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Is probiotic prophylaxis worthwhile in patients with predicted severe acute pancreatitis?

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SUMMARY

Few studies have examined probiotic prophylaxis in patients with acute pancreatitis, and those that have been performed have yielded conflicting results. In this Practice Point commentary, I discuss the findings and limitations of a study by Besselink *et al*., which assessed the effects of a multispecies probiotic preparation in patients with predicted severe acute pancreatitis. The preparation did not reduce infectious complications, and increased mortality. However, it is necessary to remember that large genetic and functional differences exist between various strains of bacteria and that only a few lactic acid bacteria (LAB) have demonstrated an ability to significantly reduce inflammation, control infection and provide health benefits to humans. Choice of LAB and dose of LAB is critical for outcome. Extensive preclinical studies are essential before recommendations for new cocktails of probiotics can be introduced in clinical practice.

KEYWORDS infectious complications, lactic acid bacteria, outcomes, probiotics, severe acute pancreatitis

COMMENTARY

Acute pancreatitis affects approximately 50 per 100,000 individuals, of whom 1 in 5 has severe acute pancreatitis (SAP).[1] Acute pancreatitis is associated with gallstone disease and alcohol abuse, but is also triggered by trauma and various drugs and infections.[1]

The first ever human study of probiotics for the treatment of pancreatitis involved 45 patients: 22 received live *Lactobacillus plantarum 299*, and 23 received heat-killed *L. plantarum 299*.[2] Infected pancreatic necroses and abscesses occurred in 1 of 22 treated, and 7 of 23 control patients ($P = 0.023$). No intention-to-treat analysis was performed. No adverse effects related to treatment were observed.

A second study[3] administered four species of lactic acid bacteria (LAB)—*Lactobacillus paracasei* subsp. *paracasei* 19, *L. plantarum* 2362, *Pediococcus pentosaceus* 5–33:3, and *Leuconostoc mesenteroides* 32–77:1 together with four prebiotic fibers to 31 patients with SAP. In total, 2 of 31 treated, and 6 of 31 control patients died. The cumulative incidence of systemic inflammatory response and multiorgan failure was significantly lower in patients who received synbiotic therapy (probiotic plus prebiotic) than in controls (8 vs 14; $P < 0.05$), and the number of patients with an uneventful recovery was significantly higher in patients on synbiotic therapy than in controls ($P < 0.05$). No treatment-related adverse effects were observed.

Besselink and colleagues' study[4] investigated the use of probiotic therapy in patients with SAP and included 298 patients. The study is very different from the previous two studies described.[2,3] A few of its characteristics deserve comment.

This multicenter, randomized, controlled study involved hundreds of doctors and nurses with little or no knowledge about probiotics or the other different standard treatments for SAP. The study groups might not have been fully comparable. Organ failure during admission was significantly more common in the probiotic group than in the placebo group (27.0% vs 16.0%, $P = 0.02$).[4] Furthermore, two investigators independently reviewed Besselink *et al*.'s data and revealed that more patients in the probiotic group had organ failure before or on the day of the first dose than did those in the placebo group (13.2% vs 4.9%, $P = 0.01$).[5]

The complication of deadly intestinal ischemia was observed in Besselink and colleagues' study population in eight patients; however, this complication has not previously been associated with probiotic treatment or pancreatitis. Intestinal ischemia is, however, associated with vasopressor treatment in patients with shock

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and/or bleeding esophageal varices. Insufficient randomization might explain why more patients in the probiotic group than the placebo group received vasopressor treatment, and explain the significantly higher rate of unexpected death because of bowel ischemia in the probiotic group versus the control group (8 vs 0, respectively). The mortality rate in the probiotic group was therefore higher than in the placebo group (16% vs 6%, $P = 0.01$).[4]

The composition of the probiotic therapy used in Besselink *et al.*'s study was different to that commonly used (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium 762 bifidum*, and *Bifidobacterium lactis*).[4] Only a few of the thousands of bacteria that have been investigated as potential probiotics have probiotic and anti-inflammatory properties. Different, and sometimes opposing, effects are found between strains, even those that carry the same name. When 46 *L. lactis* strains were investigated for their ability to produce pro-inflammatory and anti-inflammatory cytokines, different and opposing effects were observed.

Some LAB—*L. paracasei* subsp. *paracasei, L. plantarum,* and *P. pentosaceus*—are more likely to have clinical efficacy. In particular, *L. paracasei* has been shown to induce cellular immunity and stimulate the production of the suppressive cytokines TGF-β and interleukin 10, suppress T_H2 activity and CD4 T-cells, suppress splenocyte proliferation and decrease antigen-specific IgE and IgG_1. *L. paracasei* was shown to be the strongest inducer of T_H1 cytokines and repressor of T_H2 cytokines out of >100 LAB strains. When the ability of four different strains of bacteria—*L. paracasei*, *Lactobacillus johnsonii*, *Bifidobacterium longum*, and *B. lactis*—were studied for their ability to control *Trichinella spiralis*-induced infection, only *L. paracasei* was shown to be able to reduce the infection-associated T_H2 response, levels of TGF-β, cyclo-oxygenase-2 and prostaglandin E_2 in muscle, and to attenuate infection-induced muscle hyper-contractility. *L. paracasei* NCC2461, in contrast to *B. lactis* NCC362 and *L. johnsonii* NCC533, has been shown to effectively restore normal gut permeability and to significantly reduce stress-induced visceral hyperalgesia and pain.

L. plantarum also has an excellent record of clinical efficacy. Fifty different LAB were examined for their ability to control 23 different *Clostridium difficile* strains, but only *L. paracasei* and *L. plantarum* were shown to effectively eliminate all strains; more than half of the LAB strains were totally ineffective, and some were effective only against a few strains of *C. difficile*. A few LAB are potentiated by being given simultaneously with a supply of prebiotic fibers, and a minority of LAB have the ability to use semifermentable fibers such as oligofructans—*L. plantarum* (several strains), *L. paracasei* subsp. p*aracasei, Lactobacillus brevis* and *P. pentosaceus*.[6,7]

Probiotic formulations containing *L. plantarum*, *L. paracasei* and *P. pentoseus* are, so far, the only bacteria shown to have beneficial effects for the treatment of patients with acute pancreatitis. Their efficacy in this setting is supported by their efficacy in other categories of critical illness such as severe multitrauma, extensive surgical procedures (e.g. liver transplantation and pancreatoduodenectomies) and chronic diseases such as liver cirrhosis and encephalopathies.[6,7]

Competing interests
The author has declared an association with Medipharm AB. See the article online for full details of this relationship.

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PRACTICE POINT

Few lactic acid bacteria have been shown to reduce inflammation and control infection in patients with acute pancreatitis. *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Pediococcus pentosaceus* can be safely and effectively used as probiotics in this setting. Extensive preclinical studies are essential before recommendations for new cocktails of probiotics can be introduced in clinical practice.