Alimentary Pharmacology & Therapeutics

Review article: bacterial translocation in the critically ill – evidence and methods of prevention

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SUMMARY

Background
Delayed sepsis, systemic inflammatory response syndrome (SIRS) and multiorgan failure remain major causes of morbidity and mortality on intensive care units. One factor thought to be important in the aetiology of SIRS is failure of the intestinal barrier resulting in bacterial translocation and subsequent sepsis.

Aim
This review summarizes the current knowledge about bacterial translocation and methods to prevent it.

Methods
Relevant studies during 1966–2006 were identified from a literature search. Factors, which detrimentally affect intestinal barrier function, are discussed, as are methods that may attenuate bacterial translocation in the critically ill patient.

Results
Methodological problems in confirming bacterial translocation have restricted investigations to patients undergoing laparotomy. There are only limited data available relating to specific interventions that might preserve intestinal barrier function or limit bacterial translocation in the intensive care setting. These can be categorized broadly into pre-epithelial, epithelial and post-epithelial interventions.

Conclusions
A better understanding of factors that influence translocation could result in the implementation of interventions which contribute to improved patient outcomes. Glutamine supplementation, targeted nutritional intervention, maintaining splanchnic flow, the judicious use of antibiotics and directed selective gut decontamination regimens hold some promise of limiting bacterial translocation. Further research is required.

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INTRODUCTION

The gastrointestinal tract (GIT) has a multitude of functions other than digestion. The alimentary tract produces numerous hormones with local and systemic effects, as well as representing the single largest immunological organ of the body. The gut also serves as a barrier against living organisms and antigens within its lumen; the so-called '*intestinal barrier function*'.[1–4] The fact that luminal contents in the caecum have a bacterial concentration of the order of 10^{12} organisms/mL of faeces,[5] whilst portal blood, mesenteric lymph nodes (MLNs) and indeed tissues one cell deep to the intact intestinal mucosa are usually sterile, dramatically illustrates the efficacy of this barrier. This role of the gut serves to manage luminal antigens, encouraging the symbiotic relationship between man and enteric bacteria, while ensuring that the internal milieu remains sterile. Breakdown or overwhelming of this barrier may result in the ingress of viable bacteria and their antigens with the development of sepsis, initiation of a cytokine mediated systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), and death. This process is known as bacterial translocation and describes the so called '*gut origin of sepsis hypothesis*',[6, 7] represented graphically in Figure 1. The role of the gut as the motor of multiple organ failure may help explain the absence of a discreet focus of infection in most patients with delayed SIRS and MODS.[8] A better understanding of the mechanisms involved may delay or prevent the onset of SIRS and MODS in the critically ill. This review summarizes the current knowledge on bacterial translocation and factors which detrimentally affect intestinal barrier function. Methods of attenuating bacterial translocation and its ill effects in the intensive care setting are discussed.

SEARCH METHODS

Relevant studies during 1966–2006 were identified from a Medline, PubMed and Cochrane database search. Original articles and reviews in all languages were collated. The authors' own studies and private collections, as well as books in print were also used to identify relevant studies. Search terms included those of 'bacterial translocation', 'prevention', 'human', 'intensive care', 'critical illness', 'enteral nutrition', 'parenteral nutrition', 'immunonutrition', 'glutamine', 'sepsis' and 'multiple organ failure'.

Level 1 evidence from human studies was conspicuous by its absence. No randomized controlled trials could be identified specifically addressing the issue of bacterial translocation and its prevention in humans.

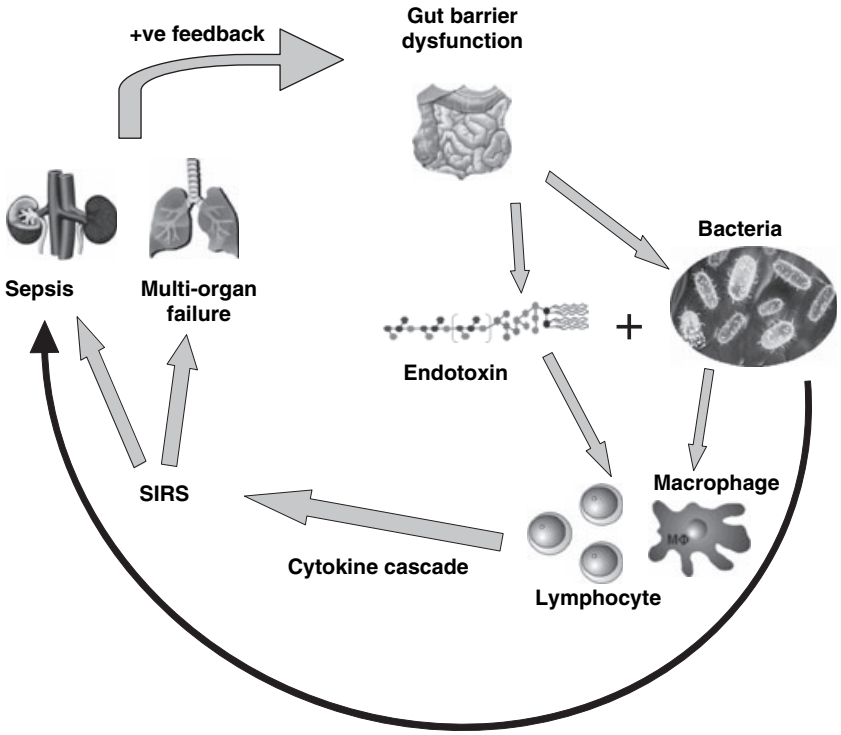

Figure 1. The gut origin of sepsis hypothesis, with bacterial translocation as a potential stimulus for ongoing inflammation.

Studies presented in this review therefore represent level 2 to level 4 evidence. Where possible, emphasis was given to human clinical studies, but trials using animal or *in vitro* models have also been included particularly where little or no human data were available.

BACTERIAL TRANSLOCATION: AN OVERVIEW

The idea that the alimentary tract, teeming with its own bacterial flora, could represent a source of sepsis under certain conditions has interested clinicians for many years. This theory, usually referred to as the *'gut origin of sepsis'* hypothesis, is not new. In the late 19th century, the idea evolved that peritonitis could result from the passage of bacteria from organs adjacent to the peritoneal cavity. In Germany this was referred to as '*durchwanderungs-peritonitis*', literally translated as 'wandering through peritonitis'. In 1891 and 1895, two separate investigators hypothesized that viable bacteria could pass through the intact gut wall *in vivo*.[9, 10] It was Berg and Garlington who in 1979 defined this phenomenon as *bacterial translocation*.[11]

Translocation is used to describe the passage of viable resident bacteria from the GIT, across the mucosa, to normally sterile tissues such as the MLNs and other internal organs.[11] The term also applies to the passage of inert particles and other antigenic macromolecules, such as lipopolysaccharide endotoxins and peptidoglycans, across the intestinal mucosal barrier. It is usually assumed that the colon, with its much higher bacterial load, must be the most probable site of bacterial translocation. It would seem unlikely that translocation would occur from other parts of the normally sterile intestinal tract but there is no clinical or experimental evidence to confirm this.

Whist it is tempting to think that any bacteria or endotoxin passing through the intestinal barrier might cause septic complications in the host, there is growing evidence to suggest that translocation may in fact be a normal phenomenon. It is possible that translocation occurs to allow the alimentary tract to be exposed to and sample antigens within the lumen such that the gut can mount a controlled local immune response helping to keep these antigens away from the internal milieu, a process known as 'oral tolerance'.[12–14] It is then only when the host's immune defences are overwhelmed or otherwise defective that septic complications arise.

Numerous modifications on the 'gut origin of sepsis hypothesis' have been put forward. Deitch proposed the 'three hit model'[15]. In this model, an initial insult results in splanchnic hypoperfusion (first hit) with the gut becoming a major site of proinflammatory factor production. Resuscitation results in reperfusion which leads to an ischaemia-reperfusion injury to the intestine (second hit) with a resultant loss of gut barrier function and an ensuing enhanced gut inflammatory response, without the need for translocation of microbes as far as the MLNs or beyond. Once bacteria or endotoxin cross the mucosal barrier, they can trigger an augmented immune response such that the gut becomes a proinflammatory organ, releasing chemokines, cytokines and other proinflammatory intermediates which affect both the local as well as the systemic immune systems (third hit), finally resulting in SIRS and MODS.

Another modification of the 'gut origin of sepsis hypothesis' is known as the 'gut-lymph theory'[16, 17] which proposes that macrophages and other immune cells in the submucosal lymphatics of the gut wall or the MLNs trap the majority of translocating bacteria. However, those that survive or the cell wall and protein components of the dead bacteria (including lipopolysaccharides and peptidoglycans) along with the cytokines and chemokines generated in the gut, travel via the mesenteric lymphatics to the cysterna chilli, and via the thoracic duct empty into the left subclavin vein to reach the right side of the heart. These inflammatory products then enter the pulmonary circulation and activate the alveolar macrophages, and in so doing contribute to acute lung injury and the progression to adult respiratory distress syndrome (ARDS) and MODS. This theory corroborates work published by Moore *et al.* who failed to demonstrate bacteria or endotoxins in portal venous blood of polytrauma patients.[18, 19] However, the mechanisms by which translocating bacteria, their antigenic components or cytokines generated in the gut set about causing sepsis and MODS remains unclear.

METHODOLOGICAL PROBLEMS IN CONFIRMING BACTERIAL TRANSLOCATION

Luminal bacteria that manage to breach the extrinsic intestinal barrier defences can cross the mucosal epithelium by taking either the transcellular or the paracellular route, or a combination of the two.[20, 21] On entering the *laminal propria*, most bacteria are destroyed by macrophages; however, those that are not enter the portal venous system and associated solid

organs, pass to the MLNs or transgress the peritoneal cavity directly. Confirmation of bacterial translocation (BT) therefore necessitates the identification of bacteria in one or more of these sites, making assessment of bacterial translocation in humans difficult as it necessitates invasive tissue sampling.

In humans, the most reliable method of assessing bacterial translocation is by culture of MLNs. This involves the limited sampling of MLNs at the time of laparotomy using aseptic techniques, and their subsequent culture on appropriate media.[22, 23] A positive culture is considered to indicate bacterial translocation. There are a number of limitations to this technique. Firstly, it restricts *in vivo* studies relating to bacterial translocation to surgical patients undergoing laparotomy. Studies investigating bacterial translocation or barrier function in other clinical conditions have often necessitated extrapolations from animal models. Secondly, there is an ethical and logistical limit to the number of lymph nodes that can be safely sampled in humans. The more extensive sampling possible in animals has resulted in a major disparity in the prevalence of translocation between animal and human studies. Bacterial translocation has been repeatedly reported to occur in approximately 10–15% of surgical patients,[22–24] while some animal studies report a prevalence of greater than 90%.[25–27]

The methodological limitations of confirming translocation in humans have major implications to the understanding of this phenomenon, and particularly so in the critically ill patient. The effects of conditions specific to the intensive care setting (such as prolonged ventilation and the use of protracted inotropic support) on the intestinal barrier and subsequent bacterial translocation are largely unknown. However, recent advances in molecular microbiology have opened new frontiers in identifying bacterial translocation by non-interventional methods. Isolation and sequencing of DNA fragments belonging to enteric bacteria from peripheral blood and other body fluids may yet permit the confirmation of translocation of enteric organisms without the need for invasive sampling.[28–34]

It is important to emphasize that the literature is full of studies using surrogate measures of intestinal barrier function. These include blood cultures with concomitant faecal cultures, intestinal immune markers, bowel scrapings, intestinal permeability measurements, and the culture of nasogastric aspirates. [35–43] It is felt that these do not represent level 1 evidence of bacterial translocation, and as such, the findings of such studies should be interpreted with caution.

FACTORS THAT PREDISPOSE TO TRANSLOCATION

Factors that influence bacterial translocation are believed to act on the delicate homeostatic equilibrium between luminal organisms and the gut barrier, promoting ingress of antigens across the intestinal barrier.[44, 45] These factors are thought to include intestinal obstruction,[23, 24, 46–48] jaundice,[23, 24, 49–52] inflammatory bowel disease,[24, 53, 54] malignancy,[55–57] pre-operative total perenteral nutrition (TPN),[23] emergency surgery,[23] and gastric colonization with microrganisms.[23, 40] Much of the evidence to substantiate these claims is available from animal studies. Further, the number and complexity of factors that interplay at the biome-epithelial interface to bring about translocation makes conclusions regarding factors which are 'independently' important for translocation exceedingly difficult. This is compounded by the fact that most trials investigating translocation have small cohort sizes, permitting only univariate analysis for association.

Increased bacterial loads and breakdown of tight junctions associated with intestinal obstruction are thought to promote bacterial translocation. First proposed by Deitch *et al.*,[47, 58] intestinal obstruction has been shown to promote bacterial overgrowth,[58] and disruption of the intestinal epithelium in animal models,[48, 59, 60] resulting in an increased prevalence of bacterial translocation on univariate analysis.[61] These observations have also been substantiated by some human studies.[23, 24, 46]

Jaundice is almost universally believed to promote translocation in humans. There is a lot of evidence from *in vitro* as well as animal studies that this may indeed be the case.[51, 62] Bile and bile salts within the lumen of the gut are believed to be protective.[52, 63, 64] Ding *et al.* showed that bacterial translocation was more common in rats whose bile ducts was ligated, but these changes were not observed in those receiving bile or bile acids orally.[63] Obstructive jaundice was also shown to impair reticuloendothelial function in rats,[65] with failure of macrophage activation,[66] Kupffer cell function,[67] as well as cause ileal mucosal disruptions,[68] disruption of desmosomes and formation of lateral spaces between enterocytes,[69] whilst also disturbing intestinal permeability and

other aspects of gut barrier function.[25] *In vitro* exposure of enteric bacteria to bile during their growth was observed to result in bacterial cells with decreased invasiveness for cultured intestinal epithelial cells.[70] Absence of bile from within the lumen of the gut was also associated with a quantitative increase in small intestinal microflora as well as disturbance of normal migratory motor complexes.[71] This evidence is further substantiated by observations that many of the ill-effects of jaundice in animals may be reversed by biliary decompression.[72, 73] There is limited information about the effects of jaundice on translocation in humans. The few studies available suggest that there may also be some degree of association.[24, 50]

Total perenteral nutrition is generally administered to patients with non-functioning intestines which cannot tolerate or absorb enteral nutrition. The association of TPN use with bacterial translocation is impossible to separate from underlying gut failure.[23, 74, 75] Likewise, the association of emergency surgery is a reflection of the influence the acute inflammatory response has on the gut barrier function.[23, 76, 77] The complex systemic upset in acute surgical conditions involves relative immunosuppression, increased intestinal permeability, and paralytic ileus, which all interplay to cause gut barrier failure.

To date, there is only one published study that investigated factors independently associated with bacterial translocation in humans. In this study, MacFie *et al*. performed a multivariate analysis on 927 surgical patients to assess factors independently associated with bacterial ingress across the intestinal barrier.[23] From the large number of variables investigated, and in agreement with previously published literature, intestinal obstruction, jaundice, inflammatory bowel disease, malignancy, pre-operative TPN and emergency surgery were all associated with an increased prevalence of bacterial translocation on univariate analysis. Following multivariate analysis, however, only emergency surgery and pre-operative TPN were shown to be independently associated with translocation (Table 1). Even then, the authors were of the opinion that as TPN and gut failure are inextricably linked, and as, to date, there exists no reliable test to identify patients with intestinal failure, the enhanced translocation noticed in this group of patients probably represented little more than underlying gut dysfunction, with TPN representing nothing more than a confounding factor.

Fong *et al*. showed that healthy volunteers on TPN had a higher TNF-α, Cachectin and C reactive protein levels compared with volunteers on enteral nutrition, suggesting that TPN and bowel rest modify the metabolic response to endotoxins in humans.[78] Furthermore animal experiments confirmed that bacterial translocation occurred more frequently after truncal vagotomy than after proximal gastric vagotomy clearly implying the role of the vagus on gut barrier dysfunction.[79] Hasko and Szabo in 1998 suggested that the production of TNF-α, interleukin 6, 10, 12 and chemokine macrophage inflammatory protein 1α are regulated by transmitters and co-transmitters of the autonomic nervous system.[80] Kevin Tracey in 2002 described the parasympathetic regulation of the inflammatory response: 'the cholinergic anti-inflammatory pathway' and demonstrated that efferent vagal nerve stimulation inhibits proinflammatory cytokine release and protects against systemic inflammation.[81] There is increasing evidence to suggest that vagal stimulation and cholinergic agonists acting via the 7α nicotinic acetylcholine (7αn AChR) receptors block endothelial cell activation and leukocyte recruitment during inflammation and improve survival in experimental sepsis.[82] Clearly, therefore, a functioning GIT remains an essential prerequisite for maintaining the integrity of the immune system and gut barrier function in critically ill patients. As TPN is primarily administered to patients with a non-functioning gut, it is not surprisingly that TPN was independently associated with gut barrier dysfunction as measured by bacterial translocation in surgical patients (Table 1).

MEASURES TO REDUCE BACTERIAL TRANSLOCATION

Theoretically, bacterial translocation may be modulated both quantitatively (decreasing the prevalence of translocation) and qualitatively (changing the spectrum of translocating organisms). There is no available 'level 1' evidence that can be used to recommend therapeutic interventions to decrease or somehow modulate bacterial translocation in humans. A number of factors may be of significance in modulating gut barrier function and consequently bacterial translocation in clinical practice. These act at the pre-epithelial, epithelial and post-epithelial levels. It is recognized that these factors may act at more than one site, and indeed at more than one level, but for purposes of clarity have been categorically assigned as summarized in Table 2.

Table 1. Variables independently associated with bacterial translocation in surgical patients

Factor	No. of patients	Bacterial translocation (%)	*P*-value univariate	*P*-value multivariate
All patients	927	130 (14.0)		
Age				
≤70 years	495	60 (12.1)	0.088	
>70 years	432	70 (16.2)		
Sex				
Male	505	62 (12.3)	0.106	
Female	422	68 (16.1)		
Surgery: mode				
Emergency	185	47 (25.4)	<0.001	0.001
Elective	742	83 (11.2)		
Malignancy				
No	384	61 (15.9)	0.180	
Yes	543	69 (12.7)		
Inflammatory bowel disease				
No	834	115 (13.8)	0.530	
Yes	93	15 (16.1)		
Jaundice				
No	872	122 (14.0)	0.843	
Yes	55	8 (14.5)		
Pre-operative TPN				
No	866	115 (13.3)	0.021	0.015
Yes	61	15 (24.6)		
Obstruction				
No	788	99 (12.6)		
Gastric outlet	17	2 (11.8)	0.921	
Small bowel	77	16 (20.8)	0.042	0.895
Large bowel	45	13 (28.9)	0.001	0.246

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Pre-epithelial factors

Luminal nutrients

It is widely recognized that early institution of nutritional support is of benefit, particularly in patients with severe malnutrition[83] and patients with prolonged or severe infirmity.[84–87] Not surprisingly, most reviewers of nutritional support therapy urge the use of enteral (EN) as opposed to parenteral (TPN) feeding. Parenteral nutrition, it is said, results in mucosal atrophy and increased intestinal permeability, which reflect damage to the intestinal barrier. The popular belief is that this predisposes to bacterial translocation and may be one explanation for increased rates of septic complications observed in some studies investigating TPN.[88, 89]

A number of assumptions are implicit in these commonly held views about TPN. Firstly, that bacterial translocation occurs more readily if intestinal barrier function is impaired and is associated with increased incidences of sepsis. Secondly, that septic morbidity is proved to be significantly higher in patients receiving TPN. And thirdly, that the absence of luminal nutrients as might occur during starvation, malnutrition or TPN is associated with deleterious consequences to the gut barrier which predispose to translocation.

There is no evidence to suggest that bacterial translocation is reduced by the use of enteral nutrition.[89–92] There is no evidence to confirm that short-term TPN is associated with villus atrophy or significant changes in intestinal permeability.[93] There is no evidence in humans to support the view that alterations in intestinal barrier function as assessed from changes in

Table 2. Factors which may affect bacterial translocation

Pre-epithelial	Enteral nutrients
	Selective bowel decontamination
	Gastric colonization
	Probiotics and prebiotics
Epithelial	Immunonutrients
	Glutamine and other gut specific nutrients
	Splanchnic blood flow
	Exogenous IgA
Post-epithelial	Vagus nerve stimulation
	Nicotine and cholinergics
	Granulocyte colony stimulating factor
	Direct haemoperfusion and haemofiltration (CHF)
Miscellaneous	Genomes
	Increased intra-abdominal pressures
	Melatonin
	Octreotide
	Lactulose
	Growth hormone
	Insulin-like growth factor 1
	Bowel manipulation
	Opiates
	Multimodal optimization

mucosal architecture or from alterations in intestinal permeability will predispose to an increased prevalence of bacterial translocation.[38] Starvation or malnutrition by themselves do not induce bacterial translocation.[91, 92] Alterations in mucosal architecture or intestinal permeability may indicate certain changes in intestinal barrier function but do not necessarily equate with alterations in the prevalence of bacterial translocation. With the exception of trauma patients,[94, 95] there is no firm evidence that septic morbidity is increased in patients receiving parenteral as opposed to enteral nutrition.[96]

The nature of the nutritional support that should be provided to critically ill patients should be determined by their tolerance to enteral nutrition and not by unfounded fears regarding TPN or unjustified assumptions concerning the role of gut barrier function. In this respect, if TPN is necessary, it should not be withheld on the wrong assumption that it will promote bacterial translocation. Indeed, unfounded fears based on early studies which reported poorer outcomes in patients receiving TPN may be related to the relative hyperglycaemia induced by overfeeding associated with early TPN regimes, as opposed to the intravenous administration of nutrients itself. [88, 89] More recent studies with TPN do not confirm these observations.[96] Clearly, a functioning GIT remains an essential prerequisite for maintaining the integrity of the immune system and gut barrier function. The precise role of luminal nutrients when compared with gut failure from whatever cause cannot be distinguished; however, to date, there is no evidence that the absence of luminal nutrients predisposes to bacterial translocation.

Selective gut decontamination

It may be possible to decrease sepsis from enteric bacteria by means of selective gut decontamination (SGD). The emphasis is on the 'selective' nature of instituted regimes, as it is considered important to diminish the counts of pathogenic Gram–negative microbes and in particular Enterobacteriaceae in preference to commensal anaerobic bacteria.[97] Selective decontamination is achieved through the combined use of oral non-absorbable antibiotics and/or short-term systemic preparations with microbial surveillance.[98] Many different antimicrobial regimes have been used separately or in combination for this purpose. These include, for example, vancomycin, neomycin, tobramycin, polymyxin E and many others.

Whilst there is strong evidence to suggest that SGD is effective in reducing both the intestinal bacterial load[99] as well as respiratory tract infections in the critically ill,[100, 101] studies to date have shown conflicting results in relation to the effects on septic complications and mortality. One possibility for this is the increased free endotoxin load (and subsequent endotoxin translocation) associated with the death of so many bacteria.[102] Another possibility is that decontamination regimes are not specific enough to preferentially eliminate pathogens, and therefore upset the balance of indigenous flora in such a way as to diminish the effects of bacterial antagonism.[103] To date, there are no published papers to indicate that SGD may influence BT; however, the authors have preliminary unpublished data to suggest that by combining SGD with bowel preparation and probiotics, one may indeed influence the spectrum of translocating organisms by decreasing the prevalence of translocation of pathogenic Enterobacteriaceae after bowel mobilization.

Gastric colonization

The proximal GIT contains only a modest number of microorganisms, comprising mainly acid-tolerant lactobacilli and streptococci.[104] The presence of enteric organisms or fungi in gastric aspirates (gastric

colonization) is abnormal and has been shown to be associated with an increased prevalence of bacterial translocation.[40] For this reason, positive nasogastric aspirates may have a role as a surrogate marker of altered intestinal barrier function.[23, 40] Critical illness is often associated with proximal gut overgrowth with enteric organisms. These organisms have been linked to nosocomial infection.[8] Indeed the similarity of organisms identified in septic foci and those cultured from gastric aspirates suggests that the infecting organisms are of gut origin. It would seem logical therefore to adopt measures that discourage bacterial overgrowth in the proximal gut. This has implications to the use of acid suppressing medications,[105–107] acidified enteral feeding,[108] continuous vs. intermittent enteral nutrition,[109–111] broad spectrum antibiotics[112, 113] and a miscellany of other interventions.

Probiotics and prebiotics

Probiotics are defined as live microbial feed supplements that beneficially affect the host by improving its microbial balance. Prebiotics are non-digestible foods, mainly plant fibres, consumed and used by gut bacteria as substrates for fermentation in the lower GIT. They selectively stimulate the growth and activity of beneficial strains of bacteria while also directly benefiting the gut.[114, 115] Furthermore, they may help in promoting gut transit which has been shown to be a determining factor for bacterial translocation in animal models.[116, 117]

The use of probiotics containing *Lactobacillus acidophilus La5*, *Lactobacillus bulgaricus*, *Bifidobacterium lactis BB-12* and *Streptococcus thermophilus* was shown to significantly decrease the prevalence of potentially pathogenic organisms in the upper GIT although this had no effect on gut barrier function as assessed by intestinal permeability measurements.[118]

Epithelial factors

Gut-specific nutrients and Immune enhancing feeds

Numerous immunonutrients, such as glutamine and arginine, that make claim to enhance immune function and improved patient outcomes have been investigated. Trials using such feeds have had inconsistent results.[119–129] The largest meta-analyses of its kind to date involving 26 studies in critically ill patients showed that study subjects randomized to receive immonutrient feeds had reduced risks of developing infectious complications, intra-abdominal abscesses (relative risk, 0.26; 95% CI, 0.12 to 0.55), nosocomial pneumonias (relative risk, 0.54; 95% CI, 0.35–0.84), and bacteraemias (relative risk, 0.45; 95% CI, 0.38–0.84), as well as reduced time on mechanical ventilation, reduced time in intensive care, and an overall reduction in hospital stay.[129] Despite these noted improvements, there was no effect on mortality (relative risk, 1.10; 95% CI, 0.85–1.42). Further, there were no convincing effects of immunonutrition on the incidence of ARDS or multiorgan failure. Whether observed benefits associated with immunonutrition relate to a decreased prevalence of bacteria translocation remains unproved.

The most investigated immunonutrient by far is glutamine. Glutamine is a conditionally essential amino acid[130] being increasingly important in catabolic states such as those found in critical illness. Its gut-specific effects on the post-absorptive small intestine as well as the proximal and distal colon are well known.[131, 132] It is a precursor of nucleotide synthesis, and an essential fuel for rapidly dividing cells including those from the gut epithelium, as well as the reticuloendothelial and immune systems.[130] It is a major substrate of enterocytes, colonoctes, as well as the gut-associated lymphoid tissue (GALT).[131, 133, 134] It has trophic effects on enterocytes, and as such may help maintain gut mucosal integrity under conditions of stress. This has been manifested by decreased intestinal permeability assays associated with glutamine supplementation in critically ill patient,[135] although the clinical relevance of this test remains unclear. Glutamine has also been hypothesized to attenuate the motor that drives gut-mediated systemic inflammation.[131] Proposed mechanisms are numerous and there is mounting experimental evidence that glutamine has direct tissue protective effects (by virtue of its trophic properties on enterocytes[136] and by enhancing heat shock protein expression[137–141]), antioxidant effects (by up-regulating glutathione levels[142, 143]), and also attenuates inducible nitric oxide synthetase expression.[144] Further, glutamine has been shown to attenuate both the gut and systemic elaboration of proinflammatory cytokines,[145–147] it may enhance gut immunoglobulin A (IgA) concentrations,[148, 149] while also preserving tissue metabolic function and ATP levels,[150, 151] and in so doing rendering organs more resilient to stress, shock and ischaemia-reperfusion injury.[152]

Because of these numerous beneficial effects, it is hardly surprising that glutamine has been pursued by investigators as one method of attenuating bacterial translocation, while also negating the negative effects of enteric bacteria that manage to cross the gut barrier. There is ample evidence from animal studies to support this. Salvalaggio *et al.* were able to show that in a rat model supplemental glutamine was associated with a significant reduction in both positive cultures from distant organs and bacteraemic episodes.[153] In humans, glutamine supplementation has been associated with amelioration of mucosal atrophy,[154] improved healing of mucosal injury following radiotherapy and chemotherapy,[155] enhanced gut and systemic immune function,[156, 157] and the direct attenuation of bacterial translocation and sepsis.[158, 159] There is a large literature base to support the observation that glutamine administration to selected intensive care patients is associated with improved outcomes and decreased hospital stays; however, the exact mechanisms responsible are contentious, and whether these relate to any effects on bacterial translocation is debatable.

Arginine, a non-essential amino acid, is important in nitrogen metabolism, the synthesis of polyamine, and ammonia disposition.[130] Arginine undergoes first-pass metabolism in the splanchnic bed, implying that the small intestine is an important site of arginine metabolism. Much of the interest in arginine is related to its role as a precursor for nitric oxide (NO), which in turn has a very wide range of metabolic functions. NO production by the constitutive form of nitric oxide synthetase has been shown to play a role in maintaining the normal intestinal mucosal barrier[160] and is also a determinant of the host defenses against Giardia lamblia[161–163] in humans. Arginine whilst being a non-essential amino acids in the healthy state, is hypothesized to be a conditionally essential nutrients in the severely ill catabolic patient. Its exact role in the critically ill remains to be clarified; however, particular concern has been raised with feeds that contain a high arginine content.[164] As a precursor of NO, arginine supplemented feeds may result in an uncoordinated vasodilatation which might have harmful effects in the critically ill. Further, NO may effect cellular oxygen consumption and utilization. Regulation of NO synthesis is thought to be important in the maintenance of the gut mucosal barrier in the critically ill,[144] with the result that overproduction of NO may cause intestinal mucosal damage, resulting in failure of the gut barrier function with ensuing bacterial translocation. Bertolini *et al.* were able to show that critically ill septic patients randomized to receive high arginine immune-modulating feeds had a significantly higher mortality.[164]

Vitamin A, with its essential roles in epithelial cell integrity and immune function, has been shown to be important in maintaining gut barrier function.[165] Zinc, a trace element and an important component in cell membrane structure and function, serves as an antioxidant and is important in regulating gene expression and protein transcription and synthesis.[130] It is essential to rapidly dividing cells such as those of the immune system and of the gut epithelium[166] and as such may protect against the ingress of bacteria from within the bowel lumen. Zinc supplements have been shown to improve markers of intestinal permeability in children with diarrhoeal diseases,[167] but as previously stated, one remains uncertain of the significance of intestinal permeability measurements as a surrogate marker of gut barrier function.

Splanchnic blood flow, dopexamine, inotropes and ischaemia-reperfusion injury

The gut is an organ that is exquisitely sensitive to systemic cardiovascular and pulmonary disturbances.[168, 169] The normal physiological response to systemic hypoperfusion is the shunting of blood away from the splanchnic circulation, towards more vital organs, despite the fact that states of diminished circulatory volume, systemic inflammation and sepsis result in a significant increase in gut and hepatic oxygen consumption.[170] Oxygenation to the villi in man is depending on a counter current exchange mechanism such that oxygen saturation at the tip of the villi is lower than that of arterial blood. This compounds the normal physiological response to hypoperfusion by rendering the villus very susceptible to ischaemia-reperfusion damage. This is central to the three-hit hypothesis leading to SIRS and MODS as proposed by Deitch.[15] Further, diminished splanchnic blood flow as seen in hypovolaemic shock, and bowel ischaemia, is associated with mucosal disruption, increased intestinal permeability and bacterial translocation, resulting in or perpetuating septic complications and multiorgan failure.[169] The potential importance of the therapeutic manipulation of splanchnic flow and its effect on outcome is illustrated in a number of recent human studies which suggest that the use of the splanchnic vasodilator

dopexamine is associated with a significant reduction in post-operative mortality.[168, 171] Further, studies investigating ischaemia-reperfusion injury during intestinal transplantation may clarify the pathophysiological mechanisms which cause this injury. It remains to be seen whether interventions shown to prevent or attenuate ischaemia-reperfusion tissue damage may also prevent bacterial translocation.

There are a number of ways to increase blood flow to the gut and liver in the critically ill, including correcting hypovolaemia and maintaining an adequate cardiac output. Various inotropic agents, including dopexamine, dobutamine, and dopamine, have vasodilatory properties and may also increase splanchnic blood flow, independent of their effects on cardiac output and blood vessels. The evidence in this respect is often conflicting,[171, 172] probably reflecting the presence of a number of confounding factors such as adequacy of resuscitation, variations in prescribed dosage, and the simultaneous administration of other inotropic agents. Further, different parts of the GIT may show variations in drug response to identical doses of the same inotropic agent.[170, 173] This is further compounded by the difficulty to directly assess splanchnic perfusion in humans. The current consensus appears to suggest that dopexamine increases splanchnic blood flow and increases intramucosal pH in sepsis.[173–177] Dopexamine may also have other beneficial effects on the gut, not clearly elucidated at this time. These may be mediated by direct anti-inflammatory properties[168, 178, 179] or its effect of decreasing amplitude of flow motion in ileal mucosal arterioles.[180] Human studies are needed to clarify the clinical significance of these latter observations. Dobutamine increases splanchnic blood flow after cardiopulmonary bypass independent of cardiac output.[181, 182] Dobutamine also improve both splanchnic oxygenation and gastric intramucosal pH in septic animals and in septic patients.[183, 184] Dopamine, on the contrary, increases splanchnic blood flow in sepsis,[185] which is mediated by numerous vascular dopaminergic receptors found throughout the GIT tract. Whether the beneficial effects of dopexamine and other inotropes may be attributed, at least in part, to a reduction in bacterial translocation remains to be elucidated.

Post-epithelial and miscellaneous factors

Numerous other factors have been shown to influence bacterial translocation in animals. Increased intra-abdominal pressures may result in increased ingress of luminal bacteria, such that measures to control acute abdominal compartment syndrome may lead to a decrease in translocation, and the eventual development of multisystem organ failure.[186] Melatonin has been reported to protect against oxidative injury after ischaemia-reperfusion, and exogenous injection has been shown to decrease bacterial translocation in rats.[187] Similar reductions in murine bacterial translocation were observed after administration of octreotide[188] and lactulose.[189] Enteral feeds supplemented with IgA have been reported to help maintain gut mucosal integrity and villus height while decreasing the *in vitro* transmucosal passage of bacteria.[190, 191] These findings were not observed with immunoglobulin G or lactoferrin administration. Similarly, growth hormone, insulin-like growth factor 1 (IGF-1) recombinant human IGF-1, glucagon-like peptide 2, as well as epidermal growth factor are known to promote enterocyte proliferation,[192, 193] reduce ileal mucosal apoptosis,[194] attenuate cytotoxic damage to the intestinal epithelium,[195] decrease intestinal permeability,[196, 197] and diminish bacterial translocation[192, 193, 195–199] in rats. Their effects on bacterial translocation in humans are unknown.

Intraoperative bowel manipulation has been shown to adversely affect gut barrier function and increase bacterial translocation in humans.[200] It is advisable to implement methods aimed at curtailing operative times, bowel manipulation and indeed the need for laparotomy in the critically ill, in an attempt to decrease bacterial translocation.

Opiate sparing protocols for analgesia are known to reduce nausea and vomiting, enhance transit times, preserve intestinal migratory motor complexes[201] as well as attenuate post-operative gut dysfunction. Because of this, it has been suggested that the use of opiates may increase bacterial translocation.[202] This has been confirmed in rats.[203, 204] Based on best current evidence, it would seem wise to decrease the use of opiates in the critically ill when suitable alternatives are available.

CONCLUSION

There would seem to be little doubt that gut function in general, and intestinal barrier function in particular, are important determinants of outcome in critically ill patients. Methodological problems in confirming bacterial translocation, which is a direct measure of

intestinal barrier function, has restricted investigations to patients undergoing laparotomy, and as such there is only limited data available relating to specific interventions that might preserve intestinal barrier function or limit bacterial translocation. Based on the best currently available knowledge, glutamine supplementation, aggressive and targeted nutritional intervention, maintaining good splanchnic flow whilst limiting other inotropic support, the judicious use of antibiotics and directed SGD regimes hold some promise of limiting bacterial translocation. Future potential in decreasing bacterial translocation and preserving intestinal barrier function may lie in targeted immunomodulation of GALT as well as other gut-directed therapies aimed at attenuating gut failure and encouraging the earlier return of normal gut function.

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