J Hepatobiliary Pancreat Surg (2003) 10:415–418
DOI 10.1007/s00534-002-0727-5

Journal of HBP Surgery

Bacterial translocation and its prevention in acute pancreatitis

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Abstract
In recent years, bacterial translocation from the gut onto pancreatic necrosis has been proposed as the main cause of pancreatic infection and the consequent sepsis. Failure of the intestinal barrier, together with bacterial overgrowth due to motility changes and immunosuppression, constitute the pathways of the continuous pancreatic contamination from bacterial translocation in patients with severe acute pancreatitis. Selective decontamination, by using a combination of oral and intravenous antibiotics, has been reported to decrease the incidence of sepsis and the related mortality. Immunostimulation is another action to be taken to enhance the ability of the immune system to prevent bacterial translocation, by the entrapment and killing, by enterocytes, of the bacteria trying to translocate through the bowel wall. To keep the mucosal barrier function intact is one of the main issues in the prevention of bacterial translocation. This could be achieved by the adequate delivery of oxygen and nutrient supplementation. Enteral nutrition is a key factor, as it has been proven to maintain mucosal integrity, along with preventing deterioration of the immune function of the intestine.

Introduction

Despite recent improvements in the treatment of acute pancreatitis, the severe form of the disease carries a death risk of 40%.[1] At present, a small number of patients die of acute organ failure during the early period after the onset, mainly due to advances in resuscitation and critical care. Sepsis remains the major factor in morbidity and late mortality, due to suprainfection of pancreatic necrosis.[2] The pathogenesis of this pancreatic infection still remains obscure.

Offprint requests to: C. Dervenis
Received: March 20, 2002 / Accepted: April 15, 2002

In recent years, bacterial translocation from the gut lumen has been suggested as the main source of bacteria that reach and contaminate the pancreatic necrosis. Consequently, sepsis and multiple organ failure is triggered, leading, in the most of the cases, to the patient's death. With no existing specific treatment, prevention of infection remains the most effective treatment so far.

The aim of this review was to explore the current knowledge of the pathogenesis of pancreatic necrosis infection and possible therapeutic strategies to prevent this deleterious phenomenon.

The role of the gut

The gut has been considered as the largest immune organ of the body. Its role is not only to protect against the ability of the lumen bacteria to penetrate through the wall but also to act as a secretory organ, secreting different pro- and anti-inflammatory cytokines. The protective role is produced by the interplay of propulsive peristalsis to prevent stasis and bacterial overgrowth and the maintenance of intact cell-to-cell junctions within the villi.

Small-bowel motility is important in regulating the enteric bacterial population. The relationship between interdigestive myoenteric activity and motility has been shown in animal experiments. The administration of a known inhibitor of coordinated myoenteric activity (morphine), caused a marked reduction in propulsion, and excessive bacterial overgrowth and bacterial translocation to mesenteric lymph modes.[3]

The integrity of the gut mucosa, preserved by the maintenance of normal enteric villi, is one of the principal factors in gut protective mechanisms. This integrity can be achieved by the adequate delivery of oxygen and nutrients by a normal blood flow. The mucosal lining consists of enterocytes and colonocytes that use glutamine and short-chain fatty acids as primary fuel.[4]

Thus, the presence of these nutrients in the lumen stimulates the proliferation of mucosal cells and enhances gut integrity.

The submucosa also plays an important role in the defense mechanism, as it barbors macrophages and the so-called gut-associated lymphoid tissue, which is one of the main producers in the body of the protective immunoglobulin A (IgA). Secretory IgA prevents bacterial penetration by trapping the bacteria in the mucus. Normally there is a balance between pro- and anti-inflammatory cytokines. Interleukin-1, tumor necrosis factor, and platelet-activating factor are produced by the immune cells of the gut and contribute to the systemic inflammatory response syndrome as part of the overall host reaction.[5]

The gut in acute pancreatitis: the bacterial translocation phenomenon

Acute pancreatitis is a typical model of sepsis associated with the systemic inflammatory response syndrome, with multiple organ failure (MOF) being the end result. In this context, the gut is one of the main factors implicated in that process. It is not clear whether the gut is a causative factor of MOF or the result. There is accumulated evidence that acute pancreatitis, at least in animal experiments, resulted in a significant delay in small-intestinal transit time, which was more pronounced 12 h after the onset of the disease.[6] It is well known that small-bowel motility is related to the bacterial ecology of the gut, as it contributes to bacterial clearance. Motility abnormalities have been reported to correlate with bacterial overgrowth and adherence to the intestinal wall, with the release of large amounts of toxins. The mechanism by which acute pancreatitis alters the motility of the gut has not been elucidated. It has been postulated that, as different gastrointestinal peptides and hormones regulate small-bowel motility, it is possible that the disturbances in the secretion of these peptides during acute pancreatitis are the cause of the decrease in gut motility. Therefore, delayed transit time and the subsequent bacterial overgrowth contribute to increased bacterial migration through the bowel wall into the area of pancreatic necrosis.

Another important factor is the impairment of the gut barrier by damage to the tight junctions and the epithelium of the enteric villi. It is well known that experimental pancreatitis is associated with gross distortion of the local and systemic microvasculature. This results in reduced oxygen delivery by the impaired blood supply to the gut. There is evidence that, because of the microcirculatory disturbances, an increase in oxygen radicals from macrophages and leucocytes is observed,[7] which leads to increased permeability to albumin.[8] Morphological studies in experimental acute pancreatitis showed damage of the apical portion of the distal small-bowel villi associated with alterations of the mucosal microvasculature.[9]

A number of recently published studies have explored the role of translocation in pancreatic necrosis contamination. There are three main pathways of translocation in pancreatitis: lymphatic,[10] hematogenous,[11] and transmural.[12] The latter was proven when isolation of the transverse colon in an impermeable plastic sac during experimental acute pancreatitis successfully prevented pancreatic infection.

In a study from Loyola University, Kazantsev et al.[13] showed, in a dog experiment with induced acute pancreatitis, that changes in the small-bowel mucosa were observed, with the consequent translocation of labelled *Escherichia coli* to the pancreas and to mesenteric lymph nodes. They concluded that ischemic damage to the intestinal mucosa might promote bacterial translocation. Mucosal impairment has been reported to be the key factor in bacterial translocation in different studies, as shown in a study by Cicalese and colleagnes,[9] in which they used fluorescent latex microspheres to detect mucosal permeability function in experimentally induced a cute pancreatitis.[14]

Another key issue is the role of immunosuppression, which, as has been shown, is associated with severe acute pancreatitis.[15] In normal subjects, bacteria that migrated from the gut lumen in small numbers were entrapped and killed by immunocompetent cells.[16] Therefore, impairment of the immune system, especially that related to the gut, facilitates the contamination of pancreatic necrosis by the gut bacteria.

In summary, failure of the intestinal barrier, together with bacterial overgrowth due to motility changes and immunosuppresion, constitute the pathways of the continuous pancreatic contamination due to bacterial translocation that occurs in patients with severe acute pancreatitis.

Prevention of bacterial translocation: the role of enteral nutrition

A number of studies have been conducted to assess the role of different therapeutic modalities in preventing bacterial translocation by altering the pathogenetic mechanisms.

Selective bowel decontamination has been used to diminish bacterial overgrowth. In a very interesting study from the Netherlands, Luiten et al.[29] found a decrease in septic complications and mortality in severe acute pancreatitis by using a combination of oral and intravenous antibiotics to decontaminate the gut in humans. The same findings have been reported in

another study, in which different regimens were used to decontaminate the gut in mice with induced acute pancreatitis.[17]

Immunostimulation is a promising future approach to prevent infection in acute pancreatitis. In a very interesting study by Foitzik et al.,[18] the role of glutamine in an experimental model was assessed. Acute pancreatitis and colitis was induced in rats, and the effect of glutamine on the colonic microcirculation and parameters reflecting gut barrier function and the translocation of bacteria to extraintestinal organs was studied. In the animals treated with glutamine, they found improvement in capillary blood flow in the colonic mucosa and a significant reduction in the prevalence of pancreatic infection in the animals with induced pancreatitis. Although randomized studies are needed to confirm these findings in humans, the administration of glutamine seems to be a very promising modality to prevent bacterial translocation in acute pancreatitis. Recent findings suggest that glucagon-like peptide 2 (GLP-2), a proglucagon-derived peptide, plays a key role in intestinal growth.[19] Kouris and colleagues[20] found that giving GLP-2 to rats with experimentally induced acute pancreatitis significantly decreased intestinal permeability and bacterial translocation.

Nutritional support in severe acute pancreatitis has two main goals. The first is to overcome the negative nitrogen balance, and the second is to protect gut barrier function and thus, to prevent bacterial translocation and secondary pancreatic (super)infection.

For many years it has been suggested that, by correcting malnutrition, mortality and morbidity would decrease. This hypothesis has never been proven, as there are no randomized trials, although some retrospective series, together with a few prospective but nonrandomized trials, have reported probable benefits from nutritional support. Therefore, more trials are needed, as no strong level 1 information (i.e., PRCTs) regarding the role of nutritional support in pancreatitis exists.

Recently, attention has been given to the possible role of the enteral route in delivering the necessary calories and nutrients. The rationale behind the concept of enteral feeding is that there is at least some evidence regarding its importance in restoring and possibly preventing the morphological changes in the intestine associated with starvation. Lack of nutrients in the gut lumen leads to loss of mucosal integrity as a result of a decrease in mucosal thickness.[21] Enteral feeding can also reverse the reduction in villus height that occurs after starvation or total parenteral nutrition (TPN). In a rat model with experimentally induced acute pancreatitis, Ringer lactate solution was infused for 48 h, followed by parenteral or enteral nutrition (EN) until day 7. Results showed lower endotoxin levels, greater villus height, and higher T-cell levels in animals that received EN compared with those that received TPN.[22]

Therefore, EN could play an important role in the treatment of severe acute pancreatitis, as it probably reduces bacterial translocation and immune failure and the consequent sepsis by enhancing gut barrier function. Since the mid 1980s, there has been some evidence from critically ill patients, especially those with severe injury, showing that EN, given very early, could favorably alter the outcome. Moore and co-workers[23] studied 32 patients with severe trauma and compared early EN with no nutritional intervention. They found a statistically significant difference in septic morbidity (9% vs 29%). Although there are theoretical advantages and some experimental evidence that enteral feeding could affect outcome in severe acute pancreatitis, there are difficulties in proving its clinical effectiveness.

There are a number of trials proving that, at least, the delivery of nutrients through the intestine is safe and well tolerated, and does not aggravate the disease in any case.

Recently, two randomized studies were published comparing enteral feeding with TPN. Kalfarentzos and co-warkers[24] studied 38 patients, all with severe acute pancreatitis, who were randomized to two groups (EN vs TPN). They found a significant reduction in total (including septic) complications in the enteral feeding group. The cost was three times lower in the EN group than in the TPN group, and they suggested that the use of EN was preferable in all patients with severe disease. The second study was from the United Kingdom,[25] evaluating 34 patients, who were also randomized to two groups, but this study included patients with moderate and severe disease. Patients who received enteral feeding fared better after 7 days, with respect to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and C-reactive protein (CRP) levels, compared with the TPN group. The authors also reported that serum IgM endotoxin core antibodies increased in the TPN group and remained unchanged in the EN group, and the total antioxidant capacity was less in the former group. They concluded that patients on EN were exposed to lower endotoxin levels. Probably this was related to preserved host defense.

Another randomized controlled trial, published by a Scottish group,[26] studied the effect of early EN on markers of the inflammatory response in predicted severe acute pancreatitis. Serum interleukin 6, tumor necrosis factor receptor I, and CRP were used as inflammatory markers. Contrary to previous findings, the authors found that early EN did not ameliorate the inflammatory response in patients with severe acute pancreatitis, compared with no nutritional intervention.

Finally, a randomized study is underway by our group, trying to identify the role of early EN, compared

with standard TPN, in reducing the need for surgery in patients with predicted severe acute pancreatitis. We reported preliminary results recently (23 patients) in which we showed that early EN seemed to reduce surgical interventions in the EN group by reducing the incidence of sepsis (9% vs 33%).[27] Traditionally, it is believed that delivery of an enteral regimen proximally into the gastrointestinal tract causes stimulation of exocrine pancreatic secretion, through cholecystokinin release, and, in acute pancreatitis, this causes exacerbation of the inflammatory process. Control animal and human studies supported this concept, as pancreatic secretion was higher when the nutrients were delivered either into the stomach or the duodenum compared with the intrajejenal route. However, in acute pancreatitis, in contrast, it is known that secretion is suppressed. Although the current practice is to use nasojejunal tubes, placed endoscopically or under radiographic screening, a recent study by the Glasgow group[28] showed that nasogastric feeding is usually possible in severe acute pancreatitis. They reported that this practice is safe and well tolerated, without causing any sign of clinical or biochemical deterioration.

Conclusions

Bacterial translocation and the subsequent contamination of pancreatic necrosis is the main risk factor for late death in severe acute pancreatitis. Therefore, the gut plays a key role in the disease process, and the prevention of gut dysfunction or failure is of great importance in reducing the mortality and morbidity of the disease. There is accumulated evidence that, together with the maintenance of adequate oxygen delivery, the use of enteral nutrition with antibiotics could prevent gut barrier dys function and, therefore, bacterial translocation. However, more trials are needed to resolve all the aspects of the efficacy of enteral nutrition in severe acute pancreatitis.

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