Bioecological Control of Disease, Especially Pancreatic Disease

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Introduction

Patients with acute pancreatitis often suffer an uncontrolled superinflammation, and as a result of that a malfunctioning innate immune system, which frequently leads to complications: severe infections, systemic inflammatory syndrome, and sometimes multiple organ failure. Among the characteristics of the superinflammation are an exuberant, e.g., exaggerated and prolonged, inflammatory response, an aberrant cellular response, and extreme elevations in levels of cytokines and acute-phase proteins but also in levels of coagulation and growth factors. The cytokine storm, which occurs during the first few hours, will almost immediately reach the lungs and other distant organs via the lymphatics [1], and will condition them to be/make them susceptible to a subsequent infection. Overgrowth of potentially pathogenic microorganisms in the stomach and intestines, due to disease, inhibition of gastric and gastrointestinal (GI) secretions, and absence of a food stream, supports microbial overgrowth and provides the source of bacteria for subsequent infection of the chest, pancreas, urinary tract, and other organs.

Instant Reaction: Narrow Therapeutic Window

The alarm reaction is instant: within minutes increases in the levels of various proinflammatory cytokines and within hours increases in the levels of various acute-phase proteins are observed, changes most often reaching their peaks within the first 24 h. It is increasingly recognized that the therapeutic window providing possibilities to control the exuberant phase response is narrow, most likely not much more than 24–36 h. Experience from liver transplantation suggests that a superinflammation observed in the late phase of

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the operation is intimately associated with subsequent sepsis. If at the end of the operation the endotoxin, the tumor necrosis factor α (TNF-α), and interleukin (IL)-6 levels were increased more than 6 times, the patients developed sepsis [2]. The conditions are similar in acute pancreatitis.

Efforts to control inflammation and subsequent complications, instituted later than 24–36 h after onset of disease, are prone to have limited preventive effects. Unfortunately patients with acute pancreatitis will often arrive at hospital 12–24 h after the onset of disease, which underlines the necessity of making efforts to control the inflammation the highest priority. It is strongly recommended that attempts are made immediately on arrival of the patient to restrict the superinflammation to the greatest extent possible. It is better to treat some patients unnecessarily than to miss the opportunity. The majority of immune cells (about 75%) are located in the GI tract, which is why enteral nutrition has proven to be a powerful tool to control the function of these cells. Studies in recent years have also demonstrated that immediate postoperative feeding is not only safe, but also prevents an increase in gut mucosal permeability, contributes to a positive nitrogen balance, and reduces the incidence of septic complications. It also reduces postoperative ileus and accelerates restitution of pulmonary performance, body composition, and physical performance [3, 4]. It has also been observed in a controlled study that delaying institution of enteral nutrition later than after 24 h leads to, compared with immediate supply, increased intestinal permeability and significantly higher incidence of multiple organ failure [5].

Choice of Treatment Strategy

Today's treatment strategy is to a large extent based on early enteral nutrition and use of antibiotics. It is increasingly observed that antibiotics have a limited if not no preventive effect on the course of disease [6]. It has long been known that the administration of antibiotics will suppress various immune functions, and especially macrophage activities such as the chemiluminescence response, chemotactic motility, and bactericidal and cytostatic ability [6, 7]. This is so with standard antibiotic administration and is probably even worse with selective digestive tract decontamination. It is a historic landmark that routine antibiotic prophylaxis has been shown to be of no benefit in reducing the risk of developing infected pancreatic necrosis [8]. Enteral supply of nutrients must be done with care, and nutrition solutions which increase blood glucose levels should be avoided, as hyperglycemia is associated with neutrophil dysfunction [9] and significantly increased infection and mortality rates, as demonstrated in trauma patients [10]. Standard commercial enteral nutrition solutions, rich in proinflammatory molecules containing dairy-derived proinflammatory molecules, should be avoided to the greatest extent possible. Total parenteral solutions and some commercial enteral diets have in animal experiments been shown to activate inducible nitric oxide synthase and disrupt the gut barrier function and the intestinal microflora and induce bacterial translocation [11].

Hospital-produced nutrition formulas, made of fresh fruits, vegetables, especially legumes, and fish/meat, and probably more suitable for enteral nutrition, have for questionable hygiene

and efficiency reasons been abandoned in hospitals in the developed world. Controlled clinical studies comparing the effects of standard nutrition solutions and hospital-made nutrition solutions on immunity and outcome are most highly desirable. Also, blood transfusions must be avoided to the greatest extent possible. A recent meta-analysis based on 20 peer-reviewed articles and more than 13,000 patients reported an average of 3.5 times increase in postoperative infections in surgical patients receiving allogenic blood transfusion [12].

Choice of Treatment

The enteral nutrition formulas used today are made mainly with the aim to provide calories and are to a large extent built on the concept used for parenteral nutrition, e.g., based on a mixture of various "chemicals." It is clear that such nutrition can never replace normal eating with its great variation in the supply of nutrients, antioxidants, plant fibers, and preventive nonpathogenic microorganisms. It is suggested that normal eating provides up to two million different molecules, which include several hundred different carotenoids and several thousand different flavonoids, some of which have an antioxidant effect 10 times or more powerful than that of vitamins such as C and E. Gastric release of nitric oxide is mandatory for maintenance of upper GI motility, for mucosal and splanchnic secretion, and for elimination of pathogens from the stomach. It is therefore of outmost importance that the nutrient solution supplied provides precursors for such production e.g., nitrate/nitrite. Eating natural food, rich in fresh fruits and vegetables, and hopefully also in fibers and probiotic bacteria, is optimal for the function of the innate system and for resistance to disease. Unfortunately, such nutrition is most often not possible in severely sick patients.

Choice of Feeding System

To improve the possibilities to provide immediate enteral nutrition, I developed a so-called self-propelling (autopositioning) and also regurgitation-resistant tube, based on a coil (spiral) in the end, which is made to maximally absorb the gastric motility for its transportation to an ideal position, just below the ligament of Trietz. It usually needs no assistance by endoscopy or X-ray. Nutrition is started as soon as the coil of the tube has been placed in the stomach without waiting for it to migrate into the intestine. Several studies have proven its superiority over other tubes, especially in patients with reduced or inhibited motility, such as patients with acute pancreatitis. A recent prospective study showed successful placement (within 24 h) in patients with normal gastric emptying in 78% of patients versus 14% of patients with a straight standard tube ($P = 0.041$), and in patients with impaired gastric emptying a 24-h success rate of 57% compared with 0% for patients with straight tubes ($P = 0.07$) [13].

Maintenance of Salivation and GI Secretion

The amount of GI secretion in an adult is as much as 10 L a day, of which 2.5 L is saliva and another 2.5 L is gastric secretion. These secretions are extremely rich in immunosupportive factors such as immunoglobulins, lactoferrin, lysozyme, fibronectin, and mucin, but are also an important source of healing factors such as epidermal growth factor. Removal of the salivary gland function results in gastric and intestinal ulcerations, poor wound healing, and poor regeneration of organs, especially the liver. From an immunological point of view, a drug that stimulates these secretions, instead of inhibiting them, should be preferred, and especially in the very sick and critically ill. Unfortunately, most drugs, especially those commonly used in intensive treatment units (ITUs), have strong antisecretory effects – for more information, including a list of drugs, see [14]. Low gastric pH is a prerequisite for gastric nitric oxide production, a function which is totally eliminated by supply of H_2 blockers and proton inhibitors [8]. Normal gastric acid production is also essential for absorption of several vitamins and antioxidants, including vitamin C and glutathione. Most important, in the absence of low pH, the stomach will become a reservoir for pathogens, which are often regurgitated into the lungs and are the cause of chest infections [15]. Use of H_2 blockers/proton inhibitors to prevent peptic ulcers was necessary in patients on total parenteral nutrition, but today with early and aggressive enteral feeding it is totally unnecessary [16–19].

Strict Blood Glucose Control

Elevated blood glucose level is deleterious to the function of the immune system and prevention of morbidity. Blood glucose levels below 8 mEq are also necessary for maintenance of normal GI motility [20] and for splanchnic and mucosal blood flow. Even though strict glucose control had been known for some time to reduce the incidence of wound infection after open heart surgery, it was not until recently that strict glucose control was adapted for modern ITU and postoperative care. For a long time, the state of the art was to tolerate blood glucose levels up to 12 mmol/L (220 mg/dL) in fed critically ill patients. However, strict glucose control to below 6.1 mmol/L has recently been shown to decrease blood stream infections by 46%, acute renal failure with need of hemofiltration by 41%, critical illness polyneuropathy by 44%, red cell transfusions by 50%, and mortality by 34% [21].

Generous Supply of Antioxidants

The tissue and blood concentrations of pro-oxidants are almost invariably high and the serum levels of various antioxidants and micronutrients low or extremely low in critically ill patients, including those with acute pancreatitis. As an example, total vitamin C and ascorbic

acid levels are reported to be less than 25% of normal values in such patients. A study performed in mainly trauma patients reported a 19% reduction in pulmonary morbidity and a 57% lower incidence of multiple organ failure in a group of patients receiving supplementation with α-tocopherol and ascorbate [22]. A recent controlled study in patients with acute pancreatitis reported significantly increased plasma levels of vitamin C in parallel with a significant reduction in levels of IL-2r, TNFα, IL-6, and IL-8 [23]. Furthermore, the ratio of CD4/CD8 and CD4 positive cells was significantly higher in the treated patients. In addition, a faster normalization of temperature and amylase level in serum and urine was observed. But more importantly the cure rate, the complication rate, and the length of hospital stay were significantly better. Thus far, most of the studies reported were done using conventional vitamins and intravenous supply. Antioxidants such as flavonoids have not been tried. As some of these are reported to have 10 times stronger antioxidant effects, it should be of the greatest interest to try these in severely sick patients such as those with acute pancreatitis. Healthy individuals receive most of their antioxidants, including exogenous glutathione, from fresh fruits and vegetables, and they are released and absorbed after fermentation by lactic acid bacteria (LAB) in the lower GI tract. As the mucosa in the lower gut almost entirely depends on nutrients from the lumen, it is likely that there is a premium in supplying antioxidants, which are delivered where they are much needed, e.g., at the mucosa of the lower GI tract.

Control of Microbial Flora

In addition to the digestion provided by saliva and GI secretion, does there exist an equally important system for digestion of food based on microbial enzymes in the lower GI tract? The colon is today recognized as an important immunological organ, and also as an important metabolic organ. Most likely it has more and certainly more complex functions than the rest of the GI tract. An indication of the complexity of the metabolic activities in the large intestine is the fact that the colonic "microbial organ" contains more than two million genes [24], to be compared with about 65,000 genes in the rest of the human body. Numerous substances, several hundred thousand, if not a million or two, are produced, released, and absorbed at the level of the lower small intestine and the large intestine. All depend on microbial fermentation for their release and absorption, which is why maintenance of flora is so important. Among these substances are various fatty acids, especially short chain fatty acids, carbohydrates, amino acids, polyamines, vitamins, antioxidants, phytoestrogens, and coagulation and growth factors. The main substrate for this production through microbial fermentation is plant fibers, fresh fruits, and vegetables. If such food cannot be provided to the sick patient, at least dried plant fibers, although much less effective, should be liberally supplied. However, one must keep in mind that many important antioxidants, such as glutathione, and amino acids such as glutamine do not sustain industrial processes such as drying or heating. High priority should, whenever possible, always be given to supplementing commercial feeding formulas with fresh fruits and vegetables, also in ITU patients, by any means possible.

The Concept of Synbiotics

All products released from consumed plant fibers (prebiotics) by the action of flora or supplemented bacteria (probiotics) are collectively called "synbiotics." Genetically, there is a large difference between different bacteria called "lactic acid bacteria" (LAB); often said to be greater than between man and a fish. Thus, it is of extreme importance that only LAB with strong and specific bioactivities are used. Most of the LAB used by the food industry have no or limited ability to ferment strong bioactive fibers such as inulin and phlein, no ability to adhere to human mucus, low antioxidant capacity, and most important do not survive the acidity of the stomach and bile acid. This is illustrated by a recent study. A standard commercial product containing *Lactobacillus acidophilus* LA5, *Bifidobacterium lactis* BP12, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus* was mixed with 7.5 g oligofructose and in a controlled study was supplied to critically ill patients. Although significant reductions in the number of potentially pathogenic organisms could be observed in the stomach of the patients treated, no influence on intestinal permeability could be demonstrated nor could any clinical benefits be demonstrated when this particular formula was supplied to a mixed group of critically ill patients [25]. See also [26].

My personal experience during the last 15 years stems from studies using two different synbiotics – combinations of prebiotics and probiotics: [1] *a one LAB/one fiber composition*, produced by fermentation of oat meal with *L. plantarum* strain 299; [2] *a four LAB/four fiber composition* (Synbiotic 2000®), consisting of a mixture of 10^{10} (more recently also as Synbiotic 2000 FORTE® with 10^{11}) of each of four LAB – *Pediococcus 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 fermentable fibers (prebiotics): β-glucan, inulin, pectin, and resistant starch.

Synbiotics in Chronic Liver Disease and Liver Transplantation

Most of the experience with synbiotic treatment stems from studies in patients with chronic liver disease. Synbiotics have the ability to reduce the production and absorption of endotoxin in the intestine, but they also downregulate production of proinflammatory cytokines. The in vitro production of TNF-α by peripheral blood mononuclear cells in response to stimulation by endotoxin or *Staphylococcus aureus* enterotoxin B was reduced by a median of 46% (range 8–67%) in eight of 11 (72.7%) cirrhotic patients supplied for 1 week with the four LAB/four fiber synbiotic composition [27]. Fifty-eight patients with so-called minimal encephalopathy were randomized into three groups and supplied for 1 month with [1] the four LAB/four fiber composition ($n = 20$), [2] only the fibers in the composition ($n = 20$), and [3] a placebo (nonfermentable, nonabsorbable fiber) ($n = 15$) [28]. Significant reductions in intestinal pH, serum endotoxin, and intestinal content of *Escherichia coli*, *Staphylococcus,* and *Fusobacterium* were observed in both treatment groups but not in *Pseudomonas* and *Enterococcus*, and were accompanied by significant improvements in ammonia/s, bil/s, liver enzymes, prothrombin time, and albumin/s. The levels of ALT

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decreased significantly from 252 ± 182 to 84 ± 65 ($P < 0.01$) in the synbiotic-treated group and to 110 ± 86 ($P < 0.05$) in the fiber-only group, but not in the placebo group. Significant improvements were observed in psychometric tests and the degree of encephalopathy.

Both the one LAB/one fiber and the four LAB/four fiber compositions have been tried in human liver transplantation. Ninety-five liver transplant patients were divided into three groups: group 1, selective digestive tract decontamination (SDD) four times daily for 6 weeks ($n = 32$); group 2, live *L. plantarum* 299 (LLP) at a dose of 10^9 plus 10 g of oat and inulin fibers ($n = 31$) supplied for 12 days postoperatively; group 3, identical to group 2, but with heat-killed *L. plantarum* 299 (HLP) ($n = 32$) [29]. Signs of infections occurred in 48% of patients (15/32) receiving SSD, in 34% of patients (11/32) receiving HLP, and in 13% of patients (4/31) receiving LLP, $P = 0.017$. The most dominant infections were cholangitis, occurring in ten patients receiving SSD, in eight patients receiving HLP, and in two patients receiving LLP, and pneumonia, occurring in six patients receiving SDD, in four patients receiving HLP, and in one patient receiving LLP. This study was followed by a study in 66 patients supplied either with [1] the four LAB/four fiber composition (4×10^{10} LAB) or [2] only the four fibers in the synbiotic composition [30]. The treatment started on the day before surgery and continued until the 14th day after surgery. One of the 33 patients in the synbiotic-treated group (3%) showed signs of infection (a slight urinary infection) during the first month compared with 17 of the 33 patients (51%) in the group supplied with the four fibers only. The need for antibiotics was also significantly reduced in the synbiotic-treated group.

Synbiotics in General Surgery

Ninety patients were randomized into three groups: group 1, LLP at a dose of 10^9 plus 10 g of oat and inulin fibers ($n = 30$) for 12 days postoperatively; group 2, identical to group 1, but with HLP ($n = 30$); and group 3, standard enteral nutrition ($n = 30$) [31]. Each group consisted of 30 patients. The 30-day sepsis rate was 10% (three of 30 patients) in the two groups receiving either live or heat-inactivated LAB, compared with 30% (nine of 30 patients) in the group receiving standard enteral nutrition ($P = 0.01$). The largest differences were observed in the numbers of patients with pneumonia: enteral nutrition – six patients, LLP – two patients, HLP – one patient. The beneficial effects of synbiotic treatment seemed to be most pronounced in gastric and pancreatic resections with a sepsis rate of 7% for patients receiving LLP, 17% for patients receiving HLP, and 50% for patients receiving enteral nutrition. The LLP patients received significantly less antibiotics ($P = 0.04$); the mean length of antibiotic treatment was 4 ± 3.7 days for LLP, 7 ± 5.2 days for HLP, and 8 ± 6.5 days for enteral nutrition. The incidence of noninfectious complications were 30% (9/30) for enteral nutrition, 17% (5/30) for HLP, and 13% (4/30) for LLP. A second study has just been concluded in abdominal cancer patients. Forty-five patients were treated for 2 days before and for 7 days after operation with [1] the four LAB/four fiber composition (4×10^{10} LAB) (LEN), [2] only the four fibers in the synbiotic composition (FEN), or [3] standard parenteral nutrition [32]. The incidence of postoperative bacterial infections was 47% for parenteral nutrition, 20% for FEN, and 6.7% for LEN. Significant improvements in

prealbumin (LEN, FEN), C-reactive protein (LEN, FEN), serum cholesterol (LEN, FEN), serum endotoxin (LEN, FEN), white cell blood count (LEN), and IgA (LEN) were observed on the third and sixth postoperative days. At these time points no statistically significant differences could be observed in the levels of IgM, IgG, and complements or in the cytokines IL-1, Il-6, and TNFα.

Use of Synbiotics in Polytrauma

Two studies in polytrauma patients have been concluded with Synbiotic 2000 and Synbiotic 2000 Forte, but the results have not yet been published. One prospective randomized study in patients with acute extensive trauma compared treatment with Synbiotic 2000 (40 billion LAB/day) with treatment by supplementation of a soluble fiber, treatment with a peptide diet, and treatment with glutamine. Treatment with Synbiotic 2000 led to, compared with treatment with a peptide diet (11 of 26 patients – 42%, $P < 0.04$), treatment with glutamine (11 of 32 patients – 34%, $P < 0.03$), and treatment with only fibers (12 of 29 patients – 41%, $P < 0.002$), a highly significant decrease in the number of chest infections (four of 26 patients – 15%) [33]. The total number of infections was also significantly decreased: Synbiotic 2000, five of 26 patients (19%); only fibers, 17 of 29 patients (59%); peptide diet, 13 of 26 patients (50%); and glutamine, 16 of 32 patients. In another study, 65 polytrauma patients were randomized to receive once daily for 15 days Synbiotic 2000 Forte or maltodextrin (placebo). Significant reductions were observed in a number of parameters, such as the number of deaths (5/35 vs. 9/30, $P < 0.02$), severe sepsis (6/35 vs. 13/30, $P < 0.02$), chest infections (19/35 vs. 24/30, $P < 0.03$), central line infections (13/32 vs. 20/30, $P < 0.02$), and ventilation days (average 15 vs. 26 days) [34].

Use of Synbiotics in Acute Pancreatitis

Patients with severe acute pancreatitis were randomized into two groups to receive daily and administered through a nasojejunal tube for the first 7 days a freeze-dried preparation of either LLP at a dose of 10^9 plus 10 g of oat and inulin fibers (group 1) or the same as for group 1 but with HLP (group 2) [35]. The study was designed to be interrupted when on repeat statistical analysis significant differences in favor of one of the two group were obtained, which occurred when a total of 45 patients had entered the study. At that time 22 patients had received treatment with LLP and 23 patients had received treatment with the HLP. Infected pancreatic necrosis and abscesses were seen in one of the 22 patients (4.5%) in the LLP group compared with seven of the 23 patients (30%) in the HLP group ($P = 0.023$). The only patient in the LLP 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 previous 8 days. The length of stay was considerably shorter in the LLP group (13.7 days vs. 21.4 days), but the limited size of the material did not allow statistical significance to be achieved. In a second study by the same group, sixty-two patients with

severe acute pancreatitis (Apache II scores, synbiotic-treated group 11.7 ± 1.9, controls 10.4 ± 1.5) were supplemented for 14 days with either two sachets per day of Synbiotic 2000 (2 × 40 billion LAB/day and in total 20 g fibers) or only the same amounts of fibers in 20 g as in Synbiotic 2000. Nine of the 33 patients (27%) in the Synbiotic 2000 treated group and 15 of the 29 patients (52%) in the only-fiber-treated group developed subsequent infections. Eight of the 33 (24%) Synbiotic 2000 treated patients and 14 of the 29 (48%) only-fiber-treated patients developed systemic inflammatory syndrome, multiple organ failure, or both ($P < 0.005$) [36].

Use of Synbiotics in Pancreatic Cancer Operations

A prospective randomized double-blind trial was undertaken involving 80 patients following pylorus-preserving pancreatoduodenectomy [37]. All patients received enteral nutrition immediately postoperatively. Group A received a composition of Synbiotic 2000, and group B received a placebo (the fibers in Synbiotic 2000, but no LAB) starting the day before surgery and continuing for 8 days. The 30-day infection rate, the length of hospital stay, the duration of antibiotic therapy, noninfectious complications, and side effects were recorded. The infections were diagnosed at a mean of 9 days (group A) and 8 days (group B) following surgery. Five of the 40 patients in the Synbiotic 2000 treated group (12.5%) and 16 of the 40 patients in the control group (40%) developed postoperative infections ($P = 0.005$). No peritonitis (control group, six patients), pneumonia (control group, four patients), sepsis (control group, two patients), cholangitis (control group, one patient), and empyema (control group, one patient) were observed in the Synbiotic 2000 treated group. Four patients in the Synbiotic 2000 treated group and six patients in the control group developed wound infections. Urinary tract infection was seen in one patient in each group. *Enterobacter cloacae* grew in eight control patients (two treated patients), *Enterococcus faecalis/faecium* in seven patients (one treated patient), *E coli* in seven patients (no treated patients), and *S. aureus* in two patients (no treated patients). *Klebsiella pneumonia* grew in two patients in each group and *Proteus mirabilis* in one patient in each group.

Conclusions

As can be judged from the limited studies available today, symbiotic treatment seems to have a great potential as a tool to control inflammation and infection in connection with surgery and in acute diseases such as acute pancreatitis. Limited experience suggests that promising effects can also be obtained when it is used in pancreatic surgery, both resections and transplantation. The results of treatment in other chronic diseases such as chronic liver disease provide hope that positive effects might also be obtained when it is tried in chronic pancreatitis. Such treatment might also prove valuable in patients on a waiting list for an operation, particularly transplantation. This treatment should be an attractive option as it is relatively inexpensive, has no side effects, and does not induce antibiotic resistance.

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Author Queries

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[AQ3] Please explain what "/s" represents.
[AQ4] Please explain what "bil" is.
[AQ5] Please explain what "/s" represents.
[AQ6] Please explain what "ALT" is.
[AQ7] Kindly update the details of reference 32.
[AQ8] Kindly update the details of the reference 34.