MUTUALLY BENEFICIAL INTERACTIONS BETWEEN GUT MICROBIOTA, THE EPITHELIUM, THE GUT BARRIER, AND THE MUCOSAL IMMUNE SYSTEM, BUT ALSO THE INTERPLAY BETWEEN LUMINAL COMMENSALS AND THE ENTERIC NERVOUS SYSTEM AND GUT MUSCLE. THAT THE MICROBIOTA MIGHT PLAY A ROLE IN SUCH GASTROINTESTINAL DISORDERS AS CELIAC DISEASE, INFLAMMATORY BOWEL DISEASE, AND FUNCTIONAL AND MOTILITY DISORDERS SHOULD THEREFORE COME AS NO SURPRISE. INDEED, THROUGH EFFECTS ON NEUROENDOCRINE IMMUNE, AND METABOLIC FUNCTIONS, A ROLE FOR THE MICROBIOTA HAS BEEN INVOKED IN DISORDERS AS DIVERSE AS ARTHRITIS AND LIVER DISEASE. THE RECENT PROPOSAL THAT INTERACTIONS BETWEEN MICROBIOTA AND GUT COULD EXTEND ALL THE WAY TO THE CENTRAL NERVOUS SYSTEM VIA WHAT IS REFERRED TO AS THE MICROBIOTA-GUT-BRAIN AXIS NOW PROVIDES A FRAMEWORK FOR THE INCrimINATION OF GUT MICROBES IN NEUROLOGICAL DISORDERS SUCH AS PARKINSON’S DISEASE. THE LIST OF MALadies IN WHICH THE MICROBIOME HAS BEEN IMPLICATED, ALbeit WITH VARYING LEVELS OF EVIDENCE, CONTINUES TO EXPAND AND NOW INCLUDES AUTISM, ALZHEIMER’S DISEASE, Atherosclerosis, Obesity, Metabolic Syndrome, Diabetes, Colon Cancer, Depression, and Anxiety. THIS IS THE CONTEXT IN WHICH ALL INTERVENTIONS, INCLUDING PREBIOTICS AND PROBIOTICS, THAT SEEK TO MODULATE THE MICROBIOTA MUST NOW BE VIEWED.

It is likely that foods and supplements that may well have exhibited prebiotic or probiotic properties have been around for centuries, if not millennia, and used empirically in health maintenance as well as in the management of gastrointestinal symptoms and disorders. Now, this unregulated and over-the-counter market in products that claim prebiotic and probiotic properties has begun to attract the scrutiny of the scientific community and the regulatory authorities. The biological effects of these substances are being investigated, plausible hypotheses for their use in health or disease developed and, albeit too slowly, rigorous clinical studies of their impact in humans are beginning to emerge.

Abbreviations used in this paper: IL, interleukin; ISAPP, International Scientific Association for Probiotics and Prebiotics.

Keywords: Microbiota; Probiotic; Prebiotic; Synbiotics.
Whether prodded by regulators or demanded by prescribers and consumers, prebiotics and probiotics are emerging from the dark and into the light of scientific scrutiny. This review will focus on recent developments in their definition, biology and clinical effects. Comments will be limited to issues pertinent to the gastrointestinal tract and its related organs.

**Definitions and Their Implications**

**Prebiotic**

The most widely quoted definition of a prebiotic is that provided by Gibson and Roberfroid in 1995 as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.” A panel of experts convened by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2016 modified this to “a substrate that is selectively utilized by host microorganisms conferring health benefit.” Selectivity is regarded as central to the prebiotic concept; in contrast to fibers, such as cellulose, pectins, and xylans, which promote the growth of many microorganisms in the gut, prebiotics such as fructo-oligosaccharides and galacto-oligosaccharides primarily stimulate the proliferation of *Lactobacillus* and *Bifidobacterium*. This has clinically important ramifications as selectivity mitigates against the promotion of potential pathogens, or of gas-producing organisms, such as *Clostridium*, that might induce unwanted side effects. An insistence on selectivity does not, as pointed out by Gibson et al, exclude effects on species or strains other than *Lactobacillus* and *Bifidobacterium*. Relationships between fibers and prebiotics can be the source of some confusion—depending on the fiber and the host that ingests it, some fibers can exert prebiotic effects whereas others, as already mentioned, do not. As prebiotics are typically “carbohydrate polymers that are neither digested nor absorbed in the human small intestine,” most prebiotics, in contrast, can be classified as fibers. Molecules classically regarded as prebiotics include human milk oligosaccharides, inulin, fructo-oligosaccharides, and galacto-oligosaccharides. The concept of selectivity has been challenged. Bindels et al proposed an alternative definition of a prebiotic as “a nondigestible compound that, through its metabolism by microorganisms in the gut, modulates composition and/or activity of the gut microbiota thus conferring a beneficial physiologic effect on the host.” In so doing, they ditched the requirement for selectivity and specificity and expanded metabolism beyond fermentation. In support of the latter, they draw attention to the demonstration of potentially beneficial effects of prebiotics which are not dependent on fermentation. They also proposed that noncarbohydrates may act as prebiotics and added the following candidate prebiotics to the usual list: resistant starch, pectin, arabinose, various dietary fibers, and noncarbohydrates that exert their action through a modulation of the gut microbiota.

For now, however, the concept of selectivity prevails but may well be refined as research progresses. Indeed, recent studies support the concept of selectivity. Thus, when Vandepitte et al examined the impact of inulin-type fructans on the fecal microbiota of healthy adults with mild constipation, they found, as expected, increased relative abundance of *Bifidobacterium* spp., but also noted increases in *Anaerostipes* spp. and a decrease in the population of *Bilophila*; the latter effect correlating with a change in stool consistency.

**Probiotic**

Though probably in existence for centuries, probiotics were first defined by Lilly and Stillwell in 1965 as “substances secreted by one microorganism which stimulate (in contrast to antibiotics) the growth of another.” This definition of a probiotic was subsequently expanded to “a preparation of, or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects on the host.” The widely quoted Food and Agricultural Organization of the World Health Organization is more succinct in defining a probiotic as being “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Another ISAPP panel recently revisited the term probiotic and came out in support of the retention of the Food and Agricultural Organization of the World Health Organization definition. They listed 4 categories of compounds or products that contain live microorganisms and are intended for human use and addressed their regulatory implications:

1. Live or active cultures
   These products, such as yogurts, simply claim that they contain live and active cultures but, unless evidence is provided that they confer a health benefit (which some do), this descriptor should not be taken to imply probiotic activity.

2. Probiotic in food or supplement without a health claim
   Such products state that they “contain probiotics.” They should be safe and provide evidence of a general health benefit in humans. In some jurisdictions, the use of the term “probiotic” has been regarded as an implied health claim (based on the aforementioned definitions of a probiotic) and, therefore, forbidden in the absence of acceptable evidence of a health benefit. Definitions do matter!

3. Probiotic in food or supplement with a specific health claim
   This category requires that the product has demonstrated convincing evidence of a specific health claim...
such as “reinforces the body’s natural defenses.” For example, in Europe, the European Food Safety Authority requires the following evidence to support a health claim:

a. Characterization of the strain or each of the strains in a probiotic mix or combination
b. Identification of the health relationship that is considered as a beneficial physiological effect to the target population (ie, the general population or a defined part of it)
c. Demonstration of health effects in a normal healthy population.

Few probiotics have met these requirements.

4. Probiotic drug

Here the probiotic is used to treat or prevent a specific disease. In the United States, and elsewhere, this is now categorized as a drug (defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease) and must satisfy all the regulatory requirements to be approved as such.

If a probiotic is intended as a dietary supplement (ie, categories 1–3 above) and is not being proposed as a drug, it is regulated in the United States under the Dietary Supplement Health and Education Act of 1994 and is regarded as a food. Dietary supplements do not require approval by the Food and Drug Administration before being marketed but, according to Dietary Supplement Health and Education Act of 1994, must provide evidence of safety and follow Current Good Manufacturing Practice requirements for dietary supplements. Serious adverse events must be reported to the Food and Drug Administration. The regulatory approach in other jurisdictions varies considerably from treating nonfood probiotics as drugs or biological agents to classifying them as functional foods. In others, there is minimal oversight.

The current definition of a probiotic has further ramifications. Two issues deserve special emphasis: the focus on “live” organisms and the insistence on conferring “a health benefit on the host.” Firstly, while it is readily acknowledged that studies in a number of animal models have demonstrated efficacy for killed bacteria, or even bacterial products or components, in generating a number of anti-inflammatory and anti-infective effects, this strategy has not, as yet, been explored or validated in humans. It seems improbable that effects of probiotics in humans will be confined to live organisms so this aspect of the definition will ultimately have to be refined or the term abandoned completely. The term pharmabiotic has been proposed to encompass all biological active moieties derived from the microbiota. Second, it is obvious from the latter part of the definition that clinical claims in humans, be they in the augmentation of health or in the treatment of disease, must be supported by credible clinical trial data.

Synbiotic

As its name suggests, a synbiotic refers to the combination of a prebiotic with a probiotic. The intent is to amplify the benefits of the probiotic as well as stimulate the growth of indigenous beneficial microbes.

Implications

The tersely worded legalize of the documents which typify the seemingly esoteric promulgations of the various regulatory bodies do have significant practical implications. In the United States, for example, where, in comparison with drugs, probiotics, prebiotics and synbiotics appear relatively unregulated, the consumer is confronted with products and formulations all claiming to be (or contain) probiotics whose range seems to be limited only by the imagination of the manufacturer. Claims deftly skirt around preventing or treating disease by the use of vague terms such as “immune boosting” or “restoring digestive balance” yet are seldom supported by any clinical data. How is the hapless consumer to differentiate between high quality products with supportive data and those which have none in an environment of such “light touch” regulation? It seems inevitable that regulatory oversight must increase.

A change in the regulatory climate may also demand a more rigorous approach to clinical trials. This will pose challenges for potential investigators; specifically, who will fund the trials which will be required to satisfy the new demands of regulatory authorities—requirements that are already beginning to emerge in Europe? If it is decided that a given probiotic product is to be regarded as a food, profit margins will be slim and the target population will, by definition, be the healthy population. Such trials will by virtue of their endpoints require very large numbers of participants and be very expensive. Within the food category one acceptable endpoint would be the demonstration of a reduction in risk for a given entity in the general population. This requires a validated biomarker of risk, of which there are few (eg, cholesterol for heart disease), not a biomarker of early disease (which immediately moves the product into the drug category). Both issues, the size of study population and need for validated biomarkers of risk pose huge problems for the food industry, which does not have a tradition of funding such trials. In other words, it may be cheaper to study probiotics as drugs for narrow indications within the pharmaceutical sector (paradoxically lower costs and higher margins on licensable product) unless new microbial biomarkers of risk emerge.

Practical Considerations

Quality Control

Any prebiotic that is recommended for use in humans should be thoroughly characterized in terms of its
structural biochemistry and it should be resistant to the effects of gastric acid, bile, and digestive enzymes so that it arrives at its proposed site of action (usually the colon) intact. Dose ranging studies should be performed to ensure that an effective dose is delivered without causing adverse effects.\textsuperscript{24} Needless to say, any and all health claims should be supported by clinical evidence and every effort should be made to establish a cause-and-effect relationship between the administration of the probiotic, changes in microbial populations and their metabolism and the health benefit.

For probiotics (and synbiotics) the guidelines for the evaluation of probiotics in food proposed in 2001 still form a reasonable basis for quality control:\textsuperscript{36,43}

1. "Identification of the genus and species of the probiotic strain by using a combination of phenotypic and genotypic tests as clinical evidence suggesting that the health benefits of probiotics maybe strain specific."

Though proposed almost 20 years ago this has proven remarkably prescient. The complete genomes of several probiotic strains have now been sequenced and, in so doing, some have even been reclassified.\textsuperscript{44,45} Knowledge of the genome also facilitates batch-by-batch testing of product to ensure consistency.

2. "In vitro testing to delineate the mechanism of the probiotic effect"

In the decades since the publication of these guidelines there have been extensive studies of the in vitro and in vivo properties and effects of a host of putative probiotic strains. Such studies have identified a number of effects of relevance to the gastrointestinal health and disease, including effects on motility, visceral sensation, gut barriers, immune responses, and the microbiota-gut-brain axis.\textsuperscript{46–50}

3. “Substantiation of the clinical health benefit of probiotic agents with human trials”

This remains an absolutely fundamental principle.

4. “Additionally, safety assessment of the probiotic should at a minimum determine:

1. Patterns of antimicrobial drug resistance
2. Metabolic activities
3. Side effects noted in humans during trials and after marketing
4. Toxin production and hemolytic potential if the probiotic strain is known to possess these properties
5. Lack of infectivity in animal models”

Also fundamental to the development of a probiotic is the demonstration of survivability in transiting the gastrointestinal tract, as well as throughout the shelf life of the product. While this painstaking approach to probiotic discovery has been adopted by investigators\textsuperscript{51–53} and reputable manufacturers, many products on the market have not been subjected to even the most basic aspects of quality control. Many other aspects of probiotic and prebiotic usage have been given scant attention, such as optimal dose and ideal formulation. Strain selection is critical. While certain bacterial properties may be common to some or all members of a given species, others, including those that may well be relevant to a given gastrointestinal ailment may well be strain specific and dependent on certain segments of the genome.\textsuperscript{54}

### Safety

Despite their widespread use over many decades by the general population, as well as by individuals harboring a broad spectrum of intestinal and systemic diseases, the safety record of probiotics, prebiotics and synbiotics has been excellent,\textsuperscript{55,56} even in potentially at risk populations.\textsuperscript{57–60} Rare instances of bacteremia, fungemia and abscesses have been reported,\textsuperscript{55–60} and 1 study associated probiotic use with increased mortality due to intestinal ischemia in a group of patients with severe acute pancreatitis.\textsuperscript{61} For all of these reason probiotics are “generally regarded as safe.”\textsuperscript{62} Though reassuring, the literature on probiotic and prebiotic safety lacks the rigor that one associates with drug safety monitoring and better, prospective data is needed.\textsuperscript{53} These optimistic views of safety also assume high standards in quality control which may not be always met.

### Economic Impact

It has been estimated that the global prebiotic market will exceed $8.5 billion by 2024 (https://www.gminsights.com/pressrelease/prebiotics-market-size) and that for probiotics will exceed $64 billion by 2022 (https://www.marketsandmarkets.com/Market-Reports/probiotic-market-advanced-technologies-and-global-market-69.html?gclid=Cj0KCQjwB_b0eAOFARIsAO5fVvH2HmbgwjWxqdbf40mBiiej2r5wHb5Unf9HbBz0aA3m-3wrYpF1zroaAppAEALw_wcB). For now, given the manner in which these products are regulated in most countries, the cost is borne by the consumer; costs that vary tremendously between products and countries.

### Mechanisms of Action

#### Prebiotics

Central to the very definition of a prebiotic are its impacts on bacterial proliferation and metabolism.\textsuperscript{54,65} Recent studies employing a variety of prebiotic molecules have consistently demonstrated increases in the
relative numbers of *Lactobacillus* and *Bifidobacterium* spp. as well as changes in bacterial metabolism, as evidenced, in particular, by an increased production of short-chain fatty acids such as butyrate and propionate (summarized in).26 Short-chain fatty acids, in turn, possess antimicrobial activity and promote homeostasis through effects on the integrity of the colonic epithelium and metabolic and immunological actions.25–27 As pointed out by Bindels et al.27 and acknowledged in the ISAPP document, the metabolic impact of probiotics extends beyond fermentation and some of the beneficial effects may rely on interactions with the epithelium or immune system through effects on bile acid metabolism, and neuroendocrine responses (summarized in Gibson et al.24 Impacts remote from the gut and within the central nervous system have also been demonstrated.66 As ever more selective prebiotic molecules are developed, targeting of very specific biological effects will become more possible.

**Probiotics**

Probiotics have been extensively studied in animal models and beneficial effect of several species and strains demonstrated in immunological, metabolic, and neuroendocrine dysfunction (Figure 1).

Many probiotics are derived from the commensal microbiota in the healthy human gut; their properties will, understandably, mimic those of the homeostatic effects of the intact microbiota. A substantial literature attests to the anti-inflammatory effects of probiotics. Probiotics engaging with the mucosal immune system via Toll-like receptors to promote type 1 T helper cell differentiation. As a consequence antibody production is increased, phagocytic and natural killer cell activity augmented, and the nuclear factor kappa-light-chain-enhancer of activated B cells (nuclear factor κB) pathway inhibited. These lead, in turn to the induction of T cell apoptosis, upregulation of anti-inflammatory cytokines, such as interleukin (IL)-10, and transforming growth factor beta and downregulation of proinflammatory cytokines such as tumor necrosis factor-alpha, interferon gamma, and IL-8.15,67–73 In this way, a probiotic mimics the tolerance induced by commensal organisms and contrasts with the inflammatory response to pathogens. *Faecalibacterium prausnitzii* has been identified as protective against inflammatory bowel disease in humans74 and has been shown to induce the anti-inflammatory interleukin, IL-10 in human and murine dendritic cells75 and suppress chronic inflammation in a murine model.26 This research has generated much interest in the potential of this organism as a probiotic for IBD.

Critical to their potential role in enteric infections probiotics have been shown to beneficially modulate the composition of the microbiota by inhibiting the growth of potentially pathogenic bacteria through the production of bacteriocins and the creation of a more acidic milieu that is inimical to proinflammatory bacteria, yet promotes the growth of beneficial species such as *Lactobacilli* and *Bifidobacteria*77–80.

The positive impacts of probiotics on gut barrier function have relevance to a number of conditions ranging from irritable bowel syndrome to inflammatory bowel disease as well as to the host of conditions that have, wrongly or rightly, been linked to a “leaky gut” and bacterial translocation. This hypothesis, is indeed central to the proposed role of the microbiota in the pathogenesis of a range of liver diseases and their complications.81 The structural, physiological, and molecular effects of various probiotics on the components of gut defense have been amply demonstrated in animal models.82–89

Effects of probiotics on processes relevant to dysmotility and functional disorders have also been demonstrated in animal models. These include reducing visceral hypersensitivity.39,90–94 Effects on smooth muscle function and transit have also been demonstrated.81,95,96

Beneficial effects on gut function could also be exerted via the microbiome-gut-brain axis and a plethora of recent studies, mostly, it must be conceded, from animal models, attest to the ability of microbes in the gut to modulate brain development, structure and function and influence emotions and behavior.77–101

Many other effects of probiotics and, most notably, those on metabolic processes have been demonstrated but are beyond the scope of this review; they may, however, be highly relevant to obesity, the metabolic syndrome and nonalcoholic fatty liver disease.21

These almost universally positive effects of probiotics in animal models should translate into tangible benefits in humans. Do they? While some success has achieved in demonstrating beneficial immunological, physiological and metabolic effects in humans, results have proven less consistent and often difficult to demonstrate. This should come as no surprise.

Studies of the administration of probiotics on the composition of the fecal microbiota have demonstrated, at best, modest effects.102,103 This should not be taken to imply that probiotic have no effects—effects of an orally administered probiotic on the systemic immune system104,105 and on brain responses106 have, indeed, been demonstrated in healthy volunteers and irritable bowel sufferers, respectively. What these findings speak to is the likelihood the probiotic effects are subtle, may occur on the mucosal surface and may even be exerted in the small intestine or stomach107 and not in the colon—phenomena that may not detected on analyzing the feces. It should also be noted, parenthetically, that the poorly absorbed antibiotic, rifaximin, is also associated with relatively minor shifts in gut microbiota populations—a further illustration of the subtlety of interventions that clearly modulate microbiota activity and benefit patients.108
Clinical Evidence

There continue to be major shortcomings in relation to clinical studies of prebiotics, probiotics, and synbiotics. Even among probiotic studies (which greatly outnumber those performed with prebiotics and synbiotics), the clinician will encounter challenges in attempting to derive clinically useful messages. Heterogeneity is the rule with studies differing widely in study protocol, selection of study population, sample size, strain or strains employed, dosage, formulation, duration of therapy and outcome measures, even for the same indication.\textsuperscript{109,110} For example, the recent systematic review with meta-analysis performed by Ford et al\textsuperscript{111} evaluating data from 43 randomized controlled trials while showing that probiotics, in general, are effective in irritable bowel syndrome, was unable to define which individual strains or species were most beneficial because of a lack of adequate comparative data.

Effects in Healthy Adults

As clinicians we are frequently asked by family, friends, and colleagues whether taking a probiotic is beneficial to otherwise healthy individuals. Khalesi et al\textsuperscript{112} recently completed a comprehensive review of

\textbf{Figure 1.} Mechanisms of action of probiotics. (A) Effects on the microbiota and luminal milieu. (B) Effects on gut barrier. (C) Immune effects. (D) Effects on neuromuscular function. (E) Impact on the microbiota-gut-brain axis. IgA, immunoglobulin A; SCFA, short-chain fatty acid; TLR, Toll-like receptor; T\textsubscript{reg}, regulatory T lymphocyte.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Endpoint(s) - Outcome</th>
<th>Preferred Strain(s)</th>
<th>Comments</th>
<th>Reference(s)</th>
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| AAD and CDAD | Prevention - effective | *Lactobacillus* GG and *S Saccharomyces boulardii* (in children) | Quality of evidence moderate to high  
Effective if background risk >5%  
Probiotics most effective if given close to the first dose of antibiotic  
No increase in AEs | 118–121 |
| Chemoradiation-induced diarrhea | Prevention - probable effect  
Treatment - possible benefit | | Some studies limited to abdominal and pelvic radiation therapy, some include chemotherapy | 122,123 |
| Crohn’s disease | Any outcome - no benefit | | Included prevention of postoperative recurrence, maintenance of remission | 124 |
| Diarrhea in children | Reduce duration of diarrhea - effective | *Lactobacillus reuteri* DSM 17938 and *Lactobacillus GG*  
May not be effective against gastroenteritis in developed countries. Limited evidence for persistent diarrhea. | | 125–127 |
| *Helicobacter pylori* | 1. Increase eradication rate as adjunctive therapy - conflicting data on efficacy  
2. Reduce antibiotic-related adverse events - more consistent data support efficacy | *Lactobacillus* - and *Bifidobacterium* -containing probiotics  
*Saccharomyces boulardii*  
*Lactobacillus* -containing probiotics  
*Saccharomyces boulardii* | Benefits may be greater in Asian populations  
Impact on compliance with eradication regimens uncertain | 128–130 |
| Hepatic encephalopathy | 1. Symptom improvement - some efficacy  
2. Reduce rate of progression of MHE to overt HE - some benefits seen | | No effect on mortality  
As effective as lactulose  
Low quality of evidence | 131 |
| IBS | 1. Overall symptom relief - effective  
2. Relief of major symptoms individually -effective | In general, evidence insufficient to distinguish between strains or products | Low quality of evidence overall | 111,132 |
| Pouchitis | Primary prevention and prevention of relapse | VSL #3 | Moderate-to-low quality of evidence | 124,133 |
| Recurrent abdominal pain in childhood | Reduce pain frequency and severity - some evidence of efficacy | | Low quality of evidence | 134 |
| Travelers’ diarrhea | Prevention - effective | VSL #3 | Effects greatest in mild-to-moderately severe UC  
As effective as 5-ASA preparations | 124 |
| UC | Induce remission in active UC - some efficacy  
Prevent relapse of UC in remission - some efficacy | | | 124 |

AAD, antibiotic-associated diarrhea; AE, adverse event; CDAD, *Clostridium difficile*–associated disease, HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid.
the literature on the impact of probiotics among healthy adults and concluded first, that probiotics had minor and transient effects on the fecal microbiota; second, that probiotics reduced the incidence, duration and symptoms of the common cold but not influenza; and third, that probiotics had little or inconclusive effects on lipid profiles, body mass index, or blood sugar or insulin levels. The effects on the common cold, they hypothesized, could be explained on the basis of positive immunological effects.

Benefits for prebiotics on satiety and metabolic parameters, including reductions in postprandial glucose and insulin concentrations, have been demonstrated in healthy adults; studies of impact on other metabolic parameters provided conflicting results. Beneficial effects have also been demonstrated in obese women.

For reasons that are, in part, related to the restrictions of the regulatory environment many probiotics are marketed employing vague promises such as “restores balance” and “boosts immunity”—claims that may have some basis in basic science experiments but are scarcely supported by clinical trial data or evidence of improved quality of life for those who consume them.

**Effects in Gastrointestinal Diseases and Disorders**

Despite the presence of considerable evidence for a role for the microbiota at a number of levels in the pathogenesis of a variety of gastrointestinal disorders and the demonstration, in the laboratory, of prebiotic and probiotic properties that should be of benefit in these same disorders, clinical evidence of efficacy still remains patchy. There is no shortage of studies; deficits in clinical design, coupled with variations between studies in product and formulation used, study population and endpoints have frustrated their interpretation. In selecting a prebiotic or probiotic for his or her patient the clinician faces additional challenges, few doseranging studies or head-to-head comparisons and great variability in the availability and cost of a given species, cocktail, or prebiotic formulation in different parts of the world.

A comprehensive review of all studies of prebiotics, probiotics, and synbiotics across the complete range of gastrointestinal disorders is beyond the scope of this review. Fortunately, The World Gastroenterology Organization Global Guideline on Probiotics and Probiotics, published in 2017, provides an up-to-date and evidence-based assessment of the value of prebiotics and probiotics in adults and children. Evidence was graded according to the system developed by the Oxford Centre for Evidence-Based Medicine with level 1, the highest level, indicating that benefits were based on the results of a systematic review of randomized trials or n-of-1 trials and level 5, the lowest, based merely on mechanism-based reasoning. Few products were supported by level 1 evidence for an indication in adults. Indications achieving level 1 evidence for a given probiotic or probiotic cocktail included the prevention of antibiotic-associated diarrhea in various clinical settings, reduction of side effects related to eradication therapy for Helicobacter pylori, prevention of postoperative sepsis in those undergoing elective gastrointestinal surgeries, maintenance of remission in pouchitis and reducing symptoms related to lactose malabsorption.

For prebiotics only 1 indication achieved level 1—lactulose in the management of hepatic encephalopathy. While other systematic reviews attest to a positive impact for probiotics, in general, in a variety of clinical scenarios, most are either guarded in their recommendation or unable to distinguish between species in terms of efficacy, due to limitations in available data. Table 1 lists gastrointestinal diseases and disorders where there is, at the very least, some evidence to permit an assessment of the impact of probiotics; other disorders, such as collagenous colitis, constipation and nonalcoholic fatty liver disease where available evidence does not allow for such an assessment are not presented.

**Conclusions**

The importance of the gut microbiome in homeostasis in health and in the pathogenesis of disease becomes ever more evident by the hour and studies in animal models continue to provide more clear-cut signals. Humans are complex, messy individuals. The same holds true for the microbiota-modulating interventions discussed here—impressive results in mice in rats while data from human studies are often conflicting and inconclusive. This frustration owes much to the inadequacies of clinical trials. That high-quality trials can be completed and yield positive and clinically meaningful results is amply illustrated by the recent study of the impact of a synbiotic on infections among high-risk children in India. It is to be hoped that well-characterized and appropriately formulated products will emerge from the laboratory supported by a clear rationale for their use in a given clinical indication. Regrettably, it is likely that progress in terms of quality control will only come from tighter regulation of the sector. Only then can the health care profession guide the consumer through the confusion that prebiotics and probiotics currently present.

**References**


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