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The world of probiotics
RAJIV K SHARMA MD

Dr. RAJIV SHARMA is a Board Certified Physician. He is a practicing Gastroenterologist with special interest in Nutrition, Healthy eating, Exercise and Wellness. He is a member of American Gastroenterological Association and American College of Gastroenterology. He received his Internal Medicine training at Loma Linda University Medical Center, California and Advanced Gastroenterology training from University of Rochester, NY.
What Are Probiotics?

"Probiotics" are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.

The GI tract contains a dynamic microbial community. Equilibrium is fragile and easily disrupted by:

- Antibiotics
- Travel
- Stress
- Diet
- Alcohol
- Smoking
- Aging
To qualify as a probiotic, the microorganisms should demonstrate:

- Resistance to gastric acidity
- Bile acid resistance (bile acids help in digestion and absorption of food nutrients)
- Attachment to mucus and/or human epithelial cells and cell lines
- Antimicrobial activity against potentially pathogenic bacteria
- Ability to reduce pathogen adhesion to surfaces
- Bile salt hydrolase activity (break down bile salts to simpler substrates)
- Resistance to spermicides (applicable to probiotics for vaginal use)

What Are Prebiotics? Synbiotics?

- **PREBIOTICS**: food for good bacteria. FOS (Fructo-oligosaccharides), GOS (Galacto-oligosaccharides). *Inulin = gold standard,* Prebiotics found in wheat, onion, bananas, garlic, asparagus and chicory.

- **SYNBIOTICS**: PREBIOTIC + PROBIOTIC COMBINATION FOR BETTER RESPONSE
What Are Probiotics?

Health Benefits of Probiotics

- Compete with pathogens
- Promote gut health
- Modulate the immune system
- Aid food digestion
- Enhance the intestinal flora
- Reduce intestinal discomfort

Gut Microbes Hold the Key to Your Health

- There are about 100 trillion microbes (mostly bacteria but also yeast) in the human gut.
- Probiotics modulate or "bring about a change" in the gut immune system.
- The concept has been there for many years but due to rapid growth of antibiotic era it did not flourish. It was first promoted by Elie Metchnikoff, a Russian born scientist about 100yrs ago.
- It seems like these bacteria could be holding a key to human health and wellness.

FDA Regulation is not stringent (unlike medical foods and drugs)

These Probiotic products are health food supplements not medical foods

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PROBIOTIC FOOD PRODUCTS

Yogurts, drinks, juices

Digestive health and wellbeing

Immune support
Combination products:
- Immune boosters
- Beauty from within

Oral health, throat

Delivery systems
The following information be described on the label:

- Genus, species and strain designation. Strain designation should not mislead consumers about the functionality of the strain.
- Minimum viable numbers of each probiotic strain at the end of the shelf life.
- The suggested serving size must deliver the effective dose of probiotics related to the health claim.

The following information be described on the label:

- Health claim(s)
- Proper storage conditions
- Corporate contact details for consumer information

Probiotics consumer product market is estimated at $23B USD and expect to grow to $32B by 2015.

- High incidence of digestive conditions in the population.
- Increased consumer interest in functional foods. Probiotics is one of the main ingredients used in this category and 81% of US consumers tie probiotics to digestive health.
- Discovery of links between the intestinal tract and increased health and wellness.
- Differentiation is shown to lead to market success. Growing opportunity outside the dairy aisle.
Third fastest growing globally
2013: US $3.25B

Global Probiotic Supplements – Top 10 Brands

Probiotic Yogurt: Top 10 Global Brands
 ARE ALL YOGURTS PROBIOTICS?

- Many yogurts contain live-active lactobacillus cultures and are considered functional food products; however, most are not considered probiotics per se.
- This term is reserved for products with an adequate number of microorganisms at time of consumption specifically shown to confer health benefits in controlled human trials.
- Yogurts fortified with an adequate number of viable bacteria shown to exert benefit in controlled trials are classified as probiotics.

 ARE ALL YOGURTS PROBIOTICS?

- Probiotic benefits appear species-specific, expected clinical end points may not be achieved by generically recommending yogurt to patients in whom a purported probiotic benefit is desired.
- It should be noted, however, that yogurt consumption has other benefits including improved lactose tolerance and the provision of protein, vitamin D, and calcium.

 HOW LONG SHOULD YOU TAKE PROBIOTICS?

- As viable microorganisms, probiotics can survive in the human gut and impact microbes which colonize the gut.
- Probiotics are often detectable in the stool by culture or gene-based assays during periods of consumption.
- However, many probiotic strains do not colonize the gut and are no longer recoverable in stool 1 to 4 weeks after stopping consumption.
PROBIOTICS & GUT MICROBIAL GENE EXPRESSION

- Probiotic products did not change the gut’s overall bacterial composition, but instead altered gene expression patterns relevant to carbohydrate metabolism in the host’s resident gut microbes.
- These changes in the human fecal “metatranscriptome” were transient, confined only to the time of the probiotic consumption.
- Thus, if sustained benefit from a probiotic is desired, continued consumption is likely required.


PRACTICAL CONSIDERATIONS

- Common side effects of probiotics: typically transient but include gas and bloating. Different probiotic strains possess unique properties for benefiting host physiology.
- One probiotic does not fit all GI illnesses. Probiotic selection should be based on the clinical indication and take into consideration the strain and dosage used in clinical trials.
- Symptomatic benefits offered by probiotics are likely to be modest; thus, probiotic therapies may best be used to supplement rather than replace conventional therapies.
- Continuous consumption throughout the period of desired effect appears required for probiotics.

SAFETY PROFILE

- 28 studies, none of which revealed significant treatment-emergent adverse events that were attributed to probiotic use. Of the 28 studies, 25 reported no relevant differences in safety between 23 specific probiotic treatments and placebo. The remaining three studies (each examining a different probiotic) are below:
  - In a study of patients with IBS, 2 patients in the probiotic group discontinued from the study because of adverse events (moderate nausea and severe exanthema). However, the most frequent adverse events (fatigue, pruritus, and diarrhea) occurred equally in the probiotic and placebo groups.
  - In a study of 13 patients with IBS, 1 participant had a short stay in hospital for cervicobrachialgia 2 weeks after the end of the specific probiotic treatment; however, there was no organic explanation and the patient continued in the trial.
  - In a study of 99 healthy athletes, there was a twofold increase in the number and duration of mild GI symptoms in the probiotic group compared with the placebo group, although severity tended to be lower.

**SAFETY PROFILE**

- Probiotic supplementation has been studied in healthy volunteers, and the data suggest that several probiotic strains may enhance nonspecific immune responses, but the effects on adaptive cellular and humoral immune responses appear to be negligible [Borchers et al. 2009]
- Sepsis (Lactobacillus)
- Fungemia (Saccharomyces bouardi)
- Risk higher when host immunocompromised or critically ill
- There are no formal clinical trials assessing the safety of probiotics as there are safety data on regulated medications

**AVOID PROBIOTICS IN THE CRITICALLY ILL AND THOSE WITH SEVERE IMMUNE COMPROMISE**

**PANDORA’S BOX: UNCLEAR QUESTIONS**

- The optimal number of colony forming units (CFUs) for each bacterial strain delivered remains unknown.
- Doses in human trials are based on those used in animal studies despite the differences in intestinal surface area
- Dose-response studies are generally lacking
- Commercially available probiotic formulations typically have at least $10^6$ CFUs, but they may range up to $10^{12}$ CFUs
PANDORA’S BOX: UNCLEAR QUESTIONS

- Very few studies have actually documented survival of an administered probiotic as it transits the gut, by means of fecal recovery studies
- One probiotic may not necessarily be translatable to other probiotic(s); for example, different Bifidobacterium species have different tolerances to acid and growth requirements and will have different fecal recovery rate
- The method of delivery, i.e., yogurt versus milk, may have an impact on the viability and number of bacterial colonies
- Example, only one strain of B. longum could survive in fermented milk for 2 weeks

USE OF PROBIOTICS

- Antibiotic associated diarrhea
- Infectious diarrhea
- C. difficile AD
- Ulcerative colitis (UC)
- Crohni’s disease
- Pouchitis
- IBS

ANTIBIOTIC INDUCED DIARRHEA

- may be prevented by co-administration of probiotics, probiotics significantly decreased incidence of AAD (RR 0.39–0.43)
- The most commonly used probiotics were S. boulardii
- One of the meta-analyses found that S. boulardii, L. rhamnosus, and multiple mixtures of two different probiotics were the most protective against AAD
- Other specific preparations have been studied to a lesser extent and that may be why their efficacy has been found to be less significant
ANTIBIOTIC INDUCED DIARRHEA

- The incidence of AAD in the probiotic group was 9% compared to 18% in the control group (2874 participants; RR 0.52; 95% CI 0.38 to 0.72; I² = 56%)
- The incidence of AAD in the probiotic group was 16% compared to 18% in the control group (3392 participants; RR 0.81; 95% CI 0.63 to 1.04; I² = 59%)
- A case subgroup analysis exploring heterogeneity indicated that high dose (>5 billion CFUs/day) is more effective than low probiotic dose (<5 billion CFUs/day), interaction P value = 0.010
- For the high dose studies the incidence of AAD in the probiotic group was 8% compared to 22% in the control group (1474 participants; RR 0.40; 95% CI 0.29 to 0.55)
- For the low dose studies the incidence of AAD in the probiotic group was 8% compared to 11% in the control group (1382 participants; RR 0.80; 95% CI 0.53 to 1.21)

CLOSTRIDIUM DIFFICILE COLITIS

- In individuals over the age of 50, combination of L. casei, L. bulgaricus, and S. thermophilus twice daily during a course of antibiotics and for 1 week after the completion of antibiotic therapy showed reduction in the incidence of CDC
- A total of 1871 studies were identified with 31 (4492 participants) meeting eligibility requirements for our review. Overall 11 studies were rated as a high risk of bias due mostly to missing outcome data. A complete case analysis (i.e. participants who completed the study) of those trials investigating CDAD (23 trials, 4214 participants) suggest that probiotics significantly reduce this risk by 64%. The incidence of CDAD was 2.0% in the probiotic group compared to 5.5% in the placebo or no treatment control group (RR 0.36; 95% CI 0.26 to 0.51).

INFECTIOUS DIARRHEA

- Duration of symptoms is decreased by about 30 hours both adults and children may be shortened by the use of probiotics
- Majority (18 out of 23 studies) of the probiotics tested were Lactobacilli with two studies using S. boulardii
- *Lactobacillus GG has good evidence

Cochrane Database Syst Rev. 2013 May 31;5:CD006095 Goldenberg JZ
CLOSTRIDIUM DIFFICILE COLITIS

- Adverse events were assessed in 26 studies (3964 participants). Pooled complete case analysis indicates probiotics reduce the risk of adverse events by 20% (RR 0.80; 95% CI 0.68 to 0.95)
- The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated

INFLAMMATORY BOWEL DISEASE (IBD)

- Treatment with antibiotics is fraught by variable efficacy
- Genetic polymorphisms (NOD2/CARD15) in CD play a role in bacterial peptidoglycan recognition
- May be responsive to alterations in enteric flora and thus be important in the pathogenesis and maintenance of IBD
- Cochrane database systematic reviewed, and concluded that probiotics when combined with other therapies did not improve remission rates.
- However, this analysis showed a reduction in disease activity in mild to moderately severe UC.

ULCERATIVE COLITIS

- Systematic review also suggested a similar efficacy profile between probiotics and anti-inflammatory agents
- With regard to maintenance of UC remission, probiotics have been tested in a larger number of patients. One trial by Krus et al tested E. coli Nissle 1917 and found no difference in relapse rates in patients on a probiotic versus mesalamine
- Zocco and colleagues found no difference in relapse rates at 6 or 12 months when comparing Lactobacillus GG with mesalamine with a combination of the two. Those patients who took the probiotic did appear to have a longer time to relapse.
- All of these studies support the idea that probiotics may be as effective as mesalamine in maintaining remission in the short-term trials
CROHN’S DISEASE

- The literature on the induction and maintenance of remission in CD is heterogeneous and difficult to interpret
- Very few studies examined the additive effect probiotics may have on active CD
- In one study with only 11 patients, probiotics provided no additional benefit to steroids and antibiotics in inducing remission [Schultz et al. 2004]
- An open-label study with 10 patients who were refractory to prednisolone and aminosalicylates, were tried on a combination of probiotics (B. breve, B. longum, and L. casei) and a prebiotic (psyllium) simultaneously. A complete response was found in 6 of 10 patients without any adverse consequences [Fujimori et al. 2007]
- Several meta-analyses and systematic reviews have shown that probiotics were ineffective in maintenance of remission in CD [Rahimi et al. 2008; Rolle et al. 2008]

CROHN’S DISEASE

- More controlled studies have been performed on the maintenance of remission in adults with CD but in general these studies fail to show any benefit of probiotic administration.
- Data are even more robust on the prevention of relapse following surgical intervention, but again probiotics fail to prevent endoscopic or clinical recurrence

POUCHITIS

- The strongest evidence for the use of probiotics in IBD is in prevention and treatment of pouchitis [Mimura et al. 2004; Kuisma et al. 2003; Gionchetti et al. 2000, 2003].
- After proctocolectomy with ileal pouch–anal anastomosis, pouchitis or acute and chronic inflammation of the ileal reservoir is the most frequent long-term complication of this operation, occurring in up to 20% of patients at 1 year. Studies of the microflora in the pouch have revealed deficiency of Streptococcal species [Komanduri et al. 2007]
- A number of prospective controlled clinical trials of a probiotic, VSL#3 for 9–12 months, in the prevention and treatment of pouchitis [Gionchetti et al. 2000, 2003; Mimura et al. 2004]
- These studies show consistently a decrease in incidence and relapse of inflammatory response. One uncontrolled trial in patients with mild active pouchitis who were treated with VSL#3 showed a remission rate of 69% [Gionchetti et al. 2007].
- In contrast, a single species of Lactobacillus GG failed to show efficacy in a 3-month trial [Kuisma et al. 2003].
IRRITABLE BOWEL SYNDROME (IBS)

• A multisymptom GI disorder with unclear etiology and pathogenesis
• Changes in GI microflora in IBS patients have been reported by a number of investigators [Kassinen et al. 2007; Shanahan, 2007]
• Recently, reports on variable prevalences of small intestinal bacterial overgrowth (SIBO) in IBS have been published [Posserud et al. 2007; Lin, 2004]
• IBS symptoms such as bloating or flatulence have been attributed to possible alterations in the intestinal microflora and probiotics have been used empirically to treat these difficult symptoms [Kim et al. 2003, 2005]
• Postinfectious IBS may begin after a bout of acute gastroenteritis suggesting that altered microflora or induction of an altered inflammatory or immune state in the bowel may lead to altered bowel function and IBS symptoms [Collins et al. 2009]

IRRITABLE BOWEL SYNDROME (IBS)

• Elevated levels of interleukin 6 (IL-6), IL-6R, IL-1Beta and tumor necrosis factor alpha (TNF-α) and a lower IL-10/IL-12 ratio have been reported in IBS patients in comparison to controls, suggesting that IBS may be associated with increased pro-inflammatory cytokine secretion. [Dinan et al. 2006; Liebregts et al. 2007, O’Mahony et al. 2005]
• Plasma cytokine levels may not necessarily reflect the expression or levels of cytokines in the mucosa of the bowel wall, but may come from activated immune cells in the spleen or liver [Nance and Sanders, 2007].
• The imbalance between IL-10 and IL-12, observed in peripheral blood mononuclear cells, was confirmed at the mucosal level in a recent study suggesting that this finding may be an underlying phenotype in IBS and a potential biomarker for a subset of IBS patients [Macsharry et al. 2008].
• B. infantis was shown to increase IL-10/IL-12 ratio in IBS patients suggesting a possible mechanism by which this probiotic may exert its effect [O’Mahony et al. 2005]

IRRITABLE BOWEL SYNDROME (IBS)

• Bifidobacterium infantis 35624 demonstrated efficacy in two appropriately designed RCTs.
• Both global and individual IBS symptoms (abdominal pain, bloating, incomplete evacuation, intestinal gas, straining, and bowel function) were significantly improved without evidence to suggest an increase in adverse events.
• No other probiotic, including isolated Lactobacillus species, showed significant improvement in IBS symptoms in appropriately designed RCTs [Brenner et al. 2009] * no effect
• Systematic review of the literature evaluating efficacy of probiotics in the treatment of IBS revealed that probiotics had a statistically significant effect in reducing IBS symptoms with a number needed to treat (NNT) of 4 (95% CI 3–12.5) [Moayyedi et al. 2010].
• Almost all probiotic combinations contained both Bifidobacteria and Lactobacilli, the latter had no effect as assessed by continuous data meta-analysis. This raises the possibility that Bifidobacteria may be the active treatment in probiotic combinations.
Gastrointestinal Microbiota and Their Contribution to Healthy Aging

- Significant changes in GI microbiota composition in older subjects have been reported in relation to diet, drug use and the settings where the older subjects are living, that is, in community nursing homes or in a hospital.
- Probiotics have been shown to be effective in restoring the microbiota changes of older subjects, promoting different aspects of health in elderly people as improving immune function and reducing inflammation.

TIPS FOR CHOOSING A PROBIOTIC

- Check the label
- Call the manufacturer
- Beware of the Internet
- Stick to well-established companies and companies you know: Attune Foods, Bicodex, Culturelle, Dannon, General Mills, Kraft, Nestle, Procter & Gamble, VSL Pharmaceuticals and Yakult.

STORAGE

- Remember to store your probiotic according to package instructions
- Make sure the product has a sell-by or expiration date
- Probiotics are living organisms. Even if they are dried and dormant, like in a powder or capsule, they must be stored properly or they will die.
- Some require refrigeration whereas others do not.
- They also have a shelf-life, so make sure you use them before the expiration date on the package.
What Lies Ahead for Probiotics

- Advances in genomics are facilitating in-depth scientific investigation of the human microbiome and the functional capacities of probiotics
- Human Microbiome Project
- Mood disorders
- Obesity
- Autism
- Diabetes
- Recent clinical trials and translational studies suggest that lactobacillus probiotics may offer epithelial cytoprotection to limit symptoms of radiation enteritis, a dose-limiting side effect for patients receiving abdominal radiation therapy for malignancy

What Lies Ahead for Probiotics

- "Turbo-probiotics" designed to secrete human cytokines
- Gene-based bacterial profiling studies from disease affected humans have identified what may be novel "probiotics" such as Faecalibacterium prausnitzii and Clostridium species IV and XIVa
- We can identify, purify, and repackage probiotic-derived soluble factors possessing proven capacity to modify biological function
- Harness the power of probiotics while averting the potential risks associated with live bacteria
- As these advances progress to real-life medicine the term pharmabiotic has been proposed by some investigators in an effort to encompass both beneficial microbes and their products
<table>
<thead>
<tr>
<th>COMMERCIAL PRODUCT</th>
<th>MEDICAL CONDITION</th>
<th>Variable effectiveness based on clinical evidence/medical literature</th>
</tr>
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<tbody>
<tr>
<td>BioGul®</td>
<td>IBS, ID treatment</td>
<td></td>
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<tr>
<td>BioK®</td>
<td>AAD prevention, CDAD prevention</td>
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<tr>
<td>Culturos®</td>
<td>AAD prevention, CDAD prevention, IBD treatment and prevention, Crohn’s disease, IBS, prevention of rotavirus-related diarrhea in children, reduces the risk of respiratory tract infections in children, useful in the prevention of atopic dermatitis in children at high risk of allergy</td>
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<tr>
<td>Enterozina®</td>
<td>Reduces adverse effects and increases tolerability of Helicobacter Pylori eradication therapy, Allergic Rhinitis in children</td>
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<tr>
<td>Metabio®</td>
<td>Inflammatory Bowel Disease, IBS, acute diarrhea, chronic constipation</td>
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<tr>
<td>Miyisan®</td>
<td>Antibiotic-associated diarrhea, reduction of side effects of H. Pylori treatment</td>
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</tbody>
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| Probiotics Plus | Relieves constipation, improves bowel function, prevents diarrhea, reduces mortality rates in elderly | Relieves constipation, improves bowel function, prevents diarrhea, reduces mortality rates in elderly |
| VSL#3®           | IBS, Ulcerative Colitis (Diarrhea and hemorrhoids), Peptic ulcer disease (and possibly for UC) prevention and maintaining remission | IBS, Ulcerative Colitis (Diarrhea and hemorrhoids), Peptic ulcer disease (and possibly for UC) prevention and maintaining remission |
| Vistra® (Formerly Sterilox) | Anti-infective prophylaxis | Anti-infective prophylaxis |
| Yakult®           | AAD prevention, CDAD prevention, IBD treatment and prevention, CDAD prevention of recurrence, Crohn’s disease (treats one AAD prevention, infectious diarrhea and prevention, CDAD prevention, CDAD prevention of recurrence, Crohn’s disease (treats one strain) | AAD prevention, infectious diarrhea and prevention, CDAD prevention, CDAD prevention of recurrence, Crohn’s disease (treats one strain) |
SUMMARY

- Probiotics are a therapeutic class being increasingly used for a variety of GI disorders.
- Probiotics appear to alter intestinal microflora and may exert their effect(s) by a variety of mechanisms.
- Many species of probiotics exist and it is generally accepted that not all probiotics are created equal.
- Efficacy may be due to a single strain or multiple strains or a combination of different probiotics.
- There is good evidence to support the efficacy of S. boulardii and LABs and the combination of the two for AAD, VSL#3 for pouchitis, and B. infantis 35624 for IBS.

SUMMARY

- Probiotics decrease the duration of symptoms in acute infectious diarrhea.
- Probiotics, including E. coli Nissle 1917, LGG, and VSL#3 have strong data similar to as standard therapy (mesalamine) in inducing or maintaining remission in UC.
- When added to standard therapy, probiotics do not provide additional benefit compared with standard therapy alone.
- Most probiotics tested to date are not more effective than placebo in inducing or maintaining IBD remission.
- Probiotics have been shown to be safe in immunocompetent hosts in an outpatient setting. However, administration of probiotics to immunocompromised, chronically ill, hospitalized patients with GI disorders, and indwelling catheters may predispose them to probiotic sepsis.
- Specifically, in GI disorders in which gut permeability and gut immunity may be compromised, adding probiotics may increase translocation of bacteria into the bloodstream.
- Until further studies become available on safety of probiotics in hospitalized patients, we should exercise caution in their use in this setting.

OTHER GOOD READS ON PROBIOTICS