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PANCREAS NEWS

Probiotics and Acute Pancreatitis: There Is Still a Long Way to Go!

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Probiotics are defined as "mono- or mixed cultures of live micro-organisms able to beneficially affect the host by improving the properties of the indigenous flora" [1]. The indigenous intestinal microflora is a complex ecosystem which develops early in life. In adulthood, this system consists of at least 500 different bacterial species with a maximum concentration of the bacteria in the ileum and colon [2]. More than 99% of the micro-organisms in the colon are strictly anaerobic, such as bifidobacteria, peptostreptococci, *Bacteroides spp*., and *Clostridium spp*. [3]. Intestinal microflora has several important functions for the host including the production of vitamins, degradation of bile acids, digestion of nutrients and the conversion of (pro)carcinogenic substances. In addition, the colonization of the intestine by commensal bacteria is also important for the development and functioning of the immune system [4]. The functions of the intestinal microflora may be positively influenced by probiotics which exert a therapeutic effect through modification of the composition of indigenous intestinal microflora and its metabolic activity, prevention of overgrowth and colonization of pathogens, and stimulation of the immune system.

In recent years, the therapeutic and preventive application of probiotics in several gastrointestinal and liver disorders has received increasing attention. Convincing evidence is available for some intestinal diseases, such as antibiotic-associated diarrhea and pouchitis, whereas the results of clinical trials are encouraging regarding irritable bowel syndrome, ulcerative colitis, Crohn's disease, lactose intolerance and constipation [5]. Probiotics have also been utilized in some liver diseases, such as non-alcoholic fatty liver disease, and for the prophylaxis of spontaneous bacterial peritonitis in cirrhotic patients. The results are promising but more evidence from clinical trials is still needed [4].

The infection of pancreatic necrosis by gut bacteria is a major cause of morbidity and mortality in patients with severe acute pancreatitis. In line with possible mechanisms for infectious complications in liver cirrhosis, bacterial translocation is also thought to be the pathway responsible for the infection of pancreatic necrosis leading to severe sepsis and multiple organ failure. Many conditions, all documented in acute pancreatitis, may cause this bacterial translocation, i.e., bacterial overgrowth, disturbed mucosal barrier and intestinal motility, and the overproduction of pro-inflammatory cytokines [6]. Different animal models showed a significantly lower rate of bacterial translocation by using probiotics and this has prompted human trials on this topic. Olah *et al*. [7] published the first controlled study on the effect of probiotics in humans in 2002. These authors found significantly less infected pancreatic necroses with live lactobacilli (5%, n=22) compared to heat-killed lactobacilli (30%, n=23) in a group of patients with acute non-biliary pancreatitis. However, this study was criticized because the sample size was small, patients with

biliary pancreatitis were excluded, the analyses were not analyzed by an intention-to-treat approach, and a subgroup of patients had concurrent use of antibiotics [8]. The same research group produced a second trial involving 62 patients with predicted severe pancreatitis [9]. Unfortunately, in this study, the difference in the rate of infectious complications seen in the first trial could not be reproduced.

Very recently, a new trial (PROPATRIA study, produced by the Dutch Acute Pancreatitis Study Group) was published on this controversial issue [10]. This well-designed and powerful trial is a multicenter, randomized and double-blind *versus* placebo study, including 296 patients with predicted severe acute pancreatitis (Acute Physiology and Chronic Health Evaluation - APACHE II - score ≥8; Imrie ≥3 or C-reactive protein >150 mg/L). The patients were randomly assigned within 72 h of the onset of symptoms to receive a multispecies probiotic preparation (n=152) or a placebo (n=144), enterally administered through a nasojejunal tube twice daily for 28 days. The probiotic mixture consisted of six different strains of freeze-dried, viable bacteria: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactobacillus lactis, Bifido-bacterium bifidum,* and *Bifidobacterium infantis*. The primary endpoint of the trial was to determine the entire range of infectious complications (infected pancreatic necrosis, bacteremia, pneumonia, urospesis, or infected ascites) during admission and 90-day follow-up. These complications occurred in 46 (30%) patients in the probiotic group and 41 (28%) of those in the placebo group (relative risk: 1.06; 95%CI: 0.75-1.51). Nine patients in the probiotic group developed bowel ischemia (8 with fatal outcome) as compared to none in the placebo group (P=0.004). The authors speculated that the mechanisms of bowel ischemia induced by probiotics may be related to: i) the increased local oxygen demand produced by the administration of 10 billion probiotic bacteria per day with a combined deleterious effect on an already critically reduced blood-flow and/or ii) aggravation of local inflammation due to the bacterial load within the intestinal lumen, again with a further reduction of capillary blood-flow and ultimately ischemia. Overall, 24 (16%) patients in the probiotic group died, compared with 9 (6%) in the placebo group (relative risk 2.53; 95%CI: 1.22-2.25). These results clearly show that probiotic prophylaxis did not reduces the risk of infectious complications and was associated with an increased risk of mortality in patients with predicted severe acute pancreatitis. The conclusion reached in the study was that probiotics must be regarded as unsafe in these critically-ill patients.

Unfortunately, the results of the large PROPATRIA study [10] were contrary to expectations. As different probiotic strains can have different effects, further insight into the functioning of various strains in experimental acute pancreatitis is required in order to be able to select well-characterized strains with specific beneficial effects in human acute pancreatitis.

... Denn alles Interesse für Tod und Krankheit ist nichts als eine Art von Ausdruck für das am Leben, ...
… All interest in disease and death is only another expression of interest in life, ...
Thomas Mann (1875-1955). Der Zauberberg, Chapter 6; 1924.

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