Calicut Medical Journal
www.calicutmedicaljournal.org

Review

Probiotics in humans – evidence based review

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ABSTRACT

Probiotics are live microbial food supplements or components of bacteria, which have been shown to have beneficial effects on human health. They are perceived to exert such effects by changing the composition of the gut microbiota. Several probiotic preparations seem to have promise in prevention or treatment of various conditions. There currently exists good evidence for the therapeutic use of probiotics in infectious diarrhea in children, recurrent Clostridium difficile induced infections and postoperative pouchitis. The possible benefit in other gastrointestinal infections, prevention of postoperative bacterial translocation, irritable bowel syndrome and inflammatory bowel disease continues to emerge. This review addresses the concept of probiotics and evidence from human clinical trials regarding the possible uses of probiotics in clinical practice.

INTRODUCTION

The primary function of the human gastrointestinal tract has long been considered as digestion and absorption of nutrients and excretion of waste end products. In recent years, however it has become accepted that the gastrointestinal tract fulfills many other functions, which are essential to our well-being. The intestinal tract of humans is host to a vast ecology of microbes and harbors more than 500 identified species that can be cultured and many bacteria that cannot be cultured and properly identified. These bacteria which are necessary for health have the potential to contribute to the development of diseases also by a variety of mechanisms [1,2]. Mucosa of the gastrointestinal (GI) tract function as a barrier excluding and eliminating numerous antigens derived from the external environment [3]. The peaceful coexistence of microbes with the host is referred to as host–microbe cross-talk, implying a benefit of the microbial presence to the host [4]. Perturbations in the intestinal epithelium can lead to an inflammatory response resulting directly from microbial products that alter the underlying epithelium or allow bacterial and food antigens to stimulate the mucosal immune system. Interactions between intestinal microbes and the host are the subject of intensive ongoing research as these changes influence a variety of diseases. There are three general methods by which the intestinal microflora can be altered: administration of antibiotics or prebiotics (ie, dietary components that promote the growth and metabolic activity of beneficial bacteria), or administration of probiotics (ie, beneficial bacteria).

Definitions

A probiotic is defined as a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract. This definition, however, was initially intended for use with animal feed products. For human nutrition, probiotics are defined as "live microbial food supplements or components of bacteria which have been shown to have beneficial effects on human health" [5]. The most frequently used genera fulfilling these criteria are lactobacilli and bifidobacteria

A prebiotic is defined as "as nonabsorbable food components that beneficially stimulate one or more of the gut-beneficial microbe groups and thus have a positive effect on human health" [6]. The most commonly used prebiotics are carbohydrate substrates (eg dietary fiber) with the ability to promote the components of the normal intestinal microflora which may evince a health benefit to the host.

Synbiotics is the word coined for the combined administration of specific prebiotics with probiotics to provide definite health benefits by synergistic action.

Table 1. Definitions

Probiotic	A live microbial food ingredient which is beneficial to health
Prebiotic	A non-digestible food ingredient which beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon having the potential to improve host health
Synbiotic	A mixture of probiotics and prebiotics which beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, and thus improving host health and wellbeing

GUT MICROBIOTA-THE SOURCE OF PROBIOTICS

The intestine's normal microflora is a metabolically active but as yet unexplored area of host defence [1,7]. Major functions of the gut microbiota include metabolic activities that result in salvage of energy and absorbable nutrients, trophic effects on the intestinal epithelium and protection of the host against invasion by harmful microbes [2,8]. The microbiota of a newborn develops rapidly after the birth and it is initially dependent mainly on the mother's microbiota, mode of delivery, birth environment and rarely genetic

factors [9,10]. The maternal vaginal and intestinal flora constitutes the source of bacteria, which colonizes the intestine of the newborn, the dominating strains being facultative anaerobes such as the enterobacteria, coliforms and lactobacilli. After weaning, the composition of the microflora gradually alters to resemble that of the adult. It has been estimated that at least 500 different microbial species exist in the GIT although on a quantitative basis about 20 genera probably predominate. These include Bacteroides, Lactobacillus, Clostridium, Fusobacterium, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Escherichia, and Veillonella. The bacterial strains with beneficial properties include mainly bifidobacteria and lactobacilli.

THERAPEUTIC MODULATION OF GUT MICROFLORA

The gut microflora is an important constituent in the intestine's defence barrier [11]. The initial compositional development of the gut microflora is considered a key determinant in the development of normal gut barrier functions [12]. Specific aberrancies in the intestinal microbiota may predispose the host to disease. Intestinal mucosal defense mechanisms acting in lumen and mucosa restrict colonization by pathogenic bacteria by interfering with the adherence of microorganisms to the mucosal surface. The normal gut microbiota can prevent the overgrowth of potential pathogens in the GI tract.

Probiotics introduce new microbes to the GI tract to enhance microbiota maintenance and modification, while most prebiotic components have been shown to enhance the growth of Bifidobacterium biota. Probiotics have been shown to amplify the gut mucosal barrier functions.

Probiotics – criteria

For organisms to be considered as probiotics, the following criteria need to be fulfilled:

(1) It should be isolated from the same species as its intended host

(2) It should have a demonstrable beneficial effect on the host

(3) It should be non-pathogenic

(4) It should be able to survive transit through the gastrointestinal tract

(5) On storage, large number of viable bacteria must be able to survive prolonged periods.

The list of such microorganisms continues to grow and includes strains of lactic acid bacilli (eg, Lactobacillus and Bifidobacterium), a nonpathogenic strain of E. coli (eg, E. coli Nissle 1917), Clostridium butyricum, Streptococcus salivarius, and Saccharomyces boulardii (a nonpathogenic strain of yeast)[13,14]. Also under development are strains of bacteria that have been genetically engineered to secrete immunomodulators (such as interleukin-10 or trefoil factors), which have the potential to favorably influence the immune system [15, 16]

Probiotics – mechanism of action

Mechanisms for the benefits of probiotics are incompletely understood. However, as a general rule, include [17]

- Adherence and colonization of the gut
- Suppression of growth or epithelial binding/invasion by pathogenic bacteria and production of antimicrobial substances
- Improvement of intestinal barrier function
- Controlled transfer of dietary antigens
- Stimulation of mucosal and systemic host immunity

Prebiotics act as an alternative for probiotics or their cofactors. Complex carbohydrates pass through the small intestine to the lower gut where they become available for some colonic bacteria but are not utilized by the majority of the bacteria present in the colon. Lactulose, galactooligosaccharides, fructooligosaccharides, inulin and its hydrolysates, maltooligosaccharides, and resistant starch are prebiotics commonly used in human nutrition. The main end products of carbohydrate metabolism are short-chained fatty acids, namely acetate, butyrate and propionate, which are further used by the host organism as an energy source.

The concept of pre and probiotics is presented in fig 1. The immunomodulatory potential of probiotics has introduced new potential therapeutic strategies for combating allergic, infectious and inflammatory conditions. Use of probiotics has the aim of dampening inflammation in the gut, which may involve anti-inflammatory mediators [18]. In fact, establishment of indigenous microbiota impacts on healthy immunophysiological regulation in the gut [19]. Aberrant gut microbiota may underlie not only nonspecific GI symptoms or acute infections, but also chronic diseases ranging from allergies to autoimmune and inflammatory diseases. Normalisation of the properties of unbalanced indigenous microflora by specific strains of the healthy gut microflora constitutes the rationale of probiotic therapy.

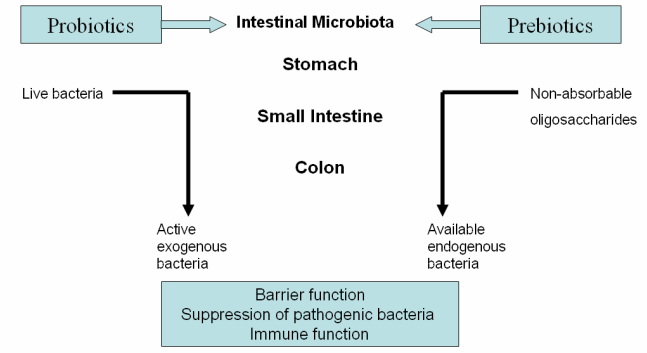

Fig 1: The probiotic and prebiotic concepts: altering the composition of intestinal microbiota by viable bacterial supplements versus nonabsorbable bacterial substrates.

CLINICAL USES OF PROBIOTICS

The hypothesis that microorganisms may have a role in maintaining human health is exciting, but it is not new. More than 100 years ago, Pasteur and Joubert observed that an antagonistic interaction occurs between bacterial strains and even suggested that nonpathogenic bacteria should be used to control pathogenic bacteria [20]. Often credited as the first advocate for probiotics, Elie Metchnikoff, the father of immunology, investigated intestinal microbes as causative agents in aging, a process he called "autointoxication." He made the observation that lactic fermentation of milk products arrested putrefaction and suggested that the consumption of those products might offer the same protection to humans [21]. Since then, scientific knowledge in the field of microbiology has expanded exponentially and the processes and consequences of bacterial fermentation have been elucidated. This has lead to attempts to manipulate the enteric microflora in a beneficial way, in the hope of achieving health benefits in the host.

PROBIOTICS IN HEALTH

Lifestyle and eating habits are partly responsible for each individual's overall health status. In ancient times, human species would have definitely eaten food with lot of live bacteria. As the concept of hygiene improved, we began eating clean food with very little live bacteria. The diet in western countries has been associated with the development of diseases such as heart disease and cancer because of its content of saturated fats and sugars and relative lack of fruits and vegetables and the desirable omega-3 fatty acids [22]. Western diet contains dramatically decreased numbers of fermented foods, exposing the host to as few as one millionth of the probiotic organisms to which human ancestors were exposed. It may not be a coincidence that the increase in inflammatory conditions, allergic conditions, obesity, heart disease and cancers has paralleled the decreased content of probiotics in the Western diet. In this context, it is to be reassessed as to whether humans need to eat sterile food instead of clean food unlike their animal counterparts

PROBIOTICS IN INTESTINAL DISEASES

DIARRHEAL DISEASES

Infective diarrhea

The most studied gastrointestinal condition treated by probiotics is acute infantile diarrhea. Rotavirus is the leading cause of infantile diarrhea worldwide and rapid oral rehydration is the primary treatment. Results of the role of probiotics have been summarized in at least three systematic reviews, all of which found an overall reduction in the duration of diarrhea by about 17 to 30 hours [23,24,25]. Several potential mechanisms have been proposed for how lactobacilli reduce the duration of rotavirus diarrhea viz; competitive blockage of receptor sites in which lactobacilli bind to receptors, enhanced immune response signal(s) from lactobacilli that regulates the secretary and motility defenses designed to remove perceived noxious substances and that lactobacilli produce substances that inactivate the viral particles. A meta-analysis performed by Huang and colleagues clearly revealed that the duration of acute infection was decreased by 1 day when a probiotics was begun at onset of diarrhea [26]. Whether these modest benefits would justify the routine use of probiotics in acute diarrheal illnesses is unclear since most acute diarrheal illnesses are self-limited. There is very little information regarding whether probiotics reduce important complications of diarrheal illness. Furthermore, the data do not provide a clear understanding of the type, dose, or duration of probiotic treatment that is required to achieve a clinical benefit. Limited data suggest that the minimal effective dose in children is 10 billion colony-forming units given within the first 48 hours. Given the positive results with Lactobacillus GG, Oberhelman and colleagues evaluated its use as a prophylactic agent in preventing diarrhea in children [27]. A lower incidence of diarrheal disease with the regular administration of a daily dose of Lactobacillus GG, 6 d a week for 15 months was evident but only in non-breast-fed infants. The use of probiotics as prophylaxis against diarrhea is an interesting concept that remains unproven.

The data on use in adults with diarrhea is limited and mixed [28,29,30]. Allan et el systematically reviewed 23 papers concerning probiotic treatment of infectious diarrhea and concluded that probiotics appear to be a useful adjunct to rehydration therapy in treating acute infectious diarrhea in adults and children [23].

Antibiotic associated diarrhea

Multiple studies have evaluated a variety of probiotics in the treatment and prevention of antibiotic associated diarrhea [31,32, 33]. At least two systematic reviews suggest that probiotics (including various bacterial species and the yeast S. boulardii) are effective in reducing the incidence of diarrhea in patients who are taking antibiotics. In a careful meta-analysis, DeSouza and colleagues pooled data showed that probiotics were more effective than placebo. However, discordant data have been published [34]. Because there is little harm from using a probiotic, it would seem that this therapy is important, significantly effective and cost-effective although routine clinical use of probiotics for all cases of antibiotic related diarrhoea cannot be justified. In addition, it remains unclear which probiotic and what doses are most effective.

Clostridium difficile associated diarrhoea

Clostridium difficile has been associated with symptomatic diarrhea since it was identified as the pathogen responsible for pseudomembranous colitis. As evidence that a normal bacterial flora can suppress the growth of C. difficile, patients have successfully been treated with fecal enemas [35]. It is reasonable to conclude that probiotic therapy could treat C. difficile infection in a similar fashion. Biller et al reported a series of four children with at least three recurrences of C. difficile successfully treated with lactobacillus [36]. The current largest, randomized, controlled trial with C. difficile-associated colitis demonstrated that S. boulardii was able to prevent disease recurrence, but only in those individuals who had more than one C. difficile sequential infection [37]

Total flora replacement (TFR) or fecal bacteriotherapy has been reported as a treatment alternative in severe C. difficile infections. It is based on transfer of fecal flora from a healthy individual, often a close relative, to a severely sick patient. TFR has been used occasionally in severe C. difficile cases, but also in severe constipation, irritable bowel syndrome and inflammatory bowel disease. The patients usually receive, after a preceding washout,

about 200 to 300 mL of fresh feces dissolved in an equal amount of saline solution. The process is repeated for about 5 to 7 days [35, 38,39]

Radiation induced diarrhea

Diarrhea is a nearly constant adverse effect of irradiation of the pelvis. Three studies in the literature report benefit of using probiotics for radiation-induced diarrhea [40,41,42]. All improved the patient status and the authors felt the probiotics were warranted and successful in decreasing radiation diarrhea. Such potentially interesting therapeutic effects should be studied more thoroughly.

Travelers diarrhea

Acute diarrhea occurs in about half of travelers who visit high-risk areas. Although most cases are mild and self-limiting, there is a considerable morbidity. Antibiotics are effective prophylaxis but are not recommended for widespread use and there is thus a need for cost-effective alternative treatments. Several studies were performed with the use of probiotics. Among the five double blind, controlled trial reported, only one trial showed significant benefit using Saccharomyces boulardii [43, 44, 45]. It is interesting that S. boulardii seems to have stronger effects on bacterial diarrhea, whereas Lactobacillus GG (LGG) has been shown to be more effective against viral and idiopathic diarrhea.

Other conditions with diarrhea

Three trials have reported a decrease in the duration of diarrhea induced by tube feeding by treatment with S. boulardii, one reported in English [46]. Two open studies proposed that lactobacilli might have some efficacy against small intestinal bacterial overgrowth [47,48], but S. boulardii was ineffective in the only randomized placebo-controlled study [49]. Elmer et al [50] reported that high doses of S. boulardii might be effective in some subjects with HIV-related chronic diarrhea; however, further evaluation is warranted before firm conclusions can be drawn.

INFLAMMATORY BOWEL DISEASE

Ingestion of probiotic bacteria has the potential to stabilize the immunological barrier in the gut mucosa by reducing the generation of local proinflammatory cytokines. There are 15 reported studies on the use of probiotics in inflammatory bowel disease (IBD) - four in ulcerative colitis, six in Crohn's disease and five in pouchitis [51,52,53,54,55,56,57]

Ulcerative colitis

Various probiotic species have shown promise in the treatment of ulcerative colitis in small studies, although a clear clinical benefit remains to be established. The four studies in ulcerative colitis were performed with Escherichia coli (Nissle), bifidobacteria plus L acidophilus and VSL#3. All studies had reported positive results. Prevention of relapse is more thoroughly documented than the treatment of active ulcerative colitis.

Crohn's disease

Probiotics in Crohn's disease have shown mixed results. Overall, four of the studies revealed definite clinical improvement and two were negative. In aggregate, the available data do not clearly demonstrate clinical effectiveness.

Pouchitis

Ileal pouch-anal anastomosis (IPAA) is the favored alternative to proctocolectomy with permanent ileostomy in ulcerative colitis (UC) and familial adenomatous polyposis. The most frequently observed long-term complication of IPAA is acute and/or chronic inflammation of the ileal reservoir, called pouchitis. Gionchetti et al. in a randomized, placebo-controlled trial in which VSL#3 was administered to 40 patients immediately after surgically formed ileal-anal pouches, achieved remission of 90% in the VSL#3-treated group versus 60% in the placebo-treated group after 12 months [56]. These studies have solidified the role of VSL#3 in the management of pouchitis [56, 57].

When the data in the 15 studies on IBD are considered, probiotic therapy appears encouraging. However further long-term studies are awaited.

IRRITABLE BOWEL SYNDROME (IBS)

IBS, as defined by the Rome II criteria, is a syndrome lasting for more than 3 months and may present with either constipation or diarrhea associated with abdominal pain. Several controlled trials of probiotics in irritable bowel syndrome (IBS) have been published [58,59,60,61,62]. The literature reveals five randomized or blinded controlled studies of which three reported a definite decrease in symptoms. Even though there is a positive trend in some of these studies, one can draw no definite conclusion on the use of probiotics in IBS in the absence of clinical improvements without statistical significance. However, it is possible that a clinically important benefit might be achieved in certain subgroups of patients, particularly those with diarrhea-predominant symptoms. Many clinicians will feel it is worth a try, but large controlled studies with different strains are needed to draw any definite conclusions.

LACTOSE INTOLERANCE

Intolerance to lactose-containing foods (primarily dairy products) is the most common disorder of intestinal carbohydrate digestion with prevalence ranging from 7 to 20 percent in Caucasians to 50% to 85% percent in African–Asians and anywhere from 90% to 100% in Asians [63]. Probiotics have been shown to improve lactose digestion by reducing the intolerance symptoms as well as by slowing oro-cecal transit [64]. During fermentation, most nonpathogenic bacteria including several strains of Lactobacillus (eg, Lactobacillus bulgaricus) and Streptococcus thermophilus produce lactase, which hydrolyses the lactose in diary products to glucose and galactose. Thus, it would seem that ingestion of probiotics can exert their lactase activity in vivo in the gut lumen, thus facilitating digestion and alleviating intolerance. This has been well shown in both adults and children [65, 66].

PREVENTION OF COLON CANCER

The consumption of probiotics and or prebiotics may have several antimutagenic effects [67,68]. Indeed the link between high fat, low fibre western diets and colon cancer may be partially explained by the alterations in fecal bacterial enzymes. The mechanisms by which lactic acid bacteria inhibit colon cancer may include alteration of the metabolic activities of intestinal microflora, alteration of physicochemical conditions in the colon,

binding and degradation of potential carcinogens, quantitative and or qualitative alterations in the intestinal microflora incriminated in the production of carcinogens, production of antitumorigenic or antimutagenic compounds, enhancing the host's immune response and effects on the physiology of the host. There is significant indirect and mechanistic evidence, based largely on laboratory animal and in vitro studies [69,70]. However, there is no evidence yet that probiotics can protect against the development of colon cancer in humans.

CONSTIPATION

Constipation is common especially in elderly people. An increase in the number of bowel movements or a decrease in transit time has been reported in controlled studies that employed probiotics for treating constipation [71,72]. The widely used laxative lactulose is a prebiotic, as it is not attacked by human disaccharidases and is substrate for the bifidobacteria in the colonic flora, that catabolise it to smaller molecules, creating an osmotic effect. However, one cannot draw any conclusion, as there is a need for larger controlled studies using probiotics and prebiotics other than lactulose.

HELICOBACTER PYLORI

Helicobacter pylori is the most common chronic bacterial infection in human and is now known to cause chronic gastritis, most peptic ulcers, gastric adenocarcinoma and lymphoma and a number of non-gastrointestinal disorders. Three reviews have been published that examine the role of probiotics in the treatment and prevention of H. pylori infection and have felt that the addition of probiotics, by enhancing immunoregulation, may be antagonistic to Helicobacter pylori infestation [73,74,75]. Many of the reports indicated there was either a suppression of H. pylori growth or a histological suppression of the gastritis but no study has identified eradication of the organism. In addition to their direct role in H. pylori, probiotics have been suggested to increase efficacy of eradication therapy by preventing antibiotic-associated side effects and thus increasing compliance [76]. Though these initial results appear promising, this requires further evaluation. At present, it is too premature to recommend the use of probiotics either alone or in combination with antibiotics for the eradication of H pylori.

LIVER DISEASE

Hepatic encephalopathy

Alteration of gut flora (either with probiotics or with prebiotics such as fermentable fiber) has been associated with improvement in hepatic encephalopathy in pilot studies [77,78]. Such therapy appears to lower blood ammonia concentrations, possibly by favoring colonization with acid-resistant, non-urease producing bacteria [79]. The role for this approach is still being studied.

Nonalcoholic fatty liver disease (NASH)

Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic hepatitis. Studies in rodent models of alcoholic fatty liver disease have demonstrated that intestinal bacteria, bacterial endotoxin and TNF-α modulate alcohol-induced liver damage. The concept that intestinal bacteria induce endogenous signals, which play a pathologic role in nonalcoholic fatty liver disease, suggests a role for novel probiotic therapy in this not so uncommon condition [80,81].

PANCREATITIS

Pancreatic necrosis and associated pancreatic infection are determinants of poor outcome in patients with severe acute pancreatitis. Colonization of the lower gastrointestinal tract and oropharynx with gram-negative organisms often precedes contamination of the inflamed pancreas. Human studies in which patients with acute pancreatitis received L. plantarum 299v showed a decrease in occurrence of pancreatic infection/abscess and a shorter hospital stay [82,83]. These human findings were supported by trials of probiotics (L. plantarum 299v and S. boulardii) in animal models of acute pancreatitis in which intestinal microbial translocation was reduced [84].

PROBIOTICS IN INFANTS

Breast-feeding protects infants from infectious disease by multiple mechanisms. Components of human milk may have an effect in modulating the composition of the intestinal flora and bifidobacteria generally constitute a significant component of normal intestinal flora in breast-fed infants [85, 86]. Breast-feeding can also affect the occurrence and virulence of colonizing pathogens [87, 88]. Thus, it appears that a combination of increased bifidobacterial counts and decreased concentrations of other enterobacteria and luminal host factors may play a role in protecting premature babies and newborns from diarrheal disease. Modification of the intestinal flora by increasing the predominance of specific nonpathogenic bacteria would seem a reasonable means of attaining a prophylactic or therapeutic effect against enteropathogens. Necrotizing enterocolitis is one devastating intestinal disorder known to occur in 10-25% of premature infants and very low birth weight babies and has a high mortality of 20-30%. Bacterial colonization or infection of the intestine by pathogens increases the risk of necrotizing enterocolitis. Trials showing reduction of necrotizing enterocolitis in population of premature newborns given supplements of Lactobacillus GG daily compared with historical control subjects have been reported [89,90]. These findings suggested a correlation between the reduction of lactobacilli and the increased risk of necrotizing enterocolitis.

USE OF PROBIOTICS BEYOND GIT

Metabolic effects- probiotics and lipid modulation

Ischemic heart disease is a major cause of morbidity and mortality that is often associated with elevated cholesterol levels and primary prevention with lipid lowering drugs or dietary modification can reduce the incidence and mortality of ischemic heart disease in healthy individuals. A wide variety of probiotic products have been used in clinical trials of serum lipid modulation [91,92,93,94]. Some of the studies report a positive effect on improving cardiovascular risk factors and there seems to be a trend towards decreasing risk factors. But more long-term evaluation would be required before firm conclusions can be drawn. At

present there is no good evidence to support the use of probiotics to modify serum lipids and to prevent atherosclerosis.

Allergy

Intestinal microflora can contribute to the processing of food antigens in the gut resulting in food hypersensitivity, of which atopic disease is a manifestation. Probiotics have the potential to modify the structure of potential antigens, reduce their immunogenicity, reduce intestinal permeability and the generation of proinflammatory cytokines that are elevated in patients with a variety of allergic disorders. There are a number of studies that evaluated probiotics in allergic conditions including rhinitis, atopic dermatitis and food allergy [95,96,97,98]. Although initial results in studies of children are promising, a definitive role for any of these indications remains unproven.

Urogenital infections and HIV

Bacterial vaginosis, yeast vaginitis and recurrent urinary tract infections (UTIs) are common urogenital problems. The normal vaginal flora in premenopausal women consists primarily of lactobacilli, which are protective against infection, but many pathophysiologic factors can cause unstable vaginal flora that may result in infection. There are only few studies with the use of probiotics in vaginal infections [99,100]. The overwhelming experiences have revealed a positive effect of L. acidophilus. Evidence from the available studies also suggests that probiotics can be beneficial for preventing recurrent UTIs in women [101]. The prevention or resolution of bacterial vaginosis is particularly important in women at risk of human immunodeficiency virus (HIV) infection. Studies have shown that women with bacterial vaginosis (no lactobacilli) are at significantly increased risk of HIV [102,103]. Thus treatment of bacterial vaginosis and promotion of vaginal lactobacilli may reduce a woman's risk of acquiring HIV-1, gonorrhea and trichomoniasis. A recent publication has shown that a human vaginal probiotic strain (Lactobacillus reuteri RC-14) can express potent functional viral inhibitors which may potentially lower the sexual transmission of HIV [104].However, further research is needed to confirm these results before the widespread use of probiotics for these indication can be recommended.

Sepsis in surgical and critically ill patients

Septic complications in surgical and intensive care patients are common. Large majorities of nosocomial infections are caused by intestinally derived organisms such as E. coli and the gut origin of sepsis hypothesis relies upon the phenomenon of bacterial translocation. There is therefore a sound theoretical basis for proposing that alterations in GI microflora might influence translocation and subsequent septic morbidity. In one of the earliest studies, using L. plantarum 299 given along with enteral fibre nutrition decreased the rate of postoperative infections in high risk liver transplant patients [105]. In another paper by Rayes et al patients undergoing major abdominal operations, including liver resection, pancreas resection, gastric resection, colon resection and intestinal bypass benefited from L. plantarum 299 in terms of fewer infections, shorter hospital stay and lower incidence of other complications [106].

PROBIOTICS IN PREGNANCY

Good nutrition during pregnancy improves the chances of having a healthy baby who will be at lower risk of diseases later in life. Bacterial vaginosis, has been suggested as a factor that increases risk of preterm labour and infant mortality and probiotics been shown to decrease risk of bacterial vaginosis and maintain normal lactobacilli vaginal flora [107,108]. In animal studies, these strains were found to be safe during pregnancy and to enhance the health of mothers and newborns [109].

Another area of interest in the use of probiotics in pregnancy is to prevent allergic reactions. Studies using *L rhamnosus* GG and *B lactis* BB12 have shown that atopic dermatitis, a condition that causes severe skin rashes in up to 15% of babies, can be prevented in 50% of cases if mothers ingest probiotics during pregnancy and newborns ingest them during the first 6 months of life [97,110,111]. Probiotics during pregnancy also have an excellent safety record [112].

OTHER POSSIBLE USES

Other health conditions that may benefit from probiotic consumption include hypertension [113,114], illness-related weight-loss [115], reducing recurrence of bladder cancer [116], collagenous colitis [117] and alcohol-induced liver damage [118]. Many other areas where probiotics may find use are currently being explored. These and many other potential benefits of probiotics remain inconclusive and controversial at present.

COMMERCIALLY AVAILABLE PROBIOTICS – SINGLE OR MULTIPLE STRAIN ?

The mechanism of action of probiotics in different situations is not well understood and so the optimal use of one or more strain cannot be precisely determined. While it seems intuitive that a combination of strains might be convenient to suite a range of indications and individual variation, this is dependent on the optimal probiotic bacterial numbers in different situations and assuming that the probiotic constituent of any cocktail are not mutually antagonistic which requires further study. Furthermore, the activities of individual components require definitions and optimization before firm recommendations can be made.

Single-strain - Saccharomyces boulardi (Laboratories Biocodex, Montrouge, France) is commonly given in doses of 2 capsules containing 250 mg morning and evening, equivalent to approximately 10 billion live organisms/d. The nonpathogenic E coli serotype O6:K5:H1 (Mutaflor;Ardeypharm GmbH, Herdecke, Germany) is referred to as Nissle 1917 is commonly given in doses of less than 10 billion LAB/d. Lactobacillus GG (LGG) (Valio, Helsinki, Finland) commonly is given in doses of 1 to 5 billion LAB/d. L acidophilus LA1 (LA1) (Nestle, Vevey, Switzerland) is commonly given in doses of less than 5 billion LAB/d (sometimes <1 billion LAB/d).

Multistrain - The probiotic cocktail VSL#3 (Sigma-Tau, Pomezia, Italy, and VSL Pharmaceuticals, Fort Lauderdale, Florida) is the only multistrain probiotic tried so far. It consists of four Lactobacillus strains (L acidophilus, L casei, L delbruecki subsp bulgaricus, and L plantarum), three Bifidobacterium strains

(B longum, B infantis, B breve), and S salivarius ssp thermophilus (5 1011 cells/g). It is commonly given in high doses,usually 1800 billion LAB and more recently up to 3600 billion LAB/d.

SAFETY ASPECTS

Probiotic supplements are easily accessible and available in the market worldwide. They are not regulated by the US Food and Drug Administration (FDA) because of their classification as a nutritional product rather than as a pharmaceutical product. This has made them available without prescription; however, the lack of regulation necessitates increased awareness from those who use them.

Probiotics are generally considered safe. As evidenced by epidemiologic studies, bacteremia or sepsis from lactobacilli is extremely rare. Numerous probiotics have a long history of safe use and no health concerns have been observed [5]. There are, however, isolated reports of fungemia with Saccharomyces following its use as a probiotic especially in immunocompromised or ICU patients [119,120]. Thus although administration of probiotics generally can be considered safe, each strain of probiotic has specific properties that should be considered before its use in any patient. Novel microbes, including probiotics and genetically modified probiotics need to be assessed for their safety on a strain-by-strain basis. The safety of probiotics in conditions where the mucosal integrity of gastrointestinal tract is compromised requires more studies before sweeping safety recommendations can be formulated.

FUTURE PERSPECTIVES

The capacity to assess the gut microbiota has expanded dramatically with the advent of molecular techniques. Real-time quantitative polymerase chain reaction procedures are among the promising tools for studies on intestinal microbiota composition. Such advancement will lead to the development of a new generation of probiotics, the action of which could be selected for defined disease-associated deviations in gut microbiota. This may also facilitate the potential use of genetically modified probiotic bacteria for pharmaceutical uses. Genetically modified lactic acid bacteria have been proposed as a vehicle to deliver vaccines in the gastro-intestinal tract. Several secretion-expression probiotic vectors have been constructed and are currently being tested in animal models. Other probiotics carrying different immunomodulating molecules are currently being tested. Also, the probiotic vector have been modified to provide a way to deliver the active ingredient at specific targets in the gastrointestinal tract. Various processing advances, such as microencapsulation and bacterial coating and addition of prebiotic compounds used as growth factors for probiotic organisms, will provide a means to optimize the delivery and survival of strains at the site of action.

CONCLUSIONS

Probiotics are live microbial food supplements or components of bacteria, which have been shown to have beneficial effects on human health. Normalization of the properties of unbalanced indigenous microflora of the intestinal tract by ingestion of specific strains of the healthy microflora forms the rationale of probiotic therapy. Prebiotic, probiotic and synbiotic treatment is still in its infancy but is rapidly moving into the mainstream. Several probiotic preparations seem to have promise in prevention or treatment of various conditions. There currently exists good evidence for the therapeutic use of probiotics in infectious diarrhea in children, recurrent Clostridium difficile induced infections and postoperative pouchitis. Evidence is also emerging for the use of probiotics in other gastrointestinal infections, prevention of postoperative bacterial translocation, irritable bowel syndrome and in ulcerative colitis and Crohn's disease. However, most studies have been in small number of patients and many have important methodological limitations, making it difficult to make unequivocal conclusions regarding efficacy, especially when compared with proven therapies. Currently no probiotic strategy is considered to represent the standard of care for any of the conditions described above. Furthermore, considerable differences exist in composition, doses and biologic activity between various commercial preparations and one consistent feature is that not all probiotic bacteria have similar therapeutic effects. The enthusiasm for probiotics has perhaps outpaced scientific support for these therapeutic approaches. They are generally regarded as safe, but physicians should monitor their use in high-risk patients. However, when used appropriately, probiotics represent a potentially beneficial adjunct to other proven therapies and with more controlled and larger studies clear data may emerge in the future.

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