Abstract

Although the word synbiotics was coined to describe the combined action of pre- and probiotics, the ability to, like antibiotics, control infection, the term is now increasingly used in a wider sense, as a name for all the substances released by microbial fermentation in the lower gut. One obvious reason is that most of the substances released seem to influence the immune defense, increase resistance to disease, and, most important, prevent complications to surgery such as infections and thrombosis. Protection layer of lactobacillus does not exist only on the GI tract mucosa, it is important at all exterior body surfaces including those of the eye, the nose, the mouth, the respiratory tract, the vagina, not to forget the skin. It is clearly reduced at all sites when the patient is in the settings of ICU.

Each human being has his/her own unique microbial collection, especially of strains of \textit{Bifidobacterium} and \textit{Lactobacillus}, and it should be possible to identify an individual on the basis of his/her personal intestinal microflora. The flora seems always to be significantly reduced in the sick, especially in connection with severe disease, care in ICU, and in patients with little food intake or on parenteral nutrition. Supply of both pre- and probiotics can modify functions such as appetite, sleep, mood and circadian rhythm, and this most likely through metabolites produced by microbial fermentation in the gut. Supply of lactic acid bacteria (LAB) can also significantly reduce serum levels of a variety of toxins such as endotoxin.

An umbrella of supplemented probiotics could provide to the patients with liver cirrhosis a tool to reduce spetic manifestations and the incidence of bleeding. LAB are effective in controlling diarrhea of both bacterial and viral origin. A series of experimental studies and se-

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veral uncontrolled clinical studies support the idea of using probiotics in patients with IBD. Ecoinmunonutrition with pre- pro- and synbiotics offer to be suitable tools in the new millenium.

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**Key words:** Econutrition. Symbiotics. Critical Care. Prebiotics. Probiotics.

Introduction

The large intestine was not long ago regarded as an organ with almost only one function - to absorb water and electrolytes. It has not been realized for long, at least not among clinicians, that the colon is a highly active metabolic organ, in which numerous metabolic processes take place and almost uncountable nutrients are released and absorbed. Here bacterial enzymes of probiotic bacteria metabolize prebiotics (various fruit and vegetable fibers, but also gastrointestinal secretions and apoptotic cell) and countless numbers of products are released and absorbed - products increasingly referred to as synbiotics.

Today colon is known as a metabolic organ with eventually more and also more complex functions than the rest of the gastrointestinal tract, where chemical processes are promoted by enzymes produced by bacterial instead of eukaryotic cells. An indication of the complexity of the metabolic activities in the large intestine is the information that the colonic “microbial organ” contains about 300 000 genes, to be compared to the about 65 000 genes in the rest of the human body. Numerous substances, several hundred thousand if not millions, are produced, released and absorbed at the level of the lower small and the large intestine. Among these are various fatty acids, especially short chain fatty acids (SCFA’s), carbohydrates, amino acids, polyamides, vitamins, antioxidants, phytoestrogens, and coagulation and growth factors. Only of polyphenols such as flavonoids exist more than four thousand and of carotenoids about six hundred.

Although the word synbiotics was coined to describe the combined action of pre- and probiotics, the ability to like antibiotics control infection, the term is now increasingly used in a wide sense, as a name for all the substances released by microbial fermentation in the lower gut. One obvious reason is that most of the substances released seem to influence the immune defense, increase resistance to disease, and, most important, prevent complications to surgery such as infections and thrombosis.

The food ingredients (fibers, complex proteins, etc.), which mainly unchanged reach the colon, are usually referred to as “colonic foods”. It is recommended that at least ten per cent of the total calorie intake should be of this type, a goal difficult to meet in the very sick patients. As prebiotic fibers are low-caloric, at least one fourth of the food eaten under healthy conditions is recommended to be of the type “food designed for the colon”, e.g. food ingredients that are not are broken down by gastrointestinal juice enzymes and absorbed in the upper small intestine. In the past it was usually regarded as ore or less impossible to provide colonic foods to patients in the ICU, a view, which in recent years has been revised.

Fibers are prebiotics

Research regarding various probiotics have in recent years exploded and information about the various probiotic bacteria is fast increasing. Prebiotics are as important, as availability and content of various fibers limits the production of symbiotic compounds produced.

Fibers are carbohydrates derived from plant cell walls, and dietary fibers are usually classified into three groups: soluble fibers such as pectins and various gums, insoluble fibers such as cellulose and mixed type fibers such as brans. The most important characteristic for them all is that they are resistant to hydrolysis by human alimentary tract enzymes, which make some of them ideal substrate for microbial fermentation in the lower GI tract. Soluble fibers (prebiotics) constitute an important source for bacterial fermentation and microbial production of nutrients, antioxidants, vitamins, and growth and other important factors. This far, the main interest has focused on the production of various short chain fatty acids (SCFAs) and fermentation by-products such as hydrogen, methane and carbon dioxide. But the content of other nutrients; various bioactive amino acids, polyamids, antioxidants and various growth factors etc are equally important.

Prebiotic fibers are slow carbohydrates, which have a strong influence glucose and fat metabolism, and cause decrease in postprandial glycemia, reduction in the concentration of free fatty acids and in serum cholesterol levels. An increase in proliferation...
of mucosa epithelial cells will occur in the caecum and in the colon as a result of increased fiber consumption, associated with a significant decrease in intraluminal pH. But fibers have also their own direct physiological effects. Common to soluble and viscous fibers is that they delay gastric emptying, increase intestinal transit time, and improve glucose tolerance. Soluble dietary fibers do also sequestrate bile salts and significantly affect lipid absorption. Here follows a short introduction to some interesting bioactive fibers.

**Pectin**

We observed, when studying a pectin solution in water, that when pH is reduced to a level of 1.0, e.g. the pH seen in the stomach, a so called two-phase separation will occur, with leading to formation of a gel phase and a watery phase. It is likely that, when this separation occurs in the stomach the gel phase will adhere to the mucosa layer and increase the protective capacity of the mucus. Banana, when green and immature, is rich in both pectin and phospholipids, both known to have strong protective effects against peptic ulcer. The effects we observed when concentrations, greater than normally seen in the fruit, were tried did not differ much from what is obtained with established drugs such as H2-blockers, proton inhibitors and surface-protecting agents. Another interesting feature of pectin is that it is a strong antioxidant, which offer mucosal protection against all three main types of oxidation damages: peroxy-, superoxide, and hydroxyl radical. This could be the mechanism by which pectin stimulates the GALT system and prevents disruption of the intestinal microflora. A disadvantage with pectin is, that it is difficult to use in tube-feeding, as it has a tendency to clog the tube.

**Betaglucans**

Another most interesting group of fibers are the betaglucans, a group of unique water soluble fibers often extracted from oat, which contains as much as up to 17% of betaglucans. This gum fiber compares favorably with other high viscosity polysaccharides such as substituted celluloses, guar gums and locust bean gums. The clinical effects of oat gums are yet not explored to the same extent as those os pectin, but are likely to be similar as described for pectin. Most clinical studies have concentrated on oat’s unique cholesterol-lowering effects, and its unique and strong antioxidant effects, extensively used in the past for food stabilizing purpose.

**Resistant starch**

Resistant starch is a type of starch, which resist digestion in the small intestine and reaches the colon, which all starches do not generally do. Resistant starch is one of the main sources of carbohydrate substrates for colonic microflora and is a good determinant of human large bowel function. It is know to release large quantitites of butyrate when fermented.

**Fructooligosacharides**

Fructooligosaccharides (FOS), composed of one molecule glucose and one to three molecules of fructose, have been shown to have unique abilities to effectively stimulate the intestinal flora. Fructooligosaccharides exist naturally in many kinds of plants such as onions, asparagus roots, tubers of Jerusalem artichoke and wheat, but also in banana, beer, burdock, chinese chives, garlic, graminae (fodder grass), honey, oat, pine, rye, chicory, stone leak, and even bacteria and yeasts. The daily intake of inulin and oligofructose by the North American populations has in a recent survey been estimated to be 2-8 g. It is important to recognize that only few lactic acid bacteria strains have the ability to ferment fructans such as phlein and inulin. When 712 LAB strains were tested, only 16 could utilize phleins and only eight inulins. Of these *L plantarum*, followed by *L paracasei* were the most effective both to ferment the fibers and to reduce pH. Beneficial effects of fructooligosacharides on serum cholesterol, triglyceride levels and blood pressure in elderly patients with hyperlipemia has been reported.

**Algal fibers**

Algal polysaccharides are receiving a newborn and fast increasing interest. Most of these fibers are resistant to hydrolysis by human endogenous digestive enzymes and should be suitable as dietary fibers. Their physiological effects have only recently begun to be investitigated. Especially their fermentative de-
gradation by the colonic flora. The soluble fibers in seaweed consist of laminarans (a sort of b-glucans associated with mannitol residues), fucans (sulphated polymers associated with xylose, galactose and glucononic acid) and alginates (mannuronic and guluronic acid polymers), whereas the isolubles algal fibers are essentially cellulose. Fermentation of alginates results in a high acetate production (80%) and laminarans have a very high yield of butyrate. Seaweed with its high content of fermentable fibers, its documented ability to produce large quantities of SCFAs and its high content of omega-3 fatty acids should be an interesting source of medical fibers, most likely soon to be explored.

**Glucomannans**

Glucomannan, a nonabsorbable polysaccharide (glucose/mannose polymer), derived from Amorphophallus konjac (english names: devil tongue, elephant yam, umbrella arum) is also receiving increasing attention for its potential health effects, most likely associated with its unique hydrosopic ability. On contact with water it swells and becomes a viscous gel. Like other soluble fibers it delays both the gastric emptying and intestinal transit time. It is also effective in decreasing the intake of digestible energy. Glycomannans are frequently used in Japan in conditions such as hypercholesterolemia, hypertension and diabetes.

**A complex flora**

It has been calculated that the human body contain more than ten times as many bacterial cells (10^14) than eukaryotic (10^13). The large intestine is supposed to be inhabited by 200 gram of live bacterial flora. But it is not only the gut, which as a “protection layer” of probiotic bacteria, is supposed to be 200 gram on our skin, about twenty gram in each of the mouth, the lung and the vagina, ten gram in the nose and about ne gram in the rectum. This “protection layer” is most often lost in the environment of ICU, and especially when treated with antibiotics and cytostatics.

About 400 bacterial species are normally found in the fecal/colonic microflora of a healthy individual, yet 30 to 40 species seem to constitute 99% of the collection in any one human subject. The bacterial genera, which are common components of the human intestinal microflora, are: Bacteroides, Bifidobacterium, Clostridium, Enterococcus, Eubacterium, Fusobacterium, Peptostreptococcus, Ruminococcus, Lactobacillus and Escherichia. It is suggested that each human being has his/her own unique microbial collection, especially of strains of Bifidobacterium and Lactobacillus, and that it should be possible to identify an individual on the basis of his/her personal intestinal microflora. The most common LAB strains found on the rectal mucosa of healthy humans living a Western lifestyle are Lactobacillus plantarum, Lactobacillus rhamnosus and Lactobacillus paracasei ssp paracasei, isolated in 52%, 26% and 17% of tested individuals respectively. The colonization rate of commonly used milk-born probiotic bacteria such Lactobacillus casei, Lactobacillus reuteri and Lactobacillus acidophilus es in the same study only 2%, 2% and 0% respectively. Lactobacillus plantarum is likely to more often colonize vegetarians (appr 2/3 of that population) than omnivorous (appr 1/4 of that population). Lactic acid bacteria (LAB) seem not to rate well modern, so called Western, lifestyle. Swedish children have a different and less rich flora than Pakistani children or Estonian children.

**Commensal flora reduced early in disease**

Cosmonauts are reported to on return from space flights have lost most of their commensal flora including Lactobacillus species such as Lactobacillus plantarum (lost to almost 100%), Lactobacillus casei (lost to almost 100%), Lactobacillus fermentum (reduced by 43%), Lactobacillus acidophilus (reduced by 27%), Lactobacillus salivarius (reduced by 22%) and Lactobacillus brevis (reduced by 12%). These changes are attributed to poor eating (dried food, no fresh fruits and vegetales) and much reduced supply of fiber and antioxidants, but also lack of exercise and mental and physical stress - conditions not very different from those of the patients in the ICU. The flora seems always to be significantly reduced in the sick, especially in connection with severe disease; care in ICU, and in patients with little food intake or on parenteral nutrition.

The reduction of the commensal flora occurs early in disease. It is observed in experimental pancreatitis — Prevents or reduces duration of diarrhea (rotavirus).
— Reduces atopic dermatitis.
— Induces remission of IBD.
— Reduces symptoms in irritable colon.
— Delays onset of diabetes (animals).
— Reduces the rate of colonic cancer (animals).
— Prevents or reduces Helicobacter infections (animals).
— Reduces the incidence and severity of pancreatic sepsis in pancreatitis (animals).
— Reduces the incidence and severity of ICU sepsis.
— Reduces the incidence and severity of sepsis after major surgery,
— Reduces biofilm.

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<th>Table II</th>
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<tr>
<td>Probiotics-clinical effects</td>
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<tr>
<td>— Prevents or reduces duration of diarrhea (rotavirus).</td>
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<tr>
<td>— Reduces atopic dermatitis.</td>
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<tr>
<td>— Reduces biofilm.</td>
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that anaerobic bacteria and lactobacilli are significantly reduced both in the distal small bowel and in the colon already within 6-12 hours after induction of disease. The changes in pattern of probiotic flora are almost instantly followed by significant increase in numbers of potentially pathogenic microorganisms (PPMs) such as Escherichia coli, and dramatic increases in mucosal barrier permeability (lumen to blood) and in endothelial permeability (blood to tissue),34, 35 both associated with increased microbial translocation and microbial growth both of mesenteric lymph nodes and, in the case of pancreatitis, the pancreatic tissue.36.

Postoperative morbidity still high - and unchanged?

The incidence following trauma and surgical treatment of major complications such as infections and venous thrombosis and of major sequelae such as formation of serosal adhesions has, seemingly in recent years not been reduced at all, or at least not as much as would have been expected. Almost every second patient subjected to transplantation, especially bone marrow, liver, pancreas and intestinal transplantation, every third patient subjected to major liver and pancreatic resection, and every fifth patient having extensive gastric and large intestinal surgery suffer episodes of infection.34, 35 Also laryngopharyngeal, orthopedic and cardiac surgery do often report a double digit incidence of infections. Accumulating evidence suggest that the occurrence of septic complications in intimately associated with a reduced immunological protection of the patient, and a large proportion of the complications are seen in patients over the age of 65 and in immuno-compromised patients.

Venous thrombosis is a frequent complication even today. It is true that clinical manifestations of thrombosis can successfully be eliminated by prophylactic use of various anti-thrombotic agents, but 50 to 70 per cent of the patients will, if phlebography is performed, show signs of venous thrombosis. High incidence of thrombosis seems particularly to be associated with parenteral nutrition (PN), and especially total parenteral nutrition (TPN). Thrombosis and infection seem to be inter-related, and it has recently been suggested that "one common complication may facilitate the occurrence of another common complication by synergistic stimulation of the coagulation system".39 Also the incidence of serosal adhesions in cavities such as the peritoneum, pleura and pericardium and around tendons remains high following surgery, making reoperations more difficult and sometimes impossible, but also leading to other sever health problems such as intestinal obstruction and to infertility.

A life-style associated predisposition?

There is accumulating evidence that Western lifestyle, especially Western food habits, predisposes to super-inflammation and to subsequent clinical complications. It is rather old observation that men eating large amounts of fiber are protected from postoperative venous thrombosis.40, 41 It has also been reported that men living in rural areas and consuming large quantities of cellulose and vegetable fibers + live lactobacilli (fermented milk) have a significantly longer mean clotting time, and soft jelly-like clots compared to those living in urban areas.42 Reduced plasma levels of fibrinogen and factor X has been observed in baboons on Western diet, when supplemented with a fiber such as konjak-glucomannan.43 Decreased levels of plasma viscosity and fibrinogen are found diabetic children supplemented with another fiber, guar-gum.44 Serosal adhesions are associated with an increased endotoxin production, and with overexpression of TGFβ,45 and germ-free animals do not develop serosal

<table>
<thead>
<tr>
<th>Site of study</th>
<th>Type of patients</th>
<th>TPN</th>
<th>SBD</th>
<th>LAB + FIBER</th>
<th>Inactivated LAB + FIBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hongonk</td>
<td>Mixed ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdom. surg.</td>
<td>30% (9/30)</td>
<td>10% (3/30)**</td>
<td>10% (3/30)</td>
<td></td>
<td></td>
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<tr>
<td>Gastr. + panc.</td>
<td>50% (8/16)</td>
<td>7% (1/15)**</td>
<td>17% (3/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver transpl.</td>
<td>48% (15/32)</td>
<td>13% (4/31)**</td>
<td>34% (11/32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acut. pancreat.</td>
<td>4.5% (1/22)***</td>
<td>30% (7/23)</td>
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* not statistically significant, ** p < 0.0001, *** p = 0.017, **** p = < 0.05.
adhesions, both observations supporting an assumption that peritoneal adhesions produced in connection with trauma are associated with alterations in the intestinal environment and in the immune defense.

Increased coagulation is associated with dyslipidemia, glucose intolerance and intravascular coagulation and thrombosis. Diabetic and obese rats with insulin deficiency show raised levels of circulating free acids (FFA). Raised levels of circulating saturated FFAs stimulates fibrinogen synthesis. Insulin resistance is suggested to promote increased levels of FFA and increased fibrinogen synthesis, which can be prevented by increased intake of prebiotics; dietary fibers such as cellulose, pectin, hemicellulose, or some starches, all substrates for production in the large intestine of short chain fatty acids (SCFA), which improves insulin sensitivity.

**Diet-induced superinflammation**

Consumption of saturated fatty acids, as well as trans fatty acids, induces significant alterations in the immune response; inhibits the macrophage functions, and stimulates Th2 response relative to the Th1 response. A recent study in mice observed higher IgM and IgG antibody levels, worsened proteinuria and increased fibrinogen synthesis, which can be prevented by increased intake of prebiotics; dietary fibers such as cellulose, pectin, hemicellulose, or some starches, all substrates for production in the large intestine of short chain fatty acids (SCFA), which improves insulin sensitivity.

### Table IV

**Possible candidates for treatment with pre- pro- and symbiotics**

<table>
<thead>
<tr>
<th>Prematures.</th>
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<tbody>
<tr>
<td>Infants.</td>
</tr>
<tr>
<td>As alternative to antibiotics.</td>
</tr>
<tr>
<td>“Astronauts” e those with insufficient intake of fresh fruits and vegetables.</td>
</tr>
<tr>
<td>When treated with antibiotics or chemotherapeutics.</td>
</tr>
<tr>
<td>When irradiated or treated with cytostatics.</td>
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<tr>
<td>When treated with renal or peritoneal dialysis.</td>
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<tr>
<td>Biliary obstruction.</td>
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<tr>
<td>Liver cirrhosis, portal hypertension.</td>
</tr>
<tr>
<td>Cancer.</td>
</tr>
<tr>
<td>When allergy.</td>
</tr>
<tr>
<td>When immunodepressed.</td>
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<tr>
<td>Hematological malignancies.</td>
</tr>
<tr>
<td>HIV/Aids.</td>
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<tr>
<td>Inflammatory bowel disease.</td>
</tr>
<tr>
<td>Irritable bowel disease.</td>
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<tr>
<td>Rheumatoid arthritis.</td>
</tr>
<tr>
<td>Hepatitis.</td>
</tr>
<tr>
<td>Pancreatitis.</td>
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<tr>
<td>Stomatitis.</td>
</tr>
<tr>
<td>Diarrhea.</td>
</tr>
<tr>
<td>When infected.</td>
</tr>
<tr>
<td>After trauma.</td>
</tr>
<tr>
<td>In major surgery, especially transplantation.</td>
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<tr>
<td>In Intensive Care.</td>
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The majority of immune system in the gut

About 80% of the total immunoglobulin-producing cells of the body are localized in lamina propria of the gut, and large quantities especially of IgA are each day released to the gut lumen. The synthesis of IgA is highly dependent on T-cells and several cytokines produced by activated lymphocytes influence different steps in the IgA differentiation pathway. Transforming growth factor-β (TGF-β) has, at least in the mice, been found to be a crucial “switch” factor, but also cytokines such as IL-2, IL-5 and IL-10 are known to be involved - see further. Changes in nutrition, physical activity, sleep, mood, age, gender, circadian rhythm, body temperature, consumption of drugs, and illness are known to influence lymphocyte function and the production of immunoglobulins and hereby resistance to disease. Care in the ICU settings is most often associated, not only with dramatic changes in nutrition provided, but also in physical activity, body temperature, sleep, mood, circadian rhythm and other innate functions as well as with increased consumption of drugs, which all will have profound influence on the immune response of the patients. It is suggested in the
literature that supply of both pre- and probiotics can modify functions such as appetite, sleep, mood and circadian rhythm, and this most likely through metabolites produced by microbial fermentation in the gut. Supply of LAB can also significantly reduce serum levels of a variety of toxins such as endotoxin.

Neuroendocrine regulation of the acute phase response

Functions such a resistance to disease and size and extent of the acute phase response are unquestionably regulated from the gut, but also by the liver and to a large extent by neuroendocrine mechanisms. Knowledge regarding the complex interactions and mechanisms that regulate psychobiological states (mood, sleep, appetite, libido, etc.) in response both psychological and physical stressors such as noxious antigenic toxins and invasive microorganisms is increasing. Evidence is mounting that nervous, endocrine, immune and inflammatory systems are both anatomically and functionally interconnected. Stressors influence the immune functions and the inflammatory response to a large extent via the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.

Excessive cytokine production (IL-1, TNFα, but also IL-6) is normally down-regulated by corticosteroids. Various defects in the interaction of these systems will undoubtedly lead to increased morbidity in chronic conditions such as SIRS, MODS and MOF and in chronic conditions such as autoimmune diseases. Elimination of neuroendocrine by adrenectomy and subsequent “unrestricted” production of inflammatory cytokines increases lethality on challenge with LPS 500-fold. Whereas acute stressor in general seem to stimulate immunity, chronic stress (environmental, social, physiological or nutritional) is generally considered to down-regulate the immune system.

Enteral nutrition is today regarded as more important as a tool to control APR and immune response than as a tool to provide calories and nutrients to the very sick patient. Recent studies in surgical patients supports such an assumption. In a recent study comparing parenteral hyperalimentation (PN) and early enteral feeding (EN) after major liver resection no differences were found between the groups when studying nutritional parameters, but significant differences observed when studying immunological parameters such as natural killer cell activity, lymphocyte numbers, response to phytohemagglutinin (PHA) and natural killer cell activity. Most important the incidence of infectious complications was 8% in the EN group compared to 31% in the PN group. Similar results have been reported in patients with severe acute pancreatitis. The changes in C-reactive protein (CRP) and disease severity severity scores (APACHE II) were significantly improved with EN compared to PN. The IgM anticore endotoxin antibody (EndoCab) and total antioxidant potential (TAC) were both significantly better in the EN group compared to PN. But most important systemic inflammatory response (SIRS), sepsis, organ failure and stay in intensive care were globally improved in the EN fed patients.

Immuno-enhancing nutrition solutions controversial

The knowledge that some nutritional components such as some amino acids, polyunsaturated fatty acids, vitamins and antioxidants have all strong immuno-modulatory effects lead to commercial production of special immuno-enhancing nutrition solutions, based on a mixture of these various nutritional components. The experience so far has not been what was originally expected. Despite the fact that some compelling data have been presented in the literature, there is much to support the view of these reviewers and others that at present "routine use of these formulas cannot be recommended". There seems to be several reasons why the success has not been as expected, but the most important is probably that the need of supply the various immuno-stimulatory to the colon has been neglected, as these formulas do not contain substrate (fibers) for microbial fermentation and supply of immuno-stimulatory nutrients from microbial fermentation at the level of the colonic mucosa . It is reasonable to assume that adding fibers (prebiotics) and lactic acid bacteria (probiotics) can significantly improve the efficacy of these nutrition solutions.

In addition, EN is also often instituted too late in order to have an ability to significantly affect APR. It is also often combined with nutrition solutions rich in fat, which at least in theory should inhibit immune functions and counteract the purpose. Furthermore, EN is often combined with treatment with antibiotics, which reduces or even eliminates the important commensal flora.

Lactic acid bacteria initiates immunoglobulin production

It has been suggested that LAB during fermentation may release components that possess immuno-modulatory activities. The ability of bifidobacteria to induce production of more significant quantities of IgA by Pe-yer’s patches has been studied in vitro. It is interesting to note that only three of tested 120 strains, all isolated from human feces, had such an ability. Two of them were identified as Bifidobacterium breve and one as B. lactis. As far as I am aware no similar study has compared the ability of various Lactobacillus to initiate production of IgA. There are, however, studies, which show that at least some LAB do possess the ability to induce production of IgA. Lactobacillus GG is reported to significantly increase the IgA immune response in Crohn’s disease, and to enhance the IgA response to rotavirus. Human intake of Lactobacillus acidophilus...
is also known to result in a > 4 fold increase in IgA response, when challenged by *S typhi*.75 Supplementation of both *Lact. reuteri* (R2LC) and *Lact. plantarum* (199 V, DSM 9843) to animals with methotrexate-induced colitis does, in addition to elevating the numbers of both CD4 and CD8 T-cells, significantly increase small as well as large bowel IgA secretion, both the soluble and insoluble fractions.76

**Lactic acid bacteria restores macrophage function**

The ability of special cells to engulf, kill and eliminate invading microorganisms and/or defective cells but also to eliminate toxins, mutagens, and other poisonous substances is important to health and to outcome in ICU patients. That enteral and/or parenteral supply of fat, as mentioned above, has a profound effect on APR and inhibits immune functions is supported by several clinical observations. It is also observed that intravenous infusion of 20% of fat emulsions (Intralipid) significantly potentiates endotoxin-induced coagulation activation.77 But, also a diet too rich in polyunsaturated fatty acids can be negative. Studies in mice with standardized thermal injuries showed a significantly increased mortality on challenge with *Pseudomonas aeruginosa* when as much as 40 per cent of total calories were supplied as fish oil.78

Modern man is richly exposed to chemicals, especially pharmaceuticals. Many of these inhibit the macrophage functions, the bactericidal function as well as the production and secretion of cytokines \( \kappa \) effects, which has not been studied to the extent they should be. Antibiotics are no exception. Supply of antibiotics (150 mg/kg body weight of Mezlocillin, Bayer) did result suppression of the various macrophage functions as demonstrated by studies of chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability and of lymphocyte proliferation.79

Subsequent work80 has demonstrated that the reduction in peritoneal macrophage function and in lymphocyte proliferation after microbial decontamination of the digestive tract is significantly restituted by supply of low molecular weight peptides obtained from indigenous gastrointestinal tact microflora species such as *Bacteroïdes sp.*, *Clostridium sp.*, *Propionibacterium sp.* and from *Lactobacillus sp.*80,81 Other studies demonstrate that supply of live or nonviable bacteria or bacterial wall components such as peptidoglycan stimulates macrophage recruitment and function81 and cell-free extracts of both *Bifidobacterium longum* and *Lactobacillus acidophilus* have been shown to significantly enhance phagocytosis both of inert particles and viable *Salmonella*.82 However, not all LAB are capable of activating macrophages. As an example, an increased macrophage activation (increased expression of la antigen on the surface) was observed in mice after intraperitoneal administration of *Lactobacillus casei* or *Corynobaerium parvum*, but not after administration of *Lactobacillus fermentum*.83

**Lactic acid bacteria, and fiber, stimulate apoptosis**

Programmed cell death is one of the important mechanisms by which the body controls both infections, especially those of viral origin, but also neoplastic transformation. Diary products, rich in saturated fat and various growth factors84,85 including insulin growth factor 1 and various cow oestrogens and sometimes xenoestrogens (from prestitcides) have been suggested to inhibit or delay apoptosis and to promote malignant cell proliferation. These changes are associated with increased luminal concentrations of bile acids86 and also modifications in composition of bowel microflora. There are several reports, which demonstrate that increased consumption of prebiotics; plant fibers such as pectin, oat, wheat, rye, or chicory fibers (inulin)87 significantly increases the rate of apoptosis. Also cells infected with a virus are supposed to undergo apoptosis in order to prevent spreading of the viral infection.89 Also these various processes seem to be enhanced by supply of both fiber and LAB (symbiotics) most likely through production of SCFAs, known to enhance the process of apoptosis.90,91 As examples, it has been observed in experimental animals that feeding beans increase the SCFA production seven-fold.91

**Lactic acid bacteria modulate lymphocyte functions**

Lymphocyte proliferation studies are commonly used to evaluate the efficacy of immunosuppressive or imuno-enhancing therapies, to test chemicals for their potential immuno-toxicity and to monitor congenital immunological effects. Four probiotic lactic acid bacteria were recently tested in an animal model. Intrestingly, *Lactobacillus acidophilus* ATCC 4356 did enhance basal proliferation by 43%, while *Lactobacillus casei* (Yakult), *Lactobacillus gasseri* ATCC 33323 and *Lactobacillus thamnosus* DSM 7061 instead inhibited both basal (by 14-61%) and mitogen-stimulated proliferation by the mitogen concanavalin A (by 43-68%) and by LPS (by 23-63%), and particulary at supra-optimal concentrations.92 As appears from this study various LAB have different immune effects and experience cannot be extrapolated from one *Lactobacillus* to another *Lactobacillus* strain or species, even if they are closely related.

It is suggested that a balance between Th1 lymphocytes, primarily associated with cellular immunity, and TH2 lymphocytes, mainly associated with humoral immunity is essential for maintenance of health. Most of the studies on this balance have been done in atopic persons, a group of individuals, who also suffer an aberrant inflammation. I am not aware of any specific studies of this balance in ICU patients, but implications for the ICU patient should be obvious and future studies warranted.
Reduced microbial stimulation during early infancy and childhood, especially in developed countries, has been associated with the considerably increased prevalence of atopic diseases in children and young adults. Reduced microbial stimulation is associated with slower postnatal maturation of the immune system, a delayed development and lack of balance between Th1 and Th2 immunity. Swedes infants have as already mentioned a significantly different gut flora than both Pakistani and Estonian children. Children prone to develop allergies are also more sensitive to infections, also when in the ICU.

The super-inflammation seen in atopic diseases is thought to be caused by inappropriate generation and activation of Th2 cells, a process inhibited by IFN-γ, but also by IL-12. It is of special interest to know that some Lactobacillus species, eventually only a few, have the ability to stimulate both IFN-γ and IL-12 production and to promote of Th1-type responde, inhibit Th2-type immune response, and restore the Th-1/Th-2 balance. It was observed that stimulation of human peripheral blood mononuclear cells (PBMC) using Lactobacillus thannosus or Lactobacillus bulgaricus strains lead to induction of Th1 type cytokines IL-12, IL-18, and IFN-γ. It was also observed that supply of Lactobacillus casei and Lactobacillus plantarum totally inhibited antigen-induced IgE secretion in ovalalbumin- and casein-primed mice, an effect not obtained with Lactobacillus johnsonii. Furthermore, IL-12 production by peritoneal macrophages was enhanced, and IL-4 production of concanavalin A-stimulated spleen cells suppressed in animals treated with Lactobacillus plantarum.

Lactic acid bacteria modulate cytokine release

Oral administration of LAB seem to determine the direction and efficacy of the humoral responde, a responde is differently modulated by different LAB. Most of the attention has so far been given the cytokine production by mononuclear cells such as macrophages, but also mononuclear eukaryotic cells are important sources of cytokines. It has thus become increasingly clear that tissues such as intestinal epithelial cells and prokaryotic cells such as commensal flora and/or supplemented probiotic bacteria when challenged will secrete a spectrum of chemo-attractants and cytokines or cytokine-like molecules (sometimes called bacteriokines). As an example, it has been demonstrated in cell cultures that intestinal epithelial cells on challenge with LPS and PGE, produce significant amounts of IL-6, a process, which can be blunted by supply of indomethacin and inhibited by nitric oxide.

Supplementation with some LAB seems to significantly influence the expression of cytokines, but the response varies with strain of LAB supplied. The activity in blood mononuclear cells in healthy subjects of 2′-5′ synthetase, an expression of interferon-gamma (IFN-γ), is significantly increased (appr. 250% = 24 hours after a LAB-containing meal. Significant increases in cytokine activity compared to controls are also observed when human mononuclear cells are incubated in the presence of the yogurt bacteria; Lb bulgaricus (BUL), and S. thermophilus (Ther), alone or in combination (Yog); INF-γ: Bul 775%, Ther 2100%, Yog 570%, TNF-α: Bul 1020%, Ther 3180% Yog 970%, and in Il-1β: Bul 2120%, Ther 1540%, Yog 1920%, all indicating a significant immunno-activation after supply of these LAB. Another recent study compared both in a macrophage model and in a T-helper-cell model the in vitro ability to induce cytokine production by some LAB used by the dairy industry for yogurt production. Although there eas a considerable variation in response between various S. thermophilus strains this LAB seemed to stimulate macrophage and T-cell cytokine production to a somewhat greater extent than did Lactobacillus bulgaricus, Bifidobacterium adolescentis and Bifidobacterium bifidum. Also heat-killed Lactobacillus acidophilus (LA 1) has been shown in vitro to increase the mouse macrophage production of IL1-α (appr 300%) and TNF-α (appr 1000%) to a considerably greater extent than other Lactobacillus and Bifidobacteria tried.

It is mainly effects of mil-born LAB that has been studied, which is understandable, as in more recent years it has been mainly or only the dairy industry, which has maintained an interest in producing and supplying food products containing live LAB. One can expect, as interest in LAB with specific ability to ferment plant fibers gains popularity, that studies also with LAB such as Lactobacillus plantarum, Lactobacillus paracasei, various Lactococcus and Pentococcus strains and other related LAB, known for there special ability to metabolize fibers, will be undertaken.

Lactic acid bacteria increases mucin production

Numerous studies have demonstrated that supplied nonpathogenic bacteria of various kinds including LAB haver the ability to prevent and/or improve various infections. Several mechanisms have suggested such as release of avirous bacteriokines (cytokine-like molecules), nitric oxide, free radicals and lowering pH. Two other mechanisms have recently been suggested, blocking of receptors and inhibition of attachment to epithelial cells by intestinal mucins.

While the adherence of most LAB are via protease-sensitive mechanisms or via lipid (lactosylceramide) receptor, Lactobacillus plantarum seem to adhere via carbohydrate (mannose) adhesion mechanisms, e.g. the same receptors as Gram-negative bacteria such as E. coli, Enterobacter, Klebsiella, Salmonella, Shigella, Pseudomonas and Vidrio cholorae. This know-
Ledge offer unique possibilities to prevent infections and to reduce endotoxemia.

Binding of pathogens to mucosal epithelial cell mucins is an important defense mechanism for the host. The density of Goblet cells and the intestinal mucus production seem to increase with distance from the mouth. Several human genes are involved in mucin production, but MUC2 and MUC3 are the predominant ileo-colonic mucins. Both mucins show expression in Goblet cells in the large and small intestine, but MUC2 is suggested to be the major secreted mucin component of the colon. Increased MUC2 and MUC3 mRNA expression and inhibition of adherence of pathogenic Escherichia coli to HT29 intestinal cells, but not to non-intestinal cells, has recently been demonstrated in vitro, when the cells were incubated with Lactobacillus plantarum 299v, suggesting that the ability of probiotic agents such as L. plantarum to inhibit adherence of attaching and effacing organisms to intestinal epithelial cells is also mediated through their ability to increase expression of MUC2 and MUC3 intestinal mucins.
Lactic acid bacteria eliminate toxins and mutagens

Several studies show strong effects of various lactobacilli to significantly reduce and sometimes eliminate various toxins and mutagens. Several *lactobacillus* and *bifidobacteria* strains have proven to non-covalently bind and sequester very potent endotoxins such as aflatoxin B, both in vitro and in vivo. Also other bacterial toxins such as *E. coli* endotoxin are effectively reduced by probiotic bacteria. This is important as translocation of endotoxin and pathogenic bacteria occur in high frequency in critical conditions such as burns, hemorrhagic shock, severe pancreatitis and after larger operations such as transplantation.

Infections and endotoxemia are regarded as critical factors, responsible for the hemodynamic alterations and leading to increased risk of bleeding in subjects with liver cirrhosis, esophageal varices and portal hypertension, which was the reason why it is suggested that antibiotics treatment, might prevent bleeding. Supplementing *Lactobacillus* has been shown to reduce endotoxemia and severity of experimental Iccholic liver disease. Strong effects of supplied *Lactobacillus* is for example observed in galactosamine-induced chemical hepatitis. Supplemented *Lactobacillus rhamnosus DSM 6594 (= strain 271), Lactobacillus plantarum DSM 9843 (= strain 299v), Lactobacillus fermentum DSM 8704:3 (strain 245) and *Lactobacillus reuteri* (= strain 108), did significantly reduce the extent of liver injury but also reduce bacterial translocation. Again, the most pronounced effect was seen when supplementing *Lactobacillus plantarum*, especially if combined with arginine. Significant reduction in release of liver enzymes, extent of hepatocellular necrosis, inflammatory cell infiltration and bacterial translocation were observed parallel with a significant reduction in release of *Lactobacillus* and *bifidobacteria* enzymes, extent of hepatocellular necrosis, in vivo. Also other bacterial toxins such a *E. coli* endotoxin are effectively reduced by probiotic bacteria. This is important as translocation of endotoxin and pathogenic bacteria occur in high frequency in critical conditions such as burns, hemorrhagic shock, severe pancreatitis and after larger operations such as transplantation.

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**Lactic acid bacteria stimulate mucosal growth**

Reduced epithelial cell proliferation and mucosal atrophy are associated with increased invasion of various pathogens to peritoneal lymph nodes and to interior organs, which produces a risky situation in critically ill patients, especially those on parenteral nutrition or on elemental diet. Local degrading in the gut by microbial fermentation of fibers and proteinous material constitute the mechanisms by which SCFAs, but also lactic acid, succinic acid and ammonia are made available throughout the lower gastrointestinal tract. SCFAs do in addition to providing fuel for the enterocytes also promote sodium and water absorption and suppress colonic propulsive motility and hereby reduce diarrhea (mainly propionic and buturic acid). SCFAs derive mainly from carbohydrate degradation and ammonia and isovaleric acid from degradation of proteinous material. It seems reasonable to assume that in the absence of supply of fibers for SCFA production the remaining bacteria will ferment proteinous material, which always is available (gastrointestinal secretions, apoptotic cells), and more ammonia be produced, which is highly unwanted in the cirrhotic patient, especially when treated in the ICU for liver failure.

A recently published study suggest that probiotic bacteria, even in absence of supply of prebiotics is capable of stimulating growth of the mucosa in the lower gastrointestinal tract. Three groups of animals, all kept on elemental diet without any supply of fibers, were studied. One group served as contro, the other two were treated with two different LAB. The cell crypt production rate (CCRP) was about 25-40% higher in the jejnum and ileum, 70% higher in the caecum and more than 200% higher in the distal colon in LAB supplied than in control rats. The effect was more pronounced in jejunum when treated with *Lactobacillus casei* and in the colon when supplied *Clostridium butyricum*, again suggesting that a combination of a few LAB could be advantageous.

**Lactic acid bacteria prevents/reduces diarrhea**

There seem to be no conditions is which LAB (and fibers) have been as extensively tried as in diarrhea of various kinds, varying from rather simple tourist diarrhea to severe and life-threatening conditions such as antibiotic-associated and radiotherapey-induced diarrhea. It clear from al these studies that LAB provides a simple, inexpensive and effective tool, with no documented side effects, to be used both in prevention and treatment of all forms of diarrhea. It is obvious that LAB are effective in controlling diarrhea of both bacterial and viral origin, but seem to be slightly more effective in virus-induced diarrhea. This is promising, as an increasing number of infections today both in connection with extensive surgery such as transplantation and severe chronic disease such as HIV are of viral origin.

A larger European multi-center trial in children one month to three years of age was recently reported. One group consisting in 140 children were randomly allocated to either a control group or a probiotic group. The probiotic group received a probiotic preparation containing *Lactobacillus* and *Bifidobacterium* species. The control group received a placebo preparation. The primary outcome was the frequency of diarrheal episodes. The results showed that the probiotic group had a significantly lower frequency of diarrheal episodes than the control group. This finding is consistent with previous studies that have demonstrated the efficacy of probiotics in the prevention and treatment of diarrhea.

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allocated to oral rehydration + placebo, the other group of 147 children to oral rehydration + supply of $10^9$ cfu of Lactobacillus GG. The duration of diarrhea was 58.3 ± 27.6 hours in the LAB-treated group v. 71.9 ± 35.8 hours ($p = 0.03$). In rotavirus-positive children did in the LAB-treated group the diarrhea last 56.2 ± 1.9 hours vs 76.6 ± 41.6 in the control group ($p = 0.008$).

**Lactic acid bacteria prevents/reduces severity of colitis**

Experimental studies as well as clinical observations suggest that the contents of the intestinal luminal environment are responsible for the initiation and/or perpetuation of inflammatory bowel disease. It has been convincingly demonstrated the concentrations of endogenous *Lactobacillus* and *Bifidobacteria* are significantly reduced in patients with active Crohn’s disease, ulcerative colitis, pouchitis and experimental colitis. These observations has stimulated interest in trying various probiotic bacteria in inflammatory bowel disease (IBD).

A series of experimental studies and several uncontrolled clinical studies support the idea of using probiotics in patients with IBD, but so far few controlled studies have been reported.

A cocktail called VSL#3 consisting in four lactobacillus strains, three bifidobacteria strains plus *Streptococcus salivarius* ssp *thermophilus* (5 x $10^9$ cells/g), and most probably chosen at random without any further documentation of the molecular/immonological effects of each of the LAB was recently tried in an uncontrolled study in patients with ulcerative colitis. The patients were given 3 gram a day during one year and 15/20 patients remained in remission, one was lost to follow up and 4/20 had signs of relapse. The same LAB cocktail was also tried in a small controlled study in patients with pouchitis. Twenty patients served as controls, all showed remission within 9 months. In sharp contrast to this did only 3/20 patients develop remission during the same time period, when supplied with VSL#3 probiotic cocktail. It is reasonable to assume that if a cocktail of LAB was provided, where each bacteria would be chosen based on well documented metabolic and immunological effects, one should be able to expect even better results.

A recently published Columbian study compared the outcome of 1237 newborns (inpatients and transfer patients), who all received daily 250 million live *Lactobacillus acidophilus* and 250 million live *Bifidobacterium infantis* until they were discharged, usually after about one week. As controls served similar children treated during the year before. The incidence of necrotizing enterocolitis was with probiotic prophylaxis reduced to one third (18 vs 47, $p < 0.0005$) in the inpatients group, and by half (19 vs 38, $p < 0.03$) in the patients transferred from other hospitals (which most likely came under treatment late). It is most importante to observe that no complications could be attributed to the use of probiotic preparations even in these very sick newborn children, weighing in average 2600 gr (range < 1000 to > 4000 g), and which in as much as one third of the babies suffered from severe conditions such as sepsis, pneumonia or meningitis. It was incidentally observed that the LAB-treated children suffered significantly less diaper dermatitis.

**Lactic acid bacteria in intensive care patients**

Few studies have been performed in a mixed ICU patient population. A small study was performed by a nurse in Hongkong as a thesis for B Sc Degree in Health Studies. 19 patients received daily from within 12 hrs of arrival to the ICU $10^9$ of *Lactobacillus plantarum* 299, another 19 patients heat-killed *Lactobacillus plantarum* 299 (controls). 5/19 (26%) died in the treated group vs 8/19 (42%) in the control group, the difference did not reach statistical significance. However, it stimulated the physicians at the unit to undertake a larger study, which is under way. A somewhat larger prospective, randomized placebo controlled study was undertaken in a mixed abdominal surgery patient at the University of Berlin. Thirty patients were treated with *Lactobacillus plantarum* 299 in a daily dosis of $10^9$ and compared to 30 patients receiving inactivated heat-killed *Lactobacillus plantarum* 299. Another thirty received parenteral nutrition (PN). The rate of complications were for the various groups: PN 30%, heat-inactivated lactobacilli 17% and active lactobacilli 13%. Infections developed in 3/30 (10%) patients in each of the two treated groups vs 9/30 (30%) in the PN group ($p = 0.001$). Furthermore, significantly more antibiotics were administered to the PN group. The difference was even larger when the subgroup of patients having more extensive surgery (gastro and pancreatic surgery, mainly resections) were separately analysed. One of fifteen patients (7%) developed infections in the in the group receiving *Lactobacillus plantarum* vs 3/17 (17%) in the group receiving heat-inactivated *Lactobacillus plantarum* and 8/16 (50%) in the group on parenteral nutrition. Another and separate study was undertaken by the same group at Virchow Clinic, Charité University Hospital in patients undergoing liver transplantation. Treatment with active as well as heat-killed *Lactobacillus plantarum* 299 and inulin fiber added was compared to selective bowel decontamination (SBD), which during several years was the golden standard of the clinic. Four of 31 patients (13%) in the group receiving active *Lactobacillus plantarum*, 11/32 (34%) in the group receiving inactivated *Lactobacillus plantarum* and 15/32 (48%) in the group treated by SBD developed infection within 30 days ($p = 0.017$).

A randomized study was just concluded in Györ, Hungary in material of patients with severe pancreatitis. The rate of septic complications was significantly reduced in the group supplied live *Lactobaci-*
Lactobacillus plantarum 299 compared to the group supplied heat-inactivated Lactobacillus plantarum 299; 4.5% (1/22) vs 30.4% (7/23), p < 0.05. Similarly the rate of reoperation was significantly reduced; 4.5% (1/22) vs 26.1% (6/23), p < 0.05.

General comments: Table III summarizes the present limited experience in ICU patients. All studies have been performed with a single, but well documented bioactive LAB, Lactobacillus plantarum 299. Some of the studies discussed above were not large enough to allow statistical significance, but the trend is the same in all studies, the lowest mortality or the lowest infection rate always obtained in the group receiving supply of LAB and fiber. But the differences observed are impressive: in extensive gastric and pancreatic surgery 7% infection with and 50% without supply of pro- and prebiotics (p < 0.05, in liver transplant 13% with and 48% (p = 0.017) without supply of pro- and prebiotics, and acute pancreatitis 4.5% vs 30.4% (p < 0.05).

It has been calculated, based on the present Berlin experience, that groups of appr 30 patients are needed to reach statistical significance in mixed patient materials. Several such studies are on the way. However, when used in very sick patients, statistical significance seem to occur also with smaller groups; gastric and pancreatic surgery and severe pancreatitis resp.; appr 20 in each group. It is important to stress at this stage, that the limited documentation of clinical efficacy of treatment with Lactobacillus in very sick patient is further supported by extensive studies in experimental animals, using a variety of models.1-5

It has this far been necessary to accept that treatment of patients with Lactobacillus is done in parallel to treatment with strong antibiotics, which most likely will reduce the efficacy of LAB treatment. Although the doses of Lactobacillus supplied in the above studies were large compared to what has been given in other probiotic treatments, and even larger dose could eventually further improve the outcome. The treatment was also often instituted late and the supply of substrate (fibers) was never optimal. The supply of fibers could be both larger and more diverse, e.g. contain several different bioactive fibers.

Lactic acid bacteria to patients with fulminant MOF

Lactobacillus was supplied as a desperate action to five consecutive patients suffering from severe MOF after gastrointestinal surgery (fig. 1). The mean Apache II score fell from a mean 18 before institution of treatment to 12 and 9, after respectively 5 and 10 days of treatment. All patients left the ICU unit in improved condition. A short description of each of the patients follows:

Patient 1 (fig. 1A) 74 year old man with Parkinson disease, who suffered severe upper GI bleedings. No source of bleeding could be found at emergency laparotomy. After the laparotomy did severe gastric wall necrosis, wound dehiscence and peritonitis develop. An emergency gastric resection was performed and a feeding jejunostomy applied. The patient was referred to the University hospital with severe sepsis and signs of pulmonary and renal insufficiencies. Lactobacillus and oat fiber was administered via a jejunal feeding tube. Dramatic recovery was observed and the patient could be weaned off the ventilator after 10 days and leave the ICU.

Patient 2 (fig. 1B) 65 year old man initially operated for perforated duodenal ulcer and diffuse peritonitis. He developed postoperatively severe sspsis with pulmonary insufficiency. Repeated scans showed no signs of abscesses, and exploratory laparotomy was performed on two occasions. His general condition deteriorated with increasing leukocytosis and increasing plasma creatine levels. Daily enteral supply of Lactobacillus and oat fiber was instituted from the 22th day and a slow recovery began. He could leave the ICU after about 2 weeks of treatment.

Patient 3 (fig. 1C) 52 year old man was operated at a local hospital with an emergency partial gastrectomy and later referred to the University hospital with a leaking duodenal stump. He was reoperated, gastrectomy performed and drainage of the retroduodenal stump and PTC applied. Despite these measures did the conditions quickly deteriorate and the patient developed high fever, leukocytosis, and signs of pulmonary, renal and hepatic insufficiencies. Treatment with Lactobacillus and oat was instituted from the 45th day. An immediate but slow recovery began and continued over the following three weeks. The function of the organs did steadily improve, he could be weaned off the ventilator and leave the ICU.

Patient 4 (fig. 1D) 43 year old man, who had an emergency sigmoid resection for a perforated diverticulitis. He developed postoperative anastomotic dehiscence with fecal peritonitis, and was reoperated with a Hartmann procedure. He continued to deteriorate and developed high fever and signs of ventilatory insufficiency and was referred to the University hospital for care in the ICU. Probiotic treatment was instituted and he could leave the ICU after about one week on Lactobacillus and oat.

Patient 5 (fig. 1E) 63 year old lady suffering from diabetes and operated on with an emergency colectomy and ileostomy due to a colonic ischemia with colonic wall necrosis. She developed postoperatively abdominal abscesses, wound dehiscence and small bowel fistulas, and increasing signs of circulatory, ventilatory and renal insufficiencies. Treatment with Lactobacillus and oat was instituted. The patient recovered slowly during the following weeks and was able to leave the ICU after 24 days on pro- and prebiotics.

General Comments: None of the patient had positive blood cultures before or during the treatment. They developed all clinical signs of sepsis and organ dysfunction despite treatment with broad-spectrum anti-

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biotics, which continued in parallel to the Lactobacillus and fiber treatment. All patients had received TPN before the institution of enteral nutrition with Lactobacillus and oat. Also TPN was often continued in parallel with the enteral nutrition. A dramatic improvement in general condition and Apache II scores occurred from the day Lactobacillus and oat treatment was instituted in all cases. Especially encouraging is, that recovery was obtained even when the treatment was instituted late in the disease process (22 days in case 2 and 45 days in case 3).

Conclusions and final remarks

The molecular effects of pre-, pro- and synbiotics are well documented in the literature. The documentation of clinical effects is presently thin for all indications except diarrheal diseases. It is encouraging that the treatment seems to be even more effective in preventing viral diseases. This is important, as especially in transplantation viral complications are increasingly common. It also offers hope that the treatment can be of benefit in viral diseases such as HIV and positive experience has also been reported in this disease.134

As mentioned above the protection layer of lactobacillus does not exist only on the GI tract mucosa, it is important at all exterior body surfaces including those of the eye, the nose, the mouth, the respiratory tract, the vagina, not to forget the skin. It is clearly reduced at all sites when the patient is in the settings of ICU with its special hygienic conditions and supply of antibiotics and other drugs. Some observations support that an overflow of probiotic bacteria continuously occurs under normal hygienic conditions from the GI tract to all the other sites mentioned, but this is more unlikely to occur in the ICU, with all its vigorous hygienic conditions. Of that reason might in the future be indicated that the gastrointestinal supply is complemented use of LAB-containing gels on sensitive body surfaces and of LAB-containing aerosols for the respiratory tract, where this protection layer is much needed. The incidental observation that LAB supplementation reduces the incidence of diaper dermatitis is in this connection of interest. It is also interesting that two recent reports suggest that consumption of LAB-containing drinks prevents formation of biofilm and removes both yeast and bacteria from prothesis, in this case silicon rubber voice prostheses,135, 136 suggesting that LAB could be effective also in the prevention of catheter infections.

As the problems with antibiotic-associated microbial resistance increase, the medical world is increasingly looking for a tool to replace antibiotics, also for the sensitive and very artificial microbial world of ICU. Such a tool exists in combined use of pre- and probiotics. It is necessary to also remember that all fibers are not identical, they are each precursors for their special nutrients. It seems therefore important to provide several types of fibers and, if in any way possible, always fresh fruits and vegetables. Nor are all lactic acid bacteria similar in effects. It is said the genetic differences between two LAB can be greater than those between a fish and a human being. In addition many of ingested LAB do not survive the acidity of the stomach, the bile acids of the small intestine, nor do they adhere to the intestinal mucosa Each LAB has its own narrow metabolic spectrum, which is why the LAB are more effective in consortia. This supports the idea, that a composition of several LAB could have stronger effects than what can be obtained from administration of a single strain.

LAB cocktails for medical purpose must only be composed of bacteria with scientifically well documented bioactivities and demonstrated abilities such as a strong mucus adhesivity, great ability to ferment also semiresistant fibers such as inulin, strong antioxidant capacity and strong ability to modulate the immune response. Such LAB are normally not found in milk products, which LAB in general tend to have comparatively weak bioactivities. Instead they are found in fiber ferments such as saurkraut, sourdoughs, exotic dishes of fermented fruits and vegetables. An attempt to construct such a scientifically based composition of fibers and LAB, chosen on the basis of documented bioactivities, in which I am involved, is Symbiotic 2000. It consist in four bioactive LAB (containing 10^9 of each of four LAB Lactobacillus plantarum, Lactobacillus paracasei subsp paracasei, Pediacoccus pentoceus and Lactococcus raffinolactis) and is combined with 10 gram of bioactive fibers (2.5 grams of each of betaglucan, inulin, pectin and resistant starch). It is presently the object of extensive studies on various indications around the world.

It is likely that the settings and premises of ICU, as we move further into the new millennium, will be made less artificial and more to look natural. The physical and psychological environment will most likely be dramatically improved. Strong attempts will also be made to reduce the amount of pharmaceuticals, and to try to feed much more of natural food. The goal will be to reduce the stay in ICU and to use the home of the patient as much as possible. Patients, who not long ago where treated for long periods of time in the ICU, such as bone marrow transplant patients, are increasingly treated in an ecologically much more friendly place, their own home. Ecocunmmunutrition with pre-, pro- and symbiotics offer to be suitable tools in a continuously changing process.

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