REVIEW ARTICLE

Probiotic Clinical Considerations: Where do they fit?

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Interest in probiotic use for certain clinical conditions has substantially increased over the past few years. There is much research regarding probiotics as preventive, adjuvant, and primary therapeutic agents. While many studies have shown that probiotics have some efficacy, there is difficulty in determining a specific, evidence-based prescription. Studies have been limited by design due to limited sample sizes, high attrition rates, heterogeneous selection of probiotic type, and differing treatment lengths. It is not entirely clear which probiotic species is the best, but the evidence is promising for several clinical conditions. This article will answer some common questions concerning four broad clinical areas of suggested probiotic use: adult and pediatric diarrheal illness, genitourinary infections, atopic dermatitis, and upper respiratory tract infections. Probiotic safety and quality will also be discussed. In the age of increasing antibiotic resistance and the emerging role of the gut microbiome in health, further research is encouraged in the development of probiotics going forward.

INTRODUCTION

There is a growing interest in probiotic use for health benefits and disease treatment strategies. Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1] The term probiotic comes from the Greek word "for life" and has been identified as bacteria or yeast in certain dietary supplements and foods. The most common probiotics available include bacteria *Lactobacillus* and *Bifidobacterium*, and yeast *Saccharomyces boulardii*. Probiotics as single species or combinations of multiple species are found in products over the counter including yogurt, dairy drinks, capsules, tablets, packets, and sachet powders. Each probiotic has unique qualities but there is little evidence supporting various species combinations when advertised for synergy.[2] There is no known class effect regarding species and health benefits.[2, 3] Table 1 *(page 22)* lists the types of probiotics found in many available products.

Probiotic Mechanisms of Action

Several characteristics of probiotics have been reported to play a role in health. These include the ability to 1) transit through and survive in the gastrointestinal (GI) tract, 2) colonize and reproduce in the gut by adherence, 3) modulate the host immune system and block pathogens, and 4) balance homeostasis of the gut flora. Other important characteristics include quality manufacturing practices that ensure shelf life stability and the development of probiotics that are not pathogens.[2, 4]

Probiotic Safety

Probiotic safety and research is limited. Adverse effects reported have been minimal and are primarily GI in nature. Didari et al. conducted a systematic review in 2014 of clinical studies using common probiotic species that included *Bifidobacterium*, *Lactobacillus*, *Saccharomyces boulardii*, *Streptococci*, *Enterococcus*, *Propionibacterium*, and *Escherichia coli species Nissle 1917*. Their observations determined that "overwhelming existing evidence suggests that probiotics are safe;" however, there were some studies that reported adverse risks including fungemia, sepsis, and GI ischemia.[5] This review highlighted an important connection between serious illnesses and certain high risk patient groups including those who were hospitalized, immunocompromised, post-operative, in the intensive care unit, and critically sick infants. For example, several cases of fungemia caused by S. boulardii were identified in critically ill patients who had central venous catheters.[5] The National Institutes of Health (NIH) acknowledges many studies demonstrate probiotic safety with certain species, but advises caution about applying this to all probiotics.[2,4]

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TABLE 1:

Microorganisms Considered Probiotics[2]

Bacteria		Other	Yeast
Lactobacillus species (LAB)	*Bifidobacterium species*	*Bacillus cereus*	*Saccharomyces boulardii (S. boulardii)*
L. acidophilus	*B. adolescentis*	*Enterococcus faecalis*	
L. bulgaricus	*B. animalis*	*(considered pathogenic)*	
L. casei	*B. bifidum*	*Enterococcus faecium*	
L. cripatus	*B. breve*	*(considered pathogenic)*	
L. fermentum	*B. infantis*	*Escherichia coli Nissle (E.coli)*	
L. gasseri	*B. lactis*	*Streptococcus thermophiles*	
L. johnsonii	*B. longum*		
L. lactis			
L. pantarum			
L. reuteri (LR)			
L. rhamnosus GG (LGG)			

TABLE 2:

Yale / Harvard 2015 Workshop Probiotic Expert Recommendations[6]

A	Based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form
B	Based on positive, controlled studies but the presence of some negative studies
C	Based on some positive studies but clearly an inadequate amount of work to establish the certainty of "A" or "B"

Probiotic Quality

The majority of probiotic products are sold as dietary supplements which are not subject to Food and Drug Administration (FDA) approval before marketing. In order for a specific probiotic to be marketed as a drug for clinical treatment, more stringent studies must be performed to meet the FDA requirements. Many probiotic advertisements make online statements regarding safety and health promotion, but they cannot make disease prevention claims without FDA regulation.[2,4]

Finding high quality commercial probiotics can be challenging. First, manufacturing processes may damage viable microorganisms.[3] Second, clinical studies have raised concern regarding the species composition in current products along with the lack of universal quality assurance programs. The label or manufacturing process may state "generally recognized as safe" (GRAS), but this applies to food supplements and is not supported by FDA quality or safety standards as indicative of therapeutic benefit.[2,4] Finally, many products available online need to be stored in a cool environment which makes receiving probiotics in the mail subject to quality concern.[2,5]

This article will focus on answering common questions regarding four broad clinical areas of suggested probiotic use: adult and pediatric diarrheal illness, genitourinary infections, atopic dermatitis, and upper respiratory tract infections. Each section will include a discussion of recent evidence from meta-analyses and systematic reviews. Additionally, recommended evidence ratings from the Yale/Harvard 2015 Workshop of probiotic experts will be included *(Table 2)*.[6]

SHOULD PROBIOTICS BE RECOMMENDED FOR USE FOR GASTROINTESTINAL CONDITIONS, SUCH AS DIARRHEA, INFLAMMATORY BOWEL DISEASE, OR IRRITABLE BOWEL SYNDROME?

The administration of probiotics improves gut colonization with enteric flora. Theoretical benefits include restored gut barrier function, improved mucosal immunity, reduced inflammation, and improved bile acid metabolism.[7] A variety of probiotic formulations have been studied for gastrointestinal conditions, but each report has a high degree of variability in species, dosing, and research endpoints.

Diarrhea - Recommended for Acute Infectious Diarrhea & Antibiotic Associated Diarrhea

Acute infectious diarrhea (AID) can be viral, bacterial, or parasitic in nature. These types of infections are most commonly treated with rehydration and anti-diarrheal agents. As adjunctive therapy, probiotics modify gut pH, compete with the infectious agent for nutrients, and may improve the immune response. The use of probiotics for the treatment of AID was evaluated in a 2010 Cochrane systematic review of 63 randomized controlled trials (RCTs). Most trials evaluated *LGG* and *S. boulardii* and included AID of any

infectious origin. In addition, 18 trials specifically reported data from rotavirus infection in children. Overall, probiotics reduced the duration of diarrhea by a mean of 24.8 hours (95% CI, 15.9 to 33.6) and reduced the risk of diarrhea lasting 4 days or longer (RR 0.41, 95% CI 0.32 to 0.53).[8]

Broader studies of probiotics as adjuvant to rehydration for acute gastroenteritis in children have been found to decrease the duration of symptoms. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) supports with strong recommendation the use of *LGG* and *S. boulardii* for 5 to 7 days in otherwise healthy children. However, these recommendations are based upon low quality evidence, unclear randomization protocols and study blinding, and varying definitions of clinical endpoints.[9] The Yale/Harvard 2015 Workshop expert panel also supports the use of *LGG*, *S. boulardii*, and *L. reuteri* with an "A" recommendation. The use of *L. reuteri* is given a weaker but also positive recommendation from ESPGHAN.[6,9] Notably, ESPGHAN published a strong recommendation against the use of *E. faecium* SF 68 due to safety concerns with vancomycin resistance.[9]

Antibiotic-associated diarrhea (AAD) results from disruption of the normal gut microflora. Because discontinuation of antibiotics for a clinical condition is not usually recommended, prevention of AAD is a preferred strategy. Several recent meta-analyses evaluated the use of probiotics for prevention of AAD. Videlock et al. evaluated 34 placebo-controlled studies of probiotics and found a reduced risk of AAD (RR 0.53; 95% CI 0.44 to 0.63).[10] Hempel et al. reviewed 63 studies and found a similar risk reduction (RR 0.58; 95% CI 0.50 to 0.68).[11] Goldenberg et al. evaluated 23 trials of the use of probiotics to prevent AAD in patients up to 18 years of age, also demonstrating a lower risk of AAD (RR 0.46; 95% CI 0.35 to 0.61).[12] All authors identified significant heterogeneity between studies. Participants in the Yale/Harvard 2015 Workshop support the use of *S. boulardii*, *LGG*, and a combination of *Lactobacillus/Streptococcus thermophilus* species for AAD with an "A" recommendation.[6]

Data are more variable on the use of probiotics for the prevention of *C. difficile*-related diarrhea.[6] The American College of Gastroenterology (ACG) does not support the use of probiotics for treatment or prevention of *C. difficile* diarrhea. They further caution against probiotic use among immunocompromised patients.[13]

Irritable Bowel Syndrome (IBS) - Weakly Supported

Irritable bowel syndrome (IBS) is defined by the ACG as "abdominal discomfort associated with altered bowel habits.[14] The Rome III criteria is often applied in the research setting. This criteria specifies IBS as the recurrence of abdominal pain or discomfort for at least 3 days per month over 3 months, and the presence of at least 2 of the following findings: onset of symptoms associated with a change in either stool frequency and/or appearance and improvement of symptoms with defecation. Patients can be further categorized into four subtypes based upon bowel patterns: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed type (IBS-M), and unclassified (IBS-U).[14]

The pathophysiology of IBS is complex and not fully defined. A disruption in the gut-brain connection leading to visceral hypersensitivity has been hypothesized as an underlying cause. Additional theories have implicated serotonergic, immunologic, genetic, and psychosocial contributors. Alterations in the gut microbiome and the function of the gut barrier have been the focus of recent investigations.[7]

Therapeutic options for IBS range from dietary changes that increase fiber intake and restrict gluten or FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) to pharmacologic treatments. Traditional use of antispasmodics and antidepressants has expanded to several symptom-specific options for IBS-D (alosetron, eluxadoline) and IBS-C (linaclotide, lubiprostone).[14, 15, 16] The possible contribution of an altered gut microbiome has prompted the investigation of antimicrobial agents (e.g., rifaximin, metronidazole) and probiotics as potential therapeutic options.[14, 15]

The ACG supports a "weak" recommendation for the use of probiotics for IBS.[14] A similar grade is noted by the Yale/Harvard 2015 Workshop expert panel with a "B" recommendation for *B. infantis* and VSL #3.[6] The ACG guideline cites literature that identifies a positive impact of probiotics on "global symptoms" including abdominal pain, flatulence, and bloating.[14] The guideline does not support any recommendation for a particular probiotic over another due to variable data. A 2014 meta-analysis found probiotics were associated with a lower risk of IBS symptoms persisting after treatment when compared with placebo (RR 0.79; 95% CI 0.70 to 0.89).[17] The probiotics most commonly included *Lactobacillus*, *Bifidobacterium*, *Escherichia*, and *Streptococcus* species, but products varied widely in formulation and dosing. These probiotics appeared to be well tolerated; however, further evidence suggested a higher risk for adverse events including abdominal pain and bloating, versus placebo (RR 1.21; 95% CI 1.02 to 1.44).[17]

Many unanswered questions about the clinical role of probiotics for IBS remain. A trial of probiotics seems to be a reasonable option, particularly for patients complaining of abdominal pain, flatulence, and bloating. However, the optimal probiotic formulation and dose have not been determined, requiring further studies for clarification.

Inflammatory Bowel Disease (IBD) - Recommended for Ulcerative Colitis

Inflammatory bowel disease, including ulcerative colitis (UC) and Crohn's disease (CD), is often characterized by features of abdominal pain and diarrhea. Conventional therapeutic interventions focus on acute management of symptoms followed by maintenance of remission utilizing various anti-inflammatory and immune modulating agents.[18,19] Although pathophysiology of the two conditions is not well understood, a recent interest in the gut microflora immune and inflammatory response has stimulated investigations into the role of probiotics.

Studies of probiotics in UC have focused primarily on the use of VSL#3 and *E. coli* Nissle species. Their use has been targeted for induction and maintenance of remission. In a meta-analysis, Fujiya et al. found that probiotics appeared as effective as mesalazine for prevention of remission (RR 1.00; 95% CI 0.79 to 1.26).[20] The Yale/Harvard 2015 Workshop expert panel assigned a "B" recommendation for the induction of remission and an "A" recommendation for maintenance of remission.[6]

The prevention of pouchitis, an inflammatory condition occurring after an ileal pouch-anal anastomosis procedure for UC appears to be another promising therapeutic use. A recent systematic review showed that probiotic formulation VSL#3 (containing several *Lactobacilli* and *Bifidobacterium* species plus *S. thermophilus*) prevented pouchitis and maintained remission at higher rates than placebo.[21] Participants in the Yale/Harvard 2015 Workshop support the use of VSL #3 with an "A" recommendation.[6]

The evidence regarding the use of probiotics in CD is limited. Studies of probiotics for CD have yielded conflicting data, offering a "C" recommendation from the expert panel at the Yale/Harvard 2015 Workshop.[6] The ACG recommends that further investigation of probiotics is necessary before supporting use in CD.[18]

SHOULD PROBIOTICS BE RECOMMENDED IN FEMALE GENITOURINARY TRACT INFECTIONS: BACTERIAL VAGINOSIS, VULVOVAGINAL CANDIDIASIS, & RECURRENT URINARY TRACT INFECTIONS?

The female genitourinary tract is predominantly colonized by *Lactobacilli* (LAB) species. Changes in the vaginal microbiota can lead to genitourinary tract infections including bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and recurrent urinary tract infections (UTIs). This disruption or "vaginal dysbiosis" can be caused by the use of broad spectrum oral antibiotics, changes in sexual partners, menopause, diabetes, obesity, poor hygiene, and elevated vaginal pH. This most likely occurs through intestinal colonization by pathogenic bacteria which enter the vagina from the rectum.[2,22] The mechanisms of action (correction of dysbiosis) proposed for the predominant LAB species found in the genitourinary tract involves 1) lowering the pH by producing lactic acid and hydrogen peroxide, 2) producing bacteriocins toxic to pathogenic bacteria, and 3) blocking pathogenic bacteria adhesion to the genitourinary epithelium. Collectively, this decreases genitourinary colonization of pathogenic bacteria and maintains a healthy balance.[22, 23, 24]

Several studies using either oral or intravaginal probiotics for the treatment or prevention of genitourinary infections have been performed. Studies have used two approaches: primary therapy using probiotics alone (either single species or a combination of species) or additive therapy to conventional treatment. Interpretation of data from several well organized RCTs is challenging because variations were used in study design, probiotic species, treatment length, and patient follow-up.[23, 24, 25]

Bacterial Vaginosis - Probiotic Recommended as Adjuvant

BV is one of the most frequent vaginal infections in the world and results from the overgrowth of bacteria in the genitourinary tract, most commonly *Gardnerella*, *Atopobium*, and *Prevotella*. The overgrowth of these bacteria can raise the pH creating vaginal dysbiosis. Symptoms include pruritus, vaginal discharge, and dysuria. BV is typically treated with metronidazole or clindamycin, either orally or intravaginally. However, failure and recurrence rates are estimated at 30-40%.[2, 23]

One of the first reported meta-analyses of RCTs regarding the effects of probiotics for the treatment of BV was published in 2014 by Huang et al. This study included 1,304 individuals from 12 RCTs with a primary outcome specifically for BV cure rate. Authors concluded that "probiotics show a beneficial effect in patients who are suffering from BV" [RR 1.53; 95% CI 1.19 to 1.97]. They further examined a subgroup of the 9 highest quality studies and determined that probiotics either orally or intravaginally were effective either alone or in combination with conventional antibiotics for the treatment of BV [RR 1.60; 95% CI 1.16 to 2.22].[24] A literature review by Homayouni et al. in 2014 included several of these studies and reported similar conclusions.[25]

Many experts state the preferred probiotic delivery route should be intravaginal but online searches suggest this type of product is limited.[22, 24, 25] Several oral products are available, but the viability of probiotics to survive the gut and finally enter the GU tract was not thoroughly investigated in clinical trials. Timing of GU colonization after oral administration was not consistent and further studies are recommended.[24, 25]

Considerable heterogeneity was found among the type of probiotic used in the meta-analyses.[24] For example, Ya et al. randomized 117 Chinese women with BV to vaginal probiotic capsules (Probalac Vaginal: containing 108 CFU of *L. rhamnosus*, *L. acidophilus*, and *Streptococcus thermophilus*) versus placebo. Patients used probiotics for 7 days on and then omitted for 7 days, alternating this schedule for 30 days. Conversely in a different study, Bradshaw et al. randomized 268 women with BV to oral metronidazole 400 mg BID for 7 days followed by vaginal pessary use daily containing *L. acidophilus KS400* ≥ 107 CFU and 0.03 mg of estriol for 12 days, versus oral metronidazole 400 mg BID for 7 days followed by vaginal pessary placebo for 12 days. The women in this study were followed for 180 days.[24]

The Yale/Harvard 2015 Workshop expert panel offered a recommendation level "C" regarding probiotics for BV treatment.[6] However, given the general safety of probiotics, they should be considered as adjuvants either orally or intravaginally for women with BV.[3, 24, 25] In several studies, *L. rhamnosus* and GR-1 and *L. reuteri RC-14* were found effective for the treatment of BV when added to standard metronidazole therapy.[6,22,24,25] Similar probiotics may be found online and include UltraFlora (oral) by Metagenics, FemDophilius (vaginal) by Jarrow, and Terbiotics (oral) by Klaire Labs. *(See Table 3, page 26)* These products have not been approved by the FDA.

Vulvovaginal Candidiasis - Insufficient Evidence to Recommend

Vaginal dysbiosis may also lead to an overgrowth of *Candida* species with the most common type as *Candida albicans*.[22] VVC symptoms include vaginal discharge, dysuria, and pruritus. Many studies report the use of either oral or intravaginal *LGG*, *L. rhamnosus*, *L. reuteri*, and *L. acidophilus* for use in women with a history of recurrent VVC.[2,6,26] However, most studies to date have had small sample sizes, lacked statistical significance, or had high attrition rates.[26] Although probiotics are considered safe for use in most women, the use of probiotics for the primary treatment or added to conventional therapy has not been supported.[3,22] Furthermore, probiotics for VVC should not be used as primary treatment because LAB does not compete with *Candida* colonization. Only conventional anti-infectives will eliminate *Candida* thus allowing LAB to establish homeostasis.[22]

Recurrent Urinary Tract Infections - Weakly Supported

Urinary tract infections are common including infection of the kidney, ureter, urethra, or bladder. The most common pathologic bacteria is *E. coli*, a gram positive cocci.[27, 28] UTIs can be asymptomatic or symptomatic with cloudy urine, pyuria, urgency, frequency, and hematuria. Ascending infection may cause flank pain, fever, and chills. Mortality increases among the elderly and immunocompromised with UTIs.

Historically, probiotic research targeting UTIs increased in the 1980's. Authorities confirmed that vaginal dysbiosis, including the depletion of healthy LAB, leads to an increased rate of UTI recurrence in many patients. In the development of probiotics and in-vitro research studies, attempts to displace gram-positive cocci adhesion were made by adding *L. reuteri RC-14* to *L. rhamnosus GR-1*. Many studies showed promising results, but the quality and design of several clinical trials were questioned.[27]

In response, a 2010 Cochrane systematic review by Schwenger et. al evaluated probiotics (any formulation) versus placebo (no therapy) for prevention of UTIs in susceptible patients. They included 9 studies with 735 individuals and measured rates of UTI recurrence with probiotic or placebo. These studies were also challenged by high risk of bias, small sample sizes, and insufficient methodological detail. The authors reported that "a benefit could not be ruled out due to insufficient data" and more research in this area is needed. It has been further discussed that BV infection may increase the risk of recurrent UTIs.[29] Due to the promising use of probiotics for the treatment of BV, a plausible link between probiotics and prevention of both BV and UTIs may emerge in the near future.

SHOULD PROBIOTICS BE RECOMMENDED FOR THE PREVENTION OR TREATMENT OF ATOPIC DERMATITIS?

Recommended in Specific Clinical Situations

Atopic dermatitis (AD) is widely considered an inflammatory skin condition in all ages, but infants and children are more commonly affected. Clinical conditions vary in severity and frequent exacerbations are reported. Patients report itching, pain, and discomfort, which can significantly affect activities of daily living and sleep quality. AD standard therapy includes emollients and topical steroids.

The underlying pathophysiology of AD involves a complicated cellular immune response between the skin as a barrier and the bacteria that normally colonize the surface. Given the role of probiotics with respect to GI immune response and inflammation, and the general safety of probiotics, studies have demonstrated a possible role in AD.[30, 31, 32] Interestingly, it has also been reported that children who have slow development of both LAB and *Bifidobacterium* in the GI tract were found to be more susceptible to allergies.[32]

Specific use of probiotics LAB and *Bifobacterium* for the prevention of Pediatric Atopic Dermatitis (PAD) is recommended by the Yale/Harvard 2015 workshop experts.[6] Additionally, the World Allergy Organization (WAO) performed a systematic review in 2015 providing conditional recommendations for the prevention of PAD in high risk infants. Infants at risk were defined by having any biological parent or sibling with a history of allergic rhinitis, asthma, eczema, or food allergy.[33] The WAO further recommended for this risk group oral probiotic use by the mother during pregnancy and breastfeeding, and in infants who were not breastfed. The most significant risk reduction in PAD was reported when probiotics were used during pregnancy (RR 0.72, 95% CI 0.61 to 0.85) and when given to infants (RR 0.81, 95% CI 0.70 to 0.94).[33]

The American Academy of Dermatology published review by Baquerizo et al. reports several meta-analyses regarding the risk reduction of PAD with the use of prenatal and/or postnatal probiotics. In an analysis of 16 trials with probiotics (LAB and *Bifobacterium*) the risk of PAD was reduced by 20-24% (RR 0.79). This review recommends starting LAB orally for the mother during the last 2 weeks of pregnancy and continuing for the first three months post-delivery. The review did not state if the probiotics should be taken by the mother or the infant during post-delivery.[30] Other recommendations suggest *L. rhamnosus* orally for the mother during the last 4 weeks of pregnancy and for the first 6 months of breastfeeding with a transition to oral probiotics to the infant continuing until age 2.[34]

With respect to the treatment of AD, probiotic use has been supported by clinical trial evidence. The Yale/Harvard 2015 workshop experts support a level "A" recommendation for the use of LGG and *B. lactis* in the treatment of AD associated with cow's milk allergy.[6] In addition, a recent 2014 meta-analysis of 25 clinical trials (n=1,599) by Kim et al. assessed the treatment of all AD using probiotics. The endpoint of the study included any change in the Scoring of Atopic Dermatitis (SCORAD) symptoms scale. For all ages the SCORAD decreased by a mean of 4.51 points (95% CI -6.78 to -2.24). The most significant symptom reduction was found among patient ages 1-18 (-5.74, 95% CI -7.27 to 14.20) and was not found effective in infants <12 months. Considerable heterogeneity was found among all studies; however, probiotic species reported most beneficial included LAB or a combination of LAB with *Bifidobacterium*.[32]

SHOULD PROBIOTICS BE RECOMMENDED FOR THE PREVENTION OR TREATMENT OF UPPER RESPIRATORY TRACT INFECTIONS?

Weak support

Upper respiratory tract infections (URTIs) include viral and bacterial infections such as colds, sinusitis, and pharyngitis. Several systematic reviews have recently assessed probiotic effectiveness in prevention of or shortening duration of URTIs.[35, 36, 37] Probiotics may prevent URTIs by reducing the colonization of pathogenic bacteria in the GI tract, removing bacterial toxins, and enhancing humoral immune responses.[38, 39]

Probiotics may be more effective than placebo for prevention of URTIs in adults according to a Cochrane meta-analysis published in 2015 that included twelve RCTs (n=3,720).[35] Fewer patients in the probiotic group versus the placebo group were diagnosed with one episode of URTI (OR 0.53; 95% CI 0.37 to 0.76). The mean duration of the URTI was less in the probiotic patient group (mean difference -1.89 days; 95% CI -2.03 to -1.75). While probiotics in this review seemed to be more effective than placebo, the quality of evidence in these studies was low.[35]

Another meta-analysis reported similar results in 2014. In this review of 20 clinical trials (n= 3,350) the duration of URTI symptoms with probiotic use of *Lactobacillus* or *Bifidobacterium* versus placebo suggested shorter illness courses.[36] The duration of probiotic therapy use ranged from three weeks to seven months and patients in the probiotic intervention group had shorter illness by ½ - 1 day compared to placebo (weighted mean difference -0.77; 95% CI -1.5 to -0.04). The probiotic group had less work or school absenteeism (mean difference -0.17; 95% CI -0.31 to -0.03). Similar to the Cochrane meta-analysis, clinical trial design varied and although probiotics were more effective than placebo, the quality of evidence was low.[35, 36]

SUMMARY

Although there are many studies regarding the use of probiotics for a wide variety of conditions, there is no consensus on the most appropriate species, dose, and products to recommend. The Yale/Harvard 2015 workshop experts provide important guidance through their published evidence ratings for certain clinical conditions.[6] Some products are included in Table 3 for consideration. These products have not been fully evaluated by the FDA with quality and safety studies. In the age of increasing antibiotic resistance and the emerging role of the gut microbiome in health, further research is encouraged in the development of probiotics going forward.

TABLE 3:

Summary of Probiotic Recommendations[2, 6, 24]

Clinical Condition & Species (Harvard/Yale 2015 Workshop Rating*)	Product Examples & Species Type in Product**	Approximate Cost
Diarrhea Treatment of acute infectious diarrhea in children (A*) *L. rhamnosus (LGG)* *L. reuteri* *S. boulardii* Prevention of Antibiotic Associated Diarrhea (A*) *S. boulardii* *LGG* Combination of probiotics including: *L. bulgaricus, S. thermophiles, L. casei*	Danimals Yogurt *LGG* (amount not specified) (contains dairy) Culturelle (ConAgra Foods) *LGG* 10 Billion per tablet Florastor (Biocodex) Yeast: ***S. boulardii*** 250 mg/capsule or packet DanActive (Dannon, Canada) ***S. thermophilus, L. bulgaricus, & L. casei*** > 10 billion per 93 ml bottle - ***(Contains Milk)***	$5 for 12 pack (Walmart) www.danimals.com $21 for 30 tablets (Drugstore.com) www.culturelle.com $48 for 100 capsules (Costco) www.florastor.com $8 for a Pack of 8 bottles (Amazon) www.danone.ca/en/products/danactive
Inflammatory Bowel Disease Ulcerative Colitis (UC) Pouchitis Prevention & maintenance (A*) VSL#3 UC Maintenance of Remission (A*); Induction of Remission (B*) *E. coli Nissle or VSL#3*	VSL #3 (Sigma-Tau Pharmaceuticals) *L. casei, L. plantarum, **L. acidophilus, L. bulgarius, B. longum, B. breve, B. infantis & S. thermophilus*** 450 billion in a packet & 112.5 billion in a capsule Prescription strength (VSL#3-DS) 900 billion	$88 for 30 pack capsules or packet www.vsl3.com
Irritable bowel Syndrome (B*) *B. infantis 35624* or VSL #3	Align (Proctor and Gamble) - ***B. infantis 35624*** contains 1 billion CFU and (1 x 107 CFU) until at least the "best by" date. ***(contains milk)***	$30 for 28 capsules (Drugstore.com) www.metawellness.com
Vaginitis & Vaginosis (C*) *Lactobacillus rhamnosus GR-1* *Lactobacillus rhamnosus GR-1 & L. reuteri RC14* *L. acidophilus*	UltraFlora Women's (Metagenics) ***L. rhamnosus GR-1 and L. reuteri RC14*** 2 Billion (contains milk) Fem-Dophilus (Jarrow Formulas) ***L. rhamnosus GR-1 and L. reuteri RC14*** 5 Billion (contains dairy)	$31.95 for 30 capsules www.metagenics.com $13 for 30 capsules (Amazon) www.jarrow.com
Atopic eczema associated with cow's milk allergy Treatment & prevention (A*) *LGG* *B. lactis*	Culturelle (ConAgra Foods) *LGG* 10 Billion per tablet	$21 for 30 tablets (Drugstore.com) www.culturelle.com

**Yale/Harvard 2015 Workshop grade applies to the species type and clinical condition. It does not represent a rating for the product example listed. "A" recommendation is based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form. "B" recommendation is based on positive, controlled studies but the presence of some negative studies. "C" recommendation is based on some positive studies but clearly an inadequate amount of work to establish the certainty of "A" or "B".*

*** Product examples are commonly found in stores or online, but do not represent all available products on the market. These products have not been fully evaluated by the FDA and are not intended to diagnose, cure, treat, or prevent any disease.*

REFERENCES:

1. Food and Agriculture Organization of the United Nations and World Health Organization. Guidelines for the evaluation of probiotics in food: report of a joint FAO/WHO working group. April 30 and May 1, 2002. Available from: http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf. Accessed January 30, 2016.
2. Mizock BA. Probiotics. Dis Mon. 2015;61(7):259–290.
3. Williams NT. Probiotics. Am J Health Syst Pharm. 2010;67(6):449-458.
4. Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis. 2015; 60 Suppl 2:S129-34.
5. Didari T, Solki S, Mozaffari S, Nikfar S, Adollahi M. A systematic review of the safety of probiotics. Expert Opin Drug Saf. 2014;13(2):227-239.
6. Floch M, Walker WA, Sanders ME, et al. Recommendations for probiotic use: a 2015 update. J Clin Gastroenterol. 2015;49 Suppl 1:S69-73.
7. Quigley EM. Probiotics in irritable bowel syndrome: the science and the evidence. J Clin Gastroenterol. 2015;49 Suppl 1:S60-64.
8. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;11:CD003048.
9. Szajewska H, Guarino A, Hojsak I, et al. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2014;58(4):531-539.
10. Videlock EJ, Cremonini F. Meta-analysis: probiotics in antibiotic-associated diarrhea. Aliment Pharmacol Ther. 2012:35(12):1355-1369.
11. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea. JAMA. 2012;307(18):1959-1969.
12. Goldenberg JZ, Lytvyn L, Steurich J, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2015;12:CD004827.
13. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478-498.
14. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014;109 Suppl 1:S2-26.
15. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;147(5):1146-1148.
16. Nee J, Zakari M, Lembo AJ. Current and emerging drug options in the treatment of diarrhea predominant irritable bowel syndrome. Expert Opin Pharmacother. 2015;16(18):2781-2792.
17. Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and symbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol. 2014;109(10):1547-1561.
18. Lichtenstein GR, Hanauer SB, Sandborn WJ and Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104(2):465-483.
19. Kornbluth A, Sachar DB and Practice Parameters Committee of American College of Gastroenterology. Ulcerative colitis practice guidelines in adults. Am J Gastroenterol. 2010;105(3):501-523.
20. Fujiya M, Ueno N, Kohgo Y. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials. Clin J Gastroenterol. 2014;7(1):1-13.
21. Singh S, Stroud AM, Holubar SD, et al. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database Syst Rev 2015;11:CD001176.
22. Reid, G. Probiotic and prebiotic applications for vaginal health. J AOAC Int. 2012;95(1):31-34.
23. Borges S, Silva J, Teixeira P. The role of lactobacilli and probiotics in maintaining vaginal health. Arch Gynecol Obstet. 2014;289(3):479–489.
24. Huang H, Song L, Zhao W. Effects of probiotics for the treatment of bacterial vaginosis in adult women: A meta-analysis of randomized clinical trials. Arch Gynecol Obstet. 2014; 289(6):1225–1234.
25. Homayouni A, Bastani P, Ziyadi S, et al. Effects of probiotics on the recurrence of bacterial vaginosis: a review. J Low Genit Tract Dis. 2014;18(1):79-86.
26. Murina F, Graziottin A, Vicariotto F, De Seta F. Can Lactobacillus fermentum LF10 and Lactobacillus acidophilus LA02 in a slow-release vaginal product be useful for prevention of recurrent vulvovaginal candidiasis?: A clinical study. J Clin Gastroenterol. 2014 ;48 Suppl 1:S102-5.
27. Beerepoot MA, ter Riet G, Nys S, et al. Lactobacilli vs. antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. Arch Intern Med. 2012; 72(9):704-12.
28. Chisholm AH. Probiotics in preventing recurrent urinary tract infections in women: a literature review. Urol Nurs. 2015; 35(1): 18-21.
29. Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev. 2015;12:CD008772.
30. Baquerizo Nole KL, Yim E, Keri JE. Probiotics and prebiotics in dermatology. J Am Acad Dermatol. 2014;71(4):814-821.
31. Pandura M, Panduru NM, Salavastru CM, Tiplica GS. Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. J Eur Acad Dermatol Venereol. 2015;29:232-242.
32. Kim SO, Ah YM, Yu YM, et al. Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol. 2014;113(2):217-226.
33. Fiocchi A, Pawankar R, Cuello-Garcia G, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. World Allergy Organ J. 2015;8(1):4.
34. Crosby MS, Blattner CM, Goedken M, Murase JE. Update: do probiotics prevent or treat pediatric atopic dermatitis. Pediatr Allergy Immunol. 2016;Epub ahead of print.
35. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015;2:CD006895.
36. King S, Glanville J, Sanders ME, et al. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. Br J Nutr. 2014;112(1):41-54.
37. Ozen M, Kocabas Sandal G, Dinleyici EC. Probiotics or the prevention of pediatric upper respiratory infections: a systematic review. Expert Opin Biol Ther. 2015;15(1):9-20.
38. Patel R, DuPont HL. New approaches for bacteriotherapy: prebiotics, new-generation probiotics, and synbiotics. Clin Infect Dis. 2015;60 Suppl 2:S108-121.
39. MacFarland LV. From yaks to yogurt: the history, development and current use of probiotics. Clin Infect Dis. 2015;60 Suppl 2:S85-90.