**EDITORIAL ARTICLE**

# The role of probiotics and prebiotics in the treatment of pancreatitis

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*ABSTRACT: Acute pancreatitis is a potentially fatal condition, and its incidence is increasing. Bacterial translocation and end organ failure are the main causes of death. Gut flora have the potential for modulation of the inflammatory cascade. Fasting has a negative impact on gut flora. Animal studies suggested a role for probiotics in the treatment of severe acute pancreatitis; however, a very recent human trial showed disappointing results. Symbiotic combinations have shown variable results in the treatment of severe acute pancreatitis. Prebiotics alone are not thoroughly studied in severe acute pancreatitis. Only 1 study has shown positive results, and further studies are needed. Although probiotics are contraindicated in severe acute pancreatitis according to a recent multicenter study, strain-specific properties of probiotics should urgently be investigated, and further well-designed trials are badly needed. (Nutritional Therapy & Metabolism 2010; 28: 1-6)*

*KEY WORDS: Critical care, Pancreatitis, Prebiotic, Probiotic, Symbiotic*

*Received: October 4, 2009; Accepted: December 16, 2009*

## INTRODUCTION

Acute pancreatitis is a prevalent condition, which is characterized by severe abdominal pain and increased blood levels of pancreatic enzymes (1). The incidence of acute pancreatitis is increasing both in Europe and United States (2-4). Severe acute pancreatitis (SAP) is defined as necrosis of the pancreas and subsequent inflammatory cascade (5). This inflammation frequently leads to infection in the necrotic area and severe inflammatory response syndrome. In the first phase of SAP, mortality is closely related to multiorgan failure. However, in the late phase, infectious complications become the main etiological factor for mortality (6). Infectious complications in the late period of SAP are closely related to bacterial translocation. Antibiotic therapy often fails to decrease infectious complications. Probiotic therapy is proposed to modulate intestinal flora toward beneficial bacteria (7-9).

Multiple organ dysfunction syndrome (MODS) is the major factor for mortality in the intensive care unit (ICU), and patients with MODS (including SAP) usually have associated severe sepsis (10). In critical patients, gut flora are severely altered and pathogenic bacteria usually cover the entire intestine (11). The altered gut flora in ICU patients are the major source of bacteremia, severe inflammatory response syndrome, sepsis, and MODS.

In physiological situations, gut flora are in a state of equilibrium between commensal (anaerobic-lactic acid) bacteria. The commensal bacteria (lactobacilli and bifidobacteria, etc) prevent overgrowth and probably translocation of pathogenic bacteria. This beneficial effect is called “colonization resistance” against pathogenic bacteria (12). As one can easily imagine, altered gut flora facilitate bacterial translocation, especially in an inflamed mucosa (13). Diminished beneficial bacteria and alterations in the gut flora lead to bacterial translocation and subsequent sepsis and MODS. Probably, beneficial bacteria also attenuate the severity of the systemic inflammatory cascade by switching the T-helper immune response to a less aggressive type. For this reason, enteral nutrition including prebiotics or synbiotics beneficially affects the vulnerable gut flora and might

prevent severe immune response.

SAP is defined as necrosis of the pancreas as a result of severe inflammation of pancreatic tissue. The traditional clinical treatment was to give nothing by mouth until the patient recovers. Although this approach may be suitable for milder pancreatitis (edematous) cases, patients with SAP have severe alterations in their gut flora. Fasting beyond 24-48 hours further distorts the fine equilibrium of commensal and pathogenic bacteria in the gut.

The gut barrier plays an important role in SAP. Severe inflammation and cytokine storm disrupt the integrity of mucosal permeability (5). In this inflamed, leaky gut, colonization resistance against pathogenic bacteria is maintained by commensal bacteria, mostly anaerobic lactic acid–producing bacteria.

Gut barrier function determines the prognosis of patients with SAP. Antibiotic prophylaxis against pathogenic bacteria seems to be logical in preventing lethal complications of late infections; however, 2 meta-analyses (8, 14) and 2 high-quality trials (15,16) have failed to show a beneficial effect. Although wide-spectrum antibiotics diminish the total number of gut bacteria, probably the balance between commensal and pathogenic bacteria is impaired, and pathogenic bacteria were predominant. For this reason, instead of using antibiotics, probiotic application might restore the altered gut flora (17). Two studies by Oláh et al (18, 19) found that enteral feeding with probiotics was effective in reducing infections and mortality, as well as reducing the number of surgical interventions. However, Besselink et al found that probiotic application did not reduce the risk of infectious complications and even increased mortality (4).

There are 3 main studies of probiotics in SAP and there is only 1 study including prebiotics without probiotics (Tab. I). The main problem with the studies regarding probiotics in SAP is the lack of methodological similarity between studies. For example, Oláh et al used the Synbiotic 2000 combination in their latest study (19), whereas Besselink et al used Ecologic 641 (combination of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum,* and *Bifidobacterium lactis*) plus fiber supplementation (7). Li used a totally different probiotic, jinshuangqi, which is a traditional Chinese probiotic (not very well known in the

**TABLE I** - OVERVIEW OF THE STUDIES OF PROBIOTICS AND PREBIOTICS IN SEVERE ACUTE PANCREATITIS

| Author, year (Ref.) | Number of participants | Study design | Probiotic or prebiotic | Results |
|---|---|---|---|---|
| Besselink et al, 2008 (7) | 296 | DB-RCT | Ecologic 641 (*Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum, and Bifidobacterium lactis*) | 24 patients (16%) in the probiotics group died, compared with 9 (6%) in the placebo group (relative risk 2.53; 95% CI, 1.22-5.25) |
| Oláh et al, 2007 (19) | 62 | DB-RCT | Synbiotic 2000 | Lower rate of SIRS, MOF, and late organ failure in the probiotic group |
| Li, 2007 (20) | 25 | Unclear | Jinshuangqi | Time of abdominal pain alleviation, serum amylase restoration, incidence rate of complications, and mean in-hospital time were significantly decreased |
| Karakan et al, 2007 (21) | 60 | DB-RCT | Fructooligosaccharide | Median duration of hospital stay was shorter in the study group. Deaths occurred in 6 patients (20%), 2 in the study group and 4 in the control group |
| Oláh et al, 2002 (18) | 45 | Unclear | *Lactobacillus plantarum 299* (live bacteria and heat-killed) | Lower rate of pancreatic necrosis and abscess in the probiotic group; however, LOS is not significantly different |

DB-RCT = double-blind randomized controlled trial; LOS = length of hospital stay; MOF = multiorgan failure; 95% CI = 95% confidence interval; SIRS = systemic immune response syndrome.

literature) (20). Another underestimated issue is the dosage of probiotic preparation. Many probiotic preparations have no standard dosage, and they are usually given in minimal dosages for the probiotic organism to survive in the gut. Most of these probiotics are not thoroughly tested in clinical studies for their minimal effective dose. What is also not established is the optimal combination of probiotics with a prebiotic. Briefly, it is still not known which prebiotic is the right one for a certain probiotic.

The results of the Dutch multicenter PROPATRIA study by Besselink et al (7) – where use of multiple probiotics led to intestinal ischemia, increased multiple organ failure, and death – were startling enough in their own right, but were even more unexpected because they contradicted 2 previous studies by Oláh et al (18, 19), in which use of probiotics improved outcomes in SAP. One has to interpret the study's results as showing that the treatment itself (not an error in randomization or extraneous confounding factor) caused the negative outcome, in which the addition of bacteria infused directly into the small bowel set up an adverse cascade of events that led to organ failure and ultimately death, as indicated by McClave et al in an editorial (22). The explanation for these poor results may be related to the high incidence of gut ischemia seen in the treatment group (where the controls appeared to have no gut ischemia). Investigators fed high doses of enteral nutrition (EN), fiber, and bacteria directly into the small bowel. Pancreatitis is a notorious disease process for problems with third-spacing and difficulties in volume resuscitation. Six of the 9 patients who developed ischemia were fed on pressor agents in a setting of hypotension. Splanchnic hypoperfusion, reduced nutrient absorption, fermentation of luminal formula, and high doses of bacteria might have led to gaseous distention, increased intraluminal pressure, and intramural ischemia, a process that would promote organ failure and death. A comparison of the 2 studies (Oláh et al, 2007 (19) and Besselink et al, 2008 (4)) is shown in Table II.

Before making a strict decision on the Besselink study (4), one must remember that there may be some inherent

**TABLE II -** COMPARING 2 PROBIOTIC STUDIES IN SEVERE ACUTE PANCREATITIS

| | **Oláh et al, 2007 (19)** | | **Besselink et al, 2008 (4)** | |
|---|---|---|---|---|
| | **Probiotic (n = 33)** | **Controls (n = 29)** | **Probiotic (n = 152)** | **Controls (n = 144)** |
| APACHE II scores | 11.7 | 10.4 | 8.6 | 8.4 |
| Mean CRP levels (mg/dL) | 216 | 191 | 268 | 270 |
| Alcohol etiology (%) | 60 | 62 | 18 | 19 |
| Necrosis (%) | 60 | 62 | 30 | 24 |
| Age (years) | 47.5 | 46.0 | 60.4 | 59.0 |
| Center | Single | | Multicenter (15 centers) | |
| Feeding supplement | Nutrison fiber | | Nutrison multifiber | |
| Prebiotic | Beta-glucan, inulin, pectin, starch (10 g) | | Cornstarch, maltodextrin | |
| Probiotic organisms | *Lactobacillus pediacoccus, Leuconostoc, Lactobacillus paracasei, L. plantarum* (Synbiotic 2000) | | *Lactobacillus acidophilus Lactobacillus casei Lactobacillus salivarius Lactobacillus lactis Bifidobacterium bifidum Bifidobacterium lactis* (Ecologic 641, Winclove) | |
| Dosage | $10^{10}$ each organism | | $10^{10}$ each organism | |
| Route of administration | Nasojejunal | | Nasojejunal | |
| Duration of treatment | 1 week | | 4 weeks | |
| Outcomes | | | | |
| MOF (%) | 15.1 | 31.0 | 22 | 10 |
| Surgical intervention (%) | 12.1 | 24.1 | 18 | 10 |
| Mortality (%) | 6 | 21 | 16 | 6 |
| Septic complications (%) | 27 | 52 | 30 | 28 |
| LOS (days) | 14.9 | 19.7 | 28.9 | 23.5 |

APACHE = Acute Physiological Assessment and Chronic Health Evaluation; CRP = C-reactive protein; LOS = length of hospital stay; MOF = multiorgan failure.

risk with EN and probiotics. Factors such as old age, hypotension, splanchnic hypoperfusion, and pressor requirement of the patient might make the risk prohibitive in certain (but not all) patients. There are also some concerns about the method of randomization (9). In the Besselink study, there were more patients in the probiotic arm with organ failure before or during the first dose of probiotic. The expected time period for the beginning of a probiotic effect after ingestion is not defined in the study. The fact that the organ failure occurred in the probiotic group after the first dose of probiotic is raises suspicions.

It is important to avoid early, potentially inappropriate generalizations such as that any probiotic is dangerous in the critically ill patient, early EN is too dangerous in SAP, or probiotics have no role in the therapy of SAP.

## PREBIOTICS IN ACUTE PANCREATITIS

Prebiotics are, by definition, nondigestible foods that beneficially affect gut microbiota (23). In recent years, the definition of prebiotics has widened. There are 3 main properties of a food that make it a prebiotic: resistance to digestion by humans, fermentation by the gut bacteria, and a selective positive effect on commensal bacteria and resultant health-promoting effect in the host (24).

Prebiotics are fermented by the gut flora, and the bacteria produce end products of prebiotic fermentation. While the end products, such as butyrate are produced, further enhancement of the commensal bacterial growth is supported. It is observed that the cecal contents of animals being administered prebiotics contain relatively higher total amounts of short chain fatty acids and the proportional composition of the short chain fatty acids is shifted in the direction of more propionate and butyrate. The complete picture of intestinal bacterial secretions into the chyme is not known; there may be thousands of organisms contributing to this pool. Metabonomics is a relatively new scientific discipline that focuses on the study of these compounds and should shed more light on these aspects in the near future. Many of these bacterial metabolites are absorbed into the systemic circulation, and they have many distant systemic effects beyond their local effects (24).

In SAP, there is an overgrowth of pathogenic bacteria in the intestine (25). Mortality related to SAP mainly occurs as a result of infection of the necrotic area. The infection is mainly a consequence of translocated pathogenic bacteria. These bacteria come from leaky gut mucosa as a result of severe inflammation, and secondly, as a result of pathogenic bacterial overgrowth in the gut.

Many of the patients in the ICU have a contaminated or disrupted gut flora, in which pathogenic bacteria predominates. Lactic acid–producing bacteria can inhibit endogenous pathogens from multiplying (colonization resistance), and this effect also inhibits the degree of bacterial translocation (26, 27). Inulin and oligofructose are 2 widely used prebiotic agents that theoretically strengthen gut barrier function (28, 29). The most important property of a probiotic to exert beneficial effects is the ability to adhere to the gut mucosa. Some prebiotics have been shown to prolong the attachment and adherence of probiotic bacteria in animal models (30, 31). This enhancement of the beneficial effects of prebiotics was shown in a study by Klarin et al (32). Nine critically ill patients treated with broad-spectrum antibiotics received an oatmeal formula fermented with *Lactobacillus plantarum* 299v. Three of them showed *L. plantarum* 299v adhering to the rectal mucosa in histological analysis. The authors concluded that prebiotics increased the survival and attachment of *L. plantarum* 299v to rectal mucosa.

Prebiotics are usually combined with probiotics and applied as synbiotics in SAP (4, 19). There is only 1 study comparing prebiotic (without probiotic) versus placebo in SAP (21). In this study, 60 patients (30 SAP, 30 controls) were given isocaloric and isonitrogenous nasojejunal feeding in the early period of pancreatitis. The study group received fructooligosaccharide containing fiber (15 g/day). The median duration of hospital stay was shorter in the study group (10 ± 4 days [range 8-14 days] vs. 15 ± 6 days [range 7-26 days]; $p < 0.05$). The median number of days in the ICU was also similar in both groups (6 ± 2 days [range 5-8 days] vs. 6 ± 2 days [range 5-7 days]). The median duration of EN and APACHE II normalization was shorter in the prebiotic group.

However, further studies are needed to clarify certain issues: First, should probiotic supplementation be forbidden in SAP? If so, what is the difference between other critical patients in ICUs to whom probiotics were safely given in many studies and patients with SAP? Second, are prebiotics a safer alternative to probiotics in patients with SAP? In the near future, I hope that these questions will be answered by well-designed studies.

**Conflict of Interest:** none declared.
**Financial support:** none.

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