Synbiotic Control of Inflammation and Infection in Transplantation

Stig Bengmark

Apart from rejection, infection and inflammation are the most common threat to success in organ transplantation. The incidence of infection is high while patients are on the waiting list for transplantation and in the immediate postoperative period, as well as during several years after transplantation. The majority of immune cells are found in the gut, and insufficient gut immune functions and exuberant release of proinflammatory mediators such as cytokines are seen in combination with translocation of potentially pathogenic microorganisms (PPMs) in these patients. Specific lactic acid bacteria (probiotics) and specific plant fibers (probiotics), often in combination (synbiotics), have proven effective to reduce inflammation and infection in these patients. The supply of synbiotics to these patients is a documented effective tool to reduce the PPM flora, eliminate potential toxins and mutagens, provide through fermentation numerous antioxidants and nutrients, and stimulate the innate immune system. Recent studies suggest that inflammation can effectively be reduced in patients with chronic liver disease and inflammation and infection almost abolished just by uninterrupted—continuous—perioperative supplementation of synbiotics in connection with transplantation. A special feeding tube technology has been developed to optimize uninterrupted enteral nutrition with synbiotics in the perioperative period.

Despite obvious progress in medicopharmaceutical and surgical treatments during the last few decades, morbidity and mortality in severely ill patients, such as transplant patients, remain at an unacceptably high level. This is especially true for septic morbidity. The high incidence of sepsis has thus far remained relatively resistant to most preventive and treatment efforts. Only in the United States does severe sepsis annually affect 751,000 persons, which results in death of the patients in 29% (215,000 patients). Sepsis is currently the tenth most common cause of death in the country. Furthermore, the incidence of critical illness is rising by about 1.5% each year. More than half of critically ill patients (51%) or 383,000 are treated in special intensive therapy units (ITUs), and an additional 130,000 are ventilated in some intermediary-type care units. The extra treatment cost for each case is estimated to be $22,100 and the total annual cost in the United States is about $17 billion.

From the Institute of Hepatology and Department of Surgery, Royal Free and University College Medical School, University College London, London, United Kingdom.

Address reprint requests to Stig Bengmark, MD, PhD, Institute of Hepatology and Department of Surgery, Royal Free and University College Medical School, University College London, 69-75 Chenies Mews, London WC1E 6HX, United Kingdom.

0955-470X/$ - see front matter

doi:10.1016/j.trre.2004.01.001

Sepsis: A Major Problem in Transplantation

Bone marrow, liver, lung, and intestines are especially central to immune defense and resistance to disease. Both the function and the immunologic strength of these organs in transplant patients are often considerably reduced by disease even before the transplant and are further handicapped by the instituted treatments, especially by the supply of immunosuppressive agents and other pharmaceuticals, including antibiotics. There is a strong association between the dose of immunosuppressants given to the patient and the rate of infections. As a consequence, the incidence of infections is especially high during the first 2 to 4 weeks after transplantation, when the supply of immunosuppressants is the highest.

Bone Marrow (Stem Cell) Transplantation

Bone marrow transplantation constitutes a unique immunological situation because of the induced total lack of lymphocytes. It is estimated that each year worldwide more than 50,000 patients undergo bone marrow–stem cell transplantation, and manifestations of sepsis will develop in more than 25,000 of

them within the first 2 to 4 weeks.[1,2] The condition becomes very serious in patients who require invasive mechanical ventilation, need inotrope support, or experience development of organ dysfunction, with a reported mortality of >80%.[3,4]

Lung Transplantation

Infection is also a major problem in lung transplant patients. As with transplantation of other organs, use of immunosuppressants is responsible for a considerable suppression of humoral and cell-mediated immunity and subsequent infections. However, it is important to recognize that the function of the new lung is quite impaired and the cough blunted because of postoperative pain but also because of the fact that the new lung is without nerve supply. In addition, the lymphatic drainage is almost totally absent and the mucociliary clearance severely impaired. All of this explains why approximately 80% of postoperative infections in lung transplant patients occur within the chest, lung, mediastinum, and pleura.[5]

Heart Transplantation

Infectious complications are also commonly seen in heart transplantation and are the major reason for morbidity and mortality. They are second only to rejection as the cause of early deaths and are, in fact, the dominant cause of late deaths.[6] Among the identified risk factors for early infections are older age of the recipient (P <.0001), race of the donor (P = .0007), and positive donor serologic test results for cytomegalovirus (P = .0007).[7] Various supportive technologies such as ventilator support at the time of transplant (P <0.0001), ventricular assist device at the time of transplant (P = .02), and OKT3 induction therapy (P <.0001) add considerably to morbidity and mortality.[7] Use of various types of ventricular assist systems (VAS) will significantly increase the incidence of severe morbidity and mortality; severe infections are reported to occur in at least 50% of the patients supported by an implantable VAS and in 28% of the patients supported by short-term and externally applied VAS.[8]

Liver, Intestinal, and Multivisceral Transplantation

In the majority of patients subjected to intestinal and multivisceral transplantation, sepsis will develop during the first postoperative month.[9] Recent studies from clinical liver transplantation report infections during the first 30 days in about half of patients; the reported incidence in the literature varies between 30% and 86%. The highest incidence, 86%, was reported in a recent study in which selective digestive tract decontamination (SDD) was used. One might question whether SDD did not, in fact, add to the risk of sepsis instead of preventing it. The occurrence of surgical infections in liver transplantation has serious economic implications, in addition to its impact on morbidity, mortality, and quality of life. A recent study suggests that surgical site infections after liver transplantation incur approximately 24 additional hospital days per patient, $159,967 in excess charges, and a 10% increase in mortality. Strong evidence suggests that postoperative infections and antibacterial treatments are also associated with a significantly higher incidence of graft loss.[10]

An Infection-Rejection-Immunosuppression Connection

More than half of the early infections after transplantation are of bacterial origin. Viral and fungal infections are also frequent. There is a strong association between the dose and type of immunosuppressive agents administered and subsequent infection and rejection episodes. That the occurrence of infection also increases the rate of rejection was suggested by Simmons et al[11] in 1970. These authors made the observation that mild fever often preceded rejection, later accompanied by renal function deterioration, consistent with allograft rejection. They were especially able to show a clear-cut association between rejection episodes and herpesvirus infections.[12] The cause-and-effect relation between infection was recently reviewed by Cainelli and Vento,[10] who proposed that it is especially cytomegalovirus infections which up-regulate various adhesion molecules, cytokines, and coagulation factors, activate T lymphocytes, and damage human lymphocyte antigen (HLA)–DR expressing allograft blood vessels, which triggers rejection.

Factors Known to Decrease Resistance to Infection

Several factors are known to contribute to the sensitivity of infection.

Pre-existing Morbidity

An increasing part of the patient population treated by organ transplantation has metabolic syndrome (MS), prediabetes, manifest diabetes, or other MS-associated conditions known to be associated with

depressed immune function and depressed resistance to disease. An exaggerated immune response with increased release of proinflammatory cytokines is often seen in these patients. They also often have an increased incidence of septic morbidity (see later).

Extensive Use of Pharmaceuticals

Most transplant patients, if not all, are on a regimen of short-term or long-term drug treatment. It should be recognized that many more drugs than those labeled as immunosuppressive have significant immunodepressive effects. Among such drugs are most antibiotics. Furthermore, a large number of other pharmaceuticals that are commonly used inhibit salivation and gastrointestinal (GI) secretions, which are necessary for luminal release of important anti-inflammatory, anti-infectious, and growth-stimulatory factors normally provided with saliva and GI secretions.[13,14] Such unwanted effects are an increasing problem with increased use of modern and considerably more effective drugs.

Too Much Focus on Antibiotics

The process that leads to fulminant and severe sepsis is extremely complex and still in many aspects not fully understood. It has taken too long for us to realize that this process cannot be controlled with antibiotics and, as it appears now, also not with antagonists or inhibitors of individual proinflammatory cytokines. Even if prompt antibiotic therapy, compared with treatment instituted later, seems to slightly reduce the mortality in sepsis (10%-15%), it does not significantly reduce the unacceptably high burden of mortality in these groups of patients. After almost 30 years of efforts and more than 30 randomized clinical trials, it now seems clear that SDD is not an effective tool to prevent and combat sepsis. Although these treatments will decrease the incidence of chest infections, they will not influence outcome in critically ill patients.[15]

Late Institution of Preventive Measures

The therapeutic window for institution of effective anti-inflammatory and anti-infectious measures is narrower than earlier thought. From the onset of disease or trauma or the beginning of surgery, it is most likely not much more than 24 to 36 hours. If instituted later, it will have no or little effect on the inflammatory cascade that precedes sepsis, a cascade that, if "exuberant" (overwhelming and prolonged), is regarded as a key event in the subsequent development of multiorgan failure. The need for early and aggressive treatment is often neglected. One reason might be that early preventive measures are often instituted by several medical and surgical specialists, some of whom seem to have no knowledge or feeling for the urgency of immediate aggressive treatment. In addition, the power of early signs of sepsis varies considerably, and these are often occult and difficult to identify, which also explains why septic conditions are sometimes overlooked in the early stages.

Superinflammation and Infectious Complications

Individuals affected by MS, diabetes, or other chronic diseases will most often respond to stress with an exuberant acute or chronic superinflammation, which is manifested by an exaggerated and prolonged release of proinflammatory cytokines such as interleukin (IL) 6, acute-phase proteins such as C-reactive protein, and plasminogen activator inhibitor 1 (PAI-1).[16] Both IL-6 and PAI-1 are regarded as prognosticators of outcome in conditions such as those after operation or trauma, myocardial infarction, and pancreatitis but also in semichronic or chronic inflammatory conditions, such as arthritis, mental depression, or Alzheimer's disease. An overwhelming IL-6 response (eg, prolonged or extreme elevations of circulating IL-6) in patients with conditions like infection, burns, or trauma is significantly associated with adverse clinical events such as acute respiratory distress and multiple-organ failure (MOF). The effect of overwhelming acute-phase response on outcome has been well shown by a liver transplantation study; in all patients who during the later phase of operation already had signs of a 6-fold or larger increase in the cytokines tumor necrosis factor α (TNF-α)and IL-6, clinical sepsis did develop during subsequent postoperative days.

Among the changes observed in an overexuberant acute-phase response are augmented endothelial adhesion of polymorphonuclear (PMN) cells, increased production of intracellular adhesion molecule 1, priming of the PMNs for an oxidative burst, release of proinflammatory platelet-activating factor, and, associated with this, a delay in PMN apoptosis. Symptoms such as fatigue, somnolence, mental depression, anorexia, and daytime sleepiness are also often associated with the condition. In stress situations visceral adipocytes, compared with subcutaneous fat cells, do secrete much more free fatty acids and, most interestingly, per gram of tissue compared

with subcutaneous fat, greater than 3 times as much of the proinflammatory molecules such as IL-6 and PAI-1, which well explains the observation of the observed higher risk of disease in patients with visceral obesity. This is further elucidated by the fact that the amount of fat in the abdomen varies from a few milliliters to about 6 L in persons with gross obesity. The load of free fatty acids and these other powerful molecules on the liver can, thus, in stressful situations vary up to a thousand times.[17]

A Failing Innate Immune System

The disease-related changes in physical activity, sleep, and mood, age, gender, circadian rhythm, body temperature, drugs consumed, and food eaten are all known to influence important functions such as lymphocyte function, hemostasis, endothelial function, glucose and fat metabolism, capillary permeability, production of immunoglobulins (Ig), and general resistance to disease. The gut plays a leading role in most of these functions. It is not always realized that about 80% of the total Ig-producing cells of the body are localized in the lamina propria of the gut and that, under normal conditions each day, large amounts of Ig, especially IgA, are released to the gut lumen. Endemic chronic diseases, particularly type 2 diabetes mellitus, but also acute conditions such as severe sepsis and MOF are increasingly recognized as associated with, or caused by, a failing innate immune system. The innate or natural immune system, phylogenetically much older than adaptive or acquired immunity, constitutes a first-line defense system, identical to or closely associated with what is called *acute phase response* (APR). The relationship between chronic diseases and various acute complications is of great interest because it has been observed that the great majority of posttreatment and posttrauma morbidity does occur in patients with MS and associated conditions such as diabetes, obesity, and hypertension. Patients with chronic diseases are under the influence of a chronically elevated APR, which is better expressed as a "chronic"-phase response.[16]

The main function of the innate immune system and the APR is to instantly neutralize the stressors (tissue injury, malignancy, inflammation, infection, and so on) and restore homeostasis. The main tools in this process are so-called *acute-phase proteins*, such as C-reactive protein and fibrinogen, the production of which is stimulated through release of cytokines such as IL-1, IL-6, and TNF-α. These molecules are released from endothelium, macrophages, and monocytes but, to a large extent, also from adipocytes, especially within the abdomen. It is not fully understood why in some patients this process becomes overwhelming (exuberant) and leads to induction of a systemic inflammatory response syndrome and to distant organ injuries. Central to this process is the gut, which more or less suddenly turns into a "cytokine-generating" organ.[18] Deitch[18] recently showed that cytokines, endotoxins, pathogens originating from the intestines, and other unidentified gut-derived factors are delivered into the general circulation through the lymphatic system rather than the portal vein. The lack of the filtering function normally provided by the liver makes these compounds deleterious to distant organs and especially damaging to the lung.

Ancient Egyptian and, later, Greek medicine suggested that noxious agents, associated with feces, were the cause of disease. The concept of autointoxication was central to 18th and 19th century Western medicine. The immunologist and Nobel laureate Metchnikov suggested in the early 20th century that intestinal toxins induce disease and shorten life span; he believed these processes could be counteracted by regular consumption of lactic acid bacteria (LAB). In the early 20th century several surgeons, among them, Sir W. A. Lane, performed colectomy with the aim to prevent and cure intestinal autointoxication. History repeats itself, and evidence is currently accumulating that translocated gut-associated factors cause acute or chronic inflammation and produce "autodestruction" as in systemic inflammatory response syndrome and MOF. They also contribute to the development of thrombosis, adhesion formation, and sepsis and most likely play a role in the development of chronic diseases.

Instant APR Requires Instant Treatment

The inflammatory cascade is instant and the "therapeutic window" for preventive measures narrow, probably not much more than 24 hours. Measures to modulate the inflammatory cascade, for example, through early enteral nutrition, should be instituted, if possible, before surgery and be continued during and immediately after surgery. Because pretrauma treatment is not possible in trauma and medical emergencies, it should at least be instituted immediately on arrival to the hospital.[19,20]

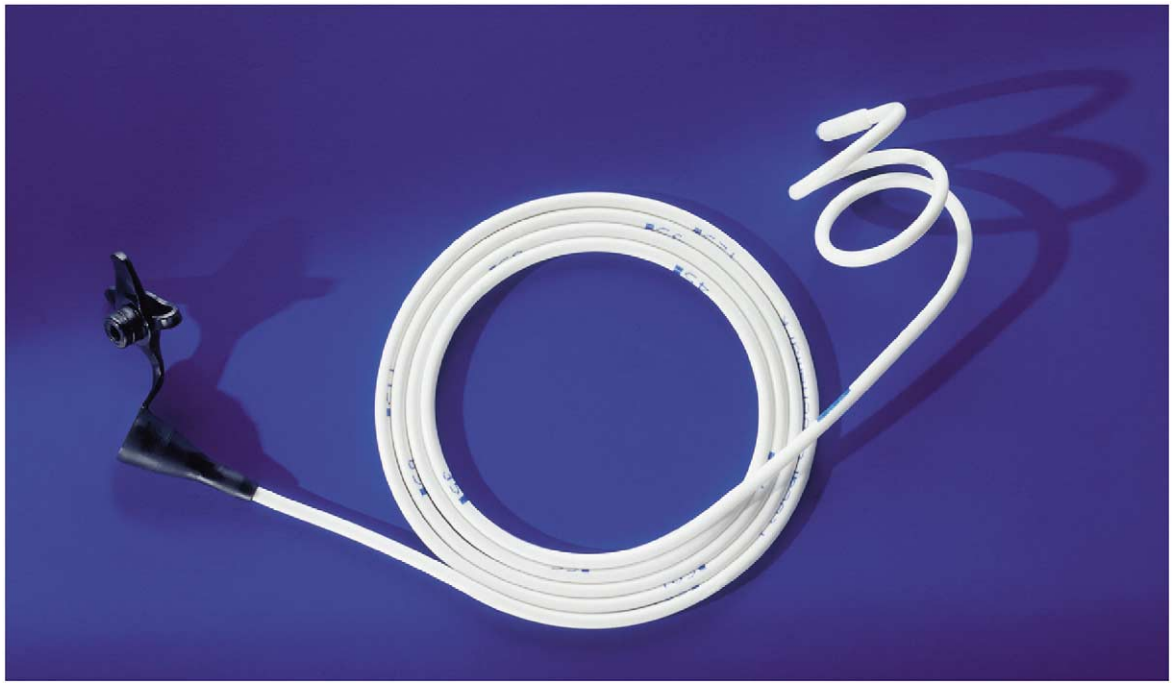

Figure 1. Autopositioning regurgitation-resistant feeding tube.

Recognition of the importance of aggressive perioperative nutrition was the reason why I invented the autopositioning and regurgitation-resistant feeding tube, developed only for the purpose of being introduced before surgery and making immediate enteral nutrition possible.[21] A coil was constructed as the head (tip) of the tube (Fig 1) instead of a balloon or a weight, which is more commonly used. It is constructed to maximally absorb gastric and duodenal motility and use it for its transportation down into the region of the ligament of Treitz. Its ability to absorb motility has been further increased with the adaptation of thin flexible fins on the outside and inside of the tube and by making the exterior surface of the coil "frosty" or "hairy," measures aimed to increase the adherence to the mucosa of the coil.[22] The coil is placed in the stomach with the aid of a guide wire and allowed to expand in the lower part of the stomach. Gastroduodenal motility is stimulated by a small meal (sandwich, pizza, spaghetti, or a vegetable juice, such as V8 [Campbell Soup Company, Camden, NJ]). The head of the tube (the coil) is in most cases within minutes, together with the bolus of the food, transported to its final and optimal position around the ligament of Treitz (Fig 2). The construction of the tube also makes it self-anchoring, which is important to prevent spontaneous regurgitation. Experience has shown that the rate of dislodgement compared with that of conventional tubes is much less. It is an advantage of this tube that no attempts are needed to verify the position of the head before the supply of nutrition is started. It has become increasingly common to start feeding immediately after the tube has been placed in the stomach, without waiting for the coil to move to its final position. The tube is available on the European market (Bengmark Flo-Care tube; Royal Numico-Nutricia Group, Zoetermeer, The Netherlands).

Although the tube was intended as a tool to be used only in patients with intact motility (eg, introduced before surgery and used in connection with elective surgery), it has increasingly been tried in patients with reduced motility and here in Europe introduced both with and without pharmacologic stimulation of motility. Gastric acidity stimulates release of nitric oxide from donor molecules, preferably nitrate or nitrite. This is why vegetable extracts such as rhubarb decoction and V8 vegetable juice, which are fluids that are known to stimulate release of nitric oxide and motility, are used to promote motility when necessary. Successful intubation has also been reported with use in critically ill patients treated in intensive care units. One such study reported successful intubation in 10 of 10 patients with

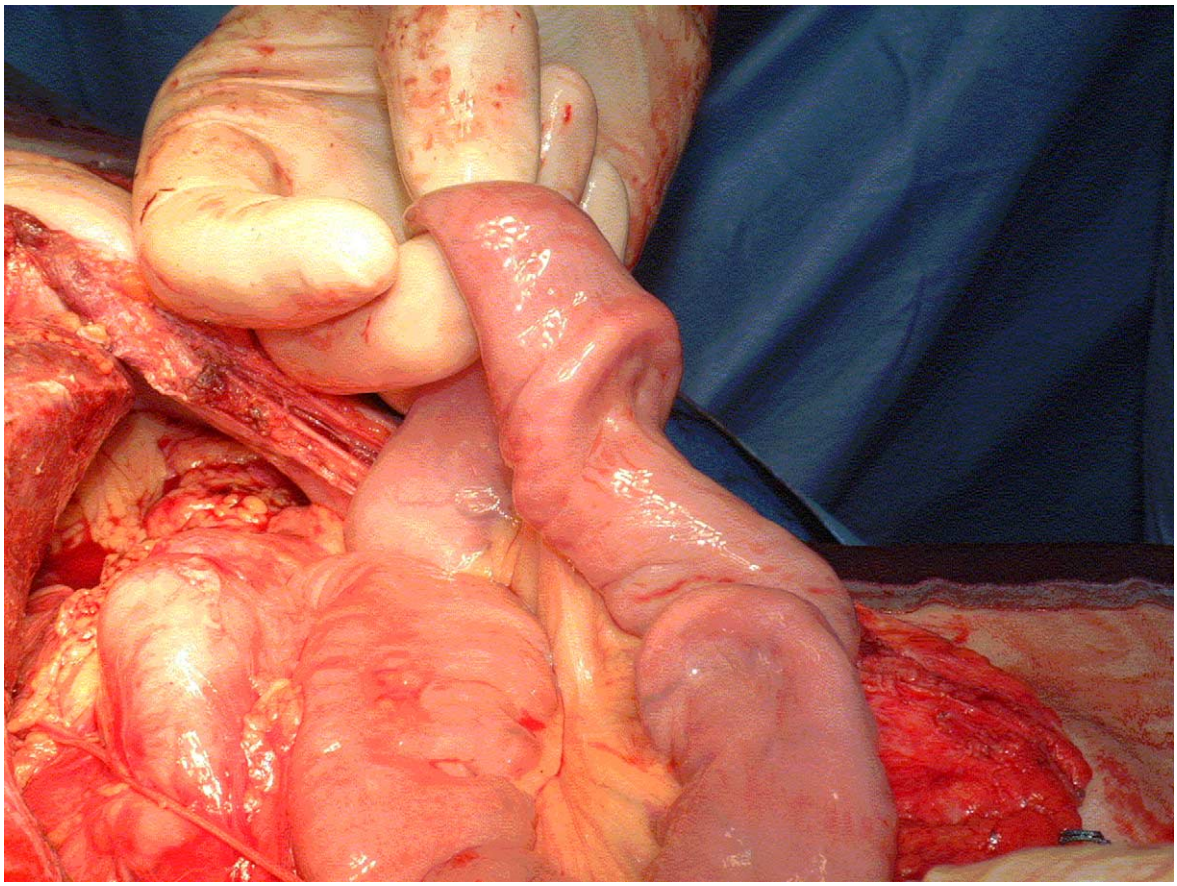

Figure 2. Feeding tube placed in ideal position with head of tube in small intestine just beyond the ligament of Treitz. (Photograph by Gerardo Mangiante, Verona, Italy.)

acute pancreatitis and in 6 of 6 patients with abdominal sepsis.[23] Although all the patients in this study showed significantly reduced GI motility, the head of the tube reached its optimal position within an average of 5.2 hours and always within 24 hours. A recent prospective study reported successful intubation in 49% of the intended intensive care unit patients, reducing the need for endoscopic placement to half,[24] and another recent randomized controlled study reported successful placement in patients with normal gastric emptying after 24 hours in 78% versus 14% with a straight standard tube ($P = .041$). In patients with impaired gastric emptying, the success rates after 24 hours were 57% versus 0% with a straight standard tube ($P = .07$).[25]

Questionable Practices Commonly Used

Several measures commonly used in perioperative and intensive care unit management and often in connection with transplantation need reconsideration. These treatments, often adapted long ago and at a time when the demand for scientific evidence was not as strict as it is today, cannot with modern criteria be regarded as evidence-based. Even if beneficial effects can sometimes be shown with the practice of some of these methods, they seem to have obvious negative consequences, which might exceed their positive value. Common to all methods discussed later is that they negatively influence immune function and resistance to infection.

Extensive Use of Antibiotics

It was shown 50 years ago that administration of antibiotics increases the susceptibility to acquire new infections.[26] Later it was proven that the administration of antibiotics suppresses macrophage functions, as documented by studies of chemiluminescence response, chemotactic motility, and bactericidal and cytostatic ability.[27,28] Appropriately timed short-term

(most often used as a "single-shot") prophylaxis is an effective tool to prevent wound infections that seemingly does not have the same negative consequences on the immune system as are seen with multiple-dose prophylaxis. Although these facts are well known, it has proven very difficult, even when the threat of microbial resistance is considered, to actually change clinical policy. Prophylactic antibiotics continue to be heavily overprescribed,[58] both in surgery and in intensive care units.

Inhibition of Salivation

An adult individual secretes as much as 10 L each day of GI secretions, as follows: saliva (2.5 L), gastric secretion (2.5 L), bile (0.5 L), pancreatic secretion (1.5 L), and small intestinal and colonic secretions (between 1.0 and 5.0 L). In children, secretion is related to body weight, and the production of GI secretions is even larger; 5-year-old children are known to secrete about 5 L a day. GI secretions are extremely rich in immunosupportive factors such as immunoglobulins, lactoferrin, lysozyme, and fibronectin but also in mucus, which is of utmost importance for mucosa protection. It must, therefore, always be remembered that these secretions constitute a main defense system against invading microorganisms and that their maintenance is important. Mucus is also an important matrix transport vehicle for ingested bacteria and an important substrate for nutrition of the commensal flora, especially when inadequate amounts of nutritional fibers are supplied. Saliva is one of the main sources in the body of important growth factors such as epidermal growth factor. Surgical or pharmaceutical removal of the salivary glands is accompanied by GI ulcerations, poor wound healing, and a poor regeneration of organs such as the liver. If possible, attempts should be made in postoperative patients and those in intensive care units to maintain and even to stimulate these secretions.[16,19,29] It is unfortunate that most drugs commonly used in intensive care units have very pronounced antisecretory effects.[29]

Inhibition of GI Secretions

Production of gastric nitric oxide is of utmost importance for maintenance of GI motility, mucosal and splanchnic blood flow, and prevention of gastric colonization with pathogens. Maintenance of low gastric pH is a prerequisite for gastric nitric oxide production, a function that is totally eliminated with histamine blockers and proton pump inhibitors. Furthermore, in the absence of acidity, the stomach will become a reservoir for pathogens, from which bacteria for chest infections are recruited and regurgitated into the lungs. Normal gastric acid production is also essential for absorption of several vitamins and antioxidants, including vitamin C and glutathione. Prevention of peptic ulcers by use of histamine blockers or proton pump inhibitors or similar drugs might be a priority issue when total parenteral nutrition is used but with aggressive enteral nutrition is no longer needed. Routine use of histamine blockers or proton pump inhibitors in partially or totally enterally fed postoperative and intensive care unit patients can no longer be regarded as evidence-based medicine.[30]

Prophylactic Nasogastric Decompression

About 70 years ago, Mayo introduced postoperative nasogastric decompression with the idea that it might prevent nausea, vomiting, and abdominal distension but also decrease postoperative ileus, prevent wound complications, and protect enteric anastomoses. This treatment modality was introduced without any scientific background, and the wisdom of routine gastric decompression was questioned early on and has continued to be questioned ever since. Today, there is accumulating evidence that this treatment is counterproductive and might both delay the return of adequate bowel function and contribute to an increased rate of septic complications. Several recent studies confirm that omission of routine nasogastric decompression is not associated with any obvious increase in morbidity or mortality. Even if a slight gastric distention occurs, no active measures should be needed because the distention will resolve spontaneously with no negative consequences and insertion of a tube is not usually required. As a matter of fact, gastric distention should not be regarded as a contraindication to the continuation of enteral feeding and high residual volumes should not automatically lead to cessation of tube feeding; if tube feeding is continued, the residual volume will most often soon decrease and disappear.[31] A meta-analysis based on 26 trials (a total of 3964 patients) concluded that routine nasogastric decompression is not supported in the literature by scientific evidence.[32] Instead, fever, atelectasis, and pneumonia are significantly less common and days to first oral intake are significantly fewer in patients managed without nasogastric tubes.[30]

Postoperative Drainage of Body Cavities

Routine use of postoperative drainage of body cavities is also not based on scientific evidence. In most cases drainage tubes serve more effectively as an entrance for microbes than as an outlet of accumulated fluids. Furthermore, most body cavities, especially the abdomen, have an extraordinarily good capacity to reabsorb leaked fluids, including blood, at least if not infected or mixed with body fluids such as urine and bile. Most studies suggest that there is no need for abdominal drainage in gastric surgery. Some controlled studies suggest no advantages of a drainage policy in liver and pancreatic surgery, and several randomized trials have documented clear benefits of a no-drainage policy in colonic surgery. Use of drains is often shown to increase the rate of complications, especially adhesions and mechanical ileus, in appendicitis-related operations. As suggested in a recent excellent review, high-quality clinical studies are necessary for solid and evidence-based recommendations re use of drainages, at least in visceral surgery.[33]

Preoperative Bowel Preparation

Availability of flora is an absolute requirement for release from consumed plant fibers and utilization in the body of various nutrients such as amino acids, other fatty acids, polyamines, vitamins and antioxidants, and coagulation and growth factors. Intestinal flora and gut immune cells are also powerful sources of proinflammatory and anti-inflammatory cytokines and are deeply involved in prevention of infection, anastomotic leakage, and formation of extensive peritoneal adhesions. Healing of intestinal anastomoses depends on luminal production of short-chain fatty acids, especially butyrate, which is released by microbial fermentation of plant fibers in the intestine. These important processes are negatively influenced by lavage or bowel preparation, as well as by administration of antibiotics. Bowel preparation and fiber-free enteral feeding also have detrimental effects on the release of important intestinal healing factors such as transforming growth factor-β1 and pro-collagen type I.

It was recently claimed that no obvious improvement in outcome after surgery for bowel cancer has occurred in recent decades. In addition, the unacceptably high postoperative infection rate also seems to have remained unchanged during several decades. Even if bowel preparation does not enhance microbial translocation, as was concluded in a recent study, several other reasons suggest that routine bowel preparation before surgery should be omitted and several studies in recent years have produced active support of the omission of bowel preparation before surgery. A recently published meta-analysis could not document any reduction in anastomotic leaks or other complications with the routine practice of preoperative bowel preparation. Instead, increasing experimental and clinical evidence suggests that reduced morbidity and considerable cost savings can be obtained by omission of bowel preparation.[34]

Transfusion With Stored Blood

Immunosuppression is increasingly recognized as a serious consequence of transfusion of allogeneic (homologous) blood in humans, including both increased recurrence rates after potentially curative cancer surgery and increased frequency of postoperative bacterial infections. We observed some 35 years ago that intraportal and intravenous infusion of hemolyzed blood to experimental animals resulted in rather immediate and extensive disseminated intravascular coagulation and fibrinolysis.[35-37]

Similar changes were obtained after induced organ hypoxia, such as intestinal or liver ischemia,[38] and after infusion of alcohol.[39] Several recent studies suggest that blood transfusion is a major risk factor for postinjury MOF.[40-42] Traumatic injuries frequently occur in alcohol-intoxicated individuals, who often also have severe shock and poor organ perfusion, and, in addition, are the objects of extensive blood transfusions. Recent studies document a strong association between the number of units transfused during the first 6 hours after trauma, age of the stored blood transfused, and outcome.[43] It is consequently recommended that, if possible, fresh blood should also be used in initial resuscitation of trauma patients. Removal of old blood cells and restoration of tissues in organs damaged by ischemia, as well as alcohol intoxication, constitute an enormous burden on the reticuloendothelial system, which results in immunoparalysis and increased sensitivity to infections. A meta-analysis based on more than 13,000 patients provided overwhelming evidence that autologous blood transfusion is associated with a significantly higher risk of postoperative bacterial infection.[44]

The phagocytic functions of neutrophils, monocytes, and macrophages are essential for protection against both chronic diseases and severe acute infections, a function considerably reduced with alcoholism, diabetes, and other chronic diseases. These

functions are all significantly impaired, especially in patients with acute tissue injuries such as burns or organ ischemia.[45] It is suggested that the increased amounts of lysophosphatidylcholine and platelet-activating factor in the stored blood induce neutrophil (PMN) priming for reactive oxygen metabolite production and induce endothelial cell damage, capillary leakage, and degranulation, which often culminate with end-organ injury and MOF.[46]

Overload With Nutrients Or Hyperalimentation

It was not long ago that hyperalimentation (eg, overload with nutrients) was regarded as a key to success in the care of the critically ill. Today, overfeeding with macronutrients is known to be regarded as much more dangerous than underfeeding, especially when applied during the first 1 or 2 weeks after operation. A series of negative metabolic consequences have been shown to be a consequence of overfeeding.[47] In intensive care unit patients, a significant association between degree of impairment in glucose and lipid metabolism and severity of illness and outcome has been documented.[48] The increased amounts of free fatty acids especially have a documented strong depressive effect on innate immune functions. The endothelial cells, which are responsible for transport to the underlying cells of nutrients such as free fatty acids and glucose, play an important role, and endothelial function is severely impaired by the inflammatory response, various toxins, and microbes.[49,50] One consequence of elevated serum free fatty acid levels is that they inhibit T-lymphocyte signaling.[51] However, the neutrophil function is reported to be considerably improved by infusion of insulin, as has been especially shown in diabetic patients after cardiac surgery.[52]

We observed some 35 years ago that high serum levels of fat and the presence of liver steatosis constitute poor risks in liver resection.[53,54] Similar observations were more recently shown in connection with liver transplantation.[55] The negative effect of dyslipidemia and steatosis is most likely independent of whether it is induced by lifestyle and constituting a part of MS, induced by the overloading of calories, such as seen in total parenteral nutrition, or caused by an exaggerated APR.

Often-Neglected Measures

Maximizing the function of the immune system, enforcing the innate immune functions, and improving resistance to diseases through enteral nutrition with specific nutrients is currently regarded to be of utmost importance. We are increasingly becoming aware that proper supply of a variety of food components is important for a satisfactory outcome in critically ill patients and those who have undergone operation and also as a measure to prevent chronic illnesses. Some important components, especially in fresh food but also in live microorganisms, have the ability to preserve and augment cellular immunity and modify production of inflammatory mediators.[56]

Aggressive Perioperative Enteral Nutrition

As already stated, all attempts to control the APR must be instituted early because the reaction to trauma is instant. It is well supported by scientific studies that immediate postoperative feeding is safe, prevents an increased gut mucosal permeability, contributes to a positive nitrogen balance, reduces the incidence of septic complications, reduces postoperative ileus, and accelerates restitution of pulmonary physical performance.[57-59] Delaying the institution of enteral nutrition for a few hours is shown to result in increased intestinal permeability; increased microbial translocation; and, compared with immediate enteral nutrition, a significantly higher incidence of MOF.[60] An intensive and uninterrupted supply through feeding tubes of enteral nutrition, especially when it contains plant fibers, during the night before surgery, during the operation, and immediately thereafter will most likely significantly improve immune functions and increase the resistance to complications.[19,30,61,62]

Tight Control of Blood Glucose Levels

Hyperglycemia is known to predispose to infectious complications[63] and serve as an independent marker of in-hospital mortality,[64] as well as to predict myocardial infarction in patients on a regimen of hypertensive treatment.[65] Even though the value of strict glucose control has been known for some time to reduce the incidence of wound infection in surgery,[66] it was not until recently that such control had been adapted in modern intensive care units and postoperative care. The state of the art was until rather recently to tolerate, in fed critically ill patients, blood glucose levels up to 12 mmol/L (220 mg/dL). However, maintaining the blood glucose level below 6.1 mmol/L led to significant improvements such as a decrease in bloodstream infections (by 46%), in acute renal failure with a need of hemofiltration (by 41%), in critical illness polyneuropathy (by 44%), in

requirement for red blood cell transfusions (by 50%), and in mortality (by 34%).[67,68] Small elevations of blood glucose (to 8-10 mmol/L) are know to impair gut motility and function,[69] and such impairment contributes to induction and prolongation of ileus. Thus a stricter glucose control after operation and in intensive care units might also promote gut motility and GI function.

Supply of Antioxidants

The tissue and blood concentrations of pro-oxidants are almost invariably high and the levels of various antioxidants and micronutrients low or extremely low in critically ill patients. As an example, total vitamin C and ascorbic acid are reported to be <25% of normal values in these patients.[70] A study performed mainly in trauma patients reported a 19% reduction in pulmonary morbidity and a 57% lower incidence of MOF in a group of patients receiving supplementation with α-tocopherol and ascorbate.[71] The benefit of antioxidant supplementation in surgical and intensive care unit patients is also supported by several other studies.[72] Glutathione is an important antioxidant, both synthesized by the body and supplied by foods, mainly fruits and vegetables. This antioxidant is significantly decreased both postoperatively and in critically ill patients, a decrease that is associated with impaired lymphocyte and neutrophil function. Glutamine is an important source of fuel for the enterocytes of the small bowel and other rapidly dividing cells such as leukocytes and macrophages and an important substrate for production of glutathione.[73] Supplying glutamine has been shown in various experimental studies to reduce cytokine release, organ damage, and mortality[74] and also to revert the depletion of glutathione and lymphocytes in Peyer's patches.[75] Several controlled clinical studies performed in recent years show significant benefits from supplementation of glutamine, including reductions in morbidity, mortality, and length of stay in critically ill patients.[76]

Supply of Plant Fibers

Plant fibers are favored substrates for microbial fermentation in the lower digestive tract. They also have their own strong bioactivities. Unfortunately, too few studies on the effects of supplying various plant fibers to surgical and intensive care unit patients are found in the medical literature. A controlled study worth mentioning reported a significant reduction in postoperative morbidity after the administration of glucan (beta 1,3-polyglucose) with reduction in nosocomial infections from 65% to 14% and mortality from 30% to 5%.[77] There is certainly a need to explore the effects of various plant fibers when supplied to postsurgical and intensive care unit patients.

Supplementing Flora

A significant reduction of the commensal flora occurs early in the disease process and is caused both by the disease and by the pharmaceutical treatment. It has been observed in experimental pancreatitis that after the induction of disease the anaerobic bacteria and particularly the LAB are significantly reduced within 6 to 12 hours both in the distal small bowel and in the colon. The reduction in preventive flora is almost instantly accompanied by significant increases in the numbers of potentially pathogenic microorganisms (PPMs) such as *Escherichia coli* and in dramatic increases in the permeability (lumen to blood) of the mucosal barrier, as well as in the endothelial (blood to tissue) permeability,[78,79] changes associated with increased microbial translocation and microbial growth in mesenteric lymph nodes and, in the case of acute pancreatitis, in the pancreatic tissue.[80] One can take for granted that every patient who undergoes a major operation is the object of significant trauma or every patient treated with modern antibiotics has a considerable reduction in the beneficial flora often combined with an overgrowth of PPMs.

Synbiotics: A Promising New Tool

There is genetically a very large difference among various bacteria called LAB; the difference between one LAB and another can be greater than between a fish and a human. Most of the LAB used by food industry have no or limited ability to ferment strong bioactive fibers such as inulin or phlein; have no ability to adhere to human mucus; have low antioxidant capacity; and, most important, do not survive the acidity of stomach and bile acid content. Strong bioactivity cannot often be expected from LAB such as yogurt bacteria, chosen mainly for their palatability. Most of the LAB currently used in sick patients have originally been identified on plants.

My personal experience during the last 15 years stems from studies using 2 different symbiotics—combinations of prebiotics and probiotics, as follows:

1. A 1 LAB/1-fiber composition, produced by fermentation of oatmeal with *Lactobacillus plantarum* strain 299.[81] The formula was produced for our studies by Probi AB, Lund, Sweden.

2. A 4 LAB/4 fiber composition, called Synbiotic 2000, consisting of a mixture of 10^{10} (and more recently a Synbiotic FORTE with 10^{11}) of each of 4 LAB—*Pediacoccus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subsp paracasei 19, and *L plantarum* 2362)—and 2.5 g of each of the 4 fermentable fibers (prebiotics)—beta glucan, inulin, pectin, and resistant starch.[82,83] The formula is produced for our studies by Medipharm AB, Kågeröd, Sweden, and Des Moines, Iowa.

Clinical Experience With Synbiotics in Acute Conditions

Acute Pancreatitis

Patients with severe acute pancreatitis were randomized to receive daily during the first 7 days through a nasojejunal tube either a freeze-dried preparation containing live *Lb plantarum* 299 in a dose of 10^9 together with a substrate of 10 g of oat fiber or the same preparation after heat inactivation.[84] The study was designed to be interrupted when on repeat statistical analysis statistically significant differences in favor of 1 of the 2 groups were obtained, which occurred when a total of 45 patients had entered the study. At that time, 22 patients had received treatment with live and 23 with the heat-killed *Lb plantarum* 299. Infected pancreatic necrosis and abscesses were seen in 1 of 22 (4.5%) in the live LAB group versus 7 of 23 (30%) in the heat-inactivated group ($P = .023$). The only patient in the live LAB group with development of an infection had signs of urinary infection on the 15th day (eg, at a time when he had not received treatment during the last 8 days). The length of stay was considerably shorter in the live LAB group (13.7 days vs 21.4 days), but the limited size of the material did not allow statistical significance to be reached.

Abdominal Surgery

The same 1 LAB/1 fiber composition was used in a study in extensive abdominal surgical operations. The patients consisted mainly of those undergoing liver, pancreatic, and gastric resections, equally distributed among the 3 groups. Three groups were compared, as follows: (1) live LAB and oat fiber, (2) heat-inactivated LAB and oat fiber, and (3) standard enteral nutrition.[85] Each group consisted of 30 patients. The 30-day sepsis rate was 10% (3/30 patients) in the 2 groups receiving either live or heat-inactivated LAB, compared with 30% (9/30 patients) in the group receiving standard enteral nutrition ($P = .01$). The biggest differences were observed in the numbers of cases of pneumonia, as follows: enteral nutrition only, 6 patients; live LAB and fiber, 2 patients; and heat-killed LAB and fiber, 1 patient. The beneficial effects of synbiotic treatment seemed to be most pronounced in gastric and pancreatic resections with a sepsis rate of 7% with live LAB, 17% with heat-inactivated LAB, and 50% with standard enteral nutrition. The live LAB-treated patients received significantly less antibiotics ($P = .04$); the mean length of antibiotic treatment was 4 ± 3.7 days with live LAB, 7 ± 5.2 days with heat-killed LAB, and 8 ± 6.5 days with only standard enteral nutrition. The incidence of noninfectious complications was as follows: enteral nutrition, 30% (9/30); heat-inactivated LAB, 17% (5/30); and live LAB, 13% (4/30). No differences were observed in the length of hospital stay. No significant changes were observed in hemoglobin; leukocytes; C-reactive protein; blood urea nitrogen; bilirubin; albumin; total lymphocyte count in CD45 RA, CD45 RO, CD4, CD8, or natural killer cells; or CD4/CD8 ratio.

Liver Transplantation

A prospective randomized study with the same 1 LAB/1 fiber preparation was performed in 95 liver transplant patients,[86] and the following 3 groups were studied: (1) SDD 4 times daily for 6 weeks (n = 32), (2) *Lb plantarum* 299 (LLP) in a dose of 10^9 plus 10 g of oat and inulin fibers (n = 31) for 12 postoperative days, and (3) identical to group 2 but with heat-killed *Lb plantarum* 299 (HLP) (n = 32). Enteral nutrition was supplied to all patients from the second postoperative day. There were no deaths. The numbers of postoperative infections were SDD, 23; HLP, 17; and LLP, 4. Signs of infections occurred as follows: SDD, 48% (15/32); HLP, 34% (11/32); and LLP, 13% (4/31) ($P = .017$, respectively). The most dominating infections were cholangitis, occurring in 10 SDD, 8 HLP, and 2 LLP patients, respectively, and pneumonia, occurring in 6 SDD, 4 HLP, and 1 LLP patient, respectively. The most often isolated microbes were *Enterococci*, found in 8 SDD, 8 HLP, and 1 LLP patient, and *Staphylococci*, found in 6 SDD, 3 HLP, and 1 LLP patient, respectively. No *E coli* or *Klebsiella* infections were seen in the LLP group. The numbers of patients requiring hemodialysis were 8 SDD, 4 HLP, and 2 LLP, and the numbers of reoperations were 6 SDD, 2 HLP, and 4 LLP, respectively. The CD4/CD8 ratio was higher in the LLP group

compared with the other 2 groups ($P = .06$), and the intensive care unit stay, hospital stay, and length of time on a regimen of antibiotic therapy were also shorter, none of them reaching statistical significance.

The same investigators did continue their efforts and try to further reduce the morbidity in connection with liver transplantation[87]; this time with the combination of 4 LAB and 4 fibers.[82,83] In this double-blind randomized study, 33 patients were supplied synbiotics and another 33 patients received only the 4 fibers in the synbiotic composition. The treatment started on the day before surgery and continued until the 14th day after surgery. Only 1 patient in the synbiotic-treated group (3%) showed signs of infection (urinary infection) during the first month compared with 17 of 33 (51%) in the patients supplied the 4 fibers only. The use of antibiotics was also significantly shorter in the synbiotic-treated group.

Clinical Experience With Synbiotics in Chronic Conditions

There are good reasons to expect beneficial effects of synbiotic treatment in chronic conditions such as cancer, kidney disease, lung disease, and so on, but systematic studies so far have been limited to chronic liver disease.

Chronic Liver Disease: Effect on Inflammation

The grade of nonalcoholic steatohepatitis correlates well with the extent of obesity, especially visceral obesity. Fat cells, especially visceral adipocytes, are known to have an increased expression of cytokines, especially TNF-α. The amount of fat in the abdomen is known to vary from a few milliliters to 6 L, which well explains the increased exposure of TNF-α in adipose individuals, which together with overexpression of γ-interferon and underexpression of IL-10 sensitizes the liver both to endotoxins and to the toxic effects of TNF-α. Activation of macrophages by gut-derived endotoxin has been assumed to be responsible for the raised levels of TNF-α and is most likely a key factor behind the progressive liver damage seen in patients with liver cirrhosis. Probiotics and prebiotics (synbiotics) have the ability to reduce the production and absorption of endotoxin in the intestine and also to down-regulate the production of proinflammatory cytokines, including TNF-α. A long-term supply of synbiotics can be expected to reduce the inflammation of the liver and lessen the steatosis. Expression of Toll-like receptors (TLR 4 and TLR2) is critically involved in TNF-α production in response to endotoxin and gram-positive microbial stimuli. 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 of 46% (range, 8%-67%) in comparison with presupplementation levels in 8 of 11 (72.7%) patients with cirrhosis who received the synbiotic composition.[88] The administration of synbiotics to patients with advanced chronic liver disease is well tolerated, and no adverse events or changes in general clinical state have been observed. If administration of synbiotics is capable of down-regulating the expression of Toll-like receptors and reducing the production of TNF-α, synbiotics could well constitute a cheap and powerful tool with no side effects for long-term treatment of patients with liver disease.

Chronic Liver Disease: Effect on Gut Colonization, Liver Function, and Encephalopathy

Among a group of 97 patients with liver cirrhosis, 58 patients were found to have signs of so-called *minimal encephalopathy*. They were randomized into 3 treatment groups and studied when synbiotics were administered during a 1-month period, as follows: Group 1 received the 4 LAB/4 fiber synbiotic composition (n = 20), group 2 received only the fibers in the composition (n = 20), and group 3 received a placebo (nonfermentable, nonabsorbable fiber) (n = 15).[89] A 1-month supply was shown to lead to a significant increase in the intestinal LAB flora in the LAB-supplied group but not the other 2 groups. The intestinal pH was significantly reduced in both the treatment groups. Significant decreases in *E coli*, *Staphylococcus*, and *Fusobacterium*, as well as in ammonia, were seen, but such decreases were not observed in *Pseudomonas* and *Enterococcus* and the levels of endotoxin fell significantly. The levels of ALT decreased significantly from 252 ± 182 to 84 ± 65 ($P < .01$) in the synbiotic-treated group and to 110 ± 86 ($P < .05$) in the fiber-only group but not in the placebo group. The improvements in liver function were accompanied by significant improvements in psychometric tests and in the degree of encephalopathy.

Chronic Liver Disease: Effect on Liver Blood Flow and Indocyanine Green Clearance

Reducing intestinal levels of endotoxin-containing gram-negative bacteria is reported to improve systemic hemodynamic disturbance in liver cirrhosis.

Supplementation with the 4 LAB/4 fiber synbiotic composition was associated with a significant reduction in indocyanine green clearance by a median of 17.5% (range, 1.4%-65%) of baseline values in 14 of 15 (93%) patients with cirrhosis and was increased in 1 patient by 4.1%.[90] The observed improvement was most likely 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 drawn from one LAB to another because they are all different in function and genetically unrelated. Producers of probiotic products often claim health benefits from their products; in most cases these claims are unsubstantiated and not true. 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 the colonic mucosa or even temporarily colonize the stomach or intestine. It has recently become increasingly common that milk-fermenting LAB, such as yogurt bacteria and *Lb acidophilus*, are used in clinical medicine. Yogurt bacteria have, like most other LAB, a low survival in an environment with acidity and bile acids such as the upper GI tract and generally have only limited or no biologic influence on the immune system. The great differences in the ability of some LAB to survive and their ability to influence cytokine production after passage through the stomach and small intestine were well shown in a study comparing the following 4 different LAB species: *L plantarum*, *L paracasei*, *Lactobacillus rhamnosus*, and *Bifidobacter animalis*.[91] After the administration of 10^8 cells/mL of each LAB and after passage through the stomach and small intestine, there remained only between 10^7 (*L plantarum*) and 10^2 (*L rhamnosus*) bacterial cells. After passage through the small intestine, most of the strains tested showed a significantly reduced or weak (especially *L rhamnosus*) ability to influence, for example, cytokine production. If LAB such as yogurt bacteria had been studied, an even smaller survival would most likely have been expected. The absence of clinical efficacy of yogurt bacteria when used in severely ill patients was recently shown. A standard commercial product containing *Lactobacillus acidophilus LA5*, *Bifidobacterium lactis BP12*, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus* was mixed with 7.5 g oligofructose and supplied in a controlled study to critically ill patients.[92] Although significant reductions in the number of potentially pathogenic organisms could be observed in the contents of the stomach of the treated patients, no influence on intestinal permeability could be demonstrated and no clinical benefits could be shown when this particular formula was supplied to a mixed group of critically ill patients.[93]

The LAB used in the synbiotic studies mentioned earlier were all selected after extensive studies of more than 350 human fecal bacteria and more than 180 bacteria harvested from fresh-growing rye. They were chosen because of their unique and superior abilities to survive in the low pH of the stomach and in the high bile acid content of the small intestine, their unique ability to attach to colonic mucosa and to temporary colonize the large intestine, their high capacity to ferment various types of plant fibers including rather fermentation-resistant fibers such as inulin, a balanced production of both proinflammatory and anti-inflammatory molecules such as cytokines, a strong ability to produce several bioactive molecules, especially heat shock proteins, and the production of significant amounts of antioxidants. Similarly, the added fibers were chosen because of their documented bioactivities. These simultaneous fibers significantly improved the previously described functions.

Future Aspects

Synbiotic treatment as a new and promising treatment is still in its infancy. There is an urgent need for synbiotic studies to be given priority. Patients who are to undergo transplantation are affected by a significantly elevated risk of sometimes life-threatening infections long before the actual treatment. Furthermore, they continue to be at risk for bacterial, viral, and fungal infections for many years after the replacement of organ(s). One of the real benefits with synbiotics is that they can be used for years with no negative effects because their supplementation does not cause any side effects nor do they cause resistance. The promising effects from the studies in chronic liver disease suggest that patients on a waiting list for operation could well benefit from a synbiotic umbrella. Similarly, there are reasons to suggest that a synbiotic umbrella during the first few years after transplantation could offer good protection against various infectious complications. Another important group to study is patients with chronic kidney disease, especially those on hemodialysis or peritoneal dialysis. These patients, espe-

cially those on continuous ambulatory peritoneal dialysis, have a high risk of infections. In addition, the incidence of chronic diseases such as coronary heart disease and diabetes is high in this patient group. There is good reason to suggest that long-term supplementation with synbiotics could help control infections and eventually also reduce the threat of development of other chronic diseases.

Thus far, most attempts to administer synbiotic treatment have been through the oral route. Preliminary studies suggest excellent results when tried topically on skin and wounds to prevent and cure infections. When applied around tracheostomies and the entrance sites of tubes and lines, the eventual biofilm is dissolved and removed and protection is offered against infections. Excellent results have also been obtained in preliminary studies with topical application in burns. Although a daily supply of bacteria and fiber is important, a whole series of other measures must be considered for optimal care of critically ill patients. Re-evaluation of practices that have been used for decades is also urgent. There is much to gain from bringing the management of critically ill patients in line with modern bioecologic and evidence-based principles.

Acknowledgment

I thank Dr Nada Rayes and her team at Charité University Hospital in Berlin, Germany.

References

1. Sparrelid E, Hägglund H, Remberger M, et al: Bacteraemia during the aplastic phase after allogeneic bone marrow transplantation is associated with early death from invasive fungal infection. Bone Marrow Transplant 1998, 22:795
2. Faber-Langendoen K, Caplan AL, McGlave PB: Survival of adult bone marrow transplant patients receiving mechanical ventilation: A case for restricted use. Bone Marrow Transplant 1993, 12:501
3. Kress JP, Christenson J, Pohlman AS, et al: Outcomes of critically ill patients in a university hospital setting. Am J Respir Crit Care Med 1999, 160:1957
4. Huaringa AR, Shaw PJ, Rowell F, et al: Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med 2000, 28:1014
5. Alexander BD, Tapson VF: Infectious complications of lung transplantation. Transplant Infect Dis 2001, 3:128
6. Montoya JG, Giraldo LF, Efron B, et al: Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 2001, 33:629
7. Smart FW, Naftel DC, Costanzo MR, et al: Risk factors for early, cumulative, and fatal infections after heart transplantation: A multi-institutional study. J Heart Lung Transplant 1996, 15:329
8. Myers TJ, Khan T, Frazier OH: Infectious complications associated with ventricular assist systems. ASAIO J 2000, 46:28
9. Kato T, Ruiz P, Thompson JF, et al: Intestinal and multivisceral transplantation. World J Surg 2002, 26:226
10. Cainelli F, Vento S: Infections and solid organ transplant rejection: A cause-and-effect relationship? Lancet Infect Dis 2002, 2:539
11. Simmons RL, Weil R, Tallent MB, et al: Do mild infections trigger the rejection of renal allografts. Transplant Proc 1970, 2:419
12. Lopez C, Simmons RL, Mauer SM, et al: Association of renal allograft rejection with virus infections. Ann J Med 1974, 56:280
13. Mandel ID: The function of saliva. J Dent Res 1987, 66:623
14. Sreebny LM, Banoczy J, Baum BJ, et al: Saliva: Its role in health and disease. Int Dent J 1992, 42:291
15. van Nieuwenhoven CA, Buskens E, van Tiel FH, et al: Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. JAMA 2001, 286:335
16. Bengmark S: Nutritional modulation of acute and "chronic" phase response. Nutrition 2001, 17:489
17. Bengmark S, Andersson R, Mangiante G: Uninterrupted perioperative enteral nutrition. Clin Nutr 2001, 20:11
18. Deitch E: Role of the gut lymphatic system in multiple organ failure. Curr Opin Crit Care 2001, 7:92
19. Bengmark S: Aggressive peri- and intraoperative enteral nutrition—Strategy for the future, in Shikora SA, Martindale RG, Schwaitzberg SD (eds): Nutritional Considerations in the Intensive Care Unit—Science, Rationale and Practice. Dubuque, IA, Kendall/Hunt Publ Co, 2002, p 365
20. Bengmark S: Enteral nutrition in HPB surgery—Past and future. J Hepatobiliary Pancreat Surg 2002, 9:448
21. Bengmark S: Swedish patent 8700582, PTC patent 0278937, US patent 4887996
22. Bengmark S: Swedish patent 507786, Int patent application SE 98/00145
23. Mangiante G, Colucci G, Marinello P, et al: Bengmark's selfpropelling naso-jejunal tube: A new useful device for intensive enteral nutrition (abstr). Intensive Care Med 1998, 24:330
24. Berger MM, Bollmann MD, Revelly JP: Progression rate of selfpropelling feeding tubes in critically ill patients. Intensive Care Med 2002, 28:1768
25. Lai CWY, Barlow R, Barnes M, et al: Bedside placement of nasojejunal tubes: A randomized-controlled trial of spiral- vs straight-ended tubes. Clin Nutr 2003, 22:267
26. Freter R: The fatal enteric cholera infection in guinea pig achieved by inhibition of normal enteric flora. J Infect Dis 1995, 97:57
27. Roszkowski K, Ko KL, Beuth J, et al: Intestinal microflora of BALB/c-mice and function of local immune cells. Z Bakteriol Hyg 1988, 270:270
28. Pulverer G, Ko HL, Roszkowski W, et al: Digestive tract microflora liberates low molecular weight peptides with immunotriggering activity. Zentralbl Bakteriol 1990, 272:318
29. Bengmark S: Gut and the immune system: enteral nutrition and immunonutrients, in Baue AE, Faist E (eds): SIRS, MODS and MOF—Systemic Inflammatory Response Syndrome, Multiple Organ Dysfunction Syndrome, Multiple Or-

gan Failure—Pathophysiology, Prevention and Therapy. New York, NY, Fry Springer, 2000, p 420
30. Savassi-Rocha PR, Conceicao SA, Ferreira JT, et al: Evaluation of the routine use of the nasogastric tube in digestive operation by a prospective controlled study. Surg Gynecol Obstet 1992, 174:317
31. Cook DJ, Fuller HD, Guyatt GH, et al: Gastrointestinal bleeding in the critically ill: Stress ulcer prophylaxis is not for everyone. N Engl J Med 1994, 330:377
32. Cheatham ML, Chapman WC, Key SP, et al: A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg 1995, 221:469
33. Dominguez Fernandez E, Post S: Abdominal drainages (German). Chirurg 2003, 74:91
34. Bengmark S: Bio-ecological control of perioperative and ITU morbidity. Langenbecks Arch Surg 2003, Nov 7 (Epub ahead of print)
35. Bengmark S, Hafstrom L, Korsan-Bengtsen K: A trial to produce intravascular coagulation by infusion of connective-tissue homogenate and erythrocyte haemolysate–A comparative study. Br J Surg 1969, 56:619
36. Bengmark S, Hafström L, Korsan-Bengtsen K: A trial to produce disseminated intravascular coagulation with intravenous infusion of homologous haemolysate and serum in cats. Acta Chir Scand 1972, 138:453
37. Bengmark S, Hafström L, Korsan-Bengtsen K: Effects of intraportal infusion of autologous hemolysate on blood coagulation factors and fibrinolysis in the cat. Am J Surg 1972, 124:647
38. Hafström L, Korsan-Bengtsen K, Bengmark S: Changes in blood clotting and fibrinolysis after liver ischemia in pigs. Am J Surg 1974, 127:300
39. Zoucas E, Bergqvist D, Göransson G, et al: Effect of acute ethanol intoxication on primary haemostasis, coagulation factors and fibrinolytic activity. Eur Surg Res 1982, 14:33
40. Sauaia A, Moore FA, Moore EE, et al: Early predictors of postinjury multiple organ failure. Arch Surg 1994, 129:39
41. Moore FA, Moore EE, Sauaia A: Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 1997, 132:620
42. Sauaia A, Moore FA, Moore EE, et al: Multiple organ failure can be predicted as early as 12 hours after injury. J Trauma 1998, 45:291
43. Zallen G, Offner PJ, Moore EE, et al: Age of transfused blood is an independent risk factor for postinjury failure. Am J Surg 1999, 178:570
44. Hill GE, Frawley WH, Griffith KE, et al: Allogeneic blood transfusion increases the risk of postoperative bacterial infection: A meta-analysis. J Trauma 2003, 54:908
45. Engelich G, Wright DG, Hartshorn KL: Acquired disorders of phagocyte function complicating medical and surgical illnesses. Clin Infect Dis 2001, 33:2040
46. Aibochi J, Moore EE, Ciesla DJ, et al: Blood transfusion and the two-insult model pf post-injury multiple organ failure. Shock 2001, 15:302
47. Klein CJ, Stanek GS, Wiles CE: Overfeeding macronutrients to critically ill adults: Metabolic complications. J Am Diet Assoc 1998, 98:795
48. Lind L, Lithell H: Imparied glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. Clin Intensive Care 1994, 5:100
49. Steinberg HO, Tarshoby M, Monestel R, et al: Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. J Clin Invest 1997, 100:1230
50. Pleiner J, Schaller G, Mittermayer F, et al: FFA-induced endothelial dysfunction can be corrected by vitamin C. J Clin Endocrinol Metab 2002, 87:2913
51. Stulnig TM, Berger M, Roden M, et al: Elevated free fatty acid concentrations inhibit T lymphocyte signaling. FASEB J 2000, 14:939
52. Rassias AJ, Marrin CAS, Arruda J, et al: Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 1999, 88:1011
53. Almersjö O, Bengmark S, Engevik L, et al: Serum lipids after extensive liver resection in man. Acta Hepatosplenol 1968, 15:1
54. Bengmark S: Liver steatosis and liver resection. Digestion 1968, 2:304
55. Marchesini G, Forlani G: NASH: From liver disease to metabolic disorders and back to clinical hepatology. Hepatology 2002, 35:497
56. Calder PC: Immunonutrition. BMJ 2003, 327:117
57. Bisgaard T, Kehlet H: Early oral feeding after elective abdominal surgery—What are the issues? Nutrition 2002, 18: 944
58. Basse L, Raskov HH, Hjort Jakobsen D, et al: Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. Br J Surg 2002, 89:446
59. Kehlet H, Holte K: Review of postoperative ileus. Am J Surg 2001, 182(Suppl):S3
60. Kompan L, Kremzar B, Gadzijev E, et al: Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. Intensive Care Med 1999, 25:129
61. Bengmark S: Progress in perioperative enteral tube feeding. Clin Nutr 1998, 17:145
62. Bengmark S: Use of some pre-, pro-, and synbiotics in critically ill patients. Probiotics in gastroenterology. Best Pract Res Clin Gastroenterol 2003, 17:833
63. McCowen KC, Malhotra A, Bistrian BR: Stress-induced hyperglycemia. Crit Care Clin 2001, 17:107
64. Umpierrez GE, Isaacs SD, Bazargan N, et al: Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002, 87:978
65. Dunder K, Lind L, Zethelius B, et al: Increase in blood glucose concentration during hypertensive treatment as a predictor of myocardial infarction: Population based cohort study. BMJ 2003, 326:681
66. Zerr KJ, Furnary AP, Grunkemeier GL, et al: Glucose control lowers the risk of wound infection in diabetes after open heart operations. Ann Thorac Surg 1997, 63:356
67. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. N Engl J Med 2001, 345:1359
68. Mesotten D, Van den Berghe G: Clinical potential of insulin therapy in critically ill patients. Drugs 2003, 63:625
69. Rayner CK, Jones KL, Samsom N, et al: Relationship of upper gastrointestinal motor and sensory function with glycemic control. Diabetes Care 2001, 24:371
70. Schorah CJ, Downing C, Piripitsi A, et al: Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill. Am J Clin Nutr 1996, 63:760

71. Nathens AB, Neff MJ, Jurkovich GJ, et al: Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 2002, 236:814
72. Baines M, Shenkin A: Use of antioxidants in surgery: a measure to reduce postoperative complications. Curr Opin Nutr Metab 2002, 5:665
73. Cao Y, Feng F, Hoos A, et al: Glutamine enhances gut glutathione production. J Parenteral Enteral Nutr 1998, 22:224
74. Wischmeyer PE, Kahana M, Wolfson R, et al: Glutamine reduces cytokine release, organ damage, and mortality in a rat model of endotoxemia. Shock 2001, 16:398
75. Manhart N, Vierlinger K, Spittler A, et al: Oral feeding with glutamine prevents lymphocyte and glutathione depletion of Peyer's patches in endotoxemic mice. Ann Surg 2001, 234:92
76. Kelly D, Wischmeyer PE: Role of L-glutamine in critical illness: New insights. Curr Opin Nutr Metab 2003, 6:217
77. de Fellippe J, da Rocha e Silva M, Maciel FMB, et al: Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1-3 polyglucose (glucan). Surg Gynecol Obstet 1993, 177:383
78. Andersson R, Wang X, Ihse I: The influence of abdominal sepsis on acute pancreatitis in rats: A study on mortality, permeability, arterial blood pressure and intestinal blood flow. Pancreas 1995, 11:365
79. Leveau P, Wang X, Soltesz V, et al: Alterations in intestinal permeability and microflora in experimental acute pancreatitis. Int J Pancreatol 1996, 20:119
80. De Souza LJ, Sampietre SN, Figueiredo S, et al: Bacterial translocation during acute pancreatitis in rats (in Portuguese, with English summary). Rev Hosp Clin Fac Med Sao Paolo 1996, 51:116
81. Johansson ML, Molin G, Jeppsson B, et al: Administration of different lactobacillus strains in fermented oatmeal soup: In vivo colonization of human intestinal mucosa and effect on the indigenous flora. Appl Environ Microbiol 1993, 59:15
82. Kruszewska K, Lan J, Lorca G, et al: Selection of lactic acid bacteria as probiotic strains by in vitro tests. Microecol Ther 2002, 29:37
83. Ljungh Å, Lan J-G, Yamagisawa N: Isolation, selection and characteristics of *Lactobacillus paracasei* ssp paracasei isolate F19. Microb Ecol Health Dis 2002, 3(Suppl):4
84. Oláh A, Belágyi T, Issekutz Á, et al: Early enteral nutrition with specific lactobacillus and fibre reduces sepsis in severe acute pancreatitis. Br J Surg 2002, 89:1103
85. Rayes N, Hansen S, Boucsein K, et al: Early enteral supply of fibre and lactobacilli vs parenteral nutrition—A controlled trial in major abdominal surgery patients. Nutrition 2002, 18:609
86. Rayes N, Hansen S, Seehofer D, et al: Early enteral supply of *Lactobacillus* and fibre vs selective bowel decontamination (SBD)—A controlled trial in liver transplant recipients. Transplantation 2002, 74:123
87. Rayes N, Seehofer D, Theruvath T, et al: Combined perioperative enteral supply of bioactive pre- and probiotics abolishes postoperative bacterial infections in human liver transplantation—A randomised, double blind clinical trial. In press 2004
88. Riordan SM, Skinner N, Nagree A, et al: Peripheral blood mononuclear cell expression of Toll-like receptors and relation to cytokine levels in cirrhosis. Hepatology 2003, 37:1154
89. Qing L, Zhong PD, Da Kang H, et al: Synbiotic modulation of gut flora: Effect on minimal hepatic encephalopathy in patients with liver cirrhosis. Hepatology. In press 2004
90. Kurtovic J, Ruettimann U, Adamson H, et al: Improvement in indocyanine green clearance following synbiotic treatment in cirrhosis (abstr). Ear Nose Throat J 2003, 52(Suppl 3)
91. Miettinen M, Alander M, von Wright A, et al: The survival of and cytokine induction by lactic acid bacteria after passage through a gastrointestinal model. Microb Ecol Health Dis 1998, 10:41
92. Jain PK, McNaught CE, Anderson ADG, et al: Influence of synbiotic containing Lactobacillus acidophilus LA5, Bifidobacterium lactis BP12, Streptococcus thermophilus, Lactobacillus bulgaricus and oligofructose on gut barrier function and sepsis in critically ill patients: A randomized controlled trial. Clin Nutr. In press 2004
93. Bengmark S: Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients. Clin Nutr. In press 2004