Review

Hell J Surg. 2023 Jul-Sep;93(1):11–29
doi: 10.59869/23003

Synbiotics (prebiotics and probiotics) in the nutrition of critically ill patients

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ABSTRACT

Background: It is well known, nowadays, that intestinal microbiota is considered to be a synbiotic partner that maintains the host's health. Probiotics are live microorganisms and prebiotics are selectively fermentable non-digestible oligosaccharides or food ingredients that when adequately present, provide health benefit for the host. The mechanisms in which these microorganisms are involved are gastrointestinal barrier function improvement, gut flora modification by antimicrobial peptides inducted by host cells, antimicrobial factors released by probiotics, epithelial adherence competition, and immunomodulation that advantages the host. Synbiotics are a synergic combination of probiotic bacteria and prebiotic ingredients that promote the growth of the former.
Methods: In the present study, the existing evidence regarding the beneficial role of probiotics, prebiotics, and synbiotics in critically ill patients was evaluated.
Results: The results were rather encouraging about the early use of pro/pre/synbiotics in daily care of critically ill patients but still controversial due to the lack of specific supportive evidence and strain specificity.
Conclusions: Despite the positive effect of pro/pre/synbiotics supplementation, they cannot be widely applied in critical care clinical practice until well-designed prospective and randomized controlled trials are performed.

Key Words: *Probiotics; prebiotics; synbiotics; critically ill; nutrition*

INTRODUCTION

Nutrition support of critically ill patients is very important for their favourable progression. In the past, herbal medicines were almost the only possibility of therapeutic intervention, even for critically ill patients and, therefore, the gastrointestinal tract was the only route for the administration of both food and treatment. The appearance of appropriate tubes made it possible to administer nutritional factors from the rectum in patients who could not be fed per os for various reasons. This practice was quite common in the 19th and the early 20th century. Intravenous administration of nutritional solutions was a new approach in the field of perioperative nutrition, which was established in clinical practice during the mid-20th century

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Submission: 01.05.2023, Acceptance: 13.06.2023

[1]. During this period, great efforts were made for the development of exclusively intravenous feeding techniques for critically ill patients, as at the same time there was no interest in the use of the gastrointestinal system and natural feeding per os. Despite all these efforts, the design and implementation of a perfect, effective and safe parenteral nutrition system failed for several reasons. The effect of parenteral nutrition on the immune system and the need for intestinal mucosal barrier integrity and functionality maintenance were not evaluated as they should. The value of nutrients and antioxidants produced from the enzymes of the lower gastrointestinal tract microbial population was overlooked and the necessity to maintain the normal production of more than 100 gastrointestinal (GI) secretions, necessary for the immune system adequacy and local infection control was not evaluated [2]. Only in the last 20 years, research and biotechnology have focused on the gastrointestinal tract and the importance of microbial flora in the restoration and maintenance of health. Also, it was recognised that important therapeutic manipulations, such as antimicrobial chemotherapy and radiation were characterised by devastating effects on the immune system, gastrointestinal mucosa, and microbial gut flora. So, nowadays, several nutrient solutions for intestinal artificial feeding are produced, which, apart from the basic nutritional substrates (amino acids, carbohydrates, fats, vitamins, and minerals) in micro molar or macromolecular form, contain various ingredients such as fibers, which by fermentation from colon microbes produce nutrients both for the body (short-chain fatty acids, antioxidants) and the gut microbial flora. The intestinal bacterial system can be affected via the interaction of administered prebiotics with the symbiotic intestinal bacteria, especially the colon, where anaerobic bacteria can ferment non-absorbable dietary carbohydrates. By the fermentation, intestinal pH is reduced and that stimulates the non-pathogenic bacteria growth (prebiotic effect) and releases short chain fatty acids (butyric, acetic, and propionic acid). Butyrate is the main energy source for epithelial colon cells and inhibits Nf-kB activation. This prevents the expression of specific genes that encode cytokines promoting inflammatory response [3]. Additionally, butyrate increases the inflammatory cell apoptosis [4].

Homeostasis and intestinal tract

It is known that health and well-being are determined by the overall homeostasis of the organism, meaning maintaining balance between the physiological systems that control the entire body's functions range [5].

Modern dietetic habits differ significantly from that of Paleolithic men. Our distant ancestor annually included in his diet more than 500 plant species, while today we use less than 50. The food was usually rough and wet, while today we consume preserved, dried, or cooked foods, processes that can destroy many sensitive dietetic factors and antioxidants. It is estimated that the Paleolithic man consumed five to ten times more fiber, at least tenfold greater amount of antioxidants, fifty times more omega-3 fatty acids and even eventually million times more bacteria and fungi. The main source of food was the ground and the food was usually "infected" with microbial material. A protective layer of microbial flora covers all surfaces of the body, including the gastrointestinal tract which is important for the prevention of infections and inflammatory reactions. The gastrointestinal tract is covered by 1-2 kgs of microbial flora and the skin by about 200 gr of bacterial populations. Other important body parts of protective microbial flora are the oral cavity and pharynx, the tracheobronchial tree, and the vagina. Each one of these positions is estimated to be colonised by 20 g of microorganisms, approximately. Excessive cleanliness disrupts this defensive layer of microorganisms and subsequently, susceptibility to opportunistic bacterial infections is more likely. The animal instinct to lick their wounds is based on the salivary protective flora and growth factors that can be inoculated on the wound.

The gastrointestinal tract microbial flora has five significant functions: a) reduction or attenuation of potential pathogens, b) reduction or attenuation of various exogenous or endogenous toxins, mutagens, carcinogens, etc., c) immunological modulation, d) maintenance of the normal apoptotic process and e) release of a large number of dietary antioxidants and growth factors [6].

In recent years, the disorder of the intestinal environment (flora or mucosal barrier) was recognised as one of the main causes of allergic and autoimmune diseases and of underlying inflammation. Patients undergoing long-term medication or major surgery tend to be merely affected by this disorder. A considerable number of experimental studies attribute the increased morbidity of these conditions to bacterial migration. However, the interpretation of the different responses of patients to significant septic complications is poor. It is assumed that two factors are equally important: a) the previous capability of the immunological response and b) the increased toxicity of potentially pathogenic microorganisms which are present in patients' flora [7].

Autoimmune diseases, gastrointestinal cancer, obesity, and cardiovascular diseases, among others, are linked to derangements in composition, numbers, or habitat of the gut microbiota due to lack of probiotics-synbiotics. Resetting the gut microbiota to the prior state, despite hardly feasible, can be achieved by the use of probiotics, as well-designed clinical studies indicate [8-10]. It is well known that intestinal microbiota play a major role in the pathogenesis of inflammatory bowel disease (IBD) and colonic cancer. Research indicates that probiotics and/or prebiotics could be used as prophylaxis in suspected or established IBD and carcinogenesis, due to their aforementioned physiologic characteristics and lack of side effects [11].

For years, it was believed that as long as the bacteria are restricted to the lumen of the gastrointestinal or respiratory system, they cannot be dangerous to the body. This view has been recently challenged by Alverdy et al [12]. It was observed that the injection of microbial culture, quantitatively and qualitatively similar to the bacteria of the intestinal tract, into the systemic circulation (intravenously, intraperitoneally or in the mesenteric lymph nodes) of healthy or under stress animals, resulted in a limited only systemic inflammatory response without organs dysfunction and was followed by speedy full recovery [12]. On the other hand, since the mid-70s, it has been found that injecting a small amount of Pseudomonas Aeruginosa culture into the cecum had fatal outcomes. This dose was much lower compared to the intravenous lethal dose [13]. It has also been observed that intratracheal instillation of the same culture of pseudomonas caused the death of all animals, which was not the case with the intravenous administration of an equal amount of the same strain culture [13].

It is known that artificial nutrition with pro/prebiotics positively influences intestinal mucosal barrier functionality, reducing infections and improving patient's clinical outcomes [14,15]. Dysbiotic microbiota has been associated with IBD and also with obesity and metabolic syndrome. Microbial manipulation (probiotic, prebiotic) impacts colorectal carcinogenesis [10]. Simren et al presented a hypothesis that abnormal microbiota activates immunological response, and subsequently increases epithelial permeability and dysregulates the enteric nervous system. These phenomena can be reversed with probiotic and synbiotic supplements administration [16].

It is also widely accepted that haematogenous infections have relatively little impact on the overall progress of the patient, the rate of organ failure, and mortality. On the other hand, the dramatic increase in the toxicity of potentially pathogenic microorganisms of the intestinal lumen or respiratory system plays a significant role in the patients' outcome. The modification of the toxicity of potentially pathogenic microorganisms of the gastrointestinal tract occurs due to the environmental changes of the intestinal lumens, caused by the disease, the lack of the foods' pH, the local redox state, the reduced osmolality and the compensatory secretion of hormones. Also under severe metabolic stress, the increase of locally secreted noradrenaline enhances intraluminal bacteria toxicity [17]. It is believed that potentially pathogenic microorganisms, which in normal conditions are inactive colonisers of the human body, alter their phenotypic characteristics under stress conditions and become pathogenic and life-threatening [1]. Alverdy et al, referring to Escherichia coli, suggested that these bacteria adhere to the host's cells for feeding reasons and cause activation of the transcription pathways in the mucosal cells, thereby causing an increase in innate immunological inflammatory response [12].

Antibiotics as therapeutic agents

Antibiotics are used to prevent and treat infections in patients with severe acute inflammatory conditions, such as severe acute pancreatitis, extensive burns, blunt trauma patients, patients with major surgery, and ICU patients. Most often this effort has only a limited impact on morbidity, mortality, and overall disease progression. In the last 20 years, selective sterilisation of the gastrointestinal tract (Selective Gut Decontamination, SGD) has been widely accepted, as a therapeutic approach to reduce the rate of septic complications and it was followed by prophylactic eradication of potentially pathogenic microorganisms of the GI tract, from the oropharynx to the rectum, without simultaneously undermining the natural anaerobic microflora [18]. In this approach, an orally administered combination of three or more non-absorbable antibiotics such as colistin, tobramycin, nystatin, gentamicin, or amphotericin B is administered alongside the same antibiotics as a local ointment for "sterilization" of the oropharyngeal cavity. The treatment is repeated every six hours for at least four-six weeks. So far, more than 30 clinical studies have been performed that were evaluated by two recent meta-analyses [19,20]. Both of these confirm a slight but still statistically significant reduction in the frequency of hospital-acquired pneumonia and an improvement in survival in certain critically ill patients. In contrast, two randomised controlled trials [21,22], did not confirm the positive effects of selective gut decontamination in liver transplant patients. In the first study, a complication rate of 32.4%, versus 27.9% in the control group was found, while in the other rates were 86% and 84.5 % respectively.

Impaired nutrition and reduced immune resistance

During the last two decades, clinical studies [23,24] indicate that 50 % of ICU patients exhibit severe malnutrition and signs of immunological deduction. Thus, these patients exhibit, postoperative or posttraumatic significantly higher complication rate, leading to a significant increase in the ICU time (patients with normal nutritional status 3±2 days vs 44±36 days for heavily malnourished patients), an extension of mechanical ventilation time dependence (2±2 days vs 41±37 days), an extension of the total hospitalisation time (31±24 days vs 82±40 days), higher frequency of tracheostomy (0% vs 67%) and a greater mortality rate (0% vs 28%). Furthermore, apart from malnutrition, other factors are involved in the high ratio of septic complications in ICU patients. Such factors include reduced patient resistance due to immune suppression, advanced age and severe underlying disease, presence of prosthetic material such as endotracheal tube, venous and bladder catheters, administration of antibiotics, and other drugs that modulate the resistance to microbial infections and long-term ICU stay, favouring the risk of cross infection. Septic complications appear in four areas: respiratory system (about 30% -65%), urinary tract (about 25%), haematogenous infections (about 15%), and surgical trauma (about 8%). They usually occur after a major trauma, a major surgery, or prolonged specific medication, for example liver and stem-cell transplantation (50% -85% of patients), after major esophagus, stomach and colon surgery (20% of patients), as well as after coronary artery bypass (in about 10 % of patients) [25].

Early enteral nutrition as a therapeutic intervention

The administration of enteral nutrients and antioxidants in ICU patients is accepted as a prerequisite for the avoidance of sepsis and other complications. Because the purpose of this therapeutic intervention is to reduce the intensity of stress response and the therapeutic window appears to be extremely narrow, the administration of enteral nutrition should commence the earliest possible [22,26]. More than a hundred years ago, Andresen et al., based on clinical experience, recommended enteral administration of 200-250 ml of nutrient solution, from the time of surgery, followed by continuous administration postoperatively [27]. He believed that such intervention was safe and that in this way he could prevent postoperative paralytic ileus and contribute towards the faster recovery of patients.

Approximately 80% of total immunoglobulin amount produced by the body, is located in the lamina propria of the intestinal mucosa [28], and significant quantities, especially IgA immunoglobulin, are released into the lumen of the gastrointestinal tract. IgA biosynthesis depends to a significant extent on T - lymphocytes and various cytokines that are produced by activated lymphocytes, which mediate IgA differentiation [29]. Dietary changes, physical activity, sleep, depression, age, sex, body temperature, medications, and various diseases can affect lymphocytes functionality, immunoglobulin production, and disease resistance. Hospitalisation in ICU causes major nutritional and mobilisation changes and practically deteriorates all body functions. This fact, together with the administration of a plethora of pharmaceutical agents, causes a significant immune response reduction.

In the past, critically ill patients were treated with hypercaloric dietary load (hyperalimentation). This is currently not used. On the contrary, we are now convinced that the administration of excessive energy load, enterally or parenterally, in critically ill patients, is extremely dangerous because it seems to be accompanied by critical or fatal consequences. Today, hypercaloric diet is very rarely recommended during the perioperative period, especially during the first two-three postoperative weeks. Furthermore, the aim of positive energy coverage and positive nitrogen balance, for surgical patients with moderate metabolic stress, has lost most of its merit. Instead, the value of enteral nutrition as a regulator of the immune defense mechanism is emphasised more.

It has been recently recognised that immunological status is more important than nitrogen uptake and caloric coverage. Windson et al., compared total parenteral nutrition vs enteral feeding in patients with acute pancreatitis and found similar results [30]. In the enteral nutrition group, there was a statistically significant improvement in the APACHE II score (6 vs 8, p <0,0001), in the levels of C-reactive protein (84 mg/lt vs 156 mg/lt, p < 0.005) in the levels of IgM antinuclear antibody against endotoxin and the total antioxidant status of the organism. Also, the intensity of the inflammatory response, sepsis and multisystem organ failure syndrome occurrence, and ICU prolonged stay were all statistically significantly improved in the enteral nutrition group. Shirabe et al., compared total parenteral nutrition vs enteral feeding in patients who underwent hepatectomy with no differences in nutritional parameters such as binding retinol protein levels, prealbumin, and 3-methylhistidine levels [31]. Instead, they found significant differences in immune parameters, such as the total number of leukocytes, response to phytohemagglutinin and activation of natural killer cells. Even more important, is the fact that the frequency of infectious complications in the enteral nutrition group was 8% compared to 3% of the parenteral hyper nutrition group and that was attributed to severe hyperglycaemia, and intense metabolic stress caused by the parenteral hyper nutrition.

A meta-analysis demonstrated that early (within 12 hours) enteral nutrition administration reduces the rate of surgical and posttraumatic infections, maintains the physiological antioxidant level of tissues, improves anabolic processes and wound repair and maintains the intestinal mucosa functional integrity [32]. Noteworthy are also the findings of Compan et al, that commencement of enteral nutrition administration in blunt trauma patients the first six hours after their admission to ICU, compared with the administration after the first day, not only ensures normal mucosal permeability of the intestine, but is also accompanied by a significant decrease in organ failure ratio [33]. It appears that the application of early enteral nutrition (< 6 hours) has positive effects on ongoing critically ill patients. As mentioned by Marik and Zaloga, even if early enteral nutrition does not reduce the rate of septic complications, neither does it increase it [32]. Enteral nutrition reduces intestinal complications such as bacterial overgrowth caused by starvation, and production of sIgA [34].

The synbiotics (probiotics and prebiotics) as a therapeutic agent

It is undeniable nowadays that the intestinal microbiota is considered to be a synbiotic partner that maintains the host's health. Probiotics are live microorganisms and prebiotics are selectively fermentable non-digestible oligosaccharides or food ingredients that enhance host's health. The mechanisms involved include improvement of gastrointestinal barrier function, modification of the flora by antimicrobial peptides induction by host cells, antimicrobial factors released by probiotics, epithelial adherence competition, and immune system regulation to the advantage of the host. Synbiotics consist of probiotic bacteria and the prebiotic nutrients that lead to the synergic activity of both. There are many benefits of prebiotics, probiotics, and synbiotics consumption as the whole human body is covered with a plethora of microorganisms [35,36].

Prebiotics and probiotics have proven beneficial in gastrointestinal diseases and specifically prebiotics (inulin, pectin, fructo and galacto oligosaccharides) are useful substrates for fermentation in gut contributes that contribute to the maintenance of the intestinal mucosal barrier, intestinal mucosa immunomodulation and immune defense enhancement against pathogenic micro-organisms [37-39]. Probiotics are non-pathogenic bacteria, which have the ability to adhere into the intestinal mucosa and stimulating the sIgA secretion and mucus production, regulate cytokines levels, produce heat shock proteins and defensins, activate macrophages and thus improve intestinal immune function [38,40,41]. The probiotic concept is the same on all sites of actions and routes of administration, as viable organisms have the same action independently of the site (mucosa-lined cavities such as mouth, colon, and vagina) [42].

Prebiotics

The early administration of enteral nutrition with only basic nutritional factors does not seem enough. The enteral feeding solutions should also contain fibers (prebiotics). Prebiotics help the development of the intestinal mucosa, to maintain its functional integrity, to maintain water and electrolytes balance in the body, to supply the body with energy and nutritional factors, and to increase resistance against pathogens. The human colon since birth depends on prebiotics administration for normal development and functionality. Breast milk has an extremely high non-digestible oligosaccharides concentration. Human breast milk is one of the richest among mammalians' milk in non-digestible oligosaccharides, which protect, due to immune modulation, infants who are fed with breast milk from infections and inflammations [43]. These non-cleavable oligosaccharides favour the development of the non-pathogenic microorganisms in the intestine of breastfeeding infants. Phytochemicals are compounds that are found in plants but without nutritional value and they are responsible for color, odor, taste and plant defense against various diseases. Popularly known phytochemicals with antioxidant properties and cell protection role from oxidative stress are lycopene in tomato, sulfides in leeks, onions, and garlic, isoflavones in soy, polyphenols in tea and grapes, and flavonoids in fruits and vegetables [42]. Dietary fibers are endogenous components of the cell walls of plant cells, polysaccharides, non-starch polysaccharides, lignin etc. These components are resistant to intestinal enzymes and cannot be digested. Thus, they provide non-digestible substrates for the small intestine, with no or minimal absorption and metabolism rate [44]. Non-digestible prebiotic hydrocarbons are various oligosaccharides such as pectin, beta glucans, inulin, fructooligosaccharides and galacto oligosaccharides, lactulose etc. Inulin, fructo and galacto oligosaccharides lead to the growth of beneficial bifidobacteria and lactobacilli strains in the colon and reduce the burden of potentially pathogenic microorganisms [37]. It has been found that glucan administration in blunt trauma patients, significantly reduces hospital infections morbidity [45].

Often in debilitated patients, it is not possible for several reasons to administer fresh fruits and vegetables but there is a great range of fiber, which can be used. One of these fibers, known for its bioactivity, is pectin, which protects muous, acts as an antioxidant, transports lactobacilli in the GI tract, and is an excellent substrate for bacterial fermentation. Bananas, particularly unripe, are rich in pectin and starch. The administration of green banana (250 gr/lt food) or pectin (2 gr/lt food) was tested in Bangladesh children, fed almost exclusively with rice which suffered from severe, persistent diarrhea syndrome [46]. In both children groups the frequency of diarrhea episodes, the duration of diarrheal syndrome, the vomiting frequency and the liquid volume (oral or intravenous) required for hydration were decreased. In the study, 59% of children who were given the green banana, and 55% of children with pectin, showed significant improvement from the third day of treatment in contrast to 15% of children fed only with rice. It is suggested that at least 10gr pectin per day should be routinely administered in all ICU patients, as an antioxidant for gut protection and restoration of gut microbial flora [23].

The intake of viscous hydrocarbons and non -digestible dietary fibers can promote some positive effects on the organism, such as an increase in saturation, slow gastric emptying, decreased appetite, lowering cholesterol, blood glucose, and low-density lipoproteins and depending on their size increasing the fecal mass, reducing the intestine transit time and generally improving the whole intestine function [47-49]. Thus, they can be used therapeutically to reduce calorie intake, control body weight, reduce cardiovascular disease, and prevent constipation and possibly colon cancer [44]. In diverticulitis, inulin improved the balance between potential pathogenic Enterobacteria and species of beneficial bifidobactiria and lactobacteria, by reducing the concentration of secondary bile acids [50]. The use of a fermentable oval Plantago solution (fibers) showed similar relapse rates in ulcerative colitis such as mesalazine [51].

Prebiotics can regulate the composition of colonic flora by increasing the number of specific bacteria (bifidobacteria). They can also modulate lipid metabolism, most likely via fermentation products [37]. The chicory fructans are beta (2-1) fructo-oligosaccharides (prebiotics) that can upregulate the number of bifidobacteria in colon flora, and affect the bioavailability of minerals and lipid metabolism. This can result in reducing the incidence of bowel disease, cardiovascular disease, metabolic syndromes, and cancer [37].

In vivo experiments have shown that fructans have anticarcinogenic properties on chemically-induced precancerous and cancerous lesions in the colon. In vitro experiments on human cells have shown that inulin-derived fermentation products can reduce cellular activity of cancer cells. This can be partially explained by the reduction of exposure to risk factors, thus driving cancer cells to earlier cellular death. It can be assumed that fructans act as both a blocking agent and a suppressing agent of chemopreventive activities [52].

Despite the vegetal diversity, the modern human chooses to take 90% of his food from only 17 plants and more than 50% of caloric and protein requirements come from just eight cereal seeds. The restricted variety of diet and the modern preservation and preparation methods of food, significantly reduce the benefits of nutrition and antioxidant reagents. The diet of patients is even more limited and that's why it is strongly supported that each solution of enteral nutrition should contain fibers. Prebiotics can induce high bifidobacteria levels in the colon at all ages. Placebo-controlled intervention studies show that high bifidobacteria levels induced by prebiotics can, for example, reduce sickness events in toddlers and gastrointestinal diseases in adults and enhance immune activity in elders. Even if they are administered prophylactically, prebiotics can alter the physical course of gastrointestinal disorders [53–55].

Probiotics

Probiotics are viable microorganisms administered to humans, aiming the mucosal floras. A probiotic product, depending on its form can be a type of food, food supplement, biological or pharmaceutical product [56]. Probiotics can affect the host by differentiating the gastrointestinal flora, improving the colonic microbial balance, and actively promoting the growth of desirable bacteria [57,58].

Probiotics may be bacteria, such as Lactobacillus, Bifidobacterium, Escherichia (strain Nissle 1917), Enterococcus (E. faecium SF68), Bacillus and Streptococcus, or certain fungus, such as Saccharomyces boulardii [50]. Probiotics such as Lactobacillus rhamnosus GG, L. reuteri, bifidobacteria and certain strains of L. casei or L. acidophilus have food production usage, such as dairy production, and also exhibit possible medical use. There is a wide genetic diversity among the different lactobacilli. Most of the lactobacteria that are consumed have limited fiber fermentation capacity, limited antioxidant properties, poor mucus adherence and are destroyed mainly by gastric acid and bile. Lactobacilli, which are contained in yoghurt are well known for their ability to grow in an environment without fibers and do not seem to have strong bioactivity, so, they are selected almost exclusively for their good flavor. In opposition to that, lactobacilli which are living and growing on plants, often under very difficult circumstances, have much stronger bioactive properties. These bacilli have the capacity to ferment fibers that are difficult to cleave. This probably explains why, eating lactobacilli from vegetables, cereals, sorrel and sourdough, as expected, exhibits much better clinical response in critically ill patients. Of great interest are the lactobacilli from seeds such as oats and rye. The number and the physiology of the bacilli in rye was studied and more than 100 species of lactobacilli were found some of which demonstrate unique bioactive properties [1].

It has been shown that probiotics are effective in various inflammatory colonic conditions, such as infantile or antibiotic-related diarrhoea, recrudescing *Clostridium difficile* colitis, Helicobacter pylori gastritis, and inflammatory bowel disease. Extracolonic diseases in which probiotics have a positive effect can be female urogenital infections, surgical site infections, allergies, AIDS, respiratory and urinary tract infection, and cancer. Even metabolic conditions have been shown to alleviate symptoms with the use of probiotics osteoporosis, obesity, and, possibly, type 2 diabetes, or even gestational allergies [14,59,60]. Preventively and therapeutically, a blend of eight probiotics has been used for diverticulitis, and others have been used in ulcerative colitis, pouchitis, or even irritable bowel syndrome for symptom alleviation [61,62].

Lactobacilli have demonstrated the ability to regulate the amount of potentially pathogenic micro-organisms, toxins, and extrinsic pathogenic factors. They can regulate the innate immunological response to pathogenic factors and microorganisms by upregulating the anabolic synthesis of growth factors and other elements of intrinsic inflammation modulation [63]. Adherence to intestinal epithelium and subsequently inhibition of pathogen's adherence and proliferation are the main mechanisms of action of probiotic bacteria. Cytokine release can be initiated by probiotics. They can also produce lactic acid and bacteriocins, which inhibit pathogen proliferation and alter the microbiota. In addition, the probiotics that produce butyric acid inhibit the adverse effects of high-protein dietary carcinogens, such as nitrosamines [58]. Sivieri et al showed the positive effect of L. acidophilus 1014 on microbial metabolism and flora composition [64].

Probiotics have been suggested to intervene in the hereditary, environmental, microbiological, and immunological factors that contribute to the occurrence of inflammatory bowel disease. Possible mechanisms include probiotic competition with or suppression of microbial pathogens, regulation of an immune response, enhancement of barrier activity, and induction of T-cell apoptosis [65]. There are several interesting studies of Crohn's disease, where the genetic modification with human genes of Lactobacillus lactis strains leads to the production of IL 10 [66,67]. In two studies, the administration of E.coli Nissle 1917 [68,69] and in a study the administration of Lactobacillus GG [70] was compared with mesalazine . Remission rates were similar to mesalazine in all of the aforementioned studies. Significant results have been obtained with the use of probiotics in patients with pouchitis. In chronic relapsing pouchitis, significant reduction in relapse rates was found by combining eight different bacteria (VSL # 3), compared with placebo [71] and further VSL # 3 use reduced postoperatively pouchitis percentage, compared with placebo [72].

In intensive care-associated conditions, such as diarrhoea associated with antibiotics consumption, ventilator-related pneumonia, and necrotising enterocolitis, various probiotic strains have been used effectively, but without a consensus on the dosages and duration of treatment [73]. However, even if they are effective in reducing these conditions' incidence, the long-term mortality rates do not seem to be significantly reduced [74].

Infection of the host has been a suspected condition concerning probiotic administration, since they are indeed live organisms. They can cause bacteraemia, and thus may induce sepsis. Despite the risk of sepsis, if considered lower than that of the pathological bacteria acquired, their use can be justified as a means of therapy [14,56]. Not all probiotics are the same and thus, they cannot cause the same adverse effects [62].

Synbiotics

Gut microbiota is closely associated with specific diet and food intake. Any change in diet can cause a chain of changes in the microbiota balance and subsequently in organ function [60]. The single or combined use of probiotics and prebiotics regulates the intestinal microbiota and by extension immunological responses [75]. Intestinal microecological disturbances (dysbacteriosis) can be treated with probiotics, prebiotics, and synbiotics used for the correction of resident normal colon microflora [76]. Combined administration of probiotics and prebiotics significantly improved intestinal flora of rats, as far as probiotic bacteria and enzymes are concerned [50]. Increasing evidence on prebiotics metabolism by probiotics and the probiotics mechanism of action in microbiota, have given the chance to specifically regulate dietary changes in specific population and disease groups [77].

Gastrointestinal glands, mucosa, and mucosa-associated lymphoid system constitute 70% of the immune system. Thus, the hypothesis of the use of synbiotics in intensive care patients for modulation of the innate immune system arises [78]. Recently, it has been exhibited that early commencement of enteral nutrition combined with synbiotics may reduce inflammatory response, regulate intestinal immunity and help infections' prevention. Oligofructose, lactulose and galactooligosaccharides are prebiotics which can regulate the gut flora balance. Critically-ill patients can be positively affected by synbiotics, with restoration of intestinal flora, improving intestinal permeability and bacterial translocation [79]. Prebiotics, probiotics, and their combination protect and cure diseases such as diarrhoea, inflammatory bowel disease, and Helicobacter infections in postoperative patients in intensive care units [6].

Synbiotic combinations can potentially regulate the microbiota as they seem to control bacteria proliferation and the short-chain fatty acids production in human colon experimental models [80,81]. Probiotic combination (L. paracasei or L. rhamnosus) with two oligosaccharide prebiotics can increase the populations of Bifidobacterium longum and B. breve, and reduce Clostridium perfringens when co-administered. This microbial shift was associated with regulation of host metabolic pathways in lipid, glucose and amino-acid metabolism, as carbohydrates were fermented by different bacterial strains. Therefore, this fact offers considerable promise for treating inflammatory bowel disease in combination with already used anti-inflammatory and immunomodulatory agents [82]. Synbiotics can restore a beneficial predominance of Lactobacillus and Bifidobacterium species. It has been shown that selected probiotics can minimise the relapse of ulcerative colitis and pouchitis [83]. A Synbiotic product (Flortec) containing Lactobacillus paracasei B21060 was admnistered in patients with diarrhoea-predominant inflammatory bowel disease and improved pain and well-being [84]. Bifidobacteria and lactobacilli are the main beneficial probiotics contributing to lactose digestion in lactose-intolerant patients, reducing symptoms and boosting immunological and anti-inflammatory responses [85]. Several studies in animal models showed the beneficial role of synbiotics. Probiotics, prebiotics and synbiotics are protective against oxidative stress and inflammation in the terminal ileum in neonatal rats, but their efficacy may be reduced when administered during hyperoxia/hypoxia insults [86]. Prebiotic and/or synbiotic supplementation in a neonatal intestinal failure piglet model showed that they can promote the functionality of the residual intestine. Synbiotics showed higher outcomes than prebiotics alone, proving the enhanced outcomes of the synergy provided by the combination of prebiotics and probiotics [87]. Rishi et al demonstrated that L. acidophilus, inulin, and their combination can have positive effects on liver damage induced by Salmonella in a murine model. Symbiotic combination decreased bacterial translocation in the liver and levels of serum aminotransferases, denoting their therapeutic contribution to the Salmonella infection therapy in mice. Even when they were administered in healthy mice, they also showed reduced lipid peroxidation levels, increased superoxide dismutase levels and glutathione, as well as decreased nitric oxide levels. Different mechanisms could be involved in the synergic effect, whereas the probiotic alone seems to be more effective [88].

Intestinal disorders and metabolic syndromes are associated with dysbiotic microbiota development and, therefore, microbial flora regulation (probiotic, prebiotic) impacts colorectal cancer development [10]. There seems to be a significant impact of prebiotics, probiotics and synbiotics on malignancy treatment in colon cancer patients by causing bio-antimutagenic and desmutagenic effect [89,90], immune response stimulation, inflammation reduction, inhibition of tumour cells formation and decrease in bacterial enzymes which hydrolyse beta-glucuronidase and other precarcinogenic substances [91,92]. Synbiotics could have a potential in the prevention and therapy of colorectal cancer affecting gut microbiota and, that way, influencing the immune system [93]. Also, synbiotics affect metabolic pathways such as the secondary bile acids deconjugation, the activities of bacterial enzymes, as well as mineral absorption [94].

Shimizu et al, found out that in critically ill patients, synbiotics that have been reported to significantly decrease sepsis, gut flora and environment are significantly altered (maintained and repaired), and the number of synbiotic anaerobes is associated with prognosis, but did not define mechanisms of probiotic/synbiotic treatment therapeutic effect and appropriate conditions for use [95]. Patients after liver and pancreas surgery or trauma patients benefited most from synbiotics; however, synbiotic preparations need extensive testing before clinical implementation to define the exact synbiotic combination and the therapy duration [73]. Prevention of infectious complications after major surgeries such as acute pancreatitis, liver transplantation, and biliary cancer has been investigated by the use of probiotics and synbiotics as post-operative treatment and concluded in the potential clinical application [96].

The understanding of these complex interactions of microbiota and eukaryotic cells can positively affect various aspects of metabolism and immunity and can further provide the knowledge of proper manipulation of a pathologic condition, if it arises [97]. It has been demonstrated that prebiotics, probiotics, and their combination can regulate the gut flora, reduce inflammation in the colon, and potentially induce disease remission [98]. Viable bacteria can be administered in high dosages in fermented products with the proper selection of prebiotics and probiotics [99], and that is leading towards a more targeted development of functional food ingredients [76].

Clinical Evaluation of Formulations with one Lactobacillus species and one kind of fiber

Lactobacillus Plantarum (LP) is commonly found in the intestinal tract of Asian and African farmers, whose diet is mainly based on fresh vegetables, rich in Lactobacillus. There is strong evidence that Western lifestyle and diet inhibit intestinal colonisation with the LP. The Lactobacillus has been detected in 2/3 of the Seventh-day Adventists, North Americans who are almost exclusively vegetarian, and only in 1/4 of North Americans with Western diet [100]. The three main types of lactobacilli isolated from jejunal biopsies in a Swedish population, are the L. Plantarum (24%), the L.Rhamnosus (12%) and L.Casei subtype of Pseudoplantarum (in 10%) [101]. Furthermore, L.Plantarum was identified in 1/3 of infants aged 3-8 weeks [102].

A team of Lund University researchers analysed the beneficial effects of synbiotics in the preparation of a specific enteral feeding solution consisting of oatmeal that was fermented by strain 299 of L. Plantarum [40]. This strain was shown to have the ability to ferment oats and without being affected by gastric fluid and bile [103]. The enteric solution based on oats and L. Plantarum 299 was tested in 3 groups of critical conditions: liver transplantation, severe pancreatitis, and recent major gastrointestinal surgery.

In 2002, the efficacy of a synbiotic mixture in patients who had undergone liver transplantation and postoperatively (from the second postoperative day) were administered early enteral nutrition was evaluated in a prospective randomised study [104]. Patients were divided into three groups. In the first, 32 patients underwent selective gut decontamination for 6 weeks before surgery. In the second, 31 patients received a specific solution of live L. Plantarum 299 strains at a dose of 10^9 with 15 gr fermented fiber for 12 days postoperatively. In the third group, 32 patients were treated for the same period (12 days) with the same special solution, but with heat-inactivated L. Plantarum. There was no postoperative mortality, although there were 23 postoperative infections in the group of selective gut decontamination, four in the group with living lactobacilli and 17 in those with inactivated lactobacilli. Clinical infection signs presented at 15 out of 32 patients in the first group (48%), four of the 31 in the second (13 %) and 11 out of 32 in the third (34 %) ($p = 0.017$). The most frequent postoperative infection was cholangitis, in ten, two and eight patients, respectively, and pneumonia in six, one and four patients from each group. The microorganisms most frequently isolated were enterococci, in eight, one and eight patients and staphylococci in six, one and three patients. E.coli or Klebsiella was not isolated in any of the second group patients Non-infectious complications were observed in 15 first group patients, 16 in the second and 19 in the third. Finally, early graft failure manifested in 10, 10 and 15 patients, respectively, and hemodialysis was necessary to eight, two and four patients of each group and 12 patients totally were operated again, six, four and two patients in each group. The CD4/CD8 ratio was better in the living Lactobacillus group ($p = 0.06$) as well as the duration of antimicrobial chemotherapy administration and the time spent in the ICU and the total time of hospitalisation, without any statistical significance of these differences.

Regarding the clinical outcome of patients with acute pancreatitis, infection of pancreatic necrotic tissues is an adverse prognostic factor, which causes a significant increase in morbidity and mortality [105,106]. Almost one week after the invasion of severe pancreatitis, pancreatic necrotic tissues are infected in 25% of patients and three weeks after 75% of the patients are infected. All therapeutic manipulations, including the administration of antibiotics and various inhibitors of cytokines that promote inflammatory reaction, failed to significantly ameliorate the progression of these patients [107-109].

In a study from Gyor in Hungary, 45 patients with severe necrotising pancreatitis were divided into two groups [110]. In the first group of 22 patients, an enteral nutrition formulation containing 10^9 live organisms of L. Plantarum strain 299 and substrate 10 gr oat fiber was administered by nasojejunal catheter twice a day for one week, The remaining 23 patients received the same enteral formulation, but the lactobacilli were inactivated by heat. Contamination of pancreatic necrotic tissues occurred in 4.5% of patients in the first group (1/22) and 30% (7/23) of the second. ($P = 0,023$). In addition, patients in the first group had shorter hospitalisation duration (13, 7 days vs 21,4 days), but not statistically significant, probably due to the small number of patients.

Lahner et al studied Lactobacillus paracasei B21060 and high fiber diet in symptomatic uncomplicated diverticular disease in a randomised, multicenter, controlled study for 6 months. Patients, aged 40-80 years, were divided into two groups. The first (24 patients) received synbiotic Lactobacillus paracasei B21060 (Flortec) once daily with high-fiber diet for six months, and the second (21 patients) received only high-fiber diet for six months. In both groups, abdominal pain was significantly decreased after six months, but in the symbiotic group the proportion of patients with less was higher. Abdominal bloating was significantly decreased in the symbiotic group, but not in the second group. Thus, a high-fiber diet is effective in decreasing abdominal pain in symptomatic diverticular disease and by the combination of high-fiber with certain synbiotics, abdominal pain and bloating can be significantly enhanced [111].

Enteral nutritional solution with live strains of L. Plantarum 299 and fermented oat fiber was used in a randomised study of patients who had undergone major surgery in the gastrointestinal system, and was compared either with the same composition but with heat-inactivated strains L. Plantarum 299 or by standard enteral nutritional solution [104]. The study included 90 patients, of whom 29 had undergone hepatectomy, 26 pancreatectomy, 22 gastrectomy, 9 colectomy and 4 intestinal bypass. The patients were divided into 3 groups, which were comparable to the number, surgery severity and metabolic and hemodynamic parameters. It was found that within one month of the study initiation, septic complications appeared at three out of 30 (10 %) patients in each group receiving either live or inactivated strains of L.Plantarum, and at 9 out of 30 (30 %) of patients in the group receiving the usual enteric artificial diet (p = 0.01). Noteworthy was the fact that the largest difference occurred in the rate of hospital pneumonia (six patients in the group of normal enteral nutrition, two in the group with live strains and one in the group with inactivated strains of L.Plantarum). The protective effect of that specific dietary solution was more evident in patients who had undergone gastrectomy or pancreatectomy. In the first group, with live strains of L.Plantarum, septic complications occurred in one of 15 patients (7 %), in the second, with the inactivated strains, in three of 17 (18 %) and in the third, with the usual nutrient solution, in eight of 16 (50 %) patients. In the first group of patients, the antibiotic dose administered was also reduced (p = 0.04) as well as the duration of antimicrobial chemotherapy (4±3.7 days, 7±5.2 days, 8±6.5 days, respectively for three patient groups). Non-infectious aetiology complications presented in 13%, 17% and 3% of each group, respectively. Additionally, there were no significant differences in hemoglobin value and the number of leukocytes, in the value of C- reactive protein, blood urea, bilirubin, albumin, total white blood cells, CD45RA, CD45RO, CD4, and CD8, of lymphocytes and natural killer cells and of CD4/CD8 ratio. Finally, there was no difference in total time of hospitalisation.

In another clinical study including surgical patients, the efficacy of fruit juice solution and synbiotic agents (PROVIVA) was evaluated. The probiotic factor was similar (L.Plantarum 299 V), but not completely the same as the L. Plantarum 299 [112]. The number of lactobacilli and oat fiber was also significantly lower than that in the previous study. In this study, the evaluated solution contained 5% mixture of lactobacilli - fermented oat fiber and 95 % fruit juice. The total content in L. Plantarum 299 V was approximately 10^7. The formulation was administered for a longer period of time than in the previous study, and at least for one week before surgery. The formulation PROVITA was administered in 64 patients and 65 were treated with the usual preoperative and postoperative care. In patients of both groups, along with the induction of anesthesia, a single dose of cefuroxime and metronidazole was administered IV. No differences were noted between the two groups in bacterial translocation (12% vs 12%, p = 0,82), the colonisation of the stomach from enteric microorganisms (11% vs 17%, p = 0,42), and septic complications morbidity (13% vs 15%, p = 0,74).

These studies differed in certain elements. The first study included patients that had undergone more severe surgical interventions with a higher risk of surgical complications. This is due to the fact that in the first study, patients in the control group (who didn't receive the synbiotic regimen) presented septic complications in a percentage of 30% (which was 50% in the cases of pancreatectomy and gastrectomy), in contrast with the patients of the control group in the second study, which included mainly patients who had undergone colectomy, and who presented septic complications in 15%. So it seems that the beneficial effect of the synbiotic regimen is more obvious in patients with a greater chance of septic complications. Moreover, in the second study, the synbiotic regimen contained lower doses of prebiotics and prebiotics. Lactobacilli quantity equal to or less than 10^7 is considered inadequate for the expression of probiotics' beneficial actions. Finally, the two studies used different types of L. Plantarum.

Clinical Evaluation of Formulations with a combination of different lactobacilli species and different types of fibers

There is evidence that the combination of different lactobacilli types with different fermentable fibers likely exerts stronger synbiotic actions. Lactobacilli growing in certain plants show different bioactivity, as natural selection results, because of their ability to fermentate these plants' fibers. Plant biologists from the University of Lund studied ecologically cultivated rye plants and found the existence of more than 180 lactobacilli species, capable of clinical use [45]. In addition, from the human gastrointestinal tract 355 other species of lactobacilli were isolated [113]. It was found that all these lactobacilli types tend to adhere to mucus, to express cell surface hydrophobicity and to adhere to collagen, fibronectin and other extracellular mesothelial tissue proteins. Eight species of lactobacilli with these properties were chosen for further study. These species are not destroyed by exposure to 20% bile solution for an hour and PH 2,5 for two hours and were able to use as the only energy substrate inulin or amylopectin in the in vitro cultures.

Three of these species produce extra beta- galactosidase, an enzyme which is known to treat lactose intolerance symptoms. Some other species produce substances bioactive against gram-positive bacteria and Helicobacter pylori. In addition, after exposure to PH 5 for an hour, they were producing protein derivatives which showed cross-reactivity to stress proteins. Finally, four of the eight lactobacilli species that were studied, were able to transcript the nuclear factor kB (NFkB) in the nucleus of macrophages V937, and that resulted in the production of cytokines that promote the inflammatory response (IL- 1b, IL-8), antiinflammatory cytokines (IL-10) and antioxidants equivalent to 100 μg of vitamin C[229]. Based on these properties, four out of the 8 lactobacilli species were selected and used to create synbiotic formulation called Synbiotic 2000. This formulation consists of 1010 from each of the 4 lactobacteria: Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L.paracasei subsp. Paracasei 19 and L. planetarium 2362 (probiotics), and 2,5 gr from each of four fermented fiber: b-glycan, inulin, pectin and non-digestible starch (prebiotics). All species of lactobacilli, except L.paracasei, are derived from rye plants.

In a clinical study involving 10 patients with severe chronic distal colitis, enemas with Synbiotic 2000 were performed twice daily and for two weeks [114]. The study was completed with 9 patients. A significant reduction in bowel movements was recorded (2,5±38 to 1,13±0,13 on day 7 p <0,05, to 1,13±23 on day 14 p <0,05, and to 0,75±0.25 on day 21, a week after discontinuation of Synbiotic 2000, p <0,01). The number of bloody stools was also decreased (from 2±0,27 to 1±0,38, p <0,05, and to 1,12±0,35, p <0,05, on the 14 and 21 days respectively). Furthermore, the bowel movement frequency during the night and the emergency bowel movements were decreased and the stool consistency was improved. Administration of Synbiotic 2000, was well tolerated, without major side effects except for mild bloating and increased gas excretion in two patients.

In a randomised double-blind study including 66 patients who had undergone liver transplantation, the efficacy of Synbiotic 2000 was compared to the administration of 4 types of fibers contained in this formulation [115]. The administration began one day before transplantation and continued for 14 days postoperatively. One patient from the group of Synbiotic 2000 presented clinical signs of infection, in contrast to 17 of the 33 (51%) patients in the fiber group.

A certain synbiotic formula (Synbiotic 2000Forte) has been shown to improve sepsis rates in critically ill intubated multiple trauma patients, thus reducing the needed time for intensive care treatment and mechanical support, with lower intestinal permeability and fewer infections [116,117].

Macrophage activation by GI tract endotoxins is believed to increase TNF- a, which may contribute to the progressive liver destruction in cirrhosis. Furthermore, overexpression of blood monocytes Toll-like receptors four and two is significantly related to increased TNF- a production after stimulation by endotoxin and gram-positive microorganisms. If synbiotics can reduce Toll-like receptors expression and decrease TNF –a production, then there could be a safe and inexpensive solution, for long-term management of liver diseases under evolution. This hypothesis can be strengthened by the study that showed that Synbiotic 2000 administration in 8 of 11 cirrhotic patients reduced by 54 % the TNF-a blood monocytes production after stimulation by endotoxin or intestine - toxin b of staphylococcus aureus [118]. Synbiotic 2000 was well tolerated without side effects and its action on chronic liver disease was also evaluated in a double-blind study with 55 patients [115]. 3 groups were studied: first, Synbiotic 2000 administration, (20 patients), second, only fiber of Synbiotic 2000 administration (20 patients) and third, administration of non-fermented fiber (placebo) (15 patients). The administration of a combination of lactobacilli and plant fibers for one month significantly increased the number of intestinal flora lactobacilli. A similar increase was not observed in the second and third groups. In the non-fermented fiber group, the stool PH decreased significantly between 6.5 and 7, while the other two ranged between 5 and 5.5. In the first two groups the Escherichia coli, Staphylococcus and Fusobacterium populations in stool were significantly reduced, but pseudomonas and enterococci populations did not. The ammonia value in serum decreased significantly in the Synbiotic 2000 group, (from 60,5+2,9 to 38,6+3,9 μmol/lt) and in the fiber group (from 63,6±3,9 to 41,5±5,2 μmol/lt), but not in the placebo group (from 60,5±2,9 to 58,6±3.9 μmol/lt). Also, in the first two groups, the endotoxin value, as well as the alanine transferase level were lower (from 252±182 to 84±65 U/lt, p <0,01 in the Synbiotic 2000 group, and 110±86 U/lt, p <0,05 in the fiber group). A similar reduction of these two parameters was not recorded in the placebo group. Finally, significant improvement was noted in the first two groups of patients in the psychometric tests results, as well as in the frequency and severity of hepatic encephalopathy.

Yokoyama et al evaluated the effect of administrating synbiotics perioperatively versus no administration on bacterial translocation to mesenteric lymph nodes (MLNs) and the manifestation of bacteraemia postoperatively after oesophagectomy in a randomised clinical trial. 42 patients with oesophageal cancer were included in the study and divided randomly in synbiotics or no synbiotics (control) groups. MLNs were taken from the jejunal mesentery before dissection (MLN-1) and after the digestive tract was restored (MLN-2). Blood and feces samples were collected pre- and postoperatively. Microorganisms from blood and feces preoperatively and postoperatively were detected using a bacterium-specific ribosomal RNA-targeted reverse transcriptase–quantitative polymerase chain reaction method. Microorganisms were detected more commonly in MLN-2 samples in the control group than in the study group (P =0.035). In addition, bacteraemia on the first postoperative day was more frequent in the control group than in the study group P =0.025). Neutrophil counts on first, second and seventh postoperative days were all significantly lower in the study group than in the control group. It was concluded that perioperative use of synbiotics reduces bacteraemia and mesenteric lymph nodes bacteria incidence, reducing the inflammatory response and providing a more uneventful postoperative course after surgery for esophageal cancer [119].

In a randomised controlled trial, the administration of the symbiotic combination of inulin, oligofructose and Lactobacillus rhamnosus and Bifidobacterium lactis was studied in patients after polypectomy. They were compared to patients with colon resection only and the results were that the symbiotic use slightly stimulated the systemic immune system [120].

The aforementioned symbiotic combination has been shown to significantly reduce necrosis in colonic cells due to fecal water deregulation and ameliorate the function of epithelial barrier in patients with polypectomy. In addition, it can regulate the flora by increasing Bifidobacterium and Lactobacillus and decreasing Clostridium perfringens [102].

Sugawara et al studied the impact of synbiotics administration perioperatively in biliary cancer patients involving the hepatic hilus undergoing high-risk hepatobiliary resection. Patients were randomised into two groups; in the first, patients received postoperative enteral feeding with synbiotics, while the second group received pre- and postoperative synbiotics. Lactulose-mannitol ratio, serum diamine oxidase activity, natural killer cell activity, interleukin-6, fecal microflora, fecal organic acid concentrations, and complications were determined pre- and postoperatively. Lactulose-mannitol ratio and serum diamine oxidase activity had similar changes in both groups. Preoperatively in the second group, natural killer cells activity, and lymphocytes increased, while interleukin-6 reduced significantly (*P* =0.05). Serum interleukin-6, white blood cell counts, and C-reactive protein postoperatively in the second group were significantly lower than in the first group (*P* =0.05). Preoperatively, fecal cultures showed significantly increased numbers of *Bifidobacterium* colonies in the second group (*P* =0.05). The second also had significantly higher total organic acid concentrations in feces postoperatively than the first (*P* =0.05). Postoperative infectious complications were recorded in 30.0% of patients in the first group and 12.1% in the second (*P* =0.05). This study concludes that immune and inflammatory responses can be reduced by preoperative administration of synbiotics, and this can lead to decreased postoperative complications after surgical treatment for biliary tract cancer [121].

In a randomised double-blind, placebo-controlled trial, eighty patients following pylorus-preserving pancreatoduodenectomy (PPPD), received enteral nutrition immediately postoperatively. The patients were randomised into two groups, in the first, they were administered a compound of four Lactobacilli and four fibers and in the second, the placebo group, received fibers only one day preoperatively and for eight days after the PPPD. In the first group, postoperative bacterial infections were significantly less (12.5%) than in the second one (fibers only, 40%). Moreover, the fibers-only group received antibiotic therapy for a shorter period [122].

In another double-blind randomised placebo-controlled trial, 68 patients, in which colorectal surgery was performed, were divided into three groups and the systemic inflammatory response was studied. In the first group, 20 patients received a synbiotic combination (multi-strain/ multi-fiber Synbiotic2000) that consisted of four lactobacilli and four prebiotics. In the second group, 28 patients received prebiotics and heat-deactivated probiotics (lactobacilli) and in the third group, 20 patients received preoperative mechanical bowel cleaning only. Values of interleukin-6 and fibrinogen were significantly higher postoperatively in the synbiotic group. It was concluded that the use of prebiotics in colorectal surgery has a similar protective anti-inflammatory effect as mechanical bowel cleaning [123].

On the other hand, another randomised clinical trial showed no measurable effect on bacterial translocation, gastric colonisation, systemic inflammation, or sepsis in elective abdominal surgery after the administration of probiotics of five different probiotic species combined with the prebiotic oligofructose [124].

Few studies have measured the synbiotics effects on critically ill patients, but their initial findings are very promising [1]. Early enteral feeding with synbiotics could hamper late complications in severe acute pancreatitis [110]. The routine treatment protocol of severe acute pancreatitis seems that can be benefited from the addition of synbiotics in the early enteral feeding [125]. However, a recent meta-analysis showed that prebiotics, probiotics or synbiotics treatment shows no significant improvement in patient outcome with acute pancreatitis [126]. The use of probiotics remains controversial and furthermore, the administration of the probiotics is not without risk, as demonstrated in critically ill patients with severe pancreatitis treated with probiotics in combination with fiber-rich enteral nutrition 2 times daily, resulting in non-obstructive necrosis of the small intestine [39,127]. In conclusion, the beneficial roles of synbiotics are summarised in Table 1.

Conclusions- Prospects

Although the exact mechanism of the beneficial clinical effects of synbiotics is not yet fully known, most of the existing evidence supports the hypothesis that are due to the important properties of both prebiotics and probiotics factors.

To this day only the bioactive properties of a limited number of fibers have been studied. We need to explore new and highly bioactive plant fibers which are in nature in great abundance. We should determine and define probiotics that could be used as a substrate for specific dietary factors production, such as glutamine, arginine and polyphenols. Until now bioactivity of a few lactobacilli was studied. It is required thus to study even more probiotic bacteria. As lactobacilli grow on plants whose fibers are mainly used for fermentation, research should be focused on plants with known substances beneficial for the body. We have to focus on new synbiotic combinations of prebiotics and probiotics with beneficial action.

So far, the synbiotic effects have been investigated in patients with severe pancreatitis, colitis, Crohn's disease, cancer, major surgery, burn victims and liver transplantation. The research should be expanded into other critically ill patient groups, such as those with stem cell transplants.

In the preoperative preparation of the colon, the potential benefits of administration of synbiotics, against the use of antibiotics or the mechanism of colon cleansing should be investigated. The synbiotics can reduce the levels of fibrinogen and activator of plasminogen -1, and thereby they can increase fibrinolysis. Thus, their therapeutic skills in treating thrombosis should be under investigation.

As the sufficient administration of prebiotics and probiotics appears to strengthen the endogenous immune

TABLE 1. Beneficial roles of synbiotics

Prophylaxis in suspected or established IBD and carcinogenesis
Positive effect in various inflammatory colonic conditions
Enhancement of Intestinal Mucosal Barrier functionality
Maintenance of intestinal mucosa immunomodulation and immune defense enhancement against pathogenic micro-organisms
Reduction of septic complications in ICU
Modification of the flora by antimicrobial peptides induction by host cells
Antimicrobial factors released by probiotics
Epithelial adherence competition
Reduced inflammatory response
Reduced cardiovascular disease rate through lipid metabolism regulation
Enhancement of intestinal mucosa development, functional integrity maintenance, water and electrolytes balance maintenance, increased resistance against pathogens
Immune system regulation to the advantage of the host
Regulation of intestinal immunity and infections' prevention
Calorie intake reduction and body weight control
Effect on metabolic pathways such as the secondary bile acids deconjugation, the activities of bacterial enzymes as well as mineral absorption
Reduction of levels of fibrinogen and activator of plasminogen -1, and increase of fibrinolysis
Restoration of intestinal flora, improved intestinal permeability and bacterial translocation

system, and the long-time administration is not accompanied by side effects, the effectiveness of synbiotics in patients suffering from endemic chronic diseases such as atherosclerosis, cancer, diabetes, chronic pulmonary diseases, liver diseases, inflammatory bowel diseases, HIV, cystic fibrosis, and hemodialysis patients should be further explored.

Acknowledgments: *The authors have no one to acknowledge.*

Funding: *No funding was received for the present study.*

Declaration of interests: *The authors declare no competing financial interests or conflicts of interest.*

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