an increased incidence of septic complications in patients with evidence of BT at surgical operation was observed first by Brooks et al and then confirmed by Sedmann et al and others[21,22,38,84] (Table 4). Proximal gut colonization, in particular, has been found to be associated with increased BT and septic morbidity.[85,86] However, the occurrence of BT did not affect mortality. In addition, it is important to note that, in the study by Sedman et al, most cases of sepsis occurred in patients without BT. This draws attention to the method of detecting BT because, in human studies in general, only one lymph node at one location is used for evaluating BT. Perhaps if multiple cultures of MLNs had been performed more positive MLNs would have been found in patients in whom sepsis later developed. The association between increased gut permeability and infectious complications, however, is more controversial (Table 5). In patients undergoing major upper gastrointestinal surgery, gut barrier dysfunction did not affect the rate of infectious complications.[87] In patients injured by burns, however, increased intestinal permeabilty was associated with a significantly higher rate of clinical infection.[23] In

Table 4. Studies on the role of BT as cause of septic complications in surgical patients.

	Patients (number), with BT, without BT	Incidence of BT (%)	Septic complications	
Brooks et al[38]	Surgical (114), 18/96	16	5/18 (28%), 13/96 (14%)	NS
Sedman et al[21]	Surgical (242), 25/217	10.3	32/242 (13.2%), 7/25 (28%), 25/217 (11.5%)	$P < 0.05$
MacFie et al[85]	Surgical (279)[a], 29/250	21	89/279 (32%), 11/29 (38%), 32/107 (30%)	NS
O'Boyle et al[22]	Surgical (448), 69/379	15.4	31/69 (45%), 73/379 (19%)	$P < 0.001$
Woodcock et al[84]	Surgical (51), 5/46	10	4/5 (80%), 9/46 (19%)	$P < 0.05$

[a] One hundred and thirty six evaluated for BT. NS = not significant.

Table 5. Studies on the role of intestinal permeability in septic complications in various populations of patients.

	Patients (number)	Intestinal permeability IP (L/M ratio)[a]	Septic complications and IP (L/M ratio)		
Roumen et al[79]	Trauma (11) or haemorrhagic shock (8) versus controls (7)	0.069 ± 0.034, 0.098 ± 0.093 versus 0.012 ± 0.005 $P < 0.005$	No association with IP		
Kanwar S et al[87]	Surgical (68)		21/68 septic post-operative	IP 0.05 [0.004–0.11] versus	
			47/68 non-septic	IP 0.05 [0.01–0.11]	NS
Pape HC et al[32]	Trauma (32) versus controls (6)	MOF: 0.51 ± 0.021 versus No MOF: 1.06 ± 0.41 N.S. 0.056 ± 0.02 $P < 0.001$	IP related to systemic inflammatory response		
LeVoyer T et al[23]	Thermal injury (15), controls (10)	0.159 ± 0.01, 0.017 ± 0.003 $P < 0.001$	9/15 infections	IP 0.153 ± 0.04 versus	
			6/15 non-infected	IP 0.044 ± 0.01	$P < 0.01$
Faries P et al[78]	Trauma (29) versus controls (10)	0.346 ± 0.699, 0.025 ± 0.008 $P < 0.01$	Increased incidence in SIRS, infectious complications, close correlation with occurrence of MOF (see Table 6)		

[a] IP (L/M ratio) = Intestinal permeability determined by the lactulose/mannitol ratio.

Table 6. Incidence of SIRS/infectious complications as a function of increase in intestinal permeability after trauma.

	Degree of increase in intestinal permeability (%)		
	Moderate (0.03 < L/M< 0.10)	Marked (L/M≤ 0.10)	*P* value
Incidence of SIRS	44	83	0.03
Incidence of infectious complications	13	58	0.01

L/M = Intestinal permeability determined by the lactulose/mannitol ratio. Reproduced from Faries PL et al (1998, *Journal of Trauma* **44**: 1031–1035) with permission.

trauma patients, both an increased (Table 6) and an unchanged rate of septic complications have been reported in relation to increases in gut permeability.[78,79] These discrepancies may well be related to differences in the severity of disease, the time-point of investigating permeability, and the number of patients studied. Nonetheless, it needs to be stressed that, so far, no causative direct link between gut barrier dysfunction and infectious complications in humans has been shown, suggesting that increased gut permeability and infective complications are, at least partly, independent phenomena. An absolute proof that BT causes infections, however, would necessitate precise phage typing of all gastrointestinal flora on a daily basis, with concomitant culture of all subsequent septic foci to show commonality and a temporal relationship.

On the other hand, the gut can also modulate local and systemic responses even in the absence of detectable translocation of bacteria. In other words, the clinical manifestation of sepsis can be a consequence of the release of endogenous mediators by the host rather than a consequence of bacteria or bacterial products per se. Evidence for the hypothesis that the gut can become a 'cytokine-releasing organ' has been obtained in different experimental models; for example, in gut ischaemia/reperfusion injury it has been demonstrated that the reperfused gut can become a source of pro-inflammatory mediators which can amplify the early SIRS independently of BT[88] (Figure 2). Moreover, inflammatory cytokines and toxic products have been demonstrated in Peyer's patches and mesenteric lymph when none could be identified in the portal or systemic circulation. Thus, it has been suggested that mesenteric lymph is an important channel for the delivery of a variety of inflammatory mediators from the gut to remote organs.[89,90] In fact, it has been proposed that the spreading of gut-derived cytokines via mesenteric lymph plays a key role in the development of shock-induced *lung injury*.[89] In animal models, ligation of the mesenteric lymph duct before induction of haemorrhagic shock prevented increases in lung permeability and injury.[91] Similarly, prevention of Gram-negative translocation has been reported to reduce the severity of hepatopulmonary syndrome in bile-duct-ligated rats.[92] Whether this concept is clinically relevant, however, remains to be seen.

In contrast to animal models, in which there is evidence of increased BT in *obstructive jaundice*[27,93,94], O'Boyle et al and Sedman et al failed to observe an increase in positive cultures of MLNs in patients with this condition.[21,22] However, Parks et al demonstrated that the increased intestinal permeability in patients with obstructive

jaundice became normal after internal biliary drainage.[27] 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 ($P < 0.05$).[95] Because positive lymph node culture was not associated with systemic infection in either group, the clinical importance and associated risk remain to be defined.

Experimental studies indicate that the bacterial contamination of pancreatic necrosis in *acute pancreatitis* occurs through translocation of intestinal bacteria.[96] However, few studies have evaluated the issue of BT in severe pancreatitis in humans. Nettelbladt et al reported a patient, suffering from haemorrhagic pancreatitis, who developed MOF with fatal outcome; in this patient the same strain of *E. coli* was found in faeces, blood, MLNs and intraperitoneal fluid, suggesting that BT was the mode of infection.[97] This may well be due to the increased intestinal permeability which has been demonstrated in patients with acute pancreatitis because the permeability is significantly more pronounced in patients with severe pancreatitis.[98] Moreover, in a prospective study on 114 patients, Beger et al observed that pancreatic necrosis was contaminated by enteric bacteria in up to 71% of cases, causing a significant increase in mortality.[99]

In *small bowel transplantation*, very traumatic surgery, ischaemia/reperfusion injury, prolonged post-operative ileus or rejection predispose to BT. In rats, BT, endotoxaemia and bacteraemia have been reported to occur within hours of transplantation.[100,101] Because inclusion of the colon to the graft increased faecal bacterial counts, and the rate of BT and infectious complications, the colon is suspected to be the predominant source of translocating organisms.[102] Few data are available for humans, but BT has been reported to occur in 44% of paediatric patients undergoing small-bowel transplantation—prolongation of cold ischaemia time strongly influencing the rate of BT.[103] Unfortunately, no statement was made on the effect of BT on outcome.

In *liver cirrhosis*, the occurrence of BT is widely accepted and is thought to play a key role in the pathogenesis of SBP and other infectious complications. In experimental models of liver cirrhosis, BT has been reported to occur with an incidence of 37–83%, and BT has clearly been related to SBP by molecular epidemiological evidence.[104,105] Data in humans are rare. In an interesting study by Cirera et al. enteric bacteria could be cultivated from MLN's in 30.8% of Child-C cirrhotic patients undergoing laparotomy as compared to less than 10% in non-cirrhotic patients and in cirrhotic patients Child A or B.[106] Regarding the mechanisms of BT involved in liver cirrhosis, the following have been demonstrated: intestinal bacterial overgrowth, increased gut permeability and a wide spectrum of alterations in the immune defence system. In detail, intestinal bacterial overgrowth of aerobic Gram-negative bacteria has been demonstrated and has been closely linked to the development of BT, SBP and endotoxaemia.[107,108] This bacterial overgrowth has been attributed, at least partly, to the decrease in small-bowel motility observed in cirrhosis.[109] Structural changes in the intestinal mucosa, including vascular congestion, oedema and inflammation, as well as widening of the intercellular spaces, have been described in cirrhosis.[110,111] However, another study, by Such et al, failed to demonstrate alterations in the ultrastructural characteristics of intestinal mucosa in cirrhotic patients.[112] This emphasizes the importance of functional impairment in the intestinal barrier. Increased intestinal permeability has been demonstrated in liver cirrhosis—interestingly, mainly in those with septic complications.[113] Intestinal mucosal oxidative damage—shown, for example, by increased lipid peroxidation and altered enterocyte mitochondrial function—as well as endotoxinaemia and the enhanced serum levels of nitric oxide observed in these patients, may play a role in mediating this hyperpermeability.[114,115] Finally, the host immune response is impaired in liver cirrhosis by decreased reticuloendothelial

phagocytic activity, reduced concentrations of intestinal IgA, and deficiencies in serum immunoglobulins, complement and qualitative neutrophil function.[116] For instance, cirrhotic patients with lower levels of serum complement (C3 and C4) and/or a low level of ascitic fluid protein have been considered to be prone to develop SBP.[117] Moreover, impaired tuftsin activity, known to modulate the biological activity of phagocytic cells, is reduced in cirrhotic patients and is associated with a higher incidence of bacterial infections.[118]

PREVENTION OF AND THERAPY FOR BACTERIAL TRANSLOCATION

A rich diversity of strategies have been investigated for the treatment of BT (Table 7). Most of them were tested in experimental models; most of the human studies were uncontrolled reports involving small numbers of patients, or studies that could not be reproduced by others. In any assumed BT, of various disorders, treatment of the underlying disease is the most effective strategy.

There is much experimental evidence linking *diet* with the maintenance of intestinal mucosal integrity. In animal models, starvation—as well as total parenteral nutrition (TPN)—promotes bacterial overgrowth, diminishes the production of intestinal mucin, decreases the levels of global gut IgA, causes mucosal atrophy (which increases intestinal permeability), attenuates the number and function of GALT lymphocytes, and accelerates oxidative stress.[119–121] Therefore, it appears that lack of enteral feeding profoundly affects the cellular and immunological status designed to protect the host from BT. In critically ill patients (trauma, burn, surgery), it is well established that early enteral nutrition diminishes septic complications. However, in the acute setting, access to the gut is limited. Therefore, enteral nutrition via a needle catheter jejunostomy has been applied. This approach has been tested in several randomized controlled trials in intensive-care patients, and it has been shown to be both feasible and associated with a significant reduction in septic morbidity.[122] More recent trials have compared immune-enhancing enteral diets to standard diets; these trials indicate that the specialized formulas of enteral diets—with immunonutrients such as glutamine, arginine and the omega-3 fatty acids—show significant additional local and systemic benefits.[123,124] This approach has been reported to result in a significant reduction in infectious complications, decreasing hospital stay and costs as compared to an isonitrogenous diet in severely injured patients (Table 8).[124] In addition, the provision of bulk-forming fibres has been shown to limit or reverse diet-induced BT[125]; this has been attributed to the production of various intestinal trophic factors and/or to a direct effect on intestinal mucus, epithelial cells and the gut flora induced by fibres.

Other enteral manoeuvres tested for the prevention of BT include supplementation with IgA, ornithine-α-ketoglutarate or fish oil. Oral supplementation of IgA completely abrogated BT in formula-fed neonatal rabbits by enhancing the gut mucosal barrier[126], and feeding a combination of IgA and IgG prevented necrotizing enterocolitis in low-birth-weight infants.[127] The administration of ornithin-α-ketoglutarate has been shown to exert beneficial effects on intestinal structure and function as well as on cellular immunity, limiting bacterial dissemination after endotoxin challenge and reducing BT after small-bowel transplantation in rats.[128,129] Modulation of the fatty-acid composition by fish-oil-enriched diets has been shown to preserve intestinal blood flow and to enhance the host's ability to kill translocated bacteria in various experimental models of BT.[130,131] This has been attributed to the increased synthesis of vasodilative *prostaglandins*, which have been reported to reverse endotoxin-induced intestinal

Table 7. Examples of therapeutic approaches for the prevention of BT.

Therapy	Disease/model	Reference
Enteral nutrition	Surgical patients	122
Immunonutrition/fibre	Severely injured patients	124,125
Immunoglobulin A	Formula-fed neonatal rabbits/low-birth-weight-infants	126,127,143
Fish oil	TPN/low endotoxin	131
Prostacyclin/prostaglandin E	Low-dose endotoxin in cat	132
	Burn injury in mice	133
Ornithine-α-ketoglutarate	Endotoxin/small-bowel transplant in rat	128,129
Lactulose		188–190
Lactobacillus/probiotics	Liver injury, short bowel, enterocolitis in rat	137–139
Hyperbaric oxygen	Intestinal obstruction, obstructive jaundice in rat	140,141
Polymyxin/anti-endotoxin	Septic/burned patients	145–147
BPI	Endotoxaemia/haemorrhagic shock in rats	149,150
	Meningococcal sepsis/trauma patients	151,152
Neutrophil depletion	Thermal injury in rats	153
Anti-L-selectin	Haemorrhagic shock in baboons	155
Xanthine oxidase inhibition	Haemorrhagic/portal hypertensive rats	191
C1-inhibitor	Thermal injury in pigs	192
IL-6	Haemorrhagic shock in mice	193
IL-11	Burn injury mice	194
ACE-inhibition (enalapril)	Thermal injury mice	195
Angiotensin-II inhibitor DuP753	Thermal injury/endotoxin in minipigs	196
Preferential iNOS inhibition	Thermal injury/endotoxaemia in rat	53,54
NOX (NO scavenger)	Endotoxinaemia in rat	197
Cholylsarcosine (conj. bile acid)	Liver cirrhosis in rat	198
Glucagon-like peptide 2	Acute necrotic pancreatitis in rat	199
Growth hormone	Acute necrotizing pancreatitis in rats	200
SGD	Critically ill, pancreatitis, liver, bone and marrow transplantation and cirrhotic patients	16,117,160–164

We apologize that, owing to limited space for citation of references in the chapter, only examples are given, and the list of references is far from complete.

vasoconstriction, enhance mucus secretion and down-regulate the synthesis of TNF.[132] Furthermore, it has been demonstrated that prostaglandin E analogues—by exerting such protective effects on the gastrointestinal mucosa—reduce the number of translocated bacteria and have been associated with improved survival in experimental thermal injury.[133] However, there have been no reports of corresponding randomized, controlled investigations on such enteral manouevres or on the use of prostaglandins in conditions promoting BT in humans.

Table 8. Effect of 'immune-enhancing-diet' on septic complications, and hospital parameters, in severely injured patients.

	IED	ISO	*P*-value
Major septic complications	5/16 (31%)	7/17 (41%)	$P < 0.02$
Antibiotic use (therapeutic, days)	2.8 ± 1.6	7.1 ± 1.7	$P < 0.02$
Hospital stay (days)	18.3 ± 2.8	32.6 ± 6.6	$P < 0.03$
Costs	80.515 ± 21.528 $	110.600 ± 19.132 $	

IED = 'Immune-enhancing-diet' via jejunostomy tube. ISO = Isonitrogenous isocaloric diet. Reproduced from Kudsk KA at al (1996, *Annals of Surgery* **224**: 531–540) with permission.

Probiotics, such as various *Lactobacillus* species, have been reported to exert many effects and to protect the gut from BT. Lactobacilli inhibit the growth of Gram-negative and pathogenic bacteria, attenuate adherence and invasion of enterovirulent bacteria in human intestinal cell lines, enhance the secretion of intestinal IgA and stabilize the gut epithelial barrier.[134,135] Moreover, lactobacilli modulate immunological defence mechanisms, enhancing host resistance against infection.[136] This battery of effects has 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 other conditions.[135,137–139] However, convincing benefits of probiotics in preventing BT in the clinical setting are lacking.

Hyperbaric oxygen(HBO_2) has been reported to prevent BT in experimental models of intestinal obstruction, burn injury, systemic inflammation and obstructive jaundice (Figure 4).[140–142] This benefit has been attributed to its bacteriostatic effect on some strains of *E. coli*, preventing bacterial overgrowth, and its anti-inflammatory properties. Moreover, HBO_2 strengthens the host's defence against infection by increasing the killing capacity of phagocytes and neutrophils—which require molecular oxygen as a substrate for microbial killing. This dramatic benefit of HBO_2 has been reported to be synergistic with that of IgA in reducing BT.[143] HBO_2 has been used successfully in individual cases of haemorrhagic shock in patients who refused blood on religious grounds[144]; however, randomized, controlled trials—and hence, clinical evidence for its use in critical illness—are absent.

The therapeutic approach of binding and *neutralizing endotoxin* has been reported to reduce mortality in patients with Gram-negative sepsis[145], but these results have been criticized and could not be confirmed.[146] Moreover, the use of endotoxin-neutralizing peptides—such as polymyxin–has been shown to reduce endotoxin levels in burn patients without effect on mortality.[147] This lack of effect has been attributed to the fact that although the antibodies bound to endotoxin they did not completely neutralize its toxic effects.[148] Additionally, 'immunoparalysis'—a well-known compensatory anti-inflammatory response to the systemic appearance of inflammatory mediators—may be excessive in some patients, causing immunosuppression which hampers the effect of antibodies against endotoxin. A physiological protein with anti-endotoxin properties is the *bactericidal/permeability-increasing protein* (BPI) which is part of the neutrophil defence system. BPI binds to, neutralizes and accelerates clearance of LPS, suppresses endotoxin-mediated cellular activation and exhibits antibacterial properties. Recombinant rBPI has been shown to reduce the incidence of BT and to attenuate vital organ damage, increasing survival in several animal models of endotoxaemia and haemorrhagic

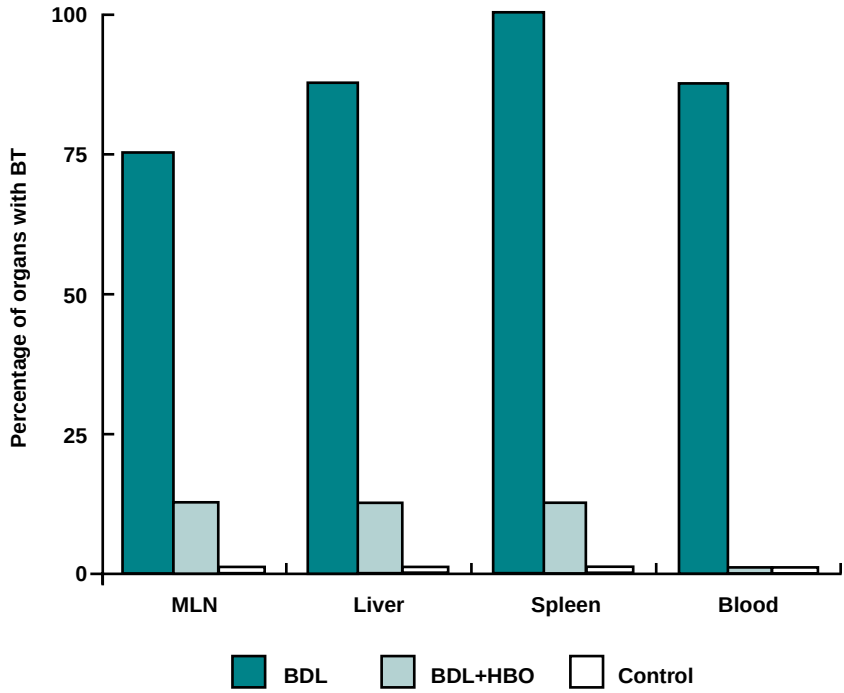


Figure 4. The effect of hyperbaric oxygenation on BT in obstructive jaundice in rats. Hyperbaric oxygenation (HBO) was applied by 2.5 ATA for 75 minutes twice daily for 7 days. BDL = Bile-duct ligation. MLN = mesenteric lymph nodes. The incidence of BT was significantly decreased by HBO_2 in all the organs studied ($P < 0.05$). Reproduced from Akin ML et al (2001, *Digestive Diseases and Sciences* **46**: 1657–1662) with permission.

shock.[149,150] rBPI has been used safely in children with severe meningococcaemia[151] and has demonstrated a favourable trend in reducing mortality or serious complications in patients with haemorrhage due to trauma.[152]

The profound effect of *neutrophil* accumulation and activation on intestinal barrier function and BT is underlined by experimental data in animal models of thermal injury and haemorrhagic shock.[153–155] Interference with neutrophil function reduced BT in experimental thermal injury[153] and improved survival time in a haemorrhagic–traumatic shock model.[155] Moreover, in the process of BT, the role of reactive oxygen species—derived, for example, from activated neutrophils–is supported by the utility of free oxygen radical scavengers, or inhibitors of xanthine, which decrease mucosal injury and reduce the incidence of BT in various animal models.[156–158] Regarding the potential risk of increased infections induced by blocking neutrophil function, a recent randomized 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.[159] This may indicate the potential use of such an approach in clinical conditions promoting BT.

A more general attempt to reduce the presumed risk of BT in critically ill patients is *selective gut decontamination* (SGD). Major targets of SGD performed typically with tobramycin, polymyxin E, amphotericin or cefotaxim are *Enterobacter*, *Pseudomonas*, *Acetobacter* and yeast. One of the first well-designed randomized studies in this area demonstrated that SGD significantly reduced the incidence of nosocomial infections in

mechanically-ventilated intensive-care patients.[160] In a large meta-analysis on the effect of oral non-absorbable antibiotics in intensive-care-unit patients, the incidence of pneumonia was found to be significantly decreased. This beneficial impact on the rate of respiratory tract infection has been firmly established.[161] However, the reduced infection rate in these studies did not result in a reduction in the length of hospital stay, the incidence of MOF or the mortality. Owing to the lack of effect on mortality and on serum endotoxin concentrations, the extra costs and the development of resistant organisms, SGD is rarely used in clinical practice in critical illness.

Nonetheless, SGD has been shown to reduce the incidence of secondary pancreatic infection and, in those expected to die, to improve survival.[162] Moreover, it has been used in patients undergoing liver transplantation and is routinely used in patients undergoing intestine and bone marrow transplantation.[163] This is based on the well-known high incidence of serious post-operative bacterial infections and the intensive immunosuppression in those patients. Furthermore, prophylactic usefulness of SGD has been shown to decrease the rate of SBP and to improve survival in cirrhotic patients with gastrointestinal haemorrhage known to be at high risk of developing severe bacterial infections.[164] Finally, owing to the excessive risk of recurrence of SBP, secondary prophylaxis is recommended in any cirrhotic patient recovering from an episode of SBP.[117] The recommended first-choice antibiotics in cirrhotics are quinolones, usually norfloxacin due to its simple administration and low cost.

CONCLUSIONS AND SUGGESTIONS

BT should not be considered as an 'on–off' or an 'all-or-nothing' phenomenon leading to clinically obvious changes under all circumstances. Extensive animal studies have reported increases in BT in a multitude of pathological entities with varying impact on outcome. In humans, data are much more scarce and the reported rates of BT are, in general, much lower. Nonetheless, BT has been shown to occur in healthy patients and has also been shown to be increased in those patients severely critically ill from extensive trauma shock, sepsis or thermal injury—as well as in those with end-stage cirrhosis. However, translation of the available data into clinical consequences is severely limited owing to:

(a) methodological problems, such as the lack of serial and multiple evaluation of MLNs in humans as well as shortcomings in sensitivity and in the practical aspects of available tools for detecting the occurrence and extent of BT;
(b) lack of agreement regarding the *clinical impact* and the prognostic relevance of BT. For instance, after a given insult one patient will develop MOF, with fatal outcome, while another will recover. However, owing to the complex nature of the process of BT and the number of host and microbial factors involved, prediction of the clinical consequence of BT, once it has occurred, is unlikely to be feasible in the foreseeable future;
(c) the lack of sufficient compelling evidence on the effect and benefit of preventing or treating BT in most of the various pathological entities referred to.

Nonetheless, despite the presence of negative data, the concept that BT contributes to morbidity remains a fruitful line of investigation. In particular, the role of the liver and lung in modulating an inflammatory response should be investigated; further studies should also be carried out on permeability changes in the colon and the lymphatic route

of BT and the delivery of inflammatory mediators beyond the MLNs. At the very least, learning about BT will provide insight into the mechanisms of cellular dysfunction of all kinds associated with ischaemia, sepsis or other causes of diffuse inflammation. At best, this avenue of investigation will lead to new treatment options for improving clinical outcome, and eventually will even help to develop preventive measures against the development of infectious complications.

Practice points

- BT occurs in healthy persons
- the clinical significance of BT is controversial and has not been substantiated so far

Research agenda

- the detection of BT in the critically ill must be further investigated
- many of the promising therapeutic measures tested in an experimental setting require further investigation in adequate, randomized, placebo-controlled clinical trials

REFERENCES

1. Berg RD & Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infection and Immunity* 1979; **23:** 403–411.
2. Alexander JW, Boyce ST, Babcock GF et al. The process of microbial translocation. *Annals of Surgery* 1990; **212:** 496–510.
3. Kane TD, Johnson SR, Alexander JW et al. Detection of intestinal bacterial translocation using PCR. *Journal of Surgical Research* 1996; **63:** 59–63.
4. Bjarnason I, MacPherson A & Hollander D. Intestinal permeability: an overview. *Gastroenterology* 1995; **108:** 1566–1581.
5. Wells CL. Relationship between intestinal microecology and the translocation of intestinal bacteria. *Antonie van Leeuwenhoek* 1990; **58:** 87–93. Review, 30 references.
6. Ljungdahl M, Lundholm M, Katouli M et al. Bacterial translocation in experimental shock is dependent on the strains in the intestinal flora. *Scandinavian Journal of Gastroenterology* 2000; **35:** 389–397.
7. Satterwhite TK, Evans DG, DuPont HL et al. Role of *Escherichia coli* colonisation factor antigen in acute diarrhoea. *Lancet* 1978; **ii:** 181–184.
8. Alverdy J, Holbrook C, Rocha F et al. Gut-derived sepsis occurs when the right pathogen with the right virulence genes meets the right host: evidence for in vivo virulence expression in Pseudomonas aeruginosa. *Annals of Surgery* 2000; **232:** 480–489.
9. Owens WE & Berg RD. Bacterial translocation from the gastrointestinal tract of athymic (nu/nu) mice. *Infection and Immunity* 1980; **27:** 461–467.
10. Brook I, MacVittie TJ & Walker RI. Recovery of aerobic and anaerobic bacteria from irradiated mice. *Infection and Immunity* 1984; **46:** 270–271.
11. Wells CL, Maddaus MA, Reynolds CM et al. Role of anaerobic flora in the translocation of aerobic and facultatively anaerobic intestinal bacteria. *Infection and Immunity* 1987; **55:** 2689–2694.
12. Steffen EK & Berg RD. Relationship between cecal population levels of indigenous bacteria and translocation to the mesenteric lymph nodes. *Infection and Immunity* 1983; **39:** 1252–1259.
13. Boedeker EC. Adherent bacteria: breaching the mucosal barrier? *Gastroenterology* 1994; **106:** 255–257.
14. Stockbruegger RW. Bacterial overgrowth as a consequence of reduced gastric acidity. *Scandinavian Journal of Gastroenterology* 1985; **111(supplement):** 7–16.

15. Nieuwenhuijs VB, Verheem A, Duijvenbode-Beumer H et al. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. *Annals of Surgery* 1998; **228:** 188–193.
* 16. Aranow JS & Fink MP. Determinants of intestinal barrier failure in critical illness. *British Journal of Anaesthesia* 1996; **77:** 71–81.
17. Spaeth G, Gottwald T, Specian RD et al. Secretory immunoglobulin A, intestinal mucin, and mucosal permeability in nutritionally induced bacterial translocation in rats. *Annals of Surgery* 1994; **220:** 798–808.
18. Slocum MM, Sittig KM, Specian RD et al. Absence of intestinal bile promotes bacterial translocation. *American Surgeon* 1992; **58:** 305–310.
19. Wells CL, Jechorek RP & Erlandsen SL. Inhibitory effect of bile on bacterial invasion of enterocytes: possible mechanism for increased translocation associated with obstructive jaundice. *Critical Care Medicine* 1995; **23:** 301–307.
20. Choudhry MA, Fazal N, Goto M et al. Gut-associated lymphoid T cell suppression enhances bacterial translocation in alcohol and burn injury. *American Journal of Physiology, Gastrointest Liver Physiol* 2002; **282:** G937–G947.
* 21. Sedman PC, MacFie J, Sagar P et al. The prevalence of gut translocation in humans (see comments). *Gastroenterology* 1994; **107:** 643–649.
22. O'Boyle CJ, MacFie J, Mitchell CJ et al. Microbiology of bacterial translocation in humans. *Gut* 1998; **42:** 29–35.
23. LeVoyer T, Cioffi WG Jr, Pratt L et al. Alterations in intestinal permeability after thermal injury. *Archives of Surgery* 1992; **127:** 26–29.
24. Riddington DW, Venkatesh B, Boivin CM et al. Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. *Journal of the American Medical Association* 1996; **275:** 1007–1012.
25. Roumen RM, van der Vliet JA, Wevers RA et al. Intestinal permeability is increased after major vascular surgery. *Journal of Vascular Surgery* 1993; **17:** 734–737.
26. Roumen RM, Hendriks T, Wevers RA et al. Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Archives of Surgery* 1993; **128:** 453–457.
27. Parks RW, Clements WD, Smye MG et al. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. *British Journal of Surgery* 1996; **83:** 1345–1349.
28. Davies GR, Wilkie ME & Rampton DS. Effects of metronidazole and misoprostol on indomethacin-induced changes in intestinal permeability. *Digestive Diseases and Sciences* 1993; **38:** 417–425.
29. O'Dwyer ST, Michie HR, Ziegler TR et al. A single dose of endotoxin increases intestinal permeability in healthy humans. *Archives of Surgery* 1988; **123:** 1459–1464.
30. Welsh FK, Farmery SM, MacLennan K et al. Gut barrier function in malnourished patients. *Gut* 1998; **42:** 396–401.
31. Harris CE, Griffiths RD, Freestone N et al. Intestinal permeability in the critically ill. *Intensive Care Medicine* 1992; **18:** 38–41.
32. Pape HC, Dwenger A, Regel G et al. Increased gut permeability after multiple trauma. *British Journal of Surgery* 1994; **81:** 850–852.
33. Salzman AL, Wang H, Wollert PS et al. Endotoxin-induced ileal mucosal hyperpermeability in pigs: role of tissue acidosis. *American Journal of Physiology* 1994; **266:** G633–G646.
34. Welsh MJ, Shasby DM & Husted RM. Oxidants increase paracellular permeability in a cultured epithelial cell line. *Journal of Clinical Investigation* 1985; **76:** 1155–1168.
35. Wilson J, Winter M & Shasby DM. Oxidants, ATP depletion, and endothelial permeability to macromolecules. *Blood* 1990; **76:** 2578–2582.
36. Pignata C, Budillon G, Monaco G et al. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. *Gut* 1990; **31:** 879–882.
37. Berg RD. Bacterial translocation from the gastrointestinal tracts of mice receiving immunosuppressive chemotherapeutic agents. *Current Microbiology* 1983; **8:** 285–292.
38. Brooks SG, May J, Sedman P et al. Translocation of enteric bacteria in humans. *British Journal of Surgery* 1993; **80:** 901–902.
39. Gautreaux MD, Gelder FB, Deitch EA et al. Adoptive transfer of T lymphocytes to T-cell-depleted mice inhibits *Escherichia coli* translocation from the gastrointestinal tract. *Infection and Immunity* 1995; **63:** 3827–3834.
40. Berg RD, Wommack E & Deitch EA. Immunosuppression and intestinal bacterial overgrowth synergistically promote bacterial translocation. *Archives of Surgery* 1988; **123:** 1359–1364.
41. Berg RD & Owens WE. Inhibition of translocation of viable *Escherichia coli* from the gastrointestinal tract of mice by bacterial antagonism. *Infection and Immunity* 1979; **25:** 820–827.

42. Berg RD. Mechanisms confining indigenous bacteria to the gastrointestinal tract. *American Journal of Clinical Nutrition* 1980; **33:** 2472–2484 (Review, 38 references).
43. Wallace JL & Miller MJ. Nitric oxide in mucosal defense: a little goes a long way. *Gastroenterology* 2000; **119:** 512–520.
44. Kubes P. Nitric oxide modulates epithelial permeability in the feline small intestine. *American Journal of Physiology* 1992; **262:** G1138–G1142.
45. Payne D & Kubes P. Nitric oxide donors reduce the rise in reperfusion-induced intestinal mucosal permeability. *American Journal of Physiology* 1993; **265:** G189–G195.
46. Alican I & Kubes P. A critical role for nitric oxide in intestinal barrier function and dysfunction. *American Journal of Physiology* 1996; **270:** G225–G237.
47. Hutcheson IR, Whittle BJ & Boughton-Smith NK. Role of nitric oxide in maintaining vascular integrity in endotoxin-induced acute intestinal damage in the rat. *British Journal of Pharmacology* 1990; **101:** 815–820.
48. Lopez-Belmonte J, Whittle BJ & Moncada S. The actions of nitric oxide donors in the prevention or induction of injury to the rat gastric mucosa. *British Journal of Pharmacology* 1993; **108:** 73–78.
49. Tepperman BL, Brown JF & Whittle BJ. Nitric oxide synthase induction and intestinal epithelial cell viability in rats. *American Journal of Physiology* 1993; **265:** G214–G218.
50. Forsythe RM, Xu DZ, Lu Q et al. Lipopolysaccharide-induced enterocyte-derived nitric oxide induces intestinal monolayer permeability in an autocrine fashion. *Shock* 2002; **17:** 180–184.
51. Salzman AL, Menconi MJ, Unno N et al. Nitric oxide dilates tight junctions and depletes ATP in cultured Caco-2BBe intestinal epithelial monolayers. *American Journal of Physiology* 1995; **268:** G361–G373.
52. Boughton-Smith NK, Evans SM, Laszlo F et al. The induction of nitric oxide synthase and intestinal vascular permeability by endotoxin in the rat. *British Journal of Pharmacology* 1993; **110:** 1189–1195.
53. Unno N, Wang H, Menconi MJ et al. Inhibition of inducible nitric oxide synthase ameliorates endotoxin-induced gut mucosal barrier dysfunction in rats. *Gastroenterology* 1997; **113:** 1246–1257.
54. Chen LW, Hsu CM, Wang JS et al. Specific inhibition of iNOS decreases the intestinal mucosal peroxynitrite level and improves the barrier function after thermal injury. *Burns* 1998; **24:** 699–705.
55. Mishima S, Xu D, Lu Q et al. Bacterial translocation is inhibited in inducible nitric oxide synthase knockout mice after endotoxin challenge but not in a model of bacterial overgrowth. *Archives of Surgery* 1997; **132:** 1190–1195.
56. Boughton-Smith NK, Evans SM, Hawkey CJ et al. Nitric oxide synthase activity in ulcerative colitis and Crohn's disease. *Lancet* 1993; **342:** 338–340.
57. Singer II, Kawka DW, Scott S et al. Expression of inducible nitric oxide synthase and nitrotyrosine in colonic epithelium in inflammatory bowel disease. *Gastroenterology* 1996; **111:** 871–885.
58. Ford H, Watkins S, Reblock K et al. The role of inflammatory cytokines and nitric oxide in the pathogenesis of necrotizing enterocolitis. *Journal of Pediatric Surgery* 1997; **32:** 275–282.
59. Wells CL, Maddaus MA, Erlandsen SL et al. Evidence for the phagocytic transport of intestinal particles in dogs and rats. *Infection and Immunity* 1988; **56:** 278–282.
60. Wells CL, Maddaus MA & Simmons RL. Role of the macrophage in the translocation of intestinal bacteria. *Archives of Surgery* 1987; **122:** 48–53.
* 61. Vazquez-Torres A, Jones-Carson J, Baumler AJ et al. Extraintestinal dissemination of Salmonella by CD18-expressing phagocytes. *Nature* 1999; **401:** 804–808.
62. Brathwaite CE, Ross SE, Nagele R et al. Bacterial translocation occurs in humans after traumatic injury: evidence using immunofluorescence. *Journal of Trauma* 1993; **34:** 586–589.
63. Lemaire LC, van Lanschot JB, Stoutenbeek CP et al. Thoracic duct in patients with multiple organ failure: no major route of bacterial translocation. *Annals of Surgery* 1999; **229:** 128–136.
64. Mainous MR, Tso P, Berg RD et al. Studies of the route, magnitude, and time course of bacterial translocation in a model of systemic inflammation. *Archives of Surgery* 1991; **126:** 33–37.
65. Deitch EA, Taylor M, Grisham M et al. Endotoxin induces bacterial translocation and increases xanthine oxidase activity. *Journal of Trauma* 1989; **29:** 1679–1683.
66. Mosenthal AC, Xu D & Deitch EA. Elemental and intravenous total parenteral nutrition diet-induced gut barrier failure is intestinal site specific and can be prevented by feeding nonfermentable fiber. *Critical Care Medicine* 2002; **30:** 396–402.
67. Fukushima R, Gianotti L & Alexander JW. The primary site of bacterial translocation. *Archives of Surgery* 1994; **129:** 53–58.
68. Powell DW. Barrier function of epithelia. *American Journal of Physiology* 1981; **241:** G275–G288.
69. Koh IH, Guatelli R, Montero EF et al. Where is the site of bacterial translocation-small or large bowel? *Transplantation Proceedings* 1996; **28:** 2661.
70. Krause W, Matheis H & Wulf K. Fungaemia and funguria after oral administration of *Candida albicans*. *Lancet* 1969; **i:** 598–599.
71. Desai MH, Herndon DN, Rutan RL et al. Ischemic intestinal complications in patients with burns. *Surgical Gynecology and Obstetrition* 1991; **172:** 257–261.

72. Winchurch RA, Thupari JN & Munster AM. Endotoxemia in burn patients: levels of circulating endotoxins are related to burn size. *Surgery* 1987; **102:** 808–812.
73. Moore FA, Moore EE, Poggetti R et al. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *Journal of Trauma* 1991; **31:** 629–636.
74. Peitzman AB, Udekwu AO, Ochoa J et al. Bacterial translocation in trauma patients. *Journal of Trauma* 1991; **31:** 1083–1086.
75. Moore FA, Moore EE, Poggetti RS et al. Postinjury shock and early bacteremia. A lethal combination. *Archives of Surgery* 1992; **127:** 893–897.
76. Rush Jr. BF, Sori AJ, Murphy TF et al. Endotoxemia and bacteremia during hemorrhagic shock. The link between trauma and sepsis? *Annals of Surgery* 1988; **207:** 549–554.
77. Endo S, Inada K, Yamada Y et al. Plasma endotoxin and cytokine concentrations in patients with hemorrhagic shock. *Critical Care Medicine* 1994; **22:** 949–955.
78. Faries PL, Simon RJ, Martella AT et al. Intestinal permeability correlates with severity of injury in trauma patients. *Journal of Trauma* 1998; **44:** 1031–1035.
79. Roumen RM, Hendriks T, Wevers RA et al. Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Archives of Surgery* 1993; **128:** 453–457.
80. Roumen RM, Frieling JT, van Tits HW et al. Endotoxemia after major vascular operations. *Journal of Vascular Surgery* 1993; **18:** 853–857.
81. Roumen RM, van der Vliet JA, Wevers RA et al. Intestinal permeability is increased after major vascular surgery. *Journal of Vascular Surgery* 1993; **17:** 734–737.
82. Goris RJ, te Boekhorst TP, Nuytinck JK et al. Multiple-organ failure. Generalized autodestructive inflammation? *Archives of Surgery* 1985; **120:** 1109–1115.
* 83. Meakins JL & Marshall JC. The gastrointestinal tract: the motor of multiple organ failure. *Archives of Surgery* 1986; **121:** 197–245.
84. Woodcock NP, Sudheer V, El Barghouti N et al. Bacterial translocation in patients undergoing abdominal aortic aneurysm repair. *British Journal of Surgery* 2000; **87:** 439–442.
85. MacFie J, O'Boyle C, Mitchell CJ et al. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* 1999; **45:** 223–228.
* 86. Marshall JC, Christou NV, Horn R et al. The microbiology of multiple organ failure. The proximal gastrointestinal tract as an occult reservoir of pathogens. *Archives of Surgery* 1988; **123:** 309–315.
87. Kanwar S, Windsor AC, Welsh F et al. Lack of correlation between failure of gut barrier function and septic complications after major upper gastrointestinal surgery. *Annals of Surgery* 2000; **231:** 88–95.
88. Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. *American Journal of Surgery* 1999; **178:** 449–453.
* 89. Magnotti LJ, Upperman JS, Xu DZ et al. Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. *Annals of Surgery* 1998; **228:** 518–527.
90. Magnotti LJ, Xu DZ, Lu Q et al. Gut-derived mesenteric lymph: a link between burn and lung injury. *Archives of Surgery* 1999; **134:** 1333–1340.
91. Sambol JT, Xu DZ, Adams CA et al. Mesenteric lymph duct ligation provides long term protection against hemorrhagic shock-induced lung injury. *Shock* 2000; **14:** 416–419.
92. Rabiller A, Nunes H, Lebrec D et al. Prevention of gram-negative translocation reduces the severity of hepatopulmonary syndrome. *American Journal of Respiratory and Critical Care Medicine* 2002; **166:** 514–517.
93. Clements WD, Parks R, Erwin P et al. Role of the gut in the pathophysiology of extrahepatic biliary obstruction. *Gut* 1996; **39:** 587–593.
94. Reynolds JV, Murchan P, Leonard N et al. Gut barrier failure in experimental obstructive jaundice. *Journal of Surgical Research* 1996; **62:** 11–16.
95. Kuzu MA, Kale IT, Col C et al. Obstructive jaundice promotes bacterial translocation in humans. *Hepatogastroenterology* 1999; **46:** 2159–2164.
96. Cicalese L, Sahai A, Sileri P et al. Acute pancreatitis and bacterial translocation. *Digestive Diseases and Sciences* 2001; **46:** 1127–1132.
97. Nettelbladt CG, Katouli M, Bark T et al. Evidence of bacterial translocation in fatal hemorrhagic pancreatitis. *Journal of Trauma* 2000; **48:** 314–315.
98. Juvonen PO, Alhava EM & Takala JA. Gut permeability in patients with acute pancreatitis. *Scandinavian Journal of Gastroenterology* 2000; **35:** 1314–1318.
99. Beger HG, Bittner R, Block S et al. Bacterial contamination of pancreatic necrosis. A prospective clinical study. *Gastroenterology* 1986; **91:** 433–438.
100. Price BA, Cumberland NS, Clark CL et al. The effect of rejection and graft-versus-host disease on small intestinal microflora and bacterial translocation after rat small bowel transplantation. *Transplantation* 1993; **56:** 1072–1076.

101. Browne BJ, Johnson CP, Roza AM et al. Endotoxemia after small bowel transplantation. *Transplantation Proceedings* 1992; **24:** 1107.
102. Spada M, Alessiani M, Fabbi M et al. Bacterial translocation is enhanced in pig intestinal transplantation when the colon is included in the graft. *Transplantation Proceedings* 1996; **28:** 2658–2659.
103. Cicalese L, Sileri P, Green M et al. Bacterial translocation in clinical intestinal transplantation. *Transplantation* 2001; **71:** 1414–1417.
104. Garcia-Tsao G, Lee FY, Barden GE et al. Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. *Gastroenterology* 1995; **108:** 1835–1841.
105. Llovet JM, Bartoli R, March F et al. Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence. *Journal of Hepatology* 1998; **28:** 307–313.
106. Cirera I, Bauer TM, Navasa M et al. Bacterial translocation of enteric organisms in patients with cirrhosis. *Journal of Hepatology* 2001; **34:** 32–37.
107. Chang CS, Chen GH, Lien HC et al. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1998; **28:** 1187–1190.
108. Bauer TM, Steinbruckner B, Brinkmann FE et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *American Journal of Gastroenterology* 2001; **96:** 2962–2967.
109. Chesta J, Defilippi C & Defilippi C. Abnormalities in proximal small bowel motility in patients with cirrhosis. *Hepatology* 1993; **17:** 828–832.
110. Astaldi G & Strosselli E. Peroral biopsy of the intestinal mucosa in hepatic cirrhosis. *American Journal of Digestive Diseases* 1960; **5:** 603–612.
111. Norman DA, Atkins JM, Seelig LL Jr et al. Water and electrolyte movement and mucosal morphology in the jejunum of patients with portal hypertension. *Gastroenterology* 1980; **79:** 707–715.
112. Such J, Guardiola JV, de Juan J et al. Ultrastructural characteristics of distal duodenum mucosa in patients with cirrhosis. *European Journal of Gastroenterology and Hepatology* 2002; **14:** 371–376.
113. Campillo B, Pernet P, Bories PN et al. Intestinal permeability in liver cirrhosis: relationship with severe septic complications. *European Journal of Gastroenterology and Hepatology* 1999; **11:** 755–759.
114. Guarner C, Runyon BA, Heck M et al. Effect of long-term trimethoprim-sulfamethoxazole prophylaxis on ascites formation, bacterial translocation, spontaneous bacterial peritonitis, and survival in cirrhotic rats. *Digestive Diseases and Sciences* 1999; **44:** 1957–1962.
115. Ramachandran A, Prabhu R, Thomas S et al. Intestinal mucosal alterations in experimental cirrhosis in the rat: role of oxygen free radicals. *Hepatology* 2002; **35:** 622–629.
* 116. Garcia-Tsao G. Spontaneous bacterial peritonitis. *Gastroenterology Clinics of North America* 1991; **21:** 257–275.
117. Rimola A, Garcia-Tsao G, Navasa M et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *Journal of Hepatology* 2000; **32:** 142–153.
118. Trevisani F, Castelli E, Foschi FG et al. Impaired tuftsin activity in cirrhosis: relationship with splenic function and clinical outcome. *Gut* 2002; **50:** 707–712.
119. Nettelbladt CG, Katouli M, Volpe A et al. Starvation increases the number of coliform bacteria in the caecum and induces bacterial adherence to caecal epithelium in rats. *European Journal of Surgery* 1997; **163:** 135–142.
120. Alverdy JC, Aoys E & Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery* 1988; **104:** 185–190.
121. Deitch EA, Xu D, Naruhn MB et al. Elemental diet and IV-TPN-induced bacterial translocation is associated with loss of intestinal mucosal barrier function against bacteria. *Annals of Surgery* 1995; **221:** 299–307.
122. Moore FA, Feliciano DV, Andrassy RJ et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. *Annals of Surgery* 1992; **216:** 172–183.
123. Jolliet P & Pichard C. Immunonutrition in the critically ill. *Intensive Care Medicine* 1999; **25:** 631–633.
124. Kudsk KA, Minard G, Croce MA et al. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. *Annals of Surgery* 1996; **224:** 531–540.
125. Spaeth G, Specian RD, Berg RD et al. Bulk prevents bacterial translocation induced by the oral administration of total parenteral nutrition solution. *Journal of Parenteral and Enteral Nutrition* 1990; **14:** 442–447.
126. Dickinson EC, Gorga JC, Garrett M et al. Immunoglobulin A supplementation abrogates bacterial translocation and preserves the architecture of the intestinal epithelium. *Surgery* 1998; **124:** 284–290.

127. Eibl MM, Wolf HM, Furnkranz H et al. Prevention of necrotizing enterocolitis in low-birth-weight infants by IgA-IgG feeding. *New England Journal of Medicine* 1988; **319:** 1–7.
128. de Oca J, Bettonica C, Cuadrado S et al. Effect of oral supplementation of ornithine-alpha-ketoglutarate on the intestinal barrier after orthotopic small bowel transplantation. *Transplantation* 1997; **63:** 636–639.
129. Schlegel L, Coudray-Lucas C, Barbut F et al. Bacterial dissemination and metabolic changes in rats induced by endotoxemia following intestinal *E. coli* overgrowth are reduced by ornithine alpha-ketoglutarate administration. *Journal of Nutrition* 2000; **130:** 2897–2902.
130. Gianotti L, Alexander JW & Eaves-Pyles T. Dietary fatty acids modulate host bacteriocidal response, microbial translocation and survival following blood transfusion and thermal injury. *Clilnical Nutrition* 1996; **15:** 291–296.
131. Pscheidl E, Schywalsky M, Tschaikowsky K et al. Fish oil-supplemented parenteral diets normalize splanchnic blood flow and improve killing of translocated bacteria in a low-dose endotoxin rat model. *Critical Care Medicine* 2000; **28:** 1489–1496.
132. Denlinger LC. Low-dose prostacyclin reverses endotoxin-induced intestinal vasoconstriction: potential for the prevention of bacterial translocation in early sepsis. *Critical Care Medicine* 2001; **29:** 453–454.
133. Fukushima R, Gianotti L, Alexander JW et al. The degree of bacterial translocation is a determinant factor for mortality after burn injury and is improved by prostaglandin analogs. *Annals of Surgery* 1992; **216:** 438–444.
134. Fuller RGG. Modification of the intestinal microflora using probiotics and prebiotics. *Scandinavian Journal of Gastroenterology* 1997; **32:** 28–31.
135. Mattar AF, Drongowski RA, Coran AG et al. Effect of probiotics on enterocyte bacterial translocation in vitro. *Pediatric Surgery International* 2001; **17:** 265–268.
136. Perdigon G, de Macias ME, Alvarez S et al. Systemic augmentation of the immune response in mice by feeding fermented milks with *Lactobacillus casei* and *Lactobacillus acidophilus*. *Immunology* 1988; **63:** 17–23.
137. Adawi D, Kasravi FB, Molin G et al. Effect of Lactobacillus supplementation with and without arginine on liver damage and bacterial translocation in an acute liver injury model in the rat. *Hepatology* 1997; **25:** 642–647.
138. Eizaguirre I, Urkia NG, Asensio AB et al. Probiotic supplementation reduces the risk of bacterial translocation in experimental short bowel syndrome. *Journal of Pediatric Surgery* 2002; **37:** 699–702.
139. Mao Y, Nobaek S, Kasravi B et al. The effects of Lactobacillus strains and oat fiber on methotrexate-induced enterocolitis in rats. *Gastroenterology* 1996; **111:** 334–344.
140. Akin ML, Erenoglu C, Dal A et al. Hyperbaric oxygen prevents bacterial translocation in rats with obstructive jaundice. *Digestive Diseases and Sciences* 2001; **46:** 1657–1662.
141. Akin ML, Uluutku H, Erenoglu C et al. Hyperbaric oxygen ameliorates bacterial translocation in rats with mechanical intestinal obstruction. *Diseases of the Colon and Rectum* 2002; **45:** 967–972.
* 142. Gennari R & Alexander JW. Effects of hyperoxia on bacterial translocation and mortality during gut-derived sepsis. *Archives of Surgery* 1996; **131:** 57–62.
143. Diebel LN, Liberati DM, Dulchavsky SA et al. Synergistic effect of hyperoxia and immunoglobulin A on mucosal barrier defense. *Journal of Trauma* 1999; **46:** 374–378.
144. Leach RM, Rees PJ & Wilmshurst P. Hyperbaric oxygen therapy. *British Medical Journal* 1998; **317:** 1140–1143.
145. Ziegler EJ, Fisher Jr CJ, Sprung CL et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group. *New England Journal of Medicine* 1991; **324:** 429–436.
146. Angus DC, Birmingham MC, Balk RA et al. E5 murine monoclonal antiendotoxin antibody in gram-negative sepsis: a randomized controlled trial. E5 Study Investigators. *Journal of the American Medical Association* 2000; **283:** 1723–1730.
147. Munster AM, Smith-Meek M, Dickerson C et al. Translocation. Incidental phenomenon or true pathology? *Annals of Surgery* 1993; **218:** 321–326.
148. Warren HS, Danner RL & Munford RS. Anti-endotoxin monoclonal antibodies. *New England Journal of Medicine* 1992; **326:** 1153–1157.
149. Yao YM, Bahrami S, Leichtfried G et al. Pathogenesis of hemorrhage-induced bacteria/endotoxin translocation in rats. Effects of recombinant bactericidal/permeability-increasing protein. *Annals of Surgery* 1995; **221:** 398–405.
150. Kohn FR, Ammons WS, Horwitz A et al. Protective effect of a recombinant amino-terminal fragment of bactericidal/permeability-increasing protein in experimental endotoxemia. *Journal of Infectious Diseases* 1993; **168:** 1307–1310.
151. Giroir BP, Scannon PJ & Levin M. Bactericidal/permeability-increasing protein—lessons learned from the phase III, randomized, clinical trial of rBPI21 for adjunctive treatment of children with severe meningococcemia. *Critical Care Medicine* 2001; **29:** S130–S135.

152. Demetriades D, Smith JS, Jacobson LE et al. Bactericidal/permeability-increasing protein (rBPI21) in patients with hemorrhage due to trauma: results of a multicenter phase II clinical trial. rBPI21 Acute Hemorrhagic Trauma Study Group. *Journal of Trauma* 1999; **46:** 667–676.
153. Fazal N, Shamim M, Khan SS et al. Neutrophil depletion in rats reduces burn-injury induced intestinal bacterial translocation. *Critical Care Medicine* 2000; **28:** 1550–1555.
154. Khorram-Sefat R, Goldmann C, Radke A et al. The therapeutic effect of C1-inhibitor on gut-derived bacterial translocation after thermal injury. *Shock* 1998; **9:** 101–108.
155. Schlag G, Redl HR, Till GO et al. Anti-L-selectin antibody treatment of hemorrhagic-traumatic shock in baboons. *Critical Care Medicine* 1999; **27:** 1900–1907.
156. Deitch EA, Bridges W, Baker J et al. Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. *Surgery* 1988; **104:** 191–198.
* 157. Deitch EA, Bridges W, Berg R et al. Hemorrhagic shock-induced bacterial translocation: the role of neutrophils and hydroxyl radicals. *Journal of Trauma* 1990; **30:** 942–951.
158. von Ritter C, Sekizuka E, Grisham MB et al. The chemotactic peptide *N*-formyl methionyl-leucyl-phenylalanine increases mucosal permeability in the distal ileum of the rat. *Gastroenterology* 1988; **95:** 651–656.
159. Mileski WJ, Hunt J & Kagan RJ. Clinical effects of inhibiting leukocyte adhesion with monoclonal antibody to ICAM-1 in the treatment of partial thickness burn injury. *Proceedings of the American Burn Association* 1998; **19:** S146.
160. Kerver AJ, Rommes JH, Mevissen-Verhage EA et al. Prevention of colonization and infection in critically ill patients: a prospective randomized study. *Critical Care Medicine* 1988; **16:** 1087–1093.
* 161. Selective Decontamination Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *British Medical Journal* 1993; **307:** 525–532.
162. Luiten EJ, Hop WC, Lange JF et al. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Annals of Surgery* 1995; **222:** 57–65.
163. Emre S, Sebastian A & Chodoff L. Selective decontamination of the digestive tract helps to prevent bacterial infections in the early postoperative period of liver transplant. *Mt Sinai Journal of Medicine* 1999; **66:** 310–313.
164. Bernard B, Grange JD, Khac EN et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; **29:** 1655–1661.
165. Tokyay R, Zeigler ST, Traber DL et al. Postburn gastrointestinal vasoconstriction increases bacterial and endotoxin translocation. *Journal of Applied Physiology* 1993; **74:** 1521–1527.
166. Baker JW, Deitch EA, Li M et al. Hemorrhagic shock induces bacterial translocation from the gut. *Journal of Trauma* 1988; **28:** 896–906.
167. Zhi-Yong S, Dong YL & Wang XH. Bacterial translocation and multiple system organ failure in bowel ischemia and reperfusion. *Journal of Trauma* 1992; **32:** 148–153.
168. Akcay MN, Capan MY, Gundogdu C et al. Bacterial translocation in experimental intestinal obstruction. *Journal of International Medical Research* 1996; **24:** 17–26.
169. Lichtman SN, Sartor RB, Keku J et al. Hepatic inflammation in rats with experimental small intestinal bacterial overgrowth. *Gastroenterology* 1990; **98:** 414–423.
170. Kasravi FB, Wang L, Wang XD et al. Bacterial translocation in acute liver injury induced by D-galactosamine. *Hepatology* 1996; **23:** 97–103.
171. Garcia-Tsao G, Albillos A, Barden GE et al. Bacterial translocation in acute and chronic portal hypertension. *Hepatology* 1993; **17:** 1081–1085.
172. Wang X, Andersson R, Soltesz V et al. Gut origin sepsis, macrophage function, and oxygen extraction associated with acute pancreatitis in the rat. *World Journal of Surgery* 1996; **20:** 299–307.
173. Deitch EA, Winterton J, Li M et al. The gut as a portal of entry for bacteremia. Role of protein malnutrition. *Annals of Surgery* 1987; **205:** 681–692.
174. Grant D, Hurlbut D, Zhong R et al. Intestinal permeability and bacterial translocation following small bowel transplantation in the rat. *Transplantation* 1991; **52:** 221–224.
175. Langrehr JM, Machens C, Zill E et al. Bacterial translocation during graft-versus-host disease after small bowel transplantation is reduced following inhibition of inducible nitric oxide synthesis. *Transplantation* 2000; **69:** 2415–2421.
176. Feltis BA, Garni RM & Wells CL. Clostridium difficile toxins and enterococcal translocation in vivo and in vitro. *Journal of Surgical Research* 2001; **97:** 97–102.
177. Schimpl G, Feierl G, Linni K et al. Bacterial translocation in short-bowel syndrome in rats. *European Journal of Pediatric Surgery* 1999; **9:** 224–227.
178. Shoda R, Mahalanabis D, Wahed MA et al. Bacterial translocation in the rat model of lectin induced diarrhoea. *Gut* 1995; **36:** 379–381.
179. Everson CA & Toth LA. Systemic bacterial invasion induced by sleep deprivation. *American Journal Physiology* 2000; **278:** R905–R916.

180. Deitch EA, Ma WJ, Ma L et al. Endotoxin-induced bacterial translocation: a study of mechanisms. *Surgery* 1989; **106:** 292–299. discussion 299–300.
181. Deitch EA. Simple intestinal obstruction causes bacterial translocation in man. *Archives of Surgery* 1989; **124:** 699–701.
182. Ambrose NS, Johnson M, Burdon DW et al. Incidence of pathogenic bacteria from mesenteric lymph nodes and ileal serosa during Crohn's disease surgery. *British Journal of Surgery* 1984; **71:** 623–625.
183. van Goor H, Rosman C, Grond J et al. Translocation of bacteria and endotoxin in organ donors. *Archives of Surgery* 1994; **129:** 1063–1066.
184. Niebauer J, Volk HD, Kemp M et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 1999; **353:** 1838–1842.
185. Alzieu M, Fartoux L & Zuber J. Translocation bacterienne au cours d'une intoxication parla colchicine. *La Presse Medicale* 1999; **28:** 1420.
186. Cornely OA & Schirmacher P. Clinical picture: bacterial translocation in neutropenic sepsis. *Lancet* 2001; **358:** 1842.
187. Tancrede CH & Andremont AO. Bacterial translocation and gram-negative bacteremia in patients with hematological malignancies. *Journal of Infectious Diseases* 1985; **152:** 99–103.
188. Erbil Y, Berber E, Ozarmagan S et al. The effects of sodium deoxycholate, lactulose and glutamine on bacterial translocation in common bile duct ligated rats. *Hepatogastroenterology* 1999; **46:** 2791–2795.
189. Ozaslan C, Turkcapar AG, Kesenci M et al. Effect of lactulose on bacterial translocation. *European Journal of Surgery* 1997; **163:** 463–467.
190. Ozcelik MF, Eroglu C, Pekmezci S et al. The role of lactulose in the prevention of bacterial translocation in surgical trauma. *Acta Chirologica Belgica* 1996; **96:** 44–48.
191. Schimpl G, Pesendorfer P, Steinwender G et al. Allopurinol reduces bacterial translocation, intestinal mucosal lipid peroxidation, and neutrophil-derived myeloperoxidase activity in chronic portal hypertensive and common bile duct-ligated growing rats. *Pediatric Research* 1996; **40:** 422–428.
192. Radke A, Mottaghy K, Goldmann C et al. C1 inhibitor prevents capillary leakage after thermal trauma. *Critical Care Medicine* 2000; **28:** 3224–3232.
193. Rollwagen FM, Li YY, Pacheco ND et al. Systemic bacteraemia following haemorrhagic shock in mice: alleviation with oral Interleukin 6. *Cytokine* 1996; **8:** 121–129.
194. Schindel D, Maze R, Liu Q et al. Interleukin-11 improves survival and reduces bacterial translocation and bone marrow suppression in burned mice. *Journal of Pediatric Surgery* 1997; **32:** 312–315.
195. Gennari R, Alexander JW, Boyce ST et al. Effects of the angiotensin converting enzyme inhibitor enalapril on bacterial translocation after thermal injury and bacterial challenge. *Shock* 1996; **6:** 95–100.
196. Tadros T, Traber DL, Heggers JP et al. Angiotensin II inhibitor DuP753 attenuates burn- and endotoxin-induced gut ischemia, lipid peroxidation, mucosal permeability, and bacterial translocation. *Annals of Surgery* 2000; **231:** 566–576.
197. Dickinson E, Tuncer R, Nadler E et al. NOX, a novel nitric oxide scavenger, reduces bacterial translocation in rats after endotoxin challenge. *American Journal of Physiology* 1999; **277:** G1281–G1287.
198. Lorenzo-Zuniga V, Bartoli R, Planas R et al. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. *Hepatology* 2003; **37:** 551–557.
199. Kouris GJ, Liu Q, Rossi H et al. The effect of glucagon-like peptide 2 on intestinal permeability and bacterial translocation in acute necrotizing pancreatitis. *American Journal of Surgery* 2001; **181:** 571–575.
200. Wang X, Wang B, Wu J et al. Beneficial effects of growth hormone on bacterial translocation during the course of acute necrotizing pancreatitis in rats. *Pancreas* 2001; **23:** 148–156.