Probiotics: Review of Evidence

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***Abstract*— Probiotic supplements have gained much popularity in the recent years. Media participation for the promotion of probiotic supplementation for various indications has been quite impressive as well. Traditionally, the word probiotic has been referred to in a positive manner and these supplements have been utilized as helpful resources in some way or another. The fact that makes this topic complicated and challenging, not only for the laymen but also for the healthcare providers is that there are numerous types and strains of probiotics available. Additionally, the standardization for dosing based on the indications is somewhat lacking. Few of the many questions that seem to pose challenges for today's health care providers are; which probiotic, how much of it, how long to use for and above all is there evidence to support the use of probiotics. The purpose of this article is to summarize the available evidence for Probiotic supplements for various indications and attempt to scratch the surface of probiotics data and seek answers to the pertinent probiotics related questions.**

***Index Terms*— Probiotics, Indications, Evidence**

I. Introduction

The World Health Organization defines probiotics as "live microorganisms" which when administered in adequate amounts confer a health benefit on the host. The most common types of these beneficial bacteria are Lactobacilli and Bifidobacterium. Previous studies indicate that probiotics may have a role in treating gastrointestinal illnesses, boosting immunity, treating and preventing some urogenital conditions, and preventing or slowing the development of certain types of cancer (1).

As a result of lack of consensus on various aspects of probiotics, a joint Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) formed an expert Consultation on Health and Nutritional properties of Powder milk with live lactic acid bacteria in Argentina in October, 2001. This was the first meeting of this group and the focus was on evaluation of the available scientific evidence relating to the properties, benefits, functionality, safety, and nutritional features of probiotics. This consultation referred to probiotics as 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host' (2). These probiotics/live microorganisms have been believed to play an important role in digestive, immunological as well as respiratory functions.

The word 'probiotic' originated from a Greek word meaning 'For Life'. At the forefront of inventions with regard to probiotics are attributed to two scientists; A Russian born scientist, a noble prize winner named Eli Metchnikoff and a French pediatrician Henry Tissier. Metchnikoff was responsible for the original observation of the positive role played by some selected bacteria. He suggested that "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes", Metchnikoff, 1907. Tissier observed that children with diarrhea had in their stools a low number of bacteria characterized by a peculiar, Y shaped morphology. These "bifid" bacteria were, on the contrary, abundant in healthy children He suggested that these bacteria could be administered to patients with diarrhea to help restore a healthy gut flora, Tissier, 1906 (2).

Probiotic Mechanisms

Probiotics are believed to exert their benefits on the host through growth and/or activity in the human body. However, it is not the source but the specificity of the action, of the microorganism that is important. As a matter of fact, confirming the source of a microorganism is challenging. Babies are not born with these bacteria in the intestine, and the origin of the intestinal microflora has not been fully elucidated. What is known is that the probiotics offer a barrier function for the normal microflora and this mechanism provides immunity against some diseases.

Gut microbes and intestinal epithelial and immune cells interactions are necessary for the development and maintenance of intestinal homeostasis. Immune and epithelial responses to microbes are dependent upon the species under study, the concentration of microbes used and the type of cell studied. A barrier is maintained between luminal microorganisms and the host immune system through intestinal epithelial cells, mucus and antimicrobial production, and IgA secretion. This interaction with the epithelium is through cell surface components, extracellular secreted proteins and fermentation products. Host-microbial interactions primarily involve Toll-Like Receptors (TLR) and Nucleotide-Binding Ligomerization domain and leucine-rich repeat containing proteins. In a dose and strain dependent manner, several probiotic strains directly alter tight junction protein expression and/or localization of epithelial cells in the gut through the release of secreted compounds. These host-microbial interactions at the gut mucosal surface are crucial for health and overall homeostasis and further, that probiotics may be utilized to enhance barrier and immune function to maintain health and offer protection against disease (3).

DOI: 10.5176/2345-718X_1.1.4

Most Common Indications and Evidence

Probiotics have been studied for various indications including diseases of the Gastro Intestinal (GI) tract, Allergies, Urogenital tract disorders, Cancer, as well as for overall health benefit. Available evidence will be classified using the levels of recommendations A through C where; A ***Level A recommendation*** is based on strong, positive, well-conducted controlled studies in the primary literature, which are not in abstract form. A ***Level B recommendation*** is based on positive controlled studies, but in the presence of some negative studies. A ***Level C recommendation*** is based on some positive studies, but clearly an inadequate amount of data to establish the certainty of a Level A or a Level B recommendation.

Diarrhea: Diarrhea arising from certain pathogenic bacteria and viruses is treatable and preventable by the use of probiotics. The strongest evidence of a beneficial effect of defined strains of probiotics has been established using Lactobacillus rhamnosus GG (LGG) and Bifidobacterium lactis BB-12 for prevention of acute diarrhea mainly caused by rotaviruses in children (1). Some fungal strains from the Saccharomyces such as Saccharomyces Boulardii (S. Boulardii) have also been used.

The most current evidence based recommendations for probiotics were developed based on the consensus opinion of the participants of the third Yale Workshop on probiotic use. The 2008 as well as 2011 recommendations from this panel (appendix a), validated the role of probiotics for various indications with the evidence based levels of recommendations as well as the probiotic strains (4). The recommendations for probiotic indications for diarrhea with the levels of recommendations are summarized in table I.

Diarrhea Type	**Recommendation**	**Specific Probiotic Strains**
Infectious-Childhood-Treatment	A	S. Boulardii, LGG, L Reuteri
Prevention of Infectious diarrhea	B	S. Boulardii, LGG
Prevention of AAD	A	S. Boulardii, LGG, combination of L Casei, L Bulgaricus, S. Thermophilus
Prevention of Recurrent CDAD	B/C	S. Boulardii, LGG, Bacteriotherapy
Prevention of CDAD	B/C	LGG, S Boulardii

Table I: Recommendations for Probiotic Use for Diarrhea
(Developed from Recommendations of Probiotic Use 2011, third Yale workshop)

Of particular interest are the indications for diarrhea resulting from the use of antibiotics commonly known as Antibiotic Associated Diarrhea (AAD) and Clostridium Difficile Associated Disease (CDAD), which have become a growing concern in today's health care. Several studies have been conducted and have proved the efficacy of probiotics for prevention of AAD and CDAD. Multiple meta-analysis as well as systematic reviews have also supported these results. One such metaanalysis on inpatient populations showed a Relative Risk Reduction (RRR) for AAD to be 44% meaning that use for probiotics can decrease the incidence of AAD by 44%. This reduction (RRR) for CDAD was much more significant at 71% (5). The studies used in this meta-analysis used various dosages and strains of probiotics causing the presence of heterogeneity to the meta-analysis.

Another large metaanalysis of 63 RCTs, which included 11 811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD with a relative risk of 0.58 (95% CI, 0.50 to 0.68; *P*=.001). The Number needed to treat (NNT) for this study was 13 (6)

Keeping the current available evidence for probiotics for the indication of diarrhea in perspective; the most effectively utilized strains of probiotics are; LGG, S Boulardii. The other Lactobacillus strains showing efficacy are; Reuteri, Casei, Thermophilus and Bulgaricus.

Inflammatory Bowel Disease (IBD): Since the initial research on the treatment of chronic inflammatory bowel disease (IBD) with Escherichia coli Nissle1917 in 1997, probiotic treatment for human IBD, including pouchitis, has been further investigated and reviewed extensively. At present, collective evidence suggests that the dynamic balance between microbes, mainly commensal flora, and host defensive responses at the mucosal frontier has a pivotal role in the initiation and pathogenesis of chronic IBD (7).

Best evidence for probiotics for IBD lies with the combination of multiple probiotics; mainly VSL#3 which constitutes eight different strains of probiotics; including three different strains of Bifidobacterium, four strains of Lactobacillus and one strain of Streptococcus.
Recommendations for probiotic usage along with the levels of recommendations for IBD are summarized in table II.

IBD Type	**Recommendation**	**Specific Probiotic Strains**
Pouchitis-Prevention	A	VSL#3
Pouchitis-Remission maintenance	A	VSL#3
Pouchitis-Induce Remission	C	VSL#3
Ulcerative Colitis-Induce Remission	B	E. Coli Nissle, VSL#3
Ulcerative Colitis-Maintenance	A	E. Coli Nissle, VSL#3
Crohn's Disease	C	E. Coli Nisle, S. Boulardii, LGG

Table II: Recommendation of Probiotic use for IBD (Developed from Recommendations of Probiotic Use 2011, third Yale workshop)
(VSL#3 contains 8 different strains of probiotics; Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus Bulgaricus, Streptococcus thermophilus).

Irritable Bowel Syndrome (IBS): The pathophysiology of IBS is unclear to date. However, several series of epidemiological, physiological, and clinical data suggest a role for intestinal bacteria in the pathogenesis of this disorder. Recent microbiology studies showed differences in the composition of the intestinal microbiota between patients with IBS and healthy individuals. Several RCT's comparing the effects of probiotics versus placebo in IBS have been published. Despite major differences in study designs, probiotic species used, dosing regimens, as well as reported clinical end points, the current data is in support of probiotics for improving IBS symptoms and reducing the risk of persistent IBS symptoms. There is limited data on the use of probiotics in children with IBS; however this data is also suggestive for beneficial effects (8).

To sum up the current evidence for probiotics for IBS; the best recommendations are for Bifidobacterium infantis and animalis, VSL#3, and Lactobacillus plantarum. The recommended probiotics with the level of evidence are summarized in table III.

Clinical Condition	Recommendation	Specific Probiotic Strains
IBS	B	Bifidobacterium Infantis, VSL#3
	C	Bifidobacterium Animalis, L. plantarum

Table III: Recommendations for Probiotic use for IBS (Developed from Recommendations of Probiotic Use 2011, third Yale workshop)

Necrotizing Enterocolitis: Is a potentially devastating disease affecting primarily preterm infants. It is characterized by severe inflammation and necrosis of the intestine. The mechanism of injury is believed to be the fact that the premature infant is likely to not have adequate initial ingestion of maternal vaginal and colonic flora because of rapid passage through the birth canal or because of C-section delivery. This lack of colonization with less diversity of bacteria phylla and fewer species of bacteria in the microbiota is implicated in causing the disease because of increased susceptibility to environmental pathogens (9).

The best evidence for probiotics for necrotizing Enterocolitis is with Lactobacillus acidophilus and Bifidobacterium bifidum with a level 'B' recommendation (4).

Immune Response: The GI tract functions as a barrier against antigens that arise in response to microorganisms and food. Establishment of indigenous microflora serves as a basis for the generation of immunophysiologic regulation in the gut. As a result of this finding, novel therapeutic interventions have been introduced based on the consumption of cultures of beneficial live microorganisms that act as probiotics. One of the suggested mechanisms of probiotic therapy is the promotion of a non-immunologic gut defense barrier, which includes the normalization of increased intestinal permeability and alteration in gut micro ecology. Another possible mechanism of probiotic therapy is enhancement of the intestine's immunologic barrier, particularly through intestinal immunoglobulin A responses and exclusion of intestinal inflammatory responses. All of these exhibit a gut-stabilizing effect. Many probiotic actions are mediated through immune regulation, particularly via balance control of anti-inflammatory and proinflammatory cytokines. The data show that probiotics can be utilized as innovative tools to exclude intestinal inflammation, normalize mucosal dysfunction of the gut as well as down-regulate hypersensitivity reactions. Data from more recent sources suggest that differences exist in the way particular probiotic bacteria exert immunomodulatory effects. Moreover, healthy subjects and the patients with inflammatory disease have distinct regulatory effects. These results conclude that development of clinical applications for extended target populations should take into consideration the specific immunomodulatory properties of probiotic bacteria (10).

Best evidence for probiotics for immune system enhancement is with LGG, Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium lactis and Lactobacillus johnsonii with a level 'A' recommendation (4).

Allergy: The barrier function faces an abrupt change at birth when the gut switches from processing amniotic fluid to digesting milk. Release of trophic hormones occurs as a result of food consumption and the secretion, motility, and absorption functions are activated. The immunologic hyporesponsiveness to antigens encountered through the enteric route produces oral tolerance. Several immunoregulatory aberrations favoring sensitization instead of tolerance induction prevail in early infancy. Antigen exclusion, elimination, and immune regulation mechanisms of the intestine are incomplete during a variable period after birth. This predisposes the intestine to an aberrant antigen uptake. Reduced capacity to generate IgA producing cells occurs as a result of immature immunologic protection. T-cell function in aberrancy is also present, thus profound differences exist in immune-regulatory cytokine generation between the cells of infants and those of adults. In newborns, the cytokine profile that of humoral immunity instead of cell-mediated immunity and the abundance of interleukin 4–generating cells during a critical period may change the immunologic T-cell memory to T-helper-2 phenotype. This leads to increased IgE production and possibly to atopic sensitization (10).

The best evidence for probiotics for Atopic eczema associated with cow's milk allergy for prevention as well as treatment is with LGG and Bifidobacterium lactis (4). The

summary of evidence with the levels of recommendation is summarized in Table IV.

Clinical Condition	Recommendation	Specific Probiotic Strains
Atopic Eczema associated with cow's milk allergy-Treatment	A	LGG, Bifidobacterium lactis
Atopic Eczema associated with cow's milk allergy-Prevention	A	LGG, Bifidobacterium lactis

Table IV: Probiotics for prevention and treatment of Atopic Eczema associated with cow's milk (Developed from Recommendations of Probiotic Use 2011, third Yale workshop)

Radiation Enteritis: Results from exposure of the abdominal region to ionizing radiation. Many patients undergoing radiation are affected by transient symptoms of irradiation of the bowel. Acute-phase symptoms may last for a short time; however the long-term complications can include significant clinical conditions that are associated with high morbidity. Data from some experimental studies as well as the clinical trials suggest the potential benefit for probiotics in radiation-induced enteritis and colitis. Therefore, the hypothesis that probiotics play a role in reinforcing antioxidant defense systems of normal mucosal cells exposed to ionizing radiation may explain to an extent their beneficial action (11).

The best evidence for probiotics for radiation induced enteritis is with VSL#3 and lactobacillus acidophilus, with a 'C' level of recommendation (4)

Bacterial Vaginosis (BV) and Vaginitis: According to the WHO, there is some clinical evidence to suggest that oral and vaginal administration of lactobacilli may eradicate asymptomatic and symptomatic BV. Supporting evidence for prevention of recurrent BV or W C by probiotics is limited however (12).

The best evidence for probiotics for Vaginosis and vaginitis is with Lactobacillus acidophilus, LGG and Lactobacillus Reuteri with a 'C' level recommendation (4).

Urogenital Tract Disorders: The association between abnormal vaginal microbial flora and its formidable risk in the increased incidence of urinary tract infection (UTI) underscores the value of understanding the microbial flora and the efforts needed to maintain it, to ensure urogenital health. Surprisingly in spite of the high incidence, UTI's receive very little attention from the medical fraternity. Growing awareness among common men as well as the newer advances in the medical field has brought them some attention. The significance of replenishing this depleting microbial flora with 'probiotics' has resurfaced in a big way. It would be unfair to take the value of probiotics on their face value. While probiotics cannot be considered a panacea for treating UTI's, the available data may be promising for ptobiotics as a strong option in improving and maintaining urogenital health (13).

The evidence for probiotics for urogenital tract disorders is inconclusive at this time and more research is needed to support this indication.

Coronary Artery Disease (CAD): Probiotics are believed to exert this benefit by lowering cholesterol. Suggested mechanisms for cholesterol removal by probiotics are; assimilation of cholesterol by growing cells, binding of cholesterol to cellular surface, incorporation of cholesterol into the cellular membrane, de-conjugation of bile via bile salt hydrolase, co-precipitation of cholesterol with de-conjugated bile, binding action of bile by fiber, and production of short-chain fatty acids by oligosaccharides.

More RCT's are needed to evaluate the cholesterol lowering properties of probiotics. Bifidobacterium and Lactobacillus species could potentially be studied and utilized for this indication (14).

Ventilator Associated Pneumonia: A recent metaanalysis of seven RCT's including total of 1,142 patients showed no significance of probiotics use for prevention of Ventilator Associated Pneumonia (VAP). The study showed Odds ratio (OR) for VAP to be 0.82; 95% CI (confidence interval), 0.55 to 1.24; P = .35, with low heterogeneity among the studies (I2 = 36.5%, P = .15). This study was consistent with the previously available evidence and did not appear to significantly alter any of the other meta-analysis endpoints (15).

Therefore, the use of Probiotics for prevention of VAP cannot be recommended at this time. Current literature is against the use of probiotics for prevention of VAP.

Colon Cancer: Preliminary evidence suggests that probiotic microorganisms may be able to prevent or delay the onset of certain cancers. This originates from the knowledge that members of the gut microflora are capable of producing carcinogens such as nitrosamines. Hence, administration of Lactobacilli and Bifidobacteria could theoretically modify the flora resulting in decreased glucuronidase and carcinogen levels. Furthermore, there is some evidence that suggest that the cancer recurrences at other sites, such as the urinary bladder may be reduced by intestinal instillation of probiotics including Lactobacilus casei. In vitro studies with LGG and Bifidobacteria and an in vivo study using two other Lactobacilus rhamnosus strains and propionibacterium species showed a decrease in availability of carcinogens in the lumen of the gut.

Keeping all the above in perspective, it would be interesting to follow the future research for probiotics for this indication. It is too early to make a definitive clinical conclusion

regarding the efficacy of probiotics in cancer prevention at this time (4)

Healthy People: Otherwise healthy **c**onsumers also use probiotics based on the assumption that probiotics can help retains their health and well-being, and potentially decrease their long-term risk of disease states affecting the bowel, kidney, respiratory tract and heart. There is a possibility that probiotic microorganisms could become primary colonizers that could remain long-term or even for life. While the use probiotic in premature and low birth weight infants may prevent death and serious morbidity, the alteration of flora in otherwise healthy babies is a more complex issue and needs further investigation (2)

It would also be prudent to recognize that the dosages of probiotics may not be sufficient in many commercially marketed yogurt brands. Clinicians should use manufacturer's recommendations for dosing of specific probiotics for various indications.

Most Common Probiotics Genera and Adverse Events

The Agency for Healthcare Research and Quality's (AHRQ) systematic review on the safety of products containing microorganisms believed to have probiotic properties. This review was co-sponsored by the National Institutes of Health (NIH) Office of Dietary Supplements, the NIH National Center for Complementary and Alternative Medicine (NCCAM), and the Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition. This document was a result of a systematic evidence based review of the studies monitoring the adverse health outcomes among probiotic studies, without restriction due to study design, participant, or clinical field. As per this report, the six genera of probiotics; Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus and Bacillus have been studied. Lactobacillus alone or in combination with other genera most commonly and Bifidobacterium were the most studied probiotics. There was some evidence to indicate that Streptococcus interventions may be responsible for a greater number of adverse events compared to other genera. There are no head to head trials to prove this however. The reviewers stratified RCTs that used each genus exclusively, no statistically significant difference between intervention and control group participants was observed for any of the six genera. However, published reports on the genera Enterococcus, Bacillus, Streptococcus were not available in the literature. Saccharomyces interventions and Bifidobacterium interventions were also rare, and a substantial proportion of studies were done using blends of probiotics (16).

Adverse Events: Most reported side effects were GI side effects and most of these side effects were observed within the first 3 days of treatment. There have been some case reports of infections including sepsis, bacteremia and fungemia believed to be resulting from probiotics. Most infections seem to be occurring one week to several weeks after initiation of probiotic use. Interestingly, during the subgroup analyses, there was no statistical significance that participants using probiotic organisms experienced more GI side effects, or infections compared with control group participants (see table V) (16).

Adverse Effects	RR (Relative Risk)	95% CI	p value	# of RCT's
GI	1.03	0.89-1.18	0.693	126
Infections	1.00	0.87-1.16	0.967	65
Other	1.01	0.91-1.12	0.923	131

Table V: Data from AHRQ Subgroup analyses of Adverse Effects

Interactions with Other Medications: The classes of medications that have been suspected to have interactions with probiotics in the past include; corticosteroids, antibiotics, immune suppressants, dietary therapies, chemotherapy, these have been questioned about possibly influencing the adverse events experienced by individuals taking medications from the above mentioned classes along with the probiotics. The current data suggests that the relative risk to experience an adverse event for studies with co-treatments is slightly higher but not of any statistical significance. Upon an interaction analysis of 44 studies with co-treatments the findings were as follows; Relative Risk (RR) =1.12; 95% CI: 0.99-1.26; p=0.074.

Adverse Events based on Age groups: Stratified analyses and meta-regressions did not show any increased risk of adverse events for children, adults, or elderly participants compared with adverse events observed in corresponding control groups. There were only four studies on the elderly population however (see table VI) (16).

Population	**RR**	**95% CI**	**P value**	**# of RCT's**
Children	0.96	0.88-1.04	0.296	35
Adults	0.97	0.79-1.19	0.745	40
Elderly	0.94	0.82-1.08	0.367	4

Table VI: Data from AHRQ Stratified analyses & metaregressions of adverse events by age groups

Adverse Events Based on Health Status: Health status has traditionally been thought to be associated with the experience of an adverse event when using probiotics. Case reports of serious adverse events appeared to be individuals with health-compromised status. Healthy

participants were not generally affected by serious infections caused by probiotic organisms. Therefore subgroup analyses of RCTs in medium health-compromised participants and critically ill patients was conducted and the results did not show a statistically significant increased risk of experiencing adverse events for intervention participants compared with control group participants with similar patient characteristics (see table VII) (16).

Health Status	RR	95% CI	P value
Medium Health compromise	1.03	0.94-1.13	0.491
Critically Ill	0.79	0.51-1.22	0.286

Table VII: Data from AHRQ subgroup analyses of RCT's in medium health compromised and critically ill patients

Adverse Events Based On Routes of Administration: Most common routes of administration of probiotics are oral and enteral. Intra vaginal and topical routes have also been used.

Oral route has been the most common routes of administration. During a stratified analysis, there was statistical difference found between the control and placebo groups. The relative risk of adverse events for probiotics group participants compared to control group participants was 0.98 (95% CI: 0.93-1.04; p=0.581). The corresponding risk difference between groups was also not statistically significant at-0.001 (95% CI: 0.005-0.003; p=0.207) (16).

Enteral routes of administration include naso-gastric and jejunostomy feeding tubes. The difference between the probiotic and control groups was not of any statistical significance when a pooled analysis based on adverse events was conducted. Results showed; RR= 0.84 (95% CI= 0.55-1.29; p=0.350), RD -0.002; 95% CI: -0.022, 0.017; p=0.828) (16).

Other routes of administration included intra-vaginal administration of probiotics which revealed mild-moderate additional side effects such as vaginal discharge. RR 1.06 (95% CI: 0.72-1.57), p=0.761 and RD -0.004 (95% CI: -0.054-0.046), p=0.870) (16).

Therefore, there was no evidence that a particular mechanism or route of administration of probiotic organisms was associated with an increased risk of an adverse event in intervention participants relative to control group participants (16).

Single versus Multiple Probiotics: The next question is whether to use one single strain of probiotics or a combination of multiple strains. The reality is that the combination of probiotics is used more frequently than the single probiotic and hence majority of the studies have conducted using combination of probiotics. A Meta Regression to investigate if the risk of adverse events was different among these two groups across studies. There was no statistically significant difference, showing a RR=0.93 (95% CI=0.82-1.04), p=0.205 (16).

Duration of Use of Probiotics: Duration of use of probiotics for a short term (<1month), medium term (>1 month-<1year), and long-term (1 year or more) has also been compared for the presence of adverse events among probiotics and control groups. Stratified analyses and metaregression was undertaken to explore whether the duration of intervention was associated with encountered adverse events. Short term and Medium term use seemed to have no statistically significant difference in encountered adverse events. The difference in adverse events was also not statistically significant in the long term use groups. RR and RD (Risk Difference) are presented in table VIII. An interesting finding was an isolated case report of a participant who took Saccharomyces Boulardii for over a year presented with a fever of unknown origin (FUO).

Duration	RR (95% CI), p	RD with 95% CI, p
Short term (<1month)	1.02 (0.89-1.17), 0.780	0.000 (0.005-0.004), 0.866
Medium term (>1month-<1yr)	0.98 (0.98-1.04), 0.470	-0.001(0.012-0.010,0.889
Long term (1 year or more)	0.76 (0.41, 1.39), 0.259	-0.006 (0.016-0.004), 0.259

Table VIII: Data from AHRQ stratified analyses of Adverse Events based on the duration of Use of probiotics

Based on the available evidence, it would be reasonable to say that the increased duration of use of probiotics did not increase the incidence of adverse events with less than one year of use of probiotics. It would be prudent to use some caution if the use requires over one year and the decision should be based on the indication as well as the benefits versus risks.

Storage and Safety: Even though the use of the term "probiotic" has traditionally been limited to microorganisms alive at the time of consumption, it is becoming increasingly evident that even non-viable microorganisms can confer health benefits as well (17).

Non-viable forms offer the benefit of being stable for prolonged periods of time as compared with the viable products. It is questionable, however, that all health benefits achievable by live probiotics can be achieved by non-viable forms. It is known that one strain of Lactobacillus; johnsonii is effective in reducing the activity of gastric pathogen Helicobacter (H) pylori in a fermented form but not in a pasteurized form (18). In addition to pasteurization, other methods used to prepare these non-viable forms include; sonication, high pressure treatment, and freeze thawing. Irradiation is used as well however that method is not permitted for use in food.

Probiotics stability during manufacturing and storage is dependent upon three major factors; strain robustness, process and storage conditions. Growing probiotics in an industrial medium and drying them for longer lasting storage is a common method used to improve stability by controlling the moisture content. Therefore, most liquid probiotic products are refrigerated products. The stability of probiotic-containing chilled

dairy products is well known. Products have been reported to maintain potency up-to 4–6 weeks of refrigerated storage. The shelf like improves with the drying process. The drying step represents a relatively short period during which probiotics are exposed to stressful conditions. Afterwards, they still have to remain viable in the final product for up to two years of storage. Depending on the conditions of storage and duration, the loss of probiotic viability during storage may be significantly higher than the loss during the drying process. Details of stability and storage temperatures for various probiotic forms are presented in table IX (19).

Dry/dehydrated products	**Moisture Content**	**Length of Shelf life**	**Temperatures**
Cereals, biscuits, snacks, confectionery, pet food	Intermediate (aw 0.2–0.5)	Mild climate 18–24 months	During distribution 30–40 ◦C (up to 50 ◦C)
Infant formula, milk powder, cereals	Low aw < 0.2	Hot climate 12–18 months	On Shelf
Supplements	Very low aw < 0.1	Depends on distribution	Room Temperature and higher

Table IX: Moisture content and temperature of various dehydrated products (19)

Summary

Current evidence suggests that use of probiotics is promising in prevention and or treatment of; GI diseases including; Infectious diarrhea, Pouchitis, Irritable Bowel Syndrome, Helicobacter pylori, Clostridium difficile Disease, Antibiotic Associated Diarrhea, Traveler's Diarrhea, or Necrotizing Enterocolitis (21). Evidence also supports use with less strength than the conditions mentioned above, including; the conditions of the urogenital tract, allergy, cholesterol lowering, as well as cancer prevention. More research is needed to evaluate efficacy for these indications for a superior evidence. The mechanisms of actions of probiotics on GI and various other conditions have been studied and will continue to be studied with the same pharmacologic approach as drugs (22). Clinicians must record patient's use of probiotics in the medication profiles and be vigilant and report any adverse events that may arise from their use. With the growing use of probiotics among general population for various indications, it would be prudent to enquire about use of probiotics in patient history and educate patients on storage, safety as well as monitoring for any adverse events during their use of probiotics. Clinician's should use current evidence and their clinical judgment in making recommendations for or against the use of probiotics. Ultimately, while selecting a product for use, the benefits should outweigh the risks.

REFERENCES

[1] The National Center for Complementary and Alternative Medicine. The Research Spotlight; the two studies explore the potential health benefits of probiotics, Retrieved, July. 2012. from, http://nccam.nih.gov/research/results/spotlight/110508.htm

[2] Food and Agriculture Organization of the United Nations. World Health Organization. (2001). Health and Nutritional Properties of Probiotics in Food Including Powdered milk with live Lactic acid bacteria-A report of a joint FAO/WHO Expert consultation.

[3] Madsen KL. (2011). Interactions between Microbes and the Gut Epithelium. Journal of Clinical Gastroenterology. 2011; 45:S111–S114.

[4] Floch MH, Walker WA, Madsen K, et al. Recommendations for Probiotic Use-2011 update. Journal of clinical gastroenterology. 2011; 45; S168-S171.

[5] Avadhani A, Miley H. Probiotics for Prevention of Antibiotic Associated Diarrhea and Clostridium Difficile Associated Disease-A Meta-analysis, Journal of American Academy of Nurse Practitioners, 2011; *23* (6) 269-274.

[6] Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of Antibiotic Associated Diarrhea-A systematic Review and Meta- analysis. Journal of American Medical Association. 2012; 307(18):1959-69.

[7] Meijer B J, Dieleman LA. Probiotics in the treatment of Human Inflammatory Bowel Disease-Update 2011. Journal of Clinical Gastroenterology. 2011; 45(3): S139-S144.

[8] Ringel Y, Ringel-Kulka T. The Rationale and Clinical Effectiveness Probiotics in Irritable Bowel Syndrome. Journal of Clinical Gastroenterology. 2011; 45(3): S145-S148.

[9] Ganguly K, Walker WA. Probiotics in the prevention of Necrotizing Enterocolitis, Journal of Clinical gastroenterology. 2011; 45 (3): S133-S138.

[10] Isolauri E, Sutas Y., Kankaanpaa P, et al. Probiotics: Effect on Immunity, American Journal of Clinical Nutrition. 2001; 73(suppl): 444S-450S.

[11] Spyropoulos BG, Misiakos EP, Fotiadis C, Stoidis CN. Antioxidant properties of probiotics and their protective effects in the pathogenesis of radiation-induced enteritis and colitis, Digestive Diseases and Sciences, 2011; 56(2):285-94.

[12] Jurden L, Buchanan M, Kelsberg G, Safranek S. Clinical Inquiry: Can probiotics safely prevent recurrent vaginitis? Journal of Family Practice; 2012; 61(6):357-68.

[13] Waigankar SS, Patel V. Role of Probiotics in Urogenital Care, Journal of midlife Health. 2011; 2(1):5-10.

[14] Kumar M, Nagpal R, Kumar R, et al. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases.2012; 902917.

[15] Gu WJ, Wei CY, Yin RX. (2012). Lack of Efficacy of Probiotics in Preventing Ventilator-Associated Pneumonia: A Systematic Review and meta-Analysis of Randomized Controlled Trials, Chest. 2012; 10.1378.

[16] Agency for Healthcare Research and Quality. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. Evidence Report/Technology Assessment. 2011; AHRQ Publication No. 11-E007.

[17] Adams CA, The probiotic paradox: live and dead cells are biological response modifiers. Nutrition Research Reviews. 2010; 23, 37–46.

[18] Gotteland M, Andrews M, Toledo M, et al. Modulation of Helicobacter pylori colonization with cranberry juice and

Lactobacillus johnsonii La1 in children. Nutrition. 2008; 24, 421–426.
[19] Makinen K, Berger B, Bel-Rhild R, Ananta E. Science and Technology for the mastership of probiotic applications in Food Products, Journal of Biotechnology. 2012 (Epublication ahead of print)
[20] Unites States Food and Drug Administration. Dietary Supplements, Retrieved; July, 2012 from; http://www.fda.gov/food/dietarysupplements/default.htm
[21] Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases, PLOS One. 2012; 7(4):e34938.
[22] Marteau PR, Probiotics in Clinical Conditions. Clinical Reviews in Allergy and Immunology. 2002 ;22(3):255-73.

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Research Interests:

- Areas of Research Interest: Infectious Diseases, Critical Care

- Doctoral Research: A Meta- analysis on efficacy of probiotics for prevention of Antibiotic Associated Diarrhea and Clostridium Difficile Associated Disease.

- Masters Research: Relationship between Standardized Health Education Conducted by Registered Nurses and Behavioral Changes that Modify Risk Factors and Cholesterol Levels.

- Capstone Projects Chair:
  A. Risk Factors for Surgical Site Infection among Obese Patients versus Non-obese Patients Undergoing Colorectal Surgery-Completed APR 2013
  B. Effectiveness of Self care Management Education in a Nurse Practitioner managed clinic-In progress
  C. Effectiveness of Early initiation of Stroke guidelines in improving patient outcomes

- Research in Progress:
  Randomized Controlled Trial of efficacy of probiotic; Lactobacillus Rhamnosus GG for prevention of Antibiotic Associated Diarrhea and Clostridium Difficile Associated Disease in hospitalized adults.