Current status of bacterial translocation as a cause of surgical sepsis

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Background

In recent years it has been increasingly recognized that the gastrointestinal tract has functions other than simply the digestion and excretion of foodstuffs. The gut is also a metabolic and immunological organ that serves as a barrier against living organisms and antigens within its lumen. This role is termed 'gut barrier function'. The fact that luminal contents in the caecum have a bacterial concentration of the order of $10^{12}$ organisms per millilitre of faeces, whilst portal blood and mesenteric lymph nodes are usually sterile, dramatically illustrates the efficacy of this barrier function.

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 nineteenth century, the idea developed 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.$^{2,3}$ These findings were confirmed after the Second World War by Fine and colleagues$^{4}$ who were able to detect viable bacteria in the peritoneal cavity of dogs in a haemorrhagic shock model. Schatten et al.$^{5}$ demonstrated that bacteria could migrate from the gastrointestinal tract into the portal circulation in the absence of an infective process in humans. Subsequently it has become clear that, in addition to Gram-negative bacteria, endotoxin, Gram-positive bacteria and fungi can pass through the mucosal barrier.$^{6}$ In 1979, Berg and Garlington$^{7}$ defined this phenomenon as ‘bacterial translocation’.

The term ‘bacterial translocation’ is used to describe the passage of viable resident bacteria from the gastrointestinal tract to normally sterile tissues such as the mesenteric lymph nodes and other internal organs.$^{7}$ The term also applies to the passage of inert particles and other macromolecules, such as lipopolysaccharide endotoxin, across the intestinal mucosal barrier.
Bacterial translocation: human studies

There is no doubt that bacterial translocation occurs in humans. It has a prevalence of about 15% in elective surgical patients and occurs more frequently in patients with intestinal obstruction and those who are immunocompromised. There is good evidence to show that translocation is associated with an increased incidence of septic complications, but not with mortality. Many studies have established an association between gastrointestinal microflora and nosocomial infection, supporting the concept of the gut as a reservoir of bacteria and endotoxin. However, the evidence that the mechanism of this association between enteric organisms and subsequent sepsis is bacterial translocation remains, at least in humans, largely circumstantial. This may reflect the methodological and ethical difficulties involved in obtaining samples of portal venous blood or mesenteric lymph nodes, which are necessary for unequivocal confirmation of the occurrence of translocation. To date there has been only one clinical study providing compelling evidence for a mechanistic link between translocation and the development of late sepsis. This study demonstrated that septic complications in 448 surgical patients were significantly more prevalent in those who showed bacterial translocation when compared with patients with no organisms in their mesenteric lymph nodes collected at laparotomy ($P < 0.001$). Furthermore, the spectrum of organisms responsible for septic morbidity was similar to those observed in the mesenteric lymph nodes, many being from enteric strains. These data strongly support the gut origin of sepsis hypothesis.

Whilst it is tempting to assume 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 so that the alimentary tract can 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; this process is known as ‘oral tolerance’. It is only when the host’s immune defences are overwhelmed that septic complications arise. Other authors go further and depict translocation not as the initiator of septic complications, but as a result of other insults which have triggered off a systemic inflammatory response, one of the effects of which is manifested as deterioration or breakdown of gut barrier function.

Bacterial translocation has been shown to occur in various patient populations. As already stated, it occurs in patients undergoing elective abdominal surgery, organ donors and those with intestinal obstruction, colorectal cancer, ischaemia–reperfusion injury shock and pancreatitis. Many authors suggest an increased prevalence in patients with obstructive jaundice, those receiving parenteral nutrition and the malnourished, but
Factors influencing the prevalence of bacterial translocation

Host defence: the mucosal barrier and permeability

Host defence mechanisms directed against invasion by microbes comprise many factors, such as gastric acid, pancreatic enzymes, bile, mucus, bowel motility, the antigen-specific local immune system known as gut-associated lymphoid tissue (GALT) and, arguably most important, the epithelial cell barrier. The intestinal epithelium is a polarized monolayer of enterocytes covered with mucus, a glycocalyx brush border and secretory immunoglobulin A (sIgA). It represents a specialized anatomical barrier separating the luminal contents of the bowel from the internal milieu. Physical breaches in this barrier, which can occur following ulceration, may predispose to translocation. A rapid rate of cellular turnover, specialization and migration helps the intestinal mucosa to maintain physical integrity. Translocation may occur via transcellular or paracellular routes, or a combination of the two. Transcellular translocation is under the control of specific membrane pumps and channels, whereas paracellular translocation is permitted (at least theoretically) by breakdown of tight junctions.

Transcellular migration has been shown to occur in rats where various organisms, including Escherichia coli and Proteus mirabilis, were visualized within intact enterocytes. There is in vitro evidence that opening up the gaps between enterocytes by loosening the intercellular tight junctions may increase bacterial translocation. Tight junctions can adjust their degree of ‘leakiness’ to meet physiological needs, and are also susceptible to numerous pathological stimuli that may change the intestinal permeability. However, it is important to emphasize that there are, as yet, no data from animal or human studies that directly confirm a causative relationship between changes in permeability and bacterial translocation. Similarly, there is no evidence to confirm that gross changes in villus morphology are causally related to increased rates of translocation.

Gastrointestinal microflora

The human gastrointestinal tract contains a wide variety of aerobic and anaerobic bacteria. Absolute bacterial counts vary along the length of the bowel, increasing from a concentration of \(10^8\) organisms/ml in the region of the distal ileum to \(10^{12}\) organisms/ml beyond the ileocaecal...
valve. The upper gut and stomach are usually sterile or are sparsely populated with relatively avirulent bacteria. It is a remarkable testimony to the efficiency of the intestinal barrier that large populations of indigenous bacteria reside in the healthy lower gut without causing harm. This indigenous microflora exerts an important influence in preventing colonization with exogenous pathogens, so-called colonization resistance. Many factors have been implicated in the regulation of the different populations of microflora. These include the creation of ‘microclimates’ whereby facultative bacteria, for example, utilize oxygen, thereby ensuring a suitable environment for obligate anaerobes. This has prompted suggestions that obligate anaerobic bacteria may be the principal inhibitors of translocation of E. coli and other potentially pathogenic bacteria. Disruption of the normal flora may predispose to a breakdown in colonization resistance. This may occur, for example, with antibiotic therapy and there is evidence that substrate utilization by different organisms will also influence other bacterial concentrations.

Critical illness is often associated with significant proximal gut overgrowth of enteric organisms, which may contribute to nosocomial infection. The similarity in the spectrum of organisms identified in septic foci and those cultured from gastric aspirates suggests that the infecting organisms are of gut origin. This infers, but does not prove, a role for bacterial translocation. Marshall et al. showed that >90% of their intensive care unit (ICU) patients with infection had at least one episode of infection with an organism that was simultaneously present in the upper gastrointestinal tract. In our own studies we have consistently found organisms in mesenteric lymph nodes that are similar to those identified in septic foci as overgrowth in the upper gut. All these data point to the importance of the gastrointestinal microflora in maintaining health and that disruption is associated with illness. However, it should be emphasized that the influence of enteric bacteria is not simply related to population density of specific bacteria. Gram-negative facultative anaerobes, particularly E. coli, are consistently shown to be the most common organisms identified in mesenteric lymph nodes. Obligate anaerobes are known to translocate but rarely do so despite their luminal concentrations. Thus it appears that absolute intraluminal population density is not a major determinant of translocation and therefore it is unlikely that rates of translocation will be influenced by alterations in gut permeability.

**Immune status**

Under normal circumstances, translocating bacteria should be phagocytosed before reaching mesenteric lymph nodes or lymphatic vessels. The presumption is that if the host is immunocompromised the normal
defence mechanisms fail, permitting egress and survival of these bacteria at distant extra-intestinal sites. The inference is that with increasing severity of illness, bacterial translocation occurs because of the inability of the host to deal adequately with the numbers of bacteria present. Much experimental evidence exists to support this concept. Bacterial translocation is more common in athymic mice than in control animals, suggesting a specific role for T-cell-mediated immunity in inhibiting translocation.\textsuperscript{20} Immunosuppressant agents and leukaemia have been associated with increased translocation to mesenteric lymph nodes in rodents, and leukaemia has been associated with increased translocation to blood in humans. The possibility that bacterial translocation may not be an all-or-none phenomenon has been previously suggested. There is experimental evidence in human studies attesting to the invariable presence of \textit{E.coli} \(\beta\)-galactosidase in the cytoplasm of mesenteric lymph nodes but positive cultures in only 5\% of the same patients.\textsuperscript{21} This suggests translocation and subsequent control in the mesenteric nodes. The association between multi-organism colonies and an increasing incidence of postoperative sepsis, as shown in our own studies,\textsuperscript{12} is compatible with this speculative mechanism of translocation and is probably a manifestation of immunosuppression. Furthermore, it is of some interest to note that our results show that the incidence of bacterial translocation was greatest in patients aged \(>70\) years, those undergoing urgent surgery and those with intestinal obstruction, all of whom might be expected to have a degree of impaired immunity.\textsuperscript{8,12} Bacterial translocation may thus serve as a promoter of septic morbidity, but not actually be the initiator.

\textit{Miscellaneous factors}

Many other factors have been shown to influence translocation, particularly in animals, and these have been extensively reviewed elsewhere.\textsuperscript{6,16,22} These include stress, jaundice, radiation, variations in intestinal motility and various drugs. Prokinetic agents such as cisapride and propranolol have been shown to decrease translocation, as have sucralfate, bile salts and prostaglandin analogues. Other drugs have been shown to increase translocation. These include chemotherapeutic and immunosuppressive agents as well as certain antibiotics.

\textbf{Bacterial translocation and nutritional support}

There is now a consensus that perioperative nutritional support is of benefit, particularly to patients with severe malnutrition. Most reviewers of nutritional support therapy urge the use of enteral nutrition (EN) as
opposed to parenteral nutrition (TPN), on the assumption that the latter is associated with mucosal atrophy and increased intestinal permeability which reflect damage to the intestinal barrier. This, it is often stated, predisposes to bacterial translocation and may be one explanation for increased rates of septic complications observed in some studies investigating TPN.

A number of assumptions are implicit in these commonly held views about TPN. The first assumption is that bacterial translocation does occur in humans, occurs more readily if intestinal barrier function is impaired and is associated with increased incidences of sepsis. The second is that septic morbidity has been proved to be significantly higher in patients receiving TPN. The third is that the absence of luminal nutrients, for example during starvation, malnutrition or TPN, is associated with deleterious consequences to the gut barrier which predispose to translocation.

Bacterial translocation does occur on a frequent basis in humans. It is associated with increased septic morbidity supporting the concept of the gut origin of sepsis hypothesis. However, it probably also occurs in healthy individuals but is not significant in the non-immunocompromised host. There is no evidence to suggest that bacterial translocation is reduced by the use of EN or increased in patients receiving TPN. There is no evidence to confirm that short-term TPN is associated with villus atrophy or significant changes in intestinal permeability or to support the view that alterations in intestinal barrier function, as assessed from changes in mucosal architecture or from alterations in intestinal permeability, will predispose to an increased prevalence of bacterial translocation in humans. Starvation or malnutrition by themselves do not induce bacterial translocation. Alterations in mucosal architecture or intestinal permeability may indicate changes in intestinal barrier function, but do not necessarily equate to alterations in the prevalence of bacterial translocation. With the exception of trauma patients, there is no firm evidence that septic morbidity is increased in patients receiving TPN as opposed to EN.

The nature of the nutritional support that should be provided to patients should be determined by their tolerance to EN and not by unproven assumptions concerning the role of gut barrier function.

**Gut-specific nutrients**

There is an increasing body of knowledge that suggests that certain nutrients have specific effects on gut function. These are sometimes referred to as ‘functional foods for the gastrointestinal tract’. For example, glutamine is known to be the preferred fuel source of the enterocyte and has been shown to impact on intestinal permeability, and may reduce rates of translocation in animal studies. Other ‘gut-specific nutri-
Bacterial translocation and surgical sepsis

There is now much circumstantial evidence to support the view that translocation is associated with an increase in septic morbidity. To date, however, there has been only one study attempting to prove a mechanistic link between translocation and the development of late sepsis. In this prospective controlled study of 279 surgical patients, cultures of nasogastric aspirates were compared with those from mesenteric lymph nodes taken at laparotomy and with organisms cultured from subsequent septic complications.12 Only 31% of patients had a sterile nasogastric aspirate; the most frequently identified organisms were *Candida* spp. (54%) and *E.coli* (20%). Multiple organisms were isolated in 39% of patients but were cultured more frequently in patients aged >70 years \( (P < 0.01) \), those undergoing non-elective surgery \( (P < 0.001) \) and those requiring proximal gastrointestinal surgery \( (P < 0.01) \). Postoperative sepsis was more common in these patients \( (P < 0.01) \). Bacterial translocation, assessed by culture of mesenteric lymph nodes, occurred in 21% of patients and was significantly more frequent in those with multiple organisms in their nasogastric aspirates \( (P < 0.01) \). *Escherichia coli* was the most common organism to be isolated from the lymph node specimens (48%) and septic foci (53%). Fungal translocation did not occur. An identical genus was identified in the nasogastric aspirate and septic focus in 30% of patients, in the nasogastric aspirate and the lymph node in 31%, and in the lymph node and a postoperative septic focus in 45%. The authors concluded that proximal gut colonization is associated with both increased bacterial translocation and septic morbidity. The commonality of organisms identified was considered as compelling evidence in support of the gut origin of sepsis hypothesis and confirms that bacterial translocation is associated with an increase in postoperative septic morbidity.

The potential importance of the gut origin of sepsis theory in the causation or perpetuation of multiple organ dysfunction (MOD) has been reviewed elsewhere.6,13 The data in support of MOD infections originating from the gut are strong. Epidemiological studies have convincingly demonstrated that the gut is the reservoir for pathogens in late MOD-related infections. In addition, there is much circumstantial evidence. Critically ill patients are often maintained on TPN and receive no enteral stimulation for long periods. It has been suggested, although not confirmed, that this may be associated with increased rates of septic morbidity related to bacterial translocation. These patients also frequently receive narcotics (which depress gut motility) together with antacids and...
broad-spectrum antibiotics, all of which can lead to alterations in gastrointestinal microflora which may in turn predispose to translocation. Gut-specific interventions have been shown to reduce ICU-acquired infection. Thus sucralfate, which maintains gastric acidity, may reduce nosocomial pneumonias.\(^\text{27}\) Recent work has shown that preoperative optimization of oxygen delivery with fluid and the splanchnic vasodilator dopexamine in surgical patients can also significantly reduce postoperative mortality, which may be a reflection of improved gut function.\(^\text{28}\)

Although these data support the view that the gut origin of sepsis hypothesis is valid as an explanation for some episodes of sepsis in the critically ill, are they sufficient to account for the development of systemic inflammatory response syndrome (SIRS) or MOD? There is increasing support for the concept of a ‘two-hit model’ to explain the clinical and metabolic changes that occur in multiple organ failure (MOF). In this first hit, direct cell trauma as a consequence of mechanical, thermal or cytotoxic injury, or cell ischaemia from shock, results in an inflammatory response that is appropriate and potentially advantageous. It would seem unlikely that bacterial translocation has any role in the pathogenesis of these early responses. In some patients, a second hit occurs as a result of repeated surgery, transient bacteraemia or persistent cell damage related to the initial injury. The two-hit theory suggests that the ongoing inflammatory response results in either an excessive compensatory anti-inflammatory response or an imbalance between pro- and anti-inflammatory responses. In other words, an autodestructive inflammation occurs which is the manifestation of severe and sometimes irreversible cell damage induced by cytokine mediators. Bacterial translocation has been suggested as inducing or perpetuating this continuous inflammatory state as endotoxin is known to induce the release of both pro- and anti-inflammatory cytokines.

There is substantial evidence from animal studies to support this theoretical basis of SIRS and MOD. In particular, there is good evidence to suggest that the mechanism behind continued inflammation of the gut is an ischaemia–reperfusion injury. In humans, the counter-current oxygen tension at the tip of the villus is lower than that in arterial blood. As a consequence epithelial cell injury may develop in any situation in which tissue oxygenation is diminished. This injury may permit bacterial translocation, which acts as a perpetuator of the inflammatory response. Evidence for this in human experiments is scant. Cabie \textit{et al.}\(^\text{29}\) reported significantly higher levels of tumour necrosis factor in the portal vein than in the systemic circulation in patients undergoing aortic surgery.\(^\text{29}\) Shenkar and Abraham\(^\text{30}\) described the first induction of cytokine mRNA after haemorrhage into the gut. These data are in accord with the possibility that, on reaching the lamina propria, endotoxin or bacteria encounter macrophages which locally produce cytokines without it being necessary
to first transport endotoxin or bacteria via the portal vein to the liver or mesenteric lymph nodes. This would also account for the failure of clinical studies to consistently identify endotoxin or bacteria in patients with SIRS or MOD.

Oxygenation to the villi in humans is dependent on a counter-current exchange mechanism such that oxygen saturation at the tip of the villi is lower than that of arterial blood. Consequently, any reduction in splanchnic blood flow is likely to result in ischaemia–reperfusion damage. Diminished splanchnic blood flow, as seen in hypovolaemic shock and bowel ischaemia, is associated with translocation and septic complications in animal models. The potential importance of splanchnic flow as a determinant of outcome in humans with critical illness is supported by the findings of a recent study which demonstrated that the use of the splanchnic vasodilator dopexamine was associated with a significant reduction in post-operative mortality. Whether this was a result of reduced translocation is unclear. It has been suggested that splanchnic hypoperfusion results in the gut becoming a major site of proinflammatory factor production. The possibility exists that splanchnic hypoperfusion can lead to an ischaemia–reperfusion injury to the gut, with a resultant loss of gut barrier function and an ensuing gut inflammatory response without the need for translocation of microbes as far as the mesenteric lymph nodes or beyond. Once endotoxin or bacteria cross the mucosal barrier, even if trapped within the gut wall, they can trigger an immune response such that the gut becomes a proinflammatory organ, releasing chemokines, cytokines and other proinflammatory intermediates which affect both the local and the systemic immune systems, finally giving rise to SIRS and MOF. Deitch has termed this ‘the three-hit model’ of gut inflammation. It comprises hypoperfusion, ischaemia–reperfusion injury and the loss of gut barrier function in association with a markedly increased proinflammatory response. In this model it is not considered that the gut barrier is simply a barrier to the passage of intraluminal bacteria to distant sites, but rather that bacteria or gut ischaemia, or both, cause the gut-associated lymphoid tissue to generate immuno-inflammatory factors that contribute to distant organ injury.

**Conclusion**

The gut origin of sepsis hypothesis is an attractive and simple concept that presupposes that bacteria cross the intestinal barrier and cause sepsis at distant sites. There is now good evidence from human subjects to support this theory, which confirms that translocation predisposes to an increase in septic morbidity. Bacterial and endotoxin translocation probably also occurs to a limited extent on a regular basis in healthy individuals.
In this situation translocation serves to provide an antigenic stimulus, but normal barrier function is preserved and morbidity does not ensue. Only if normal mechanisms of defence are overwhelmed does translocation occur. Therefore there seems little doubt that the phenomenon of bacterial translocation is associated with septic morbidity. However, it is very important to place this in the context of the surgical or nonsurgical patient. Septic morbidity is multifactorial. Bacterial translocation is likely to play an aetiological part in only a minority of patients. Other factors are equally important in the causation of postoperative septic morbidity. These may relate to colonization of the upper gut, aspiration or the presence of indwelling foreign material such as catheters and lines, and cannot be directly attributed to the phenomenon of translocation. Similarly, whilst it is almost certainly true that translocation is a factor in the causation of SIRS and/or MOF in those patients who survive the first insult of their trauma, it is difficult in the present state of our knowledge to define the relative importance of this compared with other factors. In particular, it is disappointing to record that the attractive simplicity of the gut origin of sepsis hypothesis, whilst confirmed in certain patients has not yet been associated with any proven beneficial therapeutic measures in patient care. In particular, attempts at selective gut decontamination, the use of pre- or probiotics, alterations in preoperative antibiotic prophylaxis and mechanical bowel preparation have not translated into benefits to patient care with particular regard to septic morbidity. Bacterial translocation remains a fascinating epiphenomenon to those with an interest in the metabolic care of the critically ill surgical patient. It is not, as yet, a reason to change clinical practice.

References


