Probiotics – with a focus on IBS (Irritable Bowel Syndrome)

Executive summary

Probiotics are based on emerging and fascinating science concerning the human gut microbiome, being the collection of organisms that live in the human gastrointestinal tract, and outnumber the number of human cells by between 10 and 100 to 1. The evidence supporting treatment of any specific gastrointestinal, or even non-gastrointestinal, disease or condition, is weak or nonexistent. Nevertheless, mainly due to commercial interests, there is a strong and growing market for probiotics, with advertising that often overstates the potential benefits.

Since evidence of efficacy of medical treatment requires randomized controlled trials, which are complex and expensive, we still (April 2018) need to wait longer for good evidence of which probiotics work well for which gastrointestinal condition. Irritable bowel syndrome has been studied the most, and randomized controlled trials to date show benefits in a minority of studies, and somewhat more often, show minimal or no benefit, either for overall improvement or specific symptoms of IBS. Nevertheless, meta-analyses (scientific combination of multiple randomized controlled trials) suggest that certain probiotics may help certain symptoms of IBS, can be used as adjunct therapy, and should be tried for approximately one month before re-evaluation. Unfortunately, probiotics are expensive, and have only temporary effect. Although the effect might continue as long as the probiotics are taken, the effect usually dissipates after stopping the probiotics.

Introduction

Probiotics sound like an excellent idea.

The probiotic theory involves taking live organisms, by mouth, which are thought to have beneficial effects for the host organism, to try to restore or improve the intestinal or gut microbiome. Prebiotics, on the other hand, are chemicals, or nutrients, taken by mouth, with the purpose of altering the components of the intestinal microbiome.

The full collection of live organisms in the human gut outnumbers the human cells by between 10 and 100 to 1. We call it the gut/intestinal microbiome or microbiota, and it includes viruses, fungi, protozoa, organisms called Archaea (that can live in so-called “hostile” environments), as well as bacteria. Some researchers use the term 'microbiota' to mean the microbes found within a specific environment and the term 'microbiome' to mean the collection of microbial genomes in an environment. Whichever term used term can indicate whether a paper has fully sequenced the genomes of the microbes it is examining or whether it has just identified them by 16S rRNA or culturing (L. Glendinning, U of Edinburgh, online). There is also a skin microbiome, an oral microbiome, a genital microbiome, and a respiratory microbiome.

These are difficult area to research because many of these organisms cannot be cultured, and can only be identified by complicated RNA/DNA technologies, eg 16S rRNA, etc.

The majority of the gut microbiota live in the colon, and the distal small bowel. While the upper small bowel was classically thought to be sterile, this is no longer felt to be true.

Nevertheless, research in several areas, (starting with inflammatory bowel disease and irritable bowel syndrome (IBS), then C. difficile infection (CDI or CDAD), colorectal cancer (CRC), adjunct therapy of H. pylori infection, and more recently, outside of gastrointestinal disease, such as cirrhosis of the liver, ischemic heart disease, allergies, and even obesity), suggest significant links between the gut microbiome and various diseases. In general, studies have shown the "normal" distribution of organisms in unaffected individuals, and the "abnormal" profile in disease patients (dysbiosis or imbalance – unfortunately this term, dysbiosis, is now misused by many "alternative practitioners"). Up to this time (Spring, 2018) there has been little if any successful research in altering the microbiome in any predictable or measurable way, and positively affecting a disease process, except for patients suffering from recurrent C. difficile infection.

The intestinal microbiome is thought to affect the host function by alterations in immune system function, and intestinal epithelial barrier function. There may also be effects by increasing beneficial bacteria, suppressing pathogenic bacteria, and recently, some evidence of effect on pain receptors, including opioid and cannabinoid receptors in the gut. Metabolites, breakdown or other cellular products, produced by the microbiota, can be absorbed, and produce local or systemic effects.

Another large area of interest and research is the clinical effect of organisms, usually bacteria, growing in the small intestine, which was previously thought to be primarily sterile, especially more proximally. This disorder, known as small intestinal bacterial overgrowth (SIBO), is recognized in certain clinical situations, (but probably over-diagnosed by some doctors, and definitely by many so-called "alternative practitioners"). Proof of this condition is difficult, and there is intense controversy surrounding the diagnosis, incidence, and treatment of this condition, especially in irritable bowel syndrome patients – the most widely studied group for SIBO.

Attempts to manipulate the intestinal microbiome can be classified into four groups, antibiotic therapy, prebiotic therapy, probiotic therapy, and fecal transplant (also known as fecal microbiotic therapy (FMT)) - synbiotics are combinations of pre- and pro-biotics.

Some of the practical hurdles in the study of probiotics have been the choice of organism, the dose, the reliability of the oral supplement, the resistance of the oral supplement to gastric acid and other digestive juices, and the successful passage of the supplement through the small intestine to the colon.

There are very few studies confirming, in reliably repeated research studies, a positive beneficial effect on a given disease.

There are different organisms, with different subspecies, or different effects even within the same species, and there are many different diseases.

Probiotics are often expensive, the effects may take several weeks to start working, and the effects usually wear off quite quickly when the probiotic is no longer ingested.

The ultimate treatment of the dysbiosis will likely be artificial stool (see this sample website; http://thepowerofpoop.com/resources/innovation/ , and specifically Re-POOPulate™, Allen-Vercoe (Guelph) https://www.uoguelph.ca/mcb/people/dr-emma-allen-vercoe and Petrof (Queens, Kingston),

https://dbms.queensu.ca/faculty/elaine_petrof). Real stool poses several potential infectious risks, although it has been the first, the most frequent, and the most successful treatment of altered microbiota, primarily in patients with recurrent C. difficile infection.

Probiotics are generally thought to be completely safe, but there are rare cases, most often in patients with suppressed immune systems, where the probiotic might enter the blood stream and cause serious infection.

An alternative to probiotics, strongly recommended as beneficial, and without toxic effect, is fermented foods. These may be more cost-effective, possibly providing a broader range of organisms, and potential health benefits, and this includes fresh natural yoghurt, kefir, kimchee, kombucha, sauerkraut, miso and tempeh or natto (the latter two derived from soybeans).

Prebiotics:

Many prebiotics are similar or identical, to compounds recognised as the common components of many high-FODMAP foods – ie inulin, oligofructose (for a discussion of FODMAP's, see the paper on our website on bloating, or check Wikipedia. Inulin is also the single component of Benefibre (GSK – Canadian, (as opposed to Benefiber (GSK - American) which is wheat dextrin), often advertised as a more palatable alternative to Metamucil/psyllium. Some patients, especially those with IBS (irritable bowel syndrome) will experience significant gas and bloating from high-FODMAP foods, from some prebiotics, and potentially from Benefibre.

Probiotics for IBS

Contrary to many strong advertising campaigns, I do not think there is strong evidence to support probiotics in most cases of gastrointestinal, or other, diseases.

For the main GI diseases that I treat, the most useful reference is (3176 studies, 70 RCT's, 23 studies of IBS, 47 other lower GI conditions, 54 different products):

"Systematic Review: Probiotics in The Management Of Lower Gastrointestinal Symptoms – An Updated Evidence-Based International Consensus", Hungin et al, Aliment Pharmacol Ther. 2018 Apr;47(8):1054-1070. doi: 10.1111/apt.14539. Epub 2018 Feb 20. PMID 29460487.

Their conclusion:

3 general recommendations for practising clinicians:

We recommend that specific probiotics have a role in the management of some IBS symptoms and can also be used as an adjunct to conventional treatment. We also recommend that probiotic strains should be selected based on the patient's symptoms, the clinical indication and the available evidence; no probiotic alleviates the full range of symptoms in IBS. Finally, we recommend that, when trying a probiotic therapy for a chronic GI problem, the product should be taken for 1 month; dose selection should be based on available evidence and manufacturers' recommendations.

Here are further details, for IBS:

Some patients with irritable bowel syndrome will, or may, experience benefit from some probiotic treatments. The most likely, supported by one large study, 12 years old now, and a small number of smaller studies, would be Bifidobacterium infantis 35624 (now called B. longum), which is Align™. Advertised as "a patented pure strain probiotic that gastroenterologists recommend most", the reference for this statement is a survey from 2016 of a group of specialists who agreed to specify which brand of probiotic they recommend most often (but not how often they recommend it, or probiotics in general). The bigger study was for 4 weeks, and 362 patients, and showed benefit at 1 of 3 doses, being the middle dose (10^8). A meta-analysis of all 5 studies of B. infantis concluded that the 3 studies of single probiotic B. infantis, including the 2006 study, did not significantly impact on abdominal pain, bloating or bowel habit satisfaction. Two studies that used a composite probiotic which included B. infantis produced significant reduction in abdominal pain, and bloating/distention.

A recent study (Ringel-Kulka et al, American Journal of Gastroenterology, January, 2017), not included in the previously mentioned meta-analysis by Hungin et al, published in January 2017, evaluated 275 "non-patients" (recruited from general communities by advertisement, 10 sites and eight American states). Subjects were given 10^9, B. infantis, and (despite funding from Proctor Gamble), was unequivocally negative in affecting symptoms of abdominal discomfort and bloating, albeit in "a non-patient population".

Another recent meta-analysis of probiotics for IBS, published in 2014 (Ford et al, American Journal of Gastroenterology, PMID: 25070051), not limited to B. infantis, and covering prebiotics, probiotics, and synbiotics, suggested that **19 of 25 studies failed to show any significant difference for probiotic treatment versus placebo for abdominal pain/global symptoms.** Nevertheless, this meta-analysis showed that the proportion of patients reporting "persistent or unimproved IBS symptoms" dropped from 73% for placebo-treated patients to 56% for probiotic treated patients, for a relative risk of symptoms persisting or remaining unimproved of 0.79, which is a statistically significant 21% reduction. Combination probiotics produced a significant effect on persistence of symptoms (RR 0.81; 95% confidence interval 0.67-0.98), and 3 of those studies used the same combination of Lactobacillus paracasei, Lactobacillus acidophilus, and B. lactis, and was noted benefit over placebo in those studies. Lactobacillus alone showed no clear benefit over placebo, except for 3 studies using Lactobacillus plantar him. Bifidobacterium showed no benefit over placebo in 2 studies.

The efficacy on global IBS or abdominal pain scores suggested a statistically significant improvement in symptoms, with a standardized main difference of -0.24, but specific combinations included VSL #3, showing no significant benefit over placebo, 3 trials with a combination of Lactobacillus paracasei, Lactobacillus acidophilus, and Bifidobacterium lactis, showed no benefit over placebo, and 2 trials using a combination of Bifidobacterium lactis, S. thermophilus, and Lactobacillus bulgaricus, showed no benefit over placebo. Overall, bloating scores were reduced by approximately 15%, flatulence reduced by approximately 23%, and urgency was not significantly reduced.

One conclusion from this meta-analysis is that in individual studies of between 20 and 300 patients, statistically significant results are rarely found, but by combining studies (meta-analysis), for example to a total of 2001 patients, (2603 IBS pts in the meta-analysis by Hungin) statistically significant effect can be shown. The clinical benefit of this statistic remains unknown. The NNT (number needed to treat) to improve one patient's symptoms was 7. Unfortunately, the evidence to support combinations, as a

group, was positive but not for any of the different combinations studied individually. There was a trend towards a beneficial effect of bifidobacterium, but a trend that is not statistically significant.

Many studies failed to identify the 3 classic subtypes of IBS, IBS-D, IBS-C, and IBS-M. There is a suggestion in the literature, that IBS-D might be more likely to respond, on the basis of some information about the composition of the bacterial species in those patients.

Tradenames

Align is B. (Bifidobacterium) infantis 25624 – now B. longum.

Tuzen, UltraFlora Intensive Care, GoodBelly Probiotic Juice Drinks, and Digestive Care Daily Probiotic are Lactobacillus plantarum.

Activia is B. regularis.

Floratrex is B. lactis.

Florastor is Saccharomyces boulardii - this probiotic may be more of use to prevent antibiotic-associated diarrhea and adults, or help patients get over acute infectious diarrhea or antibiotic-associated diarrhea.

Footnote

A useful tool in Canada may be probioticchart.ca, (funded by AEProbio, the Alliance for Education on Probiotics).

Specific references available on request: reception@drlalor.ca