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REVIEW ARTICLE

Bioecological control of organ failure: the role of enteral nutrition, probiotics and synbiotics

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Abstract

Surgical and medical emergencies, such as myocardial infarction, stroke, severe pancreatitis, trauma and burns, but also advanced medical and surgical treatments, from extensive surgical operations to stem cell transplantations, are associated with an unacceptably high morbidity and mortality. The most common cause is sepsis which, despite all advances in pharmaceutical medicine, is steadily increasing. Sepsis is mainly seen in elderly patients and patients with a malfunctioning innate immune system and subsequent elevated inflammatory response. In the past, multiple attempts have been made to control sepsis and subsequent organ failure, but with no or limited success, using branched chain amino acids, glutamine, growth hormone, insulin, insulin-like growth factor 1, various vitamins, as well as combinations of nutrients, including so-called immunoenhancing nutrition formulae. Aggressive perioperative enteral nutrition, tight control of blood sugar, supplementation of antioxidants, plant fibres and lactic acid bacteria (LAB) so far seem to offer the greatest hope to reduce the rate of sepsis, inflammation and subsequent single and multiple organ failure. Studies combining plant fibres and bioactive LAB have shown a unique ability to eliminate sepsis in severe acute pancreatitis (SAP), in connection with advanced surgical operations but also in infection-sensitive chronic diseases such as chronic liver disease. Experimental studies show prevention of sepsis-induced neutrophil infiltration of the lung and tissue destruction, the most common target for single organ failure. Clinical studies in SAP demonstrate significant reduction in systemic inflammatory responses in multiple organ failure. The effects observed are unique to specific LAB and specific fibres and cannot be reproduced with "yoghurt" bacteria. The choice of LAB is critical as most LAB do not survive the harsh climate in the stomach and upper intestine, and cannot adhere to the intestinal mucosa and reproduce.

AQ1 **Keywords:**

Abbreviations: ARDS: acute respiratory distress syndrome; ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; ITU: intensive therapy unit; LAB: lactic acid bacteria; MOF: multiple organ failure; PAF: platelet activating factor; PAI-1: plasminogen activator inhibitor-1; PMN: polymorphonuclear; PPMs: potentially pathogenic microorganisms; SAP: severe acute pancreatitis; SIRS: systemic inflammatory reaction syndrome; TNF-α: tumour necrosis factor-α

A threatening scenario

Patients with acute diseases, medical and surgical emergencies such as myocardial infarction, stroke, severe pancreatitis, trauma and burns, and those related to advanced medical and surgical treatments, such as stem cell transplantation or extensive surgical operations, suffer an unacceptably high morbidity and co-morbidity. What it worse, this morbidity is increasing; severe sepsis has increased in recent years by 15% per decade and today is the 10th most common cause of death in the USA (1). Severe and often life-threatening infections occur annually in the USA in approximately 751,000 individuals, and approximately 215,000 (29%) of these individuals succumb (1,2). As recently pointed out by Vincent et al. (3), the estimates of intensive therapy unit (ITU) mortality are conservative and deaths of ITU patients are often attributed to the original condition. Thus, the ITU mortality may in reality be higher than officially reported. More than half of patients (383,000, 51%) are treated in ITUs in

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the USA and approximately another 130,000 are managed at intermediary-type care units with facilities for ventilation. The extra treatment cost is calculated to be $22,100 per case and the annual cost in the USA only for this treatment to be about $17 billion (2).

A failing innate immune system

The majority of patients suffering critical illness already have a failing innate immune system before the acute critical illness. About half of the patients affected by sepsis are in the age group $\alpha > 65$ years, and 48% of the patients are neutropenic (4, 5). Knowledge about the innate immune system and its function and understanding of resistance to disease has increased tremendously over the past 10–15 years. Solid evidence suggests that outcome after larger surgical operations as well as in medical emergencies is intimately associated with the premorbid health and the strength of especially the innate immune system, but is also associated with the speed and depth of deterioration in function during the first few hours. A recent study suggests four variables: age, chronic health status, need for mechanical ventilation and highest serum creatinine value within 60–72 h of admission to be especially associated with poor outcome in severe acute pancreatitis (SAP) (6). Of the four factors suggested one is retrospective, but the remaining three are factors that mainly reflect the patient's premorbid condition and ability to resist disease: the robustness of the innate immune system. Imrie has recently emphasized patient-associated factors, especially obesity, and suggested for SAP a cheap but so far untested prognostic system based on body mass index, age, chest X-ray and oxygen saturation (7).

An exaggerated inflammatory response

Those who develop severe septic complication are known to respond to stress with an exuberant acute or chronic superinflammation, manifested by exaggerated and prolonged release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and acute-phase proteins such as C-reactive protein, but also of plasminogen activator inhibitor-1 (PAI-1) (8). Both IL-6 and PAI-1 are often regarded as prognosticators of outcome both in acute conditions such as after operation/trauma, myocardial infarction and pancreatitis, and also in semi-chronic or chronic inflammatory conditions, such as arthritis, mental depression and Alzheimer's disease. The overwhelming IL-6 response (e.g. prolonged and/or extreme elevations of circulating IL-6) seen in patients suffering from conditions such as infection, burns or trauma is strongly associated with severe exacerbation of the disease such as acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) (8). The effect of overwhelming acute-phase response on outcome is well demonstrated in a study in human liver transplantation; all patients who had a six-fold or larger increase in the cytokines tumour necrosis factor-α (TNF-α) and IL-6 during the later phase of the operation developed sepsis during the subsequent postoperative days (9).

Among the changes observed in overexuberant acute-phase response are augmented endothelial adhesion of polymorphonuclear (PMN) cells, increased production of intercellular adhesion molecule-1 (ICAM-1) and priming of the PMNs for an oxidative burst, release of pro-inflammatory platelet activating factor (PAF) and, associated with this, a delay in PMN apoptosis (10). Visceral adipocytes are, compared with subcutaneous fat cells, known to secrete much more free fatty acids, and three times as much IL-6 and PAI-1 per gram of tissue, observations that explain the high risk of both chronic and acute diseases in individuals with visceral obesity (11). The load on the liver of these and other pro-inflammatory and procoagulant molecules can vary thousand times or more, as the amount of fat in the abdomen varies from one individual to another between a few millilitres in lean subjects and about 6 litres in those with gross abdominal obesity (12).

Fighting immunoparesis

Using the supply of nutrients to modulate the inflammatory response and maximize the function of the immune system and hence the resistance to disease is becoming increasingly recognized as the most effective way to prevent unwanted morbidity. Proper enteral nutrition is well documented to improve outcome in critically ill and surgical patients, and is an important tool to prevent chronic illnesses. Various nutrients have been shown to preserve and augment different aspects of cellular immunity and to modify the production of inflammatory mediators. However, much research is needed before all the possibilities with immunomodulatory nutrition are fully understood and practised. Some measures have proven effective, such as aggressive perioperative enteral nutrition, tight blood glucose control, rich supply of antioxidants, rich supply of prebiotic fibres and maintenance of flora and/or supplementation of probiotic bacteria, which are summarized below.

Aggressive perioperative enteral nutrition

The inflammatory response is immediate, and all attempts to control the response must therefore be immediate. Studies in recent years have demonstrated that immediate postoperative feeding is safe, and prevents increases in gut mucosal permeability. Immediate enteral nutrition is reported to contribute to a positive nitrogen balance, to reduce the incidence of septic complications, to reduce the occurrence of postoperative ileus, and to accelerate restitution of pulmonary performance, body composition and physical performance. An important observation is that delaying institution of enteral nutrition for more than 24 h results in an significantly increased intestinal permeability and significantly higher incidence of MOF, compared with immediate enteral supply of nutrition (13). Oral/enteral supply of nutrients uninterruptedly during the night before, during surgery and immediately thereafter seems to support the immune system further and increase resistance to complications. The present author has developed an autopositioning and regurgitation-resistant tube to make such treatment easier (Fig. 1A, B). The tube is marketed in Europe by the Nutricia group.

An early study reported successful intubation in 10/10 patients with SAP; the head of the tube reaching its optimal position within an average of 5.2 h, and always within 24 h (14). A recent study achieved successful placement in patients with normal gastric emptying within 24 h in 78%, compared with 14% with a standard straight tube ($p = 0.041$), and in patients with impaired gastric emptying (as in most SAP patients) a successful placement within 24 h in 57%, compared with 0% with standard tubes ($p = 0.07$) (15). A recent study reports successful insertion in 12/16 (75%) of SAP patients with the tube reaching the Treitz ligament with a median of 12 h (16).

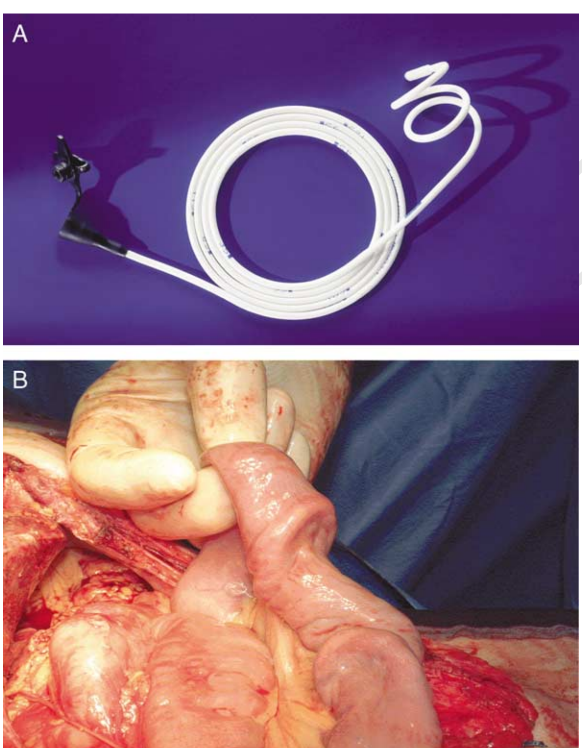

Fig. 1. Bengmark Flocare autopositioning and regurgitation-resistant feeding tube. (A) The tube before insertion; (B) the location of the head of the tube in upper jejunum (Mangiante G, personal communication).

Tight control of blood glucose

Hyperglyacemia is known as a significant marker of in-hospital mortality (17) and known to predispose to infectious complications (18). As an example, hyperglycaemia predicts myocardial infarction in patients under hypertensive treatment (19). Strict glucose control has been known for some time to reduce the incidence of wound infection in open heart surgery (20). However, it is not until recent years that strict glucose control has been more widely adopted by modern ITU and postoperative care. Until recently, the state of the art was to feed critically ill patients and not to provide exogenous insulin until blood glucose levels were above 12 mmol l^{-1} (220 mg dl^{-1}). However, studies using strict glucose control (keeping it below 6.1 mmol l^{-1}) have convincingly resulted in a decrease in bloodstream infections by 46%, critical illness polyneuropathy by 44%, acute renal failure and the need for haemofiltration by 41%, the need for red cell transfusions by 50% and mortality by 34% (21, 22). Furthermore, small elevations in blood glucose (to 8–10 mmol l^{-1}) impair gut motility and function (23) and contributes to the induction and prolongation of ileus, which has not often been recognized. Maintenance of gastrointestinal motility is another important reason for strict blood glucose control in postoperative and critically ill patients.

Supply of antioxidants

Antioxidants have numerous beneficial effects in the postoperative and ITU patient (24), including direct antioxidant, anti-inflammatory, antibacterial, antithrombotic, anticarcinogenic and vasodilatory effects. The benefits of routine supply of larger amounts of various antioxidants, especially of flavonoids, to surgical and ITU patients are as yet almost unexplored. It is well known that the tissue and blood concentrations of pro-oxidants are invariably high and the levels of various antioxidants and micronutrients low, often extremely low, in critically ill patients. As an example, total vitamin C and ascorbic acid are reported to be lass than 25% of normal values in ITU patients (25). A recently published study performed mainly in trauma patients reports an 19% reduction in pulmonary morbidity and a 57% lower incidence of MOF in a group of patients receiving supplementation with α-tocopherol and ascorbate (26; see also 27). Glutathione is an important antioxidant, synthesized by the body and supplied by food, mainly fruit and vegetables. Glutathione in serum is significantly decreased after surgery and in critically ill patients in general, and low blood levels of glutathione are associated with impaired lymphocyte and neutrophil function. Glutamine constitutes an important source of fuel in the critically ill, especially for the small bowel enterocytes, but is also a necessary substrate for production of glutathione (28). In experimental studies, supply of glutamine has been shown to reduce cytokine release, organ damage and mortality (29), and to counteract glutathione and lymphocyte depletion in Peyer's patches (30). Significant clinical results such as reductions in morbidity, mortality and length of stay are obtained by glutamine supply in critically ill patients (31). One of the main roles of lactic acid bacteria (LAB) is to ferment fruit and vegetables and to release various antioxidants. As flora is almost always absent in the critically ill, supply of probiotics, but also prebiotic plant fibres, should be mandatory.

Supply of plant fibres

Plant fibres are favoured substrates for microbial fermentation in the lower digestive tract, but also have their own strong bioactivities. Few studies on the supply of plant fibres in connection with surgery and in critically ill patients are to be found in the medical literature. An interesting controlled study, published over a decade ago, reports significant reduction in postoperative morbidity after supply of glucan(β1-3 polyglucose): nosocomial infections reduced from 65 to 14% and mortality from 30 to 5% (32). Most other studies in acute medicine in recent years have dealt mainly with combined supply of probiotics and fibres. Experimental and clinical observations provide support for prebiotics having several important functions in the body: they provide nutrients and energy for the consumer, provide nutrients and energy for the flora, provide resistance against invading pathogens, maintain water and electrolyte balance, and maintain mucosal growth and function (33, 34). The best fibres are undoubtedly those provided by eating fresh, uncooked and otherwise unprepared fruit and vegetables. However, this is most unfortunately rarely possible in the critically ill patient. The more the fibres are processed, the more they lose their potency. The fibres supplied with commercial nutrition formulae are commonly hydrolysed. This means that they are devoid of important antioxidants, various phytochemicals, glutathione and other unstable molecules such as glutamine. For that reason it is recommended that non-processed fibres should be supplemented orally. Using a mix of several different fibres it should be possible to supply 20–30 g a day, even to the critically ill. Often used prebiotics include various oligosaccharides such fructooligosaccharides, *trans*-galactosaccharides and lactulose. Oligosaccharides are especially rich in banana, artichokes, leeks, onions, garlic, asparagus and chicory. Larger molecules such as oat fibres (β-glucans), pectins and resistant starch can be expected to show great bioactivity in the body and should thus also be supplemented to the critically ill. They are usually supplied as powders, which can be diluted with water or acid fruit juices such as pineapple juice and fed through feeding tubes, or mixed with mashed fruit such as kiwi, apple, pear or banana, and eaten.

Supplementing flora

A significant reduction in the commensal flora occurs very early in the disease process, and is both induced both by the disease and stress per se and by pharmaceutical treatment. A significant reduction in anaerobic bacteria and particularly lactobacilli is observed in both the small intestine and the colon as early as 6–8 h after induction of experimental pancreatitis (35). This reduction in beneficial flora pattern is almost instantly followed by significant increases in numbers of various potentially pathogenic microorganisms (PPMs) such as *Escherichia coli.* Dramatic increases in mucosal barrier permeability (lumen to blood) and in endothelial permeability (blood to tissue) are observed (35, 36), and accompanied by increased microbial translocation and growth of PPMs, both of mesenteric lymph nodes and in the pancreatic tissue (37). For obvious ethical reasons few systematic studies have been done in patients, but most support the assumption that patients who have undergone large operations and patients who suffer major trauma or are treated with modern antibiotics suffer a considerable reduction in the beneficial flora and a significant overgrowth of PPMs. Early supplemented beneficial bacteria, so-called probiotics, are reported to counteract such negative effects. From experimental and clinical observations, it can be concluded that supplied probiotics exhibit several important bioactivities, which should be of special benefit to the critically ill (33, 34), as they reduce or eliminate

PPMs, reduce or eliminate various toxins and mutagens from the intestinal content, modulate innate and adaptive immune defence mechanisms, promote apoptosis, and release numerous nutrients, antioxidants, growth factors, coagulative and other factors from consumed fibres.

Combination of probiotics and prebiotics equals synbiotics

Supplementing enteral nutrition with both fibre and LAB has the potential to enhance further the immune system and provide protection against infectious complications. It is this author's conviction that it should always and immediately be provided to surgical patients before, during and immediately after surgery, or in the case of trauma or medical emergency immediately on arrival to the hospital. It is important to use a mixture several bioactive fibres and it is especially important to choose LAB with well-documented bioactivities.

Plant-derived synbiotics: a promising tool

Most of the LAB suggested for use in ITU patients were originally been identified on plants. Most of the LAB used by food industry have no or limited ability to ferment strong bioactive fibres such as inulin or phleins, no ability to adhere to human mucus and low antioxidant capacity and, most importantly, do not survive the acidity of stomach and bile acid content. Strong bioactivity often cannot be expected from LAB such as yoghurt bacteria, chosen mainly for their palatability. The majority of experience obtained from studies in ITU patients comes from studies using two synbiotics, combinations/mixtures of prebiotics and probiotics:

- a one-LAB/one-fibre composition, produced by fermentation of oatmeal with *Lactobacillus plantarum* strain 299 (38). The formula was produced for these studies by Probi (Lund, Sweden)
- a four-LAB/four-fibre composition, called Synbiotic 2000™, consisting of a mixture of 10^{10} (and more recently a composition with 10^{11}: Synbiotic 2000 forte™) of four different LAB: *Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subsp. *paracasei* 19 and *Lactobacillus plantarum* 2362, combined with 10 g of fibres: 2.5 g of each of four fermentable fibres: β-glucan, inulin, pectin and resistant starch (39, 40). It is common practice to supply two sachets per day, i.e. 20 g of fibre and 80,800 billion (Forte version) of LAB. The most recent experience is summarized below. The formula was produced for these studies by Medipharm (Kågeröd, Sweden) and Des Moines (Iowa, USA).

Synbiotics in surgical and intensive therapy unit patients

Acute pancreatitis

During the first 7 days, patients with SAP were randomized to receive daily, administered through a nasojejunal tube, either a freeze-dried preparation containing live *L. plantarum* 299 in a dose of 10^9 together with a substrate of oat fibre or a similar, but heat-inactivated preparation (41). The study was interrupted when on repeat statistical analysis significant differences in favour of one of the two group were obtained, which occurred after a total of 45 patients had entered the study. At that time 22 patients had received treatment with live and another 23 with the heat-killed *L. plantarum* 299. Infected pancreatic necrosis and abscesses were seen in 1/22 (4.5%) in the live LAB group versus 7/23 (30%) in the heat-inactivated group ($p = 0.023$). The only patient in the lactobacillus group who developed infection (a urinary infection) did so on the 15th day, i.e. when he had not received treatment for 8 days. The length of stay was also considerably shorter in the live LAB group (13.7 days vs 21.4 days), but the limited size of the material did not allow statistical significance to be reached.

Patients with SAP were in a second yet unpublished study by the same group supplemented for 14 days with either two sachets per day of Synbiotic 2000 (2×40 billion LAB per day, 20 g in total) or only fibre (20 g). Nine out of 33 patients (27%) in the Synbiotic 2000-treated group and 15/29 patients (52%) in the only fibre-treated group developed infections (Tables I and II). Significant reduction ($p < 0.05$) in combined SIRS + MOF was observed: 8/33 (24%) Synbiotic 2000-treated compared with 14/29 (48%) of the only fibre-treated patients (Olah A, personal communication).

Abdominal surgery

Lactobacillum plantarum 299 in a dose of 10^9 and 15 g of oat and inulin fibre was used in a study in extensive abdominal surgical operations. The patient material consisted mainly of liver, pancreatic and gastric resections, equally distributed between the groups. Three groups were compared: live LAB and fibre, heat-inactivated LAB and fibre, and standard enteral nutrition (42). Each group consisted of 30 patients. The 30 day sepsis rate was 10% (3/30 patients) in the two groups receiving either

Table I. Multistrain synbiotics in severe acute pancreatitis: summary of results from an unpublished study of patients with severe acute pancreatitis treated with either the synbiotic composition (Synbiotic 2000) or only plant fibres (the fibres in Synbiotic 2000)

	Synbiotic 2000™	Fibres only	
Total no. of infections	9/33 (27%)	15/29 (52%)	
Pancreatic abscesses	2	2	
Infected necrosis	2	6	
Chest infections	2	4	
Urinary infections	3	3	
SIRS	3	5	
MOF	5	9	
SIRS+MOF	8	14	$p<0.05$
late (>48 h) MOF	1	5	
Complications	9/33	15/29	$p<0.05$
Surgical drainage	4/33 (12%)	7/29 (24%)	
Mean hospital stay	14.9±6.5	19.7±9.3	
Dead	2/33 (6%)	6/29 (18%)	

From Olah et al. (personal communication).
SIRS: systemic inflammatory reaction syndrome; MORS: multiple organ failure.

Table II. Multistrain synbiotics in severe acute pancreatitis: summary of isolated bacteria in an unpublished study of patients with severe acute pancreatic treated with either the synbiotic composition (Synbiotic 2000) or only plant fibres (the fibres in Synbiotic 2000)

Isolated microorganism	Synbiotic 2000™	Fibres only
Pseudomonas aeruginosa	1	4
Enterococcus faecalis	1	2
Enterobacter spp.	1	1
Streptococcus spp.	2	–
Staphylococcus aureus	1	1
Enterococcus faecium	1	–
Candida spp.	–	2
Staphylococcus haemolyticus	–	1
Serratia spp.	–	2
Klebsiella spp.	–	1
Escherichia coli	–	1
Strenotrophomonas maltophilia	–	1
Citrobacter freundii	–	1
Total	7	17

From Olah et al. (personal communication).

live or heat-inactivated LAB, compared with 30% (9/30 patients) in the group on standard enteral nutrition ($p=0.01$). The largest difference was observed in the incidence of pneumonia: enteral nutrition only, six patients; live LAB and fibre, two patients; and heat-killed LAB and fibre, one patient. The beneficial effects of synbiotic treatment were seemingly most pronounced in gastric and pancreatic resections, the sepsis rate being: live LAB, 7%; heat-inactivated LAB, 17%; and standard enteral nutrition, 50%. The same pattern was observed for non-infectious complications: standard enteral nutrition only, 30% (9/30); heat-inactivated LAB, 17% (5/30); and live LAB, 13%(4/30). The supply of antibiotics to the live LAB-treated patients was significantly less ($p=0.04$), and the mean length of antibiotic treatment was considerably shorter: live LAB, 4±3.7 days; heat-killed LAB, 7±5.2 days; and standard enteral nutrition, 8±6.5 days.

In a recent study (43) in patients undergoing abdominal operations for cancer, the incidence of postoperative bacterial infections was significantly reduced from 47% with parenteral nutrition and 20% with only fibres to 6.7% with live LAB and fibre (Synbiotic 2000). Significant improvements were observed in prealbumin, C-reactive protein, serum cholesterol, white cell blood count, serum endotoxin and immunoglobulin A.

Another recent, not yet published, study in acute extensive trauma patients reports a dramatic decrease in number of chest infections with the supply of 40 billion LAB-containing Synbiotic 2000 (1/14 patients, 7%), compared with only fibres (11/28 patients, 39%), peptide (10/21 patients, 48%), or glutamine (12/37 patients, 32%). Equally, the total number of infections was decreased: Synbiotic 2000, 2/14 patients (14%); only fibres, 16/28 patients (57%); peptide, 11/21 patients (52%); and glutamine, 19/37 patients (51%) (Kompan L, personal communication).

Liver transplantation

A prospective randomized study with the same one-LAB/one-fibre preparation was performed in 95 liver transplant patients by the same group of investigators (44). Three groups of patients were studied: group 1, selective digestive tract decontamination (SDD) four times daily for 6 weeks ($n=32$); group 2, *L. plantarum* 299 (LLP) in a dose of 10^9 plus 15 g of oat and inulin fibres ($n=31$) supplied postoperatively during 12 days; and group 3, identical to group 2, but with heat-killed *L. plantarum* 299 (HLP) ($n=32$). Identical enteral nutrition was supplied to all patients from the second postoperative day. There were 23 postoperative infections in SDD, 17 in HLP and four in LLP. Signs of infections occurred in SDD 48% (15/32), HLP 34% (11/32) and LLP 13% (4/31) ($p=0.017$). The most dominating infections were cholangitis, occurring in SDD in 10, HLP in eight and LLP in two patients, and pneumonia, observed in SDD in six, HLP in four and LLP in one patient. The most often isolated microbes were *Enterococci*: SDD in eight, HLP in eight and LLP in one patient, closely followed by *Staphylococci*: SDD in six, HLP in three and LLP in one patient. No *E. coli* or *Klebsiella* infections were seen in the LLP group. Eight patients required haemodialysis in SDD, four in HLP and two in LLP, and the there were six reoperations in SDD, two in HLP and four in LLP. There were no deaths. The stay in ITU, the hospital stay and length on antibiotic therapy were shorter in the LLP group, but did not reach statistical significance. The CD4/CD8 ratio was higher in the LLP group than in the other two groups ($p = 0.06$).

The same investigators have continued their efforts to reduce the septic morbidity in liver transplantation (45). In a subsequent study the four-LAB/four-fibre combination (Synbiotic 2000) was tried. In a double-blind randomized study 33 patients were given Synbiotic 2000 and another 33 patients only the four fibres in Synbiotic 2000. The treatment started on the day before surgery and continued for 14 days after surgery. During the first postoperative month only one patient in the Synbiotic 2000-treated group (3%) showed signs of infection (urinary infection), compared with 17/33 (51%) in the patients supplied only the four fibres (Table III). The use of antibiotics was also significantly reduced in the synbiotic-treated group.

Synbiotics in chronic conditions: a new challenge

Modern medicine has failed in its ambition to prevent acute and chronic diseases. The world suffers today an epidemic of chronic diseases of a dimension never seen before. Such diseases constitute today no less than 46% of the global disease burden. Approximately 35 million individuals die each year of conditions related to chronic diseases, and the numbers increase each year. Chronic diseases are strongly associated with critical illness and MODS. The overwhelming majority of MODS is seen in patients with pre-existing chronic diseases. Early observations suggest that synbiotic treatment has great potential to improve outcome in chronically ill patients. Such treatment is reported to reduce significantly serum fibrinogen and low-density lipoprotein-cholesterol when supplied patients with moderately elevated cholesterol (46, 47). There are good reasons also to expect beneficial effects of synbiotic treatment in chronic conditions such as inflammatory bowel disease (48), cancer, chronic kidney disease (49, 50) and chronic lung disease, but systematic studies are so far to a large extent lacking. The experience to date in chronic liver disease is encouraging.

Table III. Multistrain synbiotics in liver transplantation: summary of isolated bacteria in patients after liver transplantation treated with either the synbiotic composition (Synbiotic 2000) or only plant fibres (the fibres in Synbiotic 2000)

Isolated bacterium	Synbiotic 2000™	Fibres only
Enterococcus faecalis	1	11
Escherichia coli	0	3
Enterobacter cloacae	0	2
Pseudomonas aeruginosa	0	2
Staphylococcus aureus	0	1
Total	1	18

Modified after Rayes et al. (45).

Chronic liver disease: effect on inflammation

Probiotics and prebiotics (synbiotics) have the ability to reduce the production and absorption of endotoxin in the intestine, but also down-regulate production of pro-inflammatory cytokines, including TNF-α. Long-term supply of synbiotics can be expected to reduce both the inflammation of the liver and the steatosis. It was recently observed that *in vitro* TNF-α production by peripheral blood mononuclear cells in response to stimulation by endotoxin or *Staphylococcus aureus* enterotoxin B was reduced by a median 46% (range 8–67%) compared with presupplementation levels in 8/11 (72.7%) cirrhotic patients supplied with the synbiotic composition (51). Supply of synbiotics to patients (Synbiotic 2000) with advanced chronic liver disease is well tolerated and no adverse events or changes in general clinical state have been observed. If supply of synbiotics is capable of reducing the production of TNF-α,synbiotics could well constitute a cheap and powerful tool with no side-effects for the long-term treatment of patients with liver disease.

Chronic liver disease: effect on gut colonization, liver function and encephalopathy

Out of a group of 97 patients with liver cirrhosis, 58 were found to have signs of minimal encephalopathy. They were randomized into three treatment groups and studied when supplied during 1 month. Group 1 received the four-LAB/four-fibre synbiotic composition ($n = 20$), group 2 received only the fibres in the composition ($n = 20$) and group 3 received a placebo (non-fermentable, non-absorbable fibre) ($n = 15$) (52). One-month supply was shown to lead to a significant increase in the intestinal LAB flora in the LAB-supplied group, but not in the other two groups. The intestinal pH was significantly reduced in both treatment groups. There were significant decreases in *Escherichia coli*, *Staphylococcus* and *Fusobacterium*, but not in *Pseudomonas* or *Enterococcus*, as well as in ammonia, and the levels of endotoxin fell significantly. The levels of ALT decreased, in parallel with decreases in bilirubin, from 252 ± 182 to 84 ± 65 ($p < 0.01$) in the synbiotic-treated group and to 110 ± 86 ($p < 0.05$) in the fibre-only group, but not in the placebo group. The improvements in liver function were accompanied by significant improvements in psychometric tests and in degree of encephalopathy.

Chronic liver disease: effect on liver blood flow and indocyanine clearance

Reducing intestinal levels of endotoxin-containing Gram-negative bacteria is reported to improve systemic haemodynamic disturbance in liver cirrhosis. Supplementation with the four-LAB/four-fibre synbiotic composition (Synbiotic 2000) was associated with a significant reduction in indocyanine clearance (ICG_{R15}) by a median 17.5% (range 1.4–65%) of baseline values in 14/15 (93%) cirrhotic patients and was increased in one patient by 4.1% (53). The observed improvement was probably a result of a reduced swelling of endothelial and sinusoidal cells and reduced resistance to flow.

Choice of synbiotic composition

It is important to recognize that no conclusions regarding bioactivities can be generalized from one LAB to another, as they all are different in function and genetically unrelated. Producers of probiotic products often claim health benefits from their product, which in most cases are unsubstantiated and untrue. The truth is that only a small minority of LAB have the health potentials needed for use in critical medicine. Most of the probiotic bacteria sold on the market do not survive the acidity of the stomach, or the bile acid content of the small intestine, nor do they adhere to colonic mucosa or even temporarily colonize the stomach or intestine. It has in recent become increasingly common for milk-fermenting LAB, such as yoghurt bacteria and *L. acidophilus*, to be used in clinical medicine. Like most other LAB, yoghurt bacteria have a low survival capacity in an environment with acidity and bile acids such as the upper gastrointestinal tract, and generally exhibit only limited or no biological influence on the immune system. The great differences between the ability of some LAB to survive and their ability to influence cytokine production after passage through the stomach and small intestine was well demonstrated in a study comparing four different LAB species: *L. plantarum*, *L. paracasei*, *Lactobacillus rhamnosus* and *Bifidobacter animalis* (54). Of 10^8 cells ml^{-1} of each LAB originally administered, after the passage through the stomach and small intestine only between 10^7 (*L. plantarum*) and 10^2 (*L. rhamnosus*) bacterial cells remained. After passage through the small intestine, most of the strains tested showed a significantly reduced or weak (especially *L. rhamnosus*) ability to influence cytokine production, for example. If LAB such as yoghurt bacteria had been studied an even smaller survival would have been expected.

The ability to ferment prebiotic fibres is also of great importance for the choice of probiotics. When this ability was studied only 8/712 tested LAB fermented inulin-type fibre: *L. plantarum* (several), *L. paracasei* subsp. *paracasei*, *Lactobacillus brevis* and *Pediococcus pentosaceus* (55). A recent study also suggests that only a few LAB can control pathogens such as *Clostridium difficile* (56). When the ability of 50 different LAB to control 23 different pathogenic *C. difficile* was studied, 27 were totally ineffective, eight were antagonistic to some, and only five strains proved effective against all *C. difficile* strains: three *L. plantarum* strains and two *L. paracasei* subsp. *paracasei* strains (56). These particular LAB strains have also proven effective in various other studies in inducing cellular immunity, stimulating production of suppressive cytokines (transforming growth factor-β, IL-10), suppressing CD4 T-cells, Th_2 activity and splenocyte proliferation, and decreasing specific immunoglobulin E and G_1.

"Yoghurt bacteria": no or modest effects

Attempts have been made in the past with a synbiotic composition, which appears to be composed at random without preclinical studies on biological activity; at least no such documentation is provided. Two recent controlled studies describe the effects of a standard commercial product, TREVIS™ (Chr Hansen Biosystem, Denmark), consisting of LABs commonly found in dairy products: *L. acidophilus LA5*, *Bifidobacterium lactis BP12*, *Streptococcus thermophilus*, and *L. bulgaricus* combined with 7.5 g oligofructose (57,58). Significant reductions in the number of PPMs in the stomach, but no influence on intestinal permeability and no clinical benefits, were reported in critically ill patients (45 TREVIS-treated patient and 45 controls) (57). A similarly designed study was also performed in postoperative patients, 72 TREVIS-treated (S) and 65 placebo (P), who received treatment for 2 weeks (58). Nasogastric aspirate, mesenteric lymph nodes and scrapings of the terminal ileum were harvested at surgery for microbiological analysis. No significant difference in septic morbidity and mortality (S 12.1% vs P 10.7%, $p = 0.8$), septic complications (S 32% vs P 31%, $p = 0.9$), gastric colonization (S 41% vs P 44%, $p = 0.7$), systemic inflammation or gut barrier function were observed. See also the invited commentary by the present author (59).

Synbiotic treatment reduces oxidative stress and neutrophil infiltration. The big challenge in critical illness seems to be the exuberant inflammatory response that is evoked. The organ systems most often involved in early (within 24 h) single organ failure in SAP are pulmonary [91% (60), 81% (61)], renal [4.5% (60), 5% (61)] and coagulation systems [4.5% (60), 14% (61)]. If the early superinflammation in these systems can be prevented or made transient this will contribute significantly to a favourable outcome. Host phagocytic cells, predominantly neutrophils and macrophages, play a central role in both the containment of the insult and the ensuing tissue injury (62). The degree of oxidative stress and of neutrophil activation seems to be the factor determining outcome (63), and extensive neutrophil infiltration of the lungs, but also other distant organs, is a characteristic finding in patients dying with sepsis. Pulmonary dysfunction is a most common complication in critical illness, and will in the worst scenario lead to ARDS and eventually death. It occurs as a result of pulmonary accumulation of neutrophils with secondary damage of lung tissue through various neutrophil-released products such as reactive oxygen species, proteolytic enzymes and eicosanoids, known to induce endothelial cell injuries, increased capillary permeability and hypoxia. Inflammation of lung tissue, destruction of lung tissue and pulmonary infiltration of lung tissue with neutrophils can be totally prevented by enteral supply of synbiotics (Fig. 2A–C; Ilkgul O, personal communication). The number of neutrophils in lung tissue on histology was 34.40 ± 2.49 in Synbiotic 2000 Forte-treated animals in contrast to 266.90 ± 8.92 in only fibre-treated animals and 302.20 ± 7.92 in placebo-treated animals ($p < 0.01$). Intraperitoneal injection of live *Lactobacillus* in animals with induced sepsis (caecal ligation and puncture) attenuated the chest inflammation (64). Signs of lung injury, i.e. significant increases in the number of lung tissue neutrophils, histologically documented destruction of lung tissue, TNF-α, IL-1β, myeloperoxidase activity and malondialdehyde concentrations were seen in the animals treated with saline, but not or significantly less when treated with the LAB in Synbiotic 2000. Furthermore, the reduction in neutrophil infiltration was significantly more pronounced after pretreatment for 3 days than after pretreatment for 1 day ($p < 0.01$) (64).

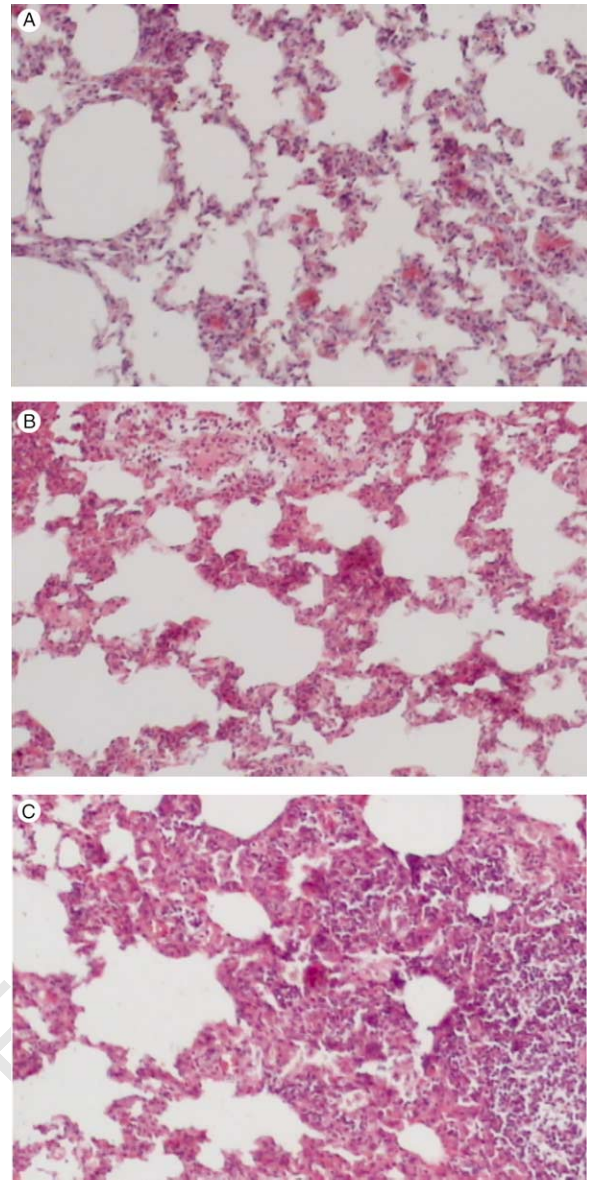

Fig. 2. Hematoxylin–eosin-stained histological sections of lung tissue obtained from rats 24 h after caecal ligation and puncture in animals pretreated for 3 weeks by daily gavage with (A) placebo (crystalline starch, a non-fermentable fibre), (B) only plant fibres (the fibres in Synbiotic 2000™), and (C) synbiotic composition (Synbiotic 2000).

Prevention and treatment of systemic inflammatory reaction syndrome and multiple organ dysfunction syndrome

Usually, no infectious focus can be identified on autopsy in patients dying of MODS (65). The understanding that one can be septic without being infected led to the recognition of what has been called the systemic inflammatory reaction syndrome (SIRS). Both conditions are difficult to predict and to prevent. However, signs of SIRS often occur earlier than those of MODS. Unexplained periods of hypotension and hypovolaemia are often seen, requiring extensive resuscitation with fluids, which later will result in fluid and retention and constitute a significant problem. During the past 10–15 years numerous attempts have been made both experimentally and clinically to reduce the metabolic consequences of hyperinflammation and to prevent and treat these conditions. These attempts include branched chain amino acids (66), glutamine (67), growth hormone (68), insulin (21,22), insulin-like growth factor-1 (69), vitamins (26,27) and combinations of nutrients, including so-called immunoenhancing nutrition formulae. Some, such as growth hormone, increased in-hospital mortality (70), others significantly reduced the ITU sepsis rate (21, 22, 26, 27), but only supplementation with α-tocopherol and ascorbate (26) has so far been shown to reduce significantly the incidence of MODS in critically ill patients.

These observations and the observation referred to above of significant reduction in combined SIRS + MODS in SAP offer hope for future progress with nutritional immunomodulation in critically ill and postoperative patients. See also Bengmark (71–73).

Future aspects

The most successful attempts so far to prevent SIRS and MODS are those that use natural substances: LAB, plant fibres and vitamins. It certainly a problem that for various reasons the nutrition of seriously ill patients is based mainly on synthetic formulae, and natural food, especially fresh fruit and vegetables, is avoided. Fruit and vegetables are rich in minerals and antioxidants, some of which are more than 10 times stronger in their antioxidant capacity than traditional vitamins such as vitamins C and E. Among these are various polyphenols and flavonoids, which are normally extracted in the intestine by microbial enzymes, absorbed and used in the body. Often neglected, they are also rich in various LAB, and often hundreds of strains can be grown from plants.

Bioecological control, supply of LAB and plants/plant fibres offer great hope for the control of critical illness and its most serious consequence, organ failure.

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