The gastrointestinal tract as a barrier in sepsis

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The gastrointestinal tract is an organ of digestion and absorption which is metabolically active and has specific nutrient requirements. In health, it has an additional function as a major barrier, protecting the body from harmful intraluminal pathogens and large antigenic molecules. In disease states, such as sepsis when the mucosal barrier is compromised, micro-organisms and their toxic products gain access to the portal and systemic circulations producing deleterious effects. Under these circumstances, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) develop leading to deterioration and death of the patient in the intensive care unit. Therapeutic strategies for such patients in the intensive care unit aim to support general immune function and maintain the structure and function of the gastrointestinal tract. For these therapies to be successful, the underlying septic or necrotic focus must be ablated using appropriate surgical or other invasive techniques.

Sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) complicate the investigation and management of several surgical diseases. These include major trauma, obstructive jaundice, inflammatory bowel disease, acute pancreatitis, intra-abdominal sepsis and major vascular surgery. These clinical conditions and their septic complications are characterised by a state of ‘hypermetabolism’, which leads to a rapid consumption of endogenous stores of protein and energy, immunological dysfunction and deterioration of organ function. These changes which affect the liver, kidney, gastrointestinal tract, heart and lungs are orchestrated by a series of neuroendocrine events and the release of cytokines, activators and mediators. The ‘gut-liver axis’ appears to have a central role in these responses.

In recent years, the gastrointestinal tract has assumed more importance in the management of the septic patient in the intensive care unit. Previously, the gastrointestinal tract was regarded as an organ that contributed little to the pathophysiology of sepsis but it is now recognised that the small intestine and colon make important contributions to the maintenance of hypermetabolism in sepsis, SIRS and MODS. This is due to changes in gastrointestinal structure and function that promote loss of intestinal barrier function and associated changes in hepatic Kupffer...
cell function. When taken in conjunction with abnormal colonisation by luminal micro-organisms, bacterial translocation and absorption of toxins due to increased intestinal permeability, there is a constant trigger to the widespread activation of pro-inflammatory cells and the release of other mediators of the metabolic response to sepsis. This produces profound systemic changes in metabolic homeostasis and immunological dysfunction. These problems appear to be enhanced by malnutrition.

Pathophysiology of sepsis

Sepsis and related conditions present a gradation of severity of illness. Minimal derangement of normal physiology and rapid restoration of metabolic homeostasis with therapy is at one end of the spectrum. At the other extreme, is massive disruption of normal organ function, which leads to progressive deterioration and death despite treatment. Central to our understanding of these events is an appreciation that initially there is a localised response to injury. If the local host defence mechanisms are inadequate or overwhelmed, this may lead subsequently to systemic manifestations. Localised infections due to bacteria, viruses, fungi and parasites stimulate the release of various mediators, e.g. cytokines, prostaglandins, thromboxanes, platelet activating factors and the complement system. These mediators help to combat infection by activating neutrophils with consequent degranulation and release of oxygen radicals, which increase local blood flow and vascular permeability allowing the influx of phagocytic cells. They also activate white blood cells and induce chemotaxis. If the severity of the infection is sufficient that these mediators spill over into the systemic circulation, a septic cascade is initiated which leads to septic shock, SIRS, and MODS. Superoxide radicals now damage host cells. Endotoxin, tumour necrosis factor, the interleukins, transforming growth factor beta and prostaglandin E2 all contribute to the initiation and maintenance of this cascade, which may be beneficial or detrimental, depending on the clinical setting.

Sepsis is not synonymous with overwhelming infection and in many patients who fit the criteria for SIRS, no micro-organism can be demonstrated or cultured. Our understanding of the development of organ failure and death has expanded greatly since originally described and we now recognise three stages in the development of SIRS. The balance between the anti-inflammatory systemic response and the pro-inflammatory systemic response is important for metabolic homeostasis, and the disruption of this equilibrium gives rise to a number of syndromes (Fig. 1). Clinical manifestations of these syndromes are cardiovascular compromise (shock), suppression of immunity, apoptosis and organ dysfunction. The balance of cytokines, their natural antagonists and
endogenous antibodies to endotoxins is important in determining outcome in patients with sepsis syndrome.\textsuperscript{11}

\section*{The gastrointestinal tract in health}

The gastrointestinal tract is regarded primarily as an organ of digestion and absorption but it is a metabolically active organ that requires specific nutrients. It has a major barrier function, protecting the body from harmful intraluminal pathogens and large antigenic molecules.\textsuperscript{12} In addition, it plays a pivotal role in the metabolism of glutamine.\textsuperscript{13} The gut mucosal barrier comprises both immunological and non-immunological protective components, the former being divided into local and systemic components and the latter comprises mechanical and chemical barriers as well as intraluminal bacteria (Table 1). The maintenance of normal epithelial cell structure prevents transepithelial migration of particles from the gut lumen, and the preservation of tight junctions between the cells prevents movement through the paracellular channels.\textsuperscript{14} Acid secretion in the stomach, alkali secretions in the small bowel and mucus production throughout the gastrointestinal tract provides additional protection. The lumen of the gut is colonised by aerobic and anaerobic micro-organisms,
### Table 1 Components of the gut mucosal barrier

<table>
<thead>
<tr>
<th>Immunological</th>
<th>Non immunological</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td><strong>Mechanical</strong></td>
</tr>
<tr>
<td>• Gut associated lymphoid tissue (GALT)</td>
<td>• Healthy enterocyte</td>
</tr>
<tr>
<td>• Intra-epithelial lymphocytes</td>
<td>• Tight junction</td>
</tr>
<tr>
<td>• Submucosal aggregates</td>
<td>• Cell turnover</td>
</tr>
<tr>
<td>• Peyer’s patches</td>
<td>• Normal motility</td>
</tr>
<tr>
<td>• Mesenteric lymph nodes</td>
<td></td>
</tr>
<tr>
<td>• Secretory IgA</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td><strong>Bacteriological</strong></td>
</tr>
<tr>
<td>• Circulatory lymphocytes</td>
<td>• Aerobic micro-organisms</td>
</tr>
<tr>
<td>• Hepatic Kupffer cells</td>
<td>• Anaerobic micro-organisms</td>
</tr>
<tr>
<td><strong>Chemical</strong></td>
<td></td>
</tr>
<tr>
<td>• Gastric acidity</td>
<td>• Salivary lysozyme</td>
</tr>
<tr>
<td>• Lactoferrin</td>
<td>• Mucous secretion</td>
</tr>
<tr>
<td>• Mucous secretion</td>
<td>• Bile salts</td>
</tr>
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and there is a progressive increase in their numbers from the stomach, where gastric acid produces an almost sterile environment, to the colon, which harbours $10^9$ aerobes and $10^{11}$ anaerobes. Under normal circumstances, these micro-organisms remain within the lumen of the bowel where they have important functions in metabolic and nutritional homeostasis. In disease states, when the mucosal barrier is compromised, these micro-organisms and their toxic products may ‘escape’ from the lumen and reach the systemic circulation to produce deleterious effects, despite the presence of other defences, e.g. the gut associated lymphoid tissue (GALT), mesenteric lymph nodes and hepatic Kupffer cells (Fig. 2).

### The gastrointestinal tract in disease

The demonstration of intestinal atrophy manifest by changes in weight, structure and mucosal content of DNA and protein have been assumed to indicate impaired intestinal barrier function, but this has not been confirmed in animal studies of protein malnutrition\(^{15}\). Recent clinical evidence demonstrates a strong association between compromise of gut barrier function and malnutrition, which suggests a mechanism that facilitates gut-derived infection and sepsis\(^{16}\). Dysfunction of the mucosal barrier is thought to result from an imbalance of aggressive and defensive factors on the gastrointestinal mucosa\(^{17}\). Genetic and environmental factors may modify the response of the gastrointestinal mucosa.
Factors influencing intestinal mucosal barrier function

Clinical studies strongly suggest that intestinal barrier dysfunction and increased permeability occur in patients with intestinal inflammation.
and other diseases associated with increased mortality and morbidity\textsuperscript{19}. The significance of this is difficult to determine, but a working hypothesis suggests that translocating micro-organisms and toxins activate a systemic inflammatory cascade and promote organ dysfunction and failure. Factors that predispose to the development of sepsis syndromes are changes in the luminal micro-environment, perfusion and oxygen defects, ischaemia reperfusion injury, malnutrition, and hepatic dysfunction.

\textit{The luminal micro-environment}

In the small intestine, peristalsis, mucus secretions rich in IgA, and resident flora help to minimise the growth of pathogenic species. The peristaltic waves discourage adherence of the organism to the bowel wall and prevent colonisation with overgrowth. The higher bacterial counts in the colon are a reflection of this decreased motility in comparison to the small bowel. The development of paralytic ileus and the formation of a blind loop allow stagnation of intraluminal contents, creating favourable conditions for microbial proliferation. The use of systemic and oral antibiotics cause a reduction in the normal colonisation-resistant resident flora and an increase in number of potentially harmful pathogenic species.

\textit{Perfusion and oxygenation defects}

The mucosa at the tip of the villi is particularly prone to ischaemia due to the counter current exchange mechanism of the vessels and occurs when there is shunting of blood during low flow states. More subtle mucosal damage detectable only microscopically may occur following mild ischaemia. In transient hypoperfusion or hypoxia, the mucosal injury is more pronounced during reperfusion when the oxygen supply is re-established. Blood loss and shock have detrimental effects on the immune and hepatic cells, reducing their capacity to clear bacteria and endotoxin. Blood transfusion can activate polymorphonuclear leucocytes which then sequestrate in various sites and has been implicated in the development of transfusion-related renal and pulmonary pathology. Autologous blood may have the same effect leading to leucocyte activation and cytokine release. The activation and accumulation of neutrophils leads to sludging of capillaries and reduction of mucosal blood flow.

Complete disruption of the bowel wall, which may occur with perforation or frank infarction, can induce profound hypotension and shock due to massive fluid losses into the bowel wall and peritoneal cavity. This may result in the intraluminal contents entering the systemic circulation either directly or indirectly. If there is minimal contamination
and haemodynamic disturbance, the initial invasion will be via the portal system with systemic bacteraemia delayed because of hepatic Kupffer cell activity. With severe intestinal wall damage, direct massive peritoneal contamination and profound shock, bacteria and endotoxin enter the systemic circulation directly from the peritoneal cavity bypassing the protective barrier of the ‘gut-liver axis’.

Ischaemia-reperfusion injury

The causes of intestinal ischaemia are diverse and may represent part of a generalised hypoperfusion insult or decreased blood flow confined to part of the splanchnic circulation. In sepsis, intestinal ischaemia may develop as a result of poor extraction and utilisation of nutrients by the intestine despite normal oxygen content and delivery. Selective splanchnic flow-dependent tissue hypoxia may develop in sepsis whereby oxygen delivery fails to meet demands and blood is shunted away from the mucosa. A reduction in blood flow to a segment of intestine may occur due to obstruction or strangulation of the bowel, or due to atherosclerosis and thromboembolic disease of the splanchnic vessels.

The ischaemic injury sustained and changes observed are dependent on the duration and severity of the ischaemia and whether these changes are reversible. Three patterns of intestinal ischaemia are apparent. These are complete vascular occlusion, compensated partial ischaemia and partial ischaemia followed by reperfusion. In complete vascular occlusion rapid progression to transmural infarction ensues. In compensated partial ischaemia, the injury may be so mild that no morphological or physiological change can be detected or there is a slight alteration in vascular permeability. An increase in intestinal capillary permeability is usually found with 1 h partial regional ischaemia but may occur after only 20 min. If significant partial ischaemia is reversed, the injury sustained by the bowel may be exacerbated by reperfusion. A decrease of intestinal arterial pressure to 25–35 mmHg for 3 h may lead to a loss of villous height and a reduction in mucosal thickness. This mucosal damage is enhanced if the ischaemic episode is followed by 1 h of reperfusion. This reperfusion injury is more severe than that produced by 4 h of ischaemia alone.

When ischaemia is relieved by reperfusion or resuscitation, oxygen-derived free radicals (ODFR) are generated by the xanthine oxidase pathway and cause direct injury to the lipid membranes of cells and hyaluronic acid of their basement membrane. Xanthine dehydrogenase occurs naturally and is found in abundance in the intestine. The dehydrogenase form catalyses the conversion of xanthine and water to uric acid with the reduction of the nicotinamide adenine dinucleotide
molecule. During ischaemia, the xanthine dehydrogenase is converted rapidly by a calcium dependent proteolytic enzyme to xanthine oxidase which generates uric acid and superoxide anion from hypoxanthine and oxygen. The accumulation of hypoxanthine during ischaemia favours the generation of ODER in response to the improvement in oxygenation during reperfusion. Evidence for the role of ODER in producing injury is supported by the reduction in villous and crypt epithelial cell necrosis by allopurinol (a xanthine oxidase inhibitor) and superoxide dismutase (a free radical scavenger) following reperfusion of ischaemic bowel.

The production of ODER together with calcium will activate the plasma membrane phospholipase A\(_2\) which releases arachidonic acid and activates the complement cascade\(^{23}\). Arachidonic acid is then converted to a leucotriene (LT) or thromboxane (TX) depending on whether it follows the lipo-oxygenase or cyclo-oxygenase pathways. Some of these arachidonic acid metabolites especially LTB\(_4\) and TXA\(_2\) and breakdown products of complement, e.g. C5\(_a\) are potent chemo-attractants and chemoactivators which can stimulate neutrophils and up-regulate adhesion molecules on the endothelial membrane. A consequence of this is the margination and adhesion of neutrophils along the wall of the vessel. This leads to the release of more ODER and other proteolytic enzymes which will cause further damage to the epithelium. Sludging and plugging of the capillaries may then occur giving rise to the ‘no re-flow’ phenomenon which will compound the ischaemic insult\(^{24}\). The role played by neutrophils in reperfusion injury is supported by the prevention of ischaemia induced intestinal mucosa injury by pretreatment of animals with monoclonal antibody against neutrophil adhesion molecules\(^{25}\). Neutropenia and inhibition of neutrophil adherence attenuates the increase in microvascular permeability\(^{26}\). The initial injury is related to the direct toxicity of ODER, independent of neutrophil activation, but later damage is dependent on neutrophil activation.

Ischaemia reperfusion injury is not confined to the bowel, and other remote organs and systems may sustain damage as a result of reduction in blood flow followed by revascularisation and successful resuscitation. The impairment sustained by remote organs is dependent on the mass of revascularised ischaemic tissue. The production of ODER and their byproducts is initially confined to the ischaemic region but subsequently spillage into the systemic circulation occurs. An increase in pulmonary permeability and hepatocellular injury have been observed when ischaemic intestine is reperfused\(^{27}\). These injuries to the lungs and liver are associated with sequestration of neutrophils but neutropenic animals are protected. A plasma chemo-activator and chemo-attractant produced following reperfusion of an ischaemic organ can stimulate ODER production by activating neutrophils and increasing microvascular permeability\(^{28}\).
An increase in plasma concentration of tumour necrosis factor (TNF) has been found with intestinal ischaemia with further increases of 5–10-fold following reperfusion. Increased portal vein endotoxin concentrations precede systemically detectable TNF, suggesting that its release may be due to hepatic stimulation by gut-derived endotoxin. TNF is a potent pyrogen and intravenous administration can cause tachycardia, hypotension and death. It activates neutrophils and enhances their phagocytic ability. Remote organ injury may be abrogated by induction of neutopenia and by the use of anti-oxidants such as superoxide dismutase and catalase. Attenuation of the increased microvascular permeability in the lungs is found by pretreating animals with anti-TNF antibody prior to bowel ischaemia reperfusion injury. Administration of anti-TNF does not prevent neutrophil sequestration in the lungs. Pretreatment with interleukin-1 receptor antagonist can reduce the injury and myeloperoxidase activity as a measure of neutrophil infiltration in both lungs and liver following ischaemia reperfusion of the bowel.

**Malnutrition**

The nutritional status of the patient has been shown to be important in determining the outcome of patients following trauma and surgical disease. Patients may present with pre-existing malnutrition due to the inability to swallow, malabsorption, poverty, self-neglect and prolonged starvation following surgery and in the intensive care unit. In patients recovering from abdominal surgery enteral feeding improves muscle function and reduces morbidity and mortality. Malnutrition and total parenteral nutrition have been shown to cause atrophy of the enterocytes and colonocytes. Although total parenteral nutrition (TPN) may improve outcome in those with intestinal failure and in the severely malnourished it may lead to atrophy of the intestinal mucosa and a reduction in IgA antibody production. This is because the enterocytes and colonocytes are better supported by enteral intraluminal infusion of nutrients. Patients who develop sepsis, SIRS and MODS very rapidly develop severe nutritional depletion due to an increase in their rate of metabolism and consumption of their endogenous stores of protein and energy, especially if no attempt is made to support their nutritional status using parenteral or enteral feeding protocols.

**Hepatic dysfunction**

Hyperbilirubinaemia is a common accompaniment to sepsis. It usually represents a direct toxic effect on liver parenchymal cells causing
inflammation in the portal triads and intrahepatic cholestasis. It may be exacerbated by hypovolaemia, the use of intravenous nutrition, drugs and excessive haemolysis. The combination of fever, rigors and obstructive jaundice should always be investigated quickly as ascending biliary sepsis can lead to rapid deterioration of the patient with onset of SIRS and MODS, especially acute renal failure. Extrahepatic biliary obstruction due to stone or stricture may cause ascending cholangitis. Acute acalculous cholecystitis may lead to gall bladder necrosis and biliary peritonitis. Unrecognised and untreated, these conditions have a high mortality so they should be investigated and treated urgently using surgical, endoscopic and radiological techniques. In the absence of extrahepatic pathology which is treatable, sepsis and hyperbilirubinaemia usually indicate severe parenchymal liver disease and/or intrahepatic cholestasis which carries a bad prognosis.

**Treatment of intestinal mucosal barrier dysfunction**

Support of the gut mucosal barrier includes adequate mucosal perfusion, optimal oxygen delivery, prevention of gastrointestinal haemorrhage and maintenance of luminal micro-ecology. These general measures together with more specific measures support enterocyte and colonocyte structure and function.

**Fluid resuscitation**

Hypotension should be reversed with the appropriate intravenous fluids. Initial management should be with crystalloids and depending on response, colloids may be given. Synthetic colloids increase the circulating volume by a greater degree per volume infused than crystalloids but carry the risk of anaphylaxis and coagulopathy. It may be necessary to supplement volume replacement with blood and fresh frozen plasma. In some cases, hypotension is resistant to fluid alone, possibly due to the generation of inflammatory mediators, e.g. TNF and myocardial depressant factor. Inotropic support with dopamine may be required. Dopamine at low doses (3–5 μg/kg/min) increases renal blood flow via its dopaminergic receptors but the effect on splanchnic perfusion remains controversial. It may reduce mucosal perfusion and accelerate the onset of intestinal ischaemia in haemorrhagic shock and in patients with congestive cardiac failure. Higher doses produce vasoconstriction by α-adrenergic stimulation off-setting the vasodilatory effect. If dopamine is inadequate noradrenaline or dobutamine should be considered. However, inotropes are no substitute for adequate fluid replacement therapy.
Tissue oxygenation

Oxygen delivery and degree of shunting due to ventilation/perfusion mismatch in the lungs can be measured from blood gas analysis and the inspired oxygen concentration. An accurate indication of tissue perfusion can be obtained using a silicone tonometer. The principles of the tonometer are based on the assumption that the partial pressure of carbon dioxide within the bowel is similar to that of the lumen, and the concentration of standard bicarbonate within the tissues is similar to that of arterial blood. The tonometer measures the intramucosal pH of the bowel which correlates well with diminished perfusion once oxygen delivery falls below a critical level. The fall in gastric intramucosal pH following cardiac surgery is associated with a higher incidence of morbidity and mortality. Tonometric measurements of gastric pH are an accepted method of monitoring systemic oxygenation and outcome in ICU patients. Sustained acidosis beyond 2 h is highly predictive of mortality and major complications in aortic surgery. Intramucosal acidosis may be an early warning of an impending complication and therapy guided by intramucosal pH measurements may significantly improve outcome in critically ill patients.

Selective digestive decontamination

Gastrointestinal haemorrhage used to be a major problem in septic patients requiring ICU management, but improvements in overall patient management have diminished the problem to an extent that prophylaxis with antacids, H₂ receptor antagonists or sucralfate are used sparingly. The use of selective digestive decontamination (SDD) of the gastrointestinal tract has its advocates. Meta-analysis of the randomised controlled trials of SDD carried out over 15 years showed that it was an effective technique for reducing infection related morbidity and mortality in ICU patients. The data showed that to prevent one respiratory tract infection you would need to treat 5 patients and to prevent one death you would need to treat 23 patients. Although SDD continues to be evaluated in specific groups of patients admitted to ICU, it has not been universally adopted due to doubts about efficacy in a general ICU population and concerns about the development of multiresistant organisms with widespread usage.

Gut barrier dysfunction improves when the intestinal pool of Gram-negative bacteria/endotoxin is reduced by the administration of non-selective or selective antibiotics, lactulose to promote non-pathogenic lactobacilli, or adsorbents to bind intraluminal endotoxin. The administration of anti-inflammatory drugs (steroids), systemically or
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Topically, may enhance the healing of mucosal inflammatory lesions. Intravenous injection of taurolidine, a drug with antiseptic, antibiotic and anti-endotoxin activity, significantly reduces systemic endotoxaemia in experimental colitis whereas systemic broad-spectrum antibiotic (metronidazole and cefuroxime) therapy was ineffective. Administration of anti-TNF antibody (cTN3) significantly reduced systemic endotoxaemia, plasma IL-6 concentration, acute phase protein response and weight loss. Repair of the intestinal barrier may be hastened by multi-targeted therapy aimed at reducing luminal aggressive factors, reducing the inflammatory response (steroids, nitric oxide synthase inhibition, anticytokines) and selective gut nutrition.

Nutritional support

The use of nutritional support techniques improves outcome of patients with sepsis and SIRS. Recently, there have been two major trends in the use of nutritional support. First there is a major shift from intravenous administration of nutrients to enteral feedings and second the quantity of nutrients being administered is decreasing and the quality of nutrient mix is improving. In sepsis, a number of studies have demonstrated that enteral feeding has a major advantage over parenteral nutrition. The beneficial effects of nutrition are its support of generalized immune function, enhancement of mucosal barrier function, reduction of bacterial translocation, modification of hepatic Kupffer cell function, cytokine release and acute phase protein production by the liver. Additional benefits of enteral nutrition are the maintenance of the structural and functional integrity of the gastrointestinal tract by stimulation of 'gut' hormone release, 'gut' motility and mucous production and maintenance of luminal milieu of nutrients, microorganisms and trophic factors that are important for normal digestion and barrier function. The theoretical advantages of enteral nutrition are sometimes undermined by an inability to deliver sufficient nutrients into the gastrointestinal tract due to prolonged ileus, bloating, abdominal distention or diarrhoea. The latter may have a small additional benefit in reducing numbers of luminal bacteria and toxins which are potentially deleterious. If diarrhoea persists, it may lead to dehydration and electrolyte imbalance.

The role of novel substrates in maintaining gut integrity has been extensively reviewed by considering their metabolism in health and disease, the effects on the gut mucosa and the experimental and clinical evidence supporting their use in clinical practice. Evidence that these substrates improve gut mucosal barrier function and increase survival does not necessarily imply that restored barrier function and improved
survival are causally linked. The substrates may exert their beneficial effects by improving nitrogen balance and metabolism or by enhancing immune function and clearance of translocated bacteria. The strongest candidates as selective gut nutrients are glutamine for the enterocyte and short chain fatty acids for the colonocyte. Recent evidence shows that glutamine supplemented parenteral nutrition improves outcome in critically ill intensive care unit patients and surgical patients. The results from studies of enteral supplementation of glutamine are disappointing, but a recent study shows encouraging results in severely injured patients with a low frequency of pneumonia, sepsis and bacteraemia. Modest intakes of standard oral diet (0.6 g nitrogen/kg daily) are sufficient to maintain gut integrity and immune function. Short chain fatty acids and n-3 polyunsaturated have modest beneficial effect in patients with intestinal inflammation. Arginine has proven immunological benefits. Despite this, oral supplementation with arginine has been shown to be detrimental in experimental colitis causing increased colonic inflammation but beneficial to mucosal barrier function and survival after experimental ischaemia/reperfusion injury. There is growing evidence that the L-arginine–nitric oxide pathway is important in the development of colonic inflammation and that this may lead to new therapeutic strategies in inflammatory bowel diseases. Arginine supplements for critically ill patients should be used cautiously at present. There is insufficient evidence from clinical studies to support the use of orthinine, branched chain amino acid or nucleotide supplementation by themselves. Supplementation of enteral diets with combinations of novel substrates is beneficial to patients in a number of different clinical situations where gut barrier function is compromised by malnutrition and hypermetabolism. The use of diets (containing fibre, fermented oats and lactobacillus) that support probiotic bacteria (microbial interference treatment) has been advocated as an important new development in the support of these patients.

**Newer therapies**

A number of new therapies have been developed based on three important theories about the sepsis syndrome namely: (i) oxygen debt causes organ injury; (ii) endotoxin is a critical mediator; and (iii) the host inflammatory response is harmful. A number of clinical trials employing new therapeutic strategies have failed to show convincing evidence of an improved outcome for patients with sepsis or septic shock and some agents have caused harm. An explanation of these therapeutic failures is that our concept of the pathophysiology of sepsis is too simplistic or incorrect and fails to consider the influence of the
compensatory anti-inflammatory response. More studies of specific diseases are clearly indicated.

**Surgical treatment**

None of the aforementioned therapies will be successful if the underlying source of infection is not controlled. This may be easy if the patient has an obvious wound infection, an abscess or soft tissue infection or a necrotic limb. Frequently, the source of the sepsis or SIRS is not apparent and intrathoracic or intra-abdominal sepsis may be difficult to diagnose. Treatment may require thoracotomy or laparotomy. Surgical exploration should be carried out after appropriate resuscitation of the patient. The extent of the surgical procedure will depend on the location and extent of the septic lesion. Adequate drainage and debridement should be carried out. In abdominal sepsis it may be necessary to consider the use of stomas, tubes or drains and, in certain circumstances, planned relaparotomy or laparostomy may be a treatment option. The chances of survival are enhanced by the early eradication of the source of sepsis or SIRS. The surgical approach is dictated by the condition of the patient and the experience of the surgeon. The survival rate for patients requiring laparotomy for abdominal sepsis in an ICU setting is approximately 40% and multiple operations are associated with diminishing returns and increasing mortality.

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