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EDITORIAL

Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients

The study reported in this issue by Jain et al.[1] is professionally well done and the observations made are of the greatest interest to all interested in immuno-nutrition and sepsis prevention. Although significant reductions in potentially pathogenic organisms (PPMs) in nasogastric aspirates were observed in the treated patients, no influence on intestinal permeability could be observed and no clinical benefits obtained when a specific synbiotic formula was supplied to a mixed group of critically ill patients. It should be emphasised that it is very important that also negative results are reported and extensively analysed.

Several factors are known to influence the efficacy of synbiotic treatment.

The time point when instituted: The most important function of synbiotic treatment is most likely to strengthen the immune response, reduce the trauma or disease-associated exuberant inflammatory cascade and ''cytokine storm'' and thereby prevent secondary morbidity, which often leads to the stage of critical illness and to care in Intensive Therapy Units (ITUs). It is observed in liver transplantation that if the increase in TNF-α and IL-6 at the end of operation is more than 6 times the preoperative values, postoperative infections are most likely to occur. Experiments in animals with induced disease such as acute pancreatitis suggest that there is a therapeutic window of no more than 24–36 h. Treatment efforts induced after that will most likely have only limited effects. This could explain the limited clinical benefit in patients, who have been in the stage of critical illness for several days. The best results of treatment will most likely be obtained if treatment is instituted before, or if not possible, as immediate as possible in acute disease process. This seems to be the reason why the best results of treatment can be expected from the use of synbiotics in elective surgical and medical treatments such as transplantations, including that of bone marrow. This could well explain if critically ill patients are more therapy-resistant than elective patients, as the acute neuro-hormonal and inflammatory cascades and immediate immune responses are already over in these patients.

However, we still do not know enough to be sure. Although several controlled clinical studies are ongoing only one small study in ITU patients has been published so far. In this study a mixture of 10^9 of *Lactobacillus plantarum* 299 and oat fibre was given to 19 critically ill patients and compared to 19 patients receiving the same formula after the lactobacillus had been heat-killed.[2] The mortality was 26% in the synbiotic-treated group compared to 42% in the group receiving the same after the LAB had been heat-killed. However, the difference did not reach statistical significance in this small material. No influence on multi-organ dysfunction and failure could be observed.

The lactic acid bacteria strains and type of fibre tried: In the study by Jain et al. a mixture of yogurt bacteria and acidophilus was used. These LAB are known as most other LAB, to have a low survival in an environment with acidity and bile acids like the upper GI tract. These LAB are also known to generally exhibit limited or no biological influence on the immune system. The fact that these LAB did not produce any clinical benefits will not exclude such benefits when other LAB are tried. It is important to remember that no conclusions regarding bioactivities can be drawn from one LAB to another as they are often very different in function and genetically unrelated. It is sometimes said that the genetic difference between one LAB and another is greater than between a fish and a human being. The great differences in survival and ability to influence cytokine production after passage through the stomach and small intestine is well demonstrated

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by a study comparing four different LAB species: *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus* and *Bifidobacter animalis*.[3] Of originally administered 10^8 cells/ml of each LAB between 10^7 (*Lactobacillus plantarum*) and 10^2 (*Lactobacillus rhamnosus*) bacterial cells only remained after the passage through the stomach and small intestine. If LAB like those used in the study by Jain et al. would have been tried an even smaller survival could have been expected. Most of the strains tested showed, after passage through the small intestine, a significantly reduced or weak (especially *Lactobacillus rhamnosus*) ability to influence, for example, cytokine production. Most interestingly *Lactobacillus plantarum*, in sharp contrast to the other LAB tested, after the passage through the stomach and small intestine, demonstrated an even greater capacity to influence cytokine production. Although the reasons for this unique effect have not been studied, it can be speculated that the low pH in the stomach could stress-activate this *Lactobacillus plantarum* strain.

The amount of lactic acid bacteria and fibre supplied: Supply of LAB in a density of 10^7 or lower is generally regarded as too small for significant clinical effects to be induced. In the present study three daily doses of totally 10^9 LAB were supplied, which should in theory be satisfactory. However, the dose of each of the four LAB was obviously much less. Cumulative effects when supplying several LAB can most often not be expected. Twice daily supply of 7.5 g of oligofructose is a most satisfactory dose. Fibres are known to exhibit significant bioactivities even when supplied without probiotics. It is, therefore, of special interest that supply of oligofructose did not alter the outcome in ITU patients.

The method of administration: The four LAB in the present study were supplied in the form of entero-capsules. There is no information about the level of release of the LAB from the capsule. Nor is there information if oral supply of the capsules could be performed in each case or if sometimes or often the content of the capsules were administered through nasogastric or nasoenteric tubes. If the goal is to influence the gastric PPM flora, it should most likely be of advantage if capsules are not used and the probiotic administered directly into the stomach. Stronger effects should be expected if the probiotic solution before administration is left in room temperature for about 1 h to let the LAB to be activated before administration.

Function of flora

It is well known that people living a Western lifestyle have a significantly reduced flora, manifested both in reduced number of strains and reduced number of bacteria compared to those who live in rural places, especially in developing countries, and who consume large amounts of fresh fruits, vegetables and live LAB. It is also known from experimental studies with induced disease such as pancreatitis that the LAB flora disappears after 6–8 h and is replaced by an overgrowth of potentially pathogenic microorganisms. Soon thereafter microbial translocation follows. A small study under publication supports the view that the majority of patients in the ITU have lost their total *Lactobacillus* flora, but it also shows that the loss can successfully be compensated by supply of a specific synbiotic preparations (Fig. 1).[4]

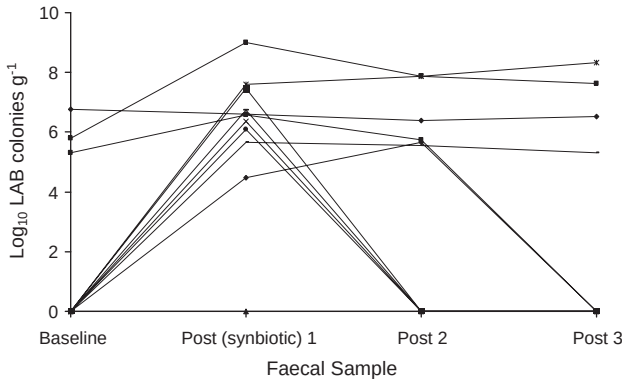

Figure 1 Number of LAB colonies in fecal before and at different intervals after two days supply of the synbiotic composition in ten ITU patients (3 General Surgery, 2 pneumonia, 2 spinal injury, 2 Neurosurgical trauma, 1 Neurology and 1 Polytrauma with ARDS). The medial APACHE II score median = 22 (11–34) Post 1 marks 2–3 days after supply of first dose.

Flora and supplied probiotics have several important functions in the body: to reduce/eliminate potentially pathogenic microorganisms/PPMs, to reduce/eliminate the content of various toxins, mutagens/carcinogens from the gut, to promote apoptosis, to release from the plant fibres numerous nutrients, antioxidants, growth, coagulation and other factors and to modulate innate and eventually adaptive immune defence mechanisms. Consumed or supplemented plant fibres have their own strong bioactivities: to maintain mucosal growth and functions, to maintain water and electrolyte balance, to provide energy and nutrients for the host, to provide energy and nutrients for the flora and to provide resistance against invading pathogens. The fermentation process in the lower GI tract releases through action of microbial enzymes numerous nutrients and antioxidants, but also various growth-, coagulation- and inflammation-controlling molecules. Antioxidants released in the lower GI tract have significant pro-regenerative, antibacterial, antithrombotic, vasodilatory, anti-inflammatory and anti-carcinogenic effects.

Choice of specific strains important

Only a few LAB have proven bioactivities to the extent needed for treatment of very sick patients. For example, when we researched about 350 human fecal bacteria and 180 bacteria from growing rye we did not find much more than a handful, which fulfilled most of the criteria needed: to survive the acidity of the stomach and the bile acid of the small intestine, to attach to colonic mucosa, to ferment various types of plant fibres, to produce both pro- and anti-inflammatory molecules such as cytokines, and to produce bioactive molecules such as heat shock proteins. It is from such extensive research in nature that we have chosen our synbiotic treatment tools.

In the first series of studies we used a one LAB/one fibre composition consisting of 10^9 *Lb plantarum* 299 and 10 g of oat fibre. Later we have been working with a four LAB/four fibre composition consisting in 10^{10} of each of the following four LAB: *Pediacoccus pentosaceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1, *Lactobacillus paracasei* subsp paracasei 19, and *Lactobacillus plantarum* 2362 and 2.5 g of each of four fermantable fibres (prebiotics): betaglucan, inulin, pectin and resistant starch.

Personal experience

I have in recent years had the privilege to work clinically with various international specialists to explore the possibilities of synbiotics to prevent disease and, especially, to prevent septic complications. Most of the work has focused on acute pancreatitis, extensive abdominal surgery, liver transplantation and chronic liver disease, conditions all known for their high rate of infection.

Severe acute pancreatitis

Forty-five patients were supplemented from a time point in the disease process defined as early as possible with the one LAB/one fibre formula containing either live or heat-killed LAB.[5] The study was interrupted when repeat statistical analysis demonstrated statistically significant differences in infection rate between the two groups. At that time 22 patients had received treatment with live and 23 with heat-killed *Lb plantarum* 299. Infected pancreatic necrosis and abscesses were seen in 1/22 (4.5%) in the live LAB group and in 7/23 (30%) in the heat-inactivated group ($P = 0.023$). The only patient in the live LAB group, who developed infection, had signs of urinary infection on the 15th day, e.g. at a time when he had not received treatment during the last eight days. The length of stay was considerably shorter in the live LAB group (13.7 days vs. 21.4 days), but the limited size of the material did not allow statistical significance to be reached.

Abdominal surgery

Live LAB and oat fibre, heat-inactivated LAB and oat fibre and Standard enteral nutrition were administered to a mixed group of patients mainly undergoing liver, pancreatic and gastric resections.[6] The 30-day sepsis rate was 10% (3/30 patients) in the two groups receiving either live or heat-inactivated LAB, compared to 30% (9/30 patients) in the group with standard enteral nutrition ($p = 0.01$), the biggest difference was observed in numbers of pneumonia: enteral nutrition only—6 patients, live LAB and fibre—2 patients, heat-killed LAB and fibre—1 patient. The beneficial effects of synbiotic treatment seemed to be most pronounced in gastric and pancreatic resections with a sepsis rate of 7% with live LAB, 17% with heat-inactivated LAB and 50% with standard enteral nutrition. The live LAB-treated patients received significantly less antibiotics ($P = 0.04$). The mean length of antibiotic

treatment was 4 ± 3.7 days with live LAB, 7 ± 5.2 days with heat-killed LAB and 8 ± 6.5 days with only standard enteral nutrition.

Liver transplantation

The 30-day infection rate after liver transplantation is usually above 50%; the most recent study reports a 30-day morbidity of 86% despite or eventually due to extensive and multiple treatment with antibiotics (selective bowel decontamination). Two randomised studies were conducted in liver transplant patients in collaboration with the University of Berlin. When the one LAB/one fibre composition was supplied, a 30 day infection rate of 13% was observed compared to 34% with heat-killed LAB and 48% with selective decontamination.[7] The infection rate was in a second study using the four LAB/four fibre composition further reduced to only 3% (1/33 patients suffered a slight urinary infection) compared to 51% in the group treated with only fibres.[8]

Chronic liver disease

Pro- and prebiotics (synbiotics) have the ability to reduce the production and absorption of endotoxin in the intestine, and to down-regulate production of pro-inflammatory cytokines, such as TNFα. In a study in collaboration with University of Sidney we recently observed that in vitro TNFα production by peripheral blood mononuclear cells, in response to stimulation by endotoxin or Staph aureus enterotoxin B, is reduced by a median 46% (range: 8–67%) in comparison to pre-supplementation levels in 8/11 (72.7%) cirrhotic patients supplied with the four LAB/four fibre composition.[9]

In another study in chronic liver disease either the four LAB/four fibre formula, only the four fibres a placebo consisting in non-fermentable, non-absorbable fibre was supplied daily during one month.[10] Significant decreases in the gut content of *Escherichia coli, Staphylococcus* and *Fusobacterium,* but not *Pseudomonas* and *Enterococcus*, were observed. Ammonia/s, levels of endotoxin/s and ALT/s fell significantly in both treatment groups and were accompanied by significant improvements in psychometric tests and in degree of encephalopathy.

Supply of synbiotics to patients with various acute and chronic conditions is almost always well-tolerated and have no adverse events or adverse changes in general clinical state of the patients. Synbiotic treatment capable to down regulate the expression of Toll-like receptors and reduce the production of TNFα seems to have the potential to be a cheap and powerful tool for both long-term treatment of patients with chronic diseases such as liver disease and for treatment of patients with various acute conditions. Efforts must continue to find the most powerful LAB and the most powerful fibres or combinations thereof.

For further information on bioecological control and synbiotic treatment—see Bengmark.[11–13]

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