Role of the Gut Barrier in Acute Pancreatitis

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Abstract: The small intestine is one of the distant organs that become damaged during severe acute pancreatitis, due to microcirculation disturbance associated with loss of fluids in the "third space," hypovolemia, splanchnic vasoconstriction, and finally an ischemia-reperfusion injury. In this scenario, the gut acts as the starter for severe systemic complications, as the failure of the intestinal barrier is associated with translocation of bacteria and inflammatory and toxic products produced in the intestinal wall, which can be responsible for sepsis and infection of the necrotic pancreas and for systemic inflammatory response. Therefore, one of the main goals of treatment in the early phases of severe acute pancreatitis should be to maintain the integrity of the gut barrier in the small intestine. These strategies include appropriate fluid resuscitation to limit the damage due to the relative hypovolemia and early enteral feeding. The role of intravenous antibiotics to prevent infection of the pancreatic necrosis is controversial and the role of probiotics, which seemed a promising tool in vitro and in early clinical trials, needs to be further investigated to better understand the effects of the single specific strains at various doses and timing before designing new clinical trials.

Key Words: acute pancreatitis, gut barrier, intestinal permeability, enteral nutrition, probiotics

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SYSTEMIC INFLAMMATION IN ACUTE PANCREATITIS

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with varying involvement of regional tissues or the remote organ system. Gallstones and alcohol consumption are the most frequent causes of AP in adults, whereas some 20% of cases remain idiopathic. AP is a relatively common disorder with an incidence of 20 to 40/100,000/y. In 80% of patients, AP is mild and it resolves without serious morbidity, but in 20% of patients the clinical course is troublesome with a high-mortality risk.[1] The inflammatory response to pancreatic injury and the presence of organ failure are the key factors, which determine the severity of the disease.

The pathogenesis of AP is caused by the inappropriate activation of trypsinogen to trypsin. These enzymes, along with free radicals, injure the acinar cells and cause the release of cytokines and vasoactive mediators, which lead to an edema as well as apoptosis. The inflammatory response in interstitial (mild) pancreatitis can cause a diffuse edema without being severe enough to cause apoptosis and necrosis. When the inflammatory cascade progresses, it is responsible for the autodigestion of acini and pancreatic islets, which cause interstitial fat necrosis and necrotizing vasculitis (necrotizing or severe pancreatitis).

These pathologic changes in the pancreatic gland are responsible for releasing active pancreatic enzymes into the bloodstream and stimulating the production of inflammatory cytokines. The release of those interleukins and the tumor necrosis factor-α from the macrophage triggers an inflammatory cascade, which leads to the systemic inflammatory response syndrome (SIRS) (Table 1). SIRS may develop into acute respiratory distress syndrome or multiorgan dysfunction syndrome (MODS).

The natural course of severe acute pancreatitis (SAP) progresses in 2 phases: the first 14 days are characterized by SIRS. It is common in patients with SAP organ failure and often occurs without infection. The second phase, beginning approximately 2 weeks after the onset of the disease, is dominated by sepsis-related complications caused by the infection of pancreatic necrosis, which carries the highest risk of patient death.[2]

The most common systemic manifestation of AP is arterial hypoxia; approximately 50% of patients with SAP will develop respiratory insufficiency. The involvement of additional systems such as the cardiovascular, renal, gastrointestinal, hematological, and neurological systems is associated with increased mortality.[3] The diagnosis of each organ insufficiency is shown in Table 1.

Most recently, it has been postulated that persistent organ failure (for >48 h) is the key determinant of severity regardless of the presence or absence of local pancreatic complications.[4]

The small intestine is one of the distant organs that become damaged during SAP, due to microcirculation disturbance associated with loss of fluids in the "third space," hypovolemia, splanchnic vasoconstriction, and finally an ischemia-reperfusion injury. The intestine, however, is not only a "victim" during SAP, but also plays an active role, as its failure worsens the course of the disease even further (Fig. 1).

THE GUT AS A "MOTOR" FOR SYSTEMIC INFLAMMATION AND INFECTED PANCREATIC NECROSIS

The mortality of patients with AP increases from $<3\%$ in patients with interstitial pancreatitis to $>15\%$ in the presence of pancreatic necrosis. A further factor worsening the prognosis of patients with necrotizing AP is the bacterial infection of the necrotic pancreas. The prevalence of infected necrosis in patients with necrotizing pancreatitis seems to be approximately 15% to 20%,[5] and the risk of death in such cases is close to 30%.[6]

Sepsis complicates approximately one third of cases of necrotizing pancreatitis and accounts for most late deaths in patients with SAP. As it is often associated with secondary infection of pancreatic and peripancreatic necrosis, attributed to gram-negative enteric bacteria, the

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TABLE 1. Features of Multiorgan Dysfunction Syndrome (MODS) and Systemic Inflammatory Response Syndrome (SIRS)

MODS: Diagnosed As	SIRS: Defined by 2 of the Followings
Shock (systolic blood pressure < 90 mm Hg)	Heart rate > 90 beats/min
Pulmonary insufficiency (PaO_2 < 60 mm Hg)	Temperature > 38 or < 36°C
Renal failure (creatinine level > 2 mg/dL)	Respiratory status: respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg
Gastrointestinal bleeding (> 500 mL/24 h)	White blood cell count > 12,000 cells/μL

risk of developing a pancreatic infection is significantly higher in patients with gram-negative microorganism intestinal colonization than in patients without it.[7]

The importance of the small intestine during the course of AP had been first suggested in the 1960s by Jacob Fine, who hypothesized that severe illness enables gut organisms to gain access to the systemic circulation passing through the intact intestinal wall. In the past few years, it has been demonstrated that bacteria itself might not need to transpose the epithelial intestinal barrier. Translocation of inflammatory compounds produced in the intestinal wall and toxic products of the gut might, therefore, be responsible for SIRS and distant organ injury.[8]

This hypothesis introduced the definition of "bacterial translocation" in relation to the intestinal permeability (IP), focusing attention on the role of the gut as the starter for SAP systemic complications.

ALTERATIONS IN INTESTINAL PERMEABILITY IN AP

Changes in the IP have been reported in both animal models of AP and in patients. In rats with experimental AP, there is an increased IP, which correlates with disease severity.[9] Various studies have investigated IP in humans with AP, with findings suggesting an increased IP in patients with SAP compared with those with mild AP.[10–12] Some of these authors also reported a significant positive correlation between mucosal permeability and endotoxinemia, confirming that not only bacteria, but its product may determine the inflammatory response and its complications.[12,13] The limitations of such studies may be represented by the fact that the different techniques used to study IP, such as measuring the urinary recovery of ethylene glycol polymers or of sugars (measuring the ratio of either mannitol, rhamnose, or lactulose), may have different results, and all these tests only provide an indirect measurement of the gut barrier damage.

At any rate, there is a certain consistency between studies, suggesting that IP increases in patients with SAP and that this is paralleled by an increased endotoxinemia. Interestingly, it has been postulated[13] that endotoxemia due to increased IP may result in a feedback, which throughout the increased production of toxic substances and cytokines, may result in further damage to the intestinal wall and increase of IP.

The increased IP and subsequent bacteraemia play a critical role during AP and determine its prognosis. In fact, in an important study evaluating 731 patients with AP, Besselink et al[14] demonstrated that most infections occurred within the first week, and that bacteraemia was an independent predictor of death and was associated with an increased risk of infected necrosis with further increased mortality. As expected, most of the isolated pathogens, either in blood or pancreatic tissue samples, originated from the gut.

More recently, Fritz et al[15] investigated a particular rat model in which after ileostomy and after treatment with selective digestive decontamination (SDD) of either the small bowel or the colon with a gentamycin and polymyxin B solution, an experimental AP was induced. Their results suggest that in this experimental model, bacterial translocation occurs far more often from the small bowel than from the colon. These results highlight that one of the main goals of the treatment in the early phases in patients with SAP should be to maintain the integrity of the gut barrier in the small intestine.

THERAPEUTIC APPROACHES TO TREAT "LEAKY" GUT IN AP AND PREVENT INFECTIOUS COMPLICATIONS

Appropriate Fluid Resuscitation

Fluid replacement is crucial in patients with SAP, because the patients may develop vascular leak syndrome with hypovolemia and hypotension, acute tubular necrosis, and renal failure. In addition, as discussed above, fluid depletion contributes to the relative intestinal ischemia and alters pancreatic microcirculation, which results in further pancreatic necrosis. This alteration in microcirculation significantly increases the degree of pancreatic ischemia, regardless of etiology, thus exacerbating the SIRS and leading to multisystem organ failure. Resuscitation is therefore critical for the treatment of AP; even if few human

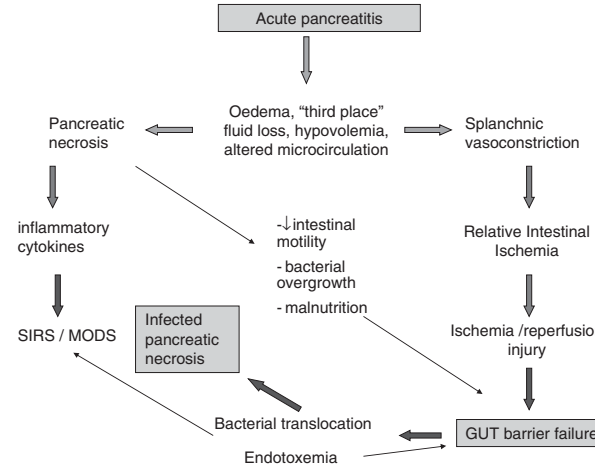

FIGURE 1. Schematic representation of the events after the onset of acute pancreatitis, underlying the importance of the intestinal barrier. The failure of the gut barrier is eventually associated with the risk of infections, including infected pancreatic necrosis, and contributes to the systemic inflammatory response, in a vicious circle, as endotoxemia and related inflammatory changes may further damage the intestinal microcirculation. MODS indicates multiorgan dysfunction syndrome; SIRS, systemic inflammatory response.

studies have addressed the role of aggressive fluid resuscitation using targeted outcome measures, and none of them have correlated the results with IP, it has been demonstrated that early fluid resuscitation is associated with reduced incidence of SIRS and organ failure at 72 hours.[16] Even the type of fluid (colloid vs. crystalloid vs. other) has not been investigated in depth, although a very recent publication suggests that resuscitation with lactated Ringer's solution may be superior to normal saline because it is associated with lower levels of inflammatory markers and a significant reduction in SIRS after 24 hours.[17] Normal saline is the preferred fluid for volume resuscitation in patients with hypercalcaemia-induced AP.

The importance of aggressive fluid resuscitation is clearly suggested by a number of studies reporting the poor outcome of patients presenting early and/or sustained hemoconcentration or increased blood urea nitrogen levels.[18,19] Accordingly, published guidelines recommend that patients with SAP should be resuscitated[20–22] with an adequate amount of fluids (not infrequently, at least 5 L/d during the first few days), adjusting the fluids amount by monitoring the urine output, which should be >0.5 mL/kg body/h.

Enteral Nutrition (EN)

Early nutritional support is an important part of the clinical management of patients with SAP, due to the need to manage the hypercatabolism secondary to extended pancreatic and extrapancreatic inflammation. However, appropriate nutritional support is also able to reduce the risk of pancreatic necrosis infection and related complications. EN should be preferred to total parenteral nutrition (TPN) in patients with SAP as it is associated with reduced mortality, lower septic complications, reduced surgical procedures and hospital stay.[23] These beneficial effects are most likely due to a trophic action on the intestinal wall, which can help the intestinal barrier to be maintained and prevent the bacterial translocation from the gut. Therefore, current guidelines suggest that EN[20–22] be preferred, which should be initiated as soon as possible in patients with predicted SAP, whereas in patients with a mild form of the disease, in whom oral feeding is likely to be possible in few days, intravenous fluids are administrated at disease onset. The optimal site to provide EN is still debated. Nasojejunal feeding, beyond the Treitz, is theoretically associated with a lower pancreatic stimulation, but the tube often requires endoscopic placement or several hours for spontaneous migration. Nasogastric feeding may, therefore, be a simpler and more convenient approach, and in the few studies performed, it was not associated with a worse outcome and/or with a higher rate of complications.[24–26]

Antibiotics

Antibiotic treatment is recommended during SAP in the presence of highly suspicious biochemical and/or imaging signs of pancreatic necrosis infection, and to treat infectious complications or sepsis, although its role to prevent bacterial superinfection in necrotizing pancreatitis is still debated.[20,22]

There have been many trials that address this issue, but their results are often hampered by a number of methodological limitations and their comparison is difficult due to differing study designs, inclusion criteria, and the antibiotics used. The most recent meta-analyses do not support a role for early preventive antibiotic prophylaxis, as it does not seem to be associated with a lower rate of infection, morbidity, and mortality.[27,28]

Interestingly, some early studies supported the use of SDD with colistin, amphotericin, and norfloxacin in patients with SAP,[29] as it is associated with decreased mortality and gram-negative pancreatic infection, and further highlighted the importance of the intestine in the clinical course of AP. However, although SDD has been proven beneficial in intensive care unit patients, it has also been associated with the emergence of antibiotic-resistant microorganisms. Therefore, other strategies to control the bacterial colonization of the small bowel and limit the damage of the gut barrier, such as the use of probiotics, have been investigated.

Probiotics

The rationale for the use of probiotics to prevent or limit intestinal damage during the course of AP resides in their beneficial effects on the gut barrier, which have been demonstrated in vitro and in vivo in a number of disorders.

The positive effect of strains of *Lactobacillus plantarum* and *Lactobacillus reuteri* on IP has been reported in a rat methotrexate-induced colitis model.[30] The oral pretreatment with *L. plantarum* one week before inducing sepsis on a rat model significantly reduced the incidence of bacterial translocation to the mesenteric lymph nodes and liver.[31] Probiotics have often been deemed effective in patients with gastrointestinal disorders typically associated with damage to the gut barrier, such as enteric infections, irritable bowel syndrome, short bowel syndrome, and inflammatory bowel disease. Some clinical studies specifically evaluated the effects of probiotics on IP, with positive results in patients with Crohn's disease,[32] with diarrhea-predominant irritable bowel syndrome,[33] and in children with atopic dermatitis.[34] Therefore, it seemed rational to test their efficacy in patients with AP, given the important role of the gut barrier in this scenario.

Interesting preclinical data have been obtained from studies evaluating the effects of probiotics in experimental models of AP. The administration of either *Saccharomyces boulardii* alone[35] or mixtures of different probiotics[36] has been proven effective in preventing bacterial translocation in rats after the chemical induction of AP.

A 6-multispecies probiotic mixture, subsequently used for the PROPATRIA trial (*Lactobacillus acidophilus* W70, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactobacillus lactis* W58, *Bifidobacterium bifidum* W23, and *Bifidobacterium lactis* W52, previously classified as *Bifidobacterium infantis*) was investigated in more detail, and was found to enhance pancreatic glutathione biosynthesis,[37] prevent intestinal barrier dysfunction,[38] and significantly reduce duodenal bacterial overgrowth of potential pathogens, bacterial translocation to extraintestinal sites, including the pancreas, and the rate of infectious complications, morbidity, and mortality in an AP rat model.[39] It is, however, interesting to point out that, in these latter studies, the probiotic mixture was administered as preventive care, that is before AP induction, and was not effective as treatment administered after the induction of AP,[40] limiting the rationale for its clinical use.

Probiotics have been tested in only a few randomized clinical trials in patients with AP, with different protocols, inclusion criteria, formulations, and with conflicting results. The main characteristics of these studies and their main results are summarized in Table 2. Two small studies were

TABLE 2. Main Characteristics of Clinical Human Studies on Acute Pancreatitis and Probiotic Treatment

References	Sample Size Calculated	Probiotic(s) Tested	Comparison	Gut Barrier Permeability			Statistically Significant Reduction of Complications				Mortality and Causes
				Tested	Method	Results	Infected Necrosis	SIRS	MODS	Any Infection	
Olàh et al[41]	No	*Lactobacillus plantarum* 299 V plus oat fiber ($10^9 \times 2$/daily dose)	EN + fibers vs. EN + symbiotic	No	—	—	No	No	No	↓ pancreatic infection requiring operation in the probiotic arm	No difference
Olàh, et al[42]	No	Multistrain (40×10^9/daily dose) and multifiber symbiotic	EN + fibers vs. EN + symbiotic	No	—	—	No	↓ SIRS + MODS in symbiotic arm		No	No difference
Qin et al[43]	Yes	*L. plantarum* (unspecified strain) (10^{10}/daily dose)	TPN vs. partial PN + EN + probiotics	Yes	Lactulose/ rhamnose urinary excretion	↓ in the probiotic arm	—	↓ SIRS in the probiotic arm	↓ MODS in the probiotic arm	↓ infective complications in the probiotic arm	No difference
Besselink et al[44]	Yes	Multistrain product (10^{10}/ daily dose) plus maltodextrins and cornstarch	Placebo vs. probiotics (through EN)	No	—	—	No	—	↑ MODS in the probiotic arm	No	↑ in the probiotic arm, due to NOMI
Sharma et al[47]	Yes	Multistrain product (10^{10}/ daily dose)	Placebo vs. probiotics (through the current mode of feeding)	Yes	Lactulose/ mannitol urinary excretion	No difference	—	—	No	↓ endotoxin core antibody IgG, IgM in the probiotic arm	No difference

EN indicates enteral nutrition; MODS, multiorgan dysfunction syndrome; NOMI, nonocclusive mesenteric ischemia; SIRS, systemic inflammatory response syndrome; TPN, total parenteral nutrition.
↓ indicates decreased; ↑, increased.

performed in Hungary by the same group.[41,42] They enrolled a relatively small population (< 40 patients/arm, without a sample size calculation) with AP, which was randomized to receive either EN only or EN plus probiotic(s) for 1 week. The main differences between these studies are that the first study excluded patients with biliary pancreatitis, enrolled patients with both mild and SAP, and used a single bacterial strain, whereas the second study enrolled only patients with SAP and used a symbiotic mixture with a multistrain bacterial mixture and 4 bioactive plant fibers. In both these studies, there was a reduction of septic complications in the probiotic arm.

In a third study,[43] performed in China, 86 patients with AP were allocated into 2 different groups receiving either TPN and placebo through a jejunal tube or TPN plus EN enriched with a single probiotic with an unspecified strain. The group receiving the enriched EN experienced a reduction in the rate of MODS, SIRS, infectious complications, and a need for antibiotics. Notably, these beneficial clinical outcomes were coupled with a reduction of IP and the rate of positive cultures of the nasogastric aspirate in the EN + probiotic group, suggesting that these effects on the gut barrier lead to the observed better prognosis.

The fourth study, published in 2008, was the multicenter randomized trial named PROPATRIA, which soon became notorious for its apparently surprising negative results.[44] Approximately, 150 patients with predictive criteria for SAP were allocated within 72 hours after the onset of symptoms into 2 arms and received either a symbiotic composition (the 6 different strains named above plus cornstarch and maltodextrins) or a placebo (sachets containing only cornstarch and maltodextrins). The treatment was administered for a maximum of 28 days, initially through a nasojejunal tube. There was no significant difference between the 2 groups either in the occurrence of infectious complications or in the pathogens cultured from biological material, but surgical intervention and MODS were significantly more frequent in the probiotics-treated group. In addition, death was more prevalent in the probiotic group, with a relative risk of 2.53 (95% confidence interval, 1.22-5.25). The principal cause of death in the 2 groups was MODS, but in the probiotics group, 8 out of 24 dead patients had nonocclusive mesenteric ischemia, with no such diagnosis in the placebo group. It was, therefore, convincibly concluded that the probiotics treatment was associated with an increased risk of fatal nonocclusive mesenteric ischemia. The reasons for this dramatic outcome are unclear but, in a later study,[45] the same authors demonstrated that the applied probiotic mixture reduced bacterial translocation (indirectly evaluated with the urinary nitrate excretion), whereas it did not affect IP assessed by a polyethylene glycol recovery. However, in the subgroup of patients with SAP and concomitant organ failure, the treatment was associated with an increased enterocyte damage (assessed by measuring the urinary concentration of intestinal fatty acid binding protein) and an increased bacterial translocation.

The authors found an association between bacterial translocation and clinical infections and the severity of AP, thus further supporting the "gut motor" hypothesis. The authors speculated that the harmful effect of the probiotic mixture could have been due to an additionally sustained inflammatory response against these new commensal bacteria, which may have led to further impairment of intestinal blood flow in patients with SAP and organ failure. The use of such a high load of this probiotic mixture, which was poorly tested in clinical trials, also makes it difficult to understand whether the damage was related to any of the specific strains or to their cumulative effects on inflammatory mediators, such as a specific cytokine.[46]

At any rate, the results of the PROPATRIA study made further investigations difficult. One other study was actually stopped prematurely, as it was underpowered with the results that were difficult to interpret.[47] The aim of the study was to evaluate the effect of probiotics or placebo on gut permeability and endotoxemia in patients with both mild and SAP, randomized in a double blind design. There was no statistically significant difference between the groups in gut permeability, but a decrease in IgM and IgG endotoxin core antibodies, which are considered to be inversely correlated with bacteraemia, possibly suggested that bacteraemia increased in the probiotic arm.

CONCLUSIONS

There is sufficient evidence to confirm that the gut barrier plays an important role during the early phases of SAP, and its dysfunction is related to infectious complications, including infection of the pancreatic necrosis, and to the risk of death. The strategies to limit the intestinal damage during SAP include appropriate fluid resuscitation to limit the damage due to the relative hypovolemia and enteral feeding. The role of intravenous antibiotics to prevent the infection of the pancreatic necrosis is controversial, and the role of probiotics, which seemed to be a promising tool in the in vitro studies and in early clinical trials, requires reflection and further investigations to better understand the effects of the single specific strains at various doses and timing. In the future, however, more studies should evaluate strategies aimed at improving the gut barrier function in SAP, either with specific EN formulations (for which a number of trials are ongoing) or using other approaches such as the use of nonabsorbable antibiotics or other SDD strategies.

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