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Can prebiotics and probiotics improve therapeutic outcomes for undernourished individuals?

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It has become clear in recent years that the human intestinal microbiota plays an important role in maintaining health and thus is an attractive target for clinical interventions. Scientists and clinicians have become increasingly interested in assessing the ability of probiotics and prebiotics to enhance the nutritional status of malnourished children, pregnant women, the elderly, and individuals with non-communicable disease-associated malnutrition. A workshop was held by the International Scientific Association for Probiotics and Prebiotics (ISAPP), drawing on the knowledge of experts from industry, medicine, and academia, with the objective to assess the status of our understanding of the link between the microbiome and under-nutrition, specifically in relation to probiotic and prebiotic treatments for under-nourished individuals. These discussions led to four recommendations:

(1) The categories of malnourished individuals need to be differentiated. To improve treatment outcomes, subjects should first be categorized based on the cause of malnutrition, additional health-concerns, differences in the gut microbiota, and sociological considerations.

(2) Define a baseline "healthy" gut microbiota for each category. Altered nutrient requirement (for example, in pregnancy and old age) and individual variation may change what constitutes a healthy gut microbiota for the individual.

(3) Perform studies using model systems to test the effectiveness of potential probiotics and prebiotics against these specific categories. These should illustrate how certain microbiota profiles can be altered, as members of different categories may respond differently to the same treatment.

(4) Perform robust well-designed human studies with probiotics and/or prebiotics, with appropriate, defined primary outcomes and sample size. These are critical to show efficacy and understand responder and non-responder outcomes. It is hoped that these recommendations will lead to new approaches that combat malnutrition.

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This report is the result of discussion during an expert workshop titled "How do the microbiota and probiotics and/or prebiotics influence poor nutritional status?" held during the 10th Meeting of the International Scientific Association for Probiotics and Prebiotics (ISAPP) in Cork, Ireland from October 1–3, 2012. The complete list of workshop attendees is shown in **Table 1**.

Introduction

Malnutrition is a term that is generally used to cover both under-nutrition and over-nutrition. It can be caused when an individual is (1) not getting enough food, (2) not getting the right balance of different sorts of food, or (3) not digesting and/or absorbing nutrients efficiently. Under-nutrition is one of the most serious problems affecting global health. The Food and Agriculture Organisation of the United Nations (FAO) estimates that about 870 million people were undernourished (in terms of supply vs. demand for dietary energy) in the 2010–12 period, representing 12.5% of the global population. Of these cases, 852 million were in the developing world, corresponding to 14.9% of those populations. For the developing world as a whole, undernourishment had dropped significantly in the period 1990–2010 (23.2–14.9%), but in certain areas the contrary was true. Most notably, the prevalence of undernourishment in sub-Saharan Africa increased from 17.0% to 27.0%.[1] Clearly new innovative strategies are required to tackle this issue.

Probiotics and prebiotics have been investigated for many years for their potential to improve digestive functions and to mitigate the effects of infectious and inflammatory conditions. Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[2] Prebiotics are non-digestible carbohydrates which are selectively fermented by the gut microbiota, leading to improvements in health outcomes.[3] Although the last few years have seen data emerge from many prebiotic human studies, a search of the Cochrane Library, Pubmed, and Scopus did not reveal any meta-analysis on malnutrition and there is general lack of prebiotic population-based studies.[4] There have however been several reviews and meeting reports highlighting the ability of prebiotics to alter the gut microbiota.[4-8] A review published in 2012 assessed the

efficacy of probiotics in treating eight distinct gastrointestinal disease states.[9] The meta-analysis of 74 randomized, placebo controlled studies showed an overall benefit of probiotic treatment. The magnitude of the effect varied between studies, possibly due to strain and formulation differences.[9] Research into the mechanisms of action and benefits of probiotics and prebiotics provides us with a stepping-stone for discovering new ways in which they could improve human health. One area where probiotic and prebiotic research may be especially useful is in preventing repeated episodes of diarrhea. Repeated incidences of lengthy episodes of diarrhea can contribute to malnutrition due to enteropathy with ineffective energy and nutrient absorption. In recent years, attention has turned to ascertaining if probiotics and/or prebiotics could be used to improve the nutritional status of malnourished individuals.

A Cochrane Review on probiotics for acute infectious diarrhea[10] found 63 randomized and quasi-randomized, placebo-controlled trials. These studies comprised 8014 participants from various geographical areas, in a wide range of settings; and also varied greatly in organisms tested, dosage supplied, and participants' characteristics. Despite these variations, the vast majority of the trials showed a reduction in diarrhea duration following probiotic treatment compared with controls, although effect sizes were highly variable between trials. The authors concluded that the difference in effect size was not explained by the known variables (study quality, probiotic strain, the number of different strains, the viability of the organisms, dosage of organisms, the causes of diarrhea, or the severity of the diarrhea, or whether the studies were done in developed or developing countries).[10] Recently acquired knowledge about the high level of inter-individual variation in the human gut microbiota may partially explain these different responses.

The human gut microbiota consists of >1000 bacterial species, with every individual host to at least 160 different species.[11-13] This represents a genetic repertoire >150-fold larger than the *Homo sapiens* hosts' complement.[14] Although the exact assortment of bacterial species in the gut varies greatly among individuals, subjects from the same geographical region tend to have more similar bacterial communities than those from different regions.[15,16] This clustering is thought to be highly influenced by the diet.[15] Therefore, when designing nutritional interventions for malnourished individuals, it is important to select specific strategies for the cohort being targeted.

The objective of the workshop was to assess the status of our understanding of the link between the microbiome and under-nutrition, specifically in relation to probiotic and prebiotic treatments for under-nourished individuals.

Micronutrient Absorption

As well as improving nutritional status by mitigating the effects of diarrhea, there is growing evidence that probiotics and prebiotics could be used to improve the absorption of micronutrients (such as calcium and iron) from ingested foods. Micronutrients are organic or inorganic compounds present in food in small amounts, such as vitamins or minerals, which are not used for energy but are nonetheless essential for good health.[17] It is estimated that at least two billion people around the world are living with micronutrient deficiencies.[18] The majority of these are impoverished and are not consuming sufficient nutrient-rich foods. In the long-term, nations will need to address how to improve nutritional strategies. In the short-term, however, nutritional interventions delivered through many channels—including humanitarian efforts—will save many lives, as well as improve the health and cognitive capacity of millions of children.[18-23] Probiotics and prebiotics increase bioavailability of micronutrients through several mechanisms and therefore represent an avenue for potentially alleviating micronutrient deficiencies.

The ability of prebiotics to increase micronutrient absorption has been examined and, although the effects were not uniform among all experiments, studies in both humans and animals showed positive effects of non-digestible oligosaccharides on mineral metabolism, bone composition, and bone architecture.[24-28] The increased short-chain fatty acid production due to prebiotic fermentation decreases the pH, increases mineral solubility and enlarges the enterocyte absorption surface. Some probiotics also appear to enhance micronutrient absorption (particularly calcium and iron) and bone development, but the effects appear to be highly dependent on the probiotic strain.[24,29-35] One placebo controlled study[34] showed that the iron status in young children could be improved significantly by intake of a milk-fortified with synbiotics (*Bifidobacterium lactis* HN019, oligosaccharide) for one year. Furthermore, the absorption of iron was improved significantly in healthy women of childbearing age after intake of probiotics (*Lactobacillus plantarum* 299v) in a placebo cross-over controlled meal study.[33] Since a large variety of probiotic strains, techniques, animal models, and patient groups have been used in these experiments, it is impossible to draw general conclusions. Clearly, there is a need for more double-blind, randomized, placebo-controlled human studies for specific subpopulations before we can assess the full potential of probiotics and prebiotics to improve the health status of individuals suffering from micronutrient deficiencies. Ideally, several studies using the same protocols and strains or supplements, in specific patient categories would provide better insight.

In some cases probiotic bacteria can have very specific beneficial effects, such as in the case of B-group vitamin production. Although B-group vitamins are present in many foods, they are easily removed or destroyed by food processing and cooking, which can lead to inadequate quantities being obtained from the diet. Genome sequencing has shown that *Lactobacillus reuteri* strains ATCC PTA 6475 and ATCC 55730 have biosynthetic pathways for Vitamin B12 and folate synthesis, and *L. reuteri* strain ATCC 55730 additionally possesses those for thiamine synthesis.[36] Folate synthesis has been also characterized in several other microorganisms including some bifidobacteria strains.[37] Further B-group vitamin-producing strains can be identified based on roseoflavin-resistance selection. Roseoflavin is a toxic riboflavin analog shown to select for spontaneous mutations in *Bacillus subtilis* strains with constitutive overproduction of riboflavin.[38] Several natural riboflavin overproducers have

been described: *Lactococcus lactis*,[39] *L. plantarum*, *Leuconosctoc mesenteroides*, and *Propionibacterium freudenreichii*.[40,41] Microbially produced vitamins thus represent a possible means of fortifying foods with additional micronutrients. This has been shown to be effective in rats fed a riboflavin-deficient diet. Most of the manifestations of ariboflavinosis (a medical condition caused by riboflavin-deficiency) observed in the riboflavin-deficient rats were eliminated when the diet was supplemented with milk fermented by *L. lactis* pNZGBAH—a strain that overproduces riboflavin during fermentation. This effect was not seen with milk fermented by a non-riboflavin-producing bacterial strain.[42]

Malnourished Children

The World Health Organisation (WHO) defines severe acute malnutrition (SAM) in childhood as a weight-for-height *z*-score (WHZ) of below -3 of the median WHO growth standards, by visible severe wasting, or by the presence of nutritional edema (kwashiorkor). Over 13 million children suffer from SAM under the age of 5 y and 1 to 2 million die each year.[43] Fatality rates of individuals undergoing hospital treatments for SAM are estimated at 20–30% but have been known to be as high as 50–60%. These fatality rates have changed little over the past 50 y.[44] Childhood under-nutrition also has long-term health consequences through programming for later disease, including the aberrant development of the immune system and cognitive function, generating enhanced risks of subsequent coronary heart disease and diabetes, and even excessive weight gain.[45] New treatments with earlier interventions are needed, even though early diagnosis of malnutrition is difficult, to prevent the development of SAM and reduce the burden of disease related to under-nutrition.

Studies involving Indian children have shown that specific probiotics can significantly reduce the duration (combinations: *Lactobacillus casei* DN-114001, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*; and *L. lactis*, *L. lactis cremoris*, and *Leuconostoc mesenteroides cremoris*)[46] and occurrence (*L. casei* strain Shirota and *Lactobacillus acidophilus*)[47,48] of diarrhea, and significantly increase the weight and height (*L. acidophilus*) of these children, relative to those fed a supplement with similar caloric value, but lacking probiotics.[47] The success of these studies raises the possibility of using probiotics (and/or prebiotics) to improve the outcomes of nutritional interventions in the treatment of undernourished children.

The PRONUT study[49] examined the ability of a mixture of four putative probiotic bacteria (*Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei* subsp. *Paracasei*, and *L. plantarum*) and four putative prebiotic substrates (inulin, pectin, oat bran, and resistant starch) to improve the outcome of nutritional interventions for Malawian children admitted to hospital suffering from SAM. This mixture was added to a high-energy and nutrient dense, ready-to-use therapeutic food (RUTF), formulated to the WHO standards for SAM treatment.[50] This was a double-blind, randomized, placebo-controlled trial, involving 795 children, almost half of whom were HIV seropositive. Although no significant differences were seen over those in the control therapeutic food intake, the study highlighted some interesting points, which should be considered for future studies. The first point was that these probiotics appear to be safe to use in HIV infected and immunodeficient malnourished children. There had been concerns that, due to the high prevalence of HIV in these subjects, probiotic administration might cause sepsis due to the immunocompromised status.[51] However, no cases of probiotic-related bacteraemia were identified, despite blood cultures being available for sick children in both treatment arms.[50] Second, it is important to consider that probiotics and prebiotics tested in one human population may have different effects on the gut microbiota of people living in different geographical locations and with distinct diets. Third, the specific interactions between probiotic bacteria and prebiotics combined in a single mixture, and how they contribute to probiotic survival in the host, have rarely been studied. In the PRONUT study, the inability of the mix to cause benefit did not mean that a different mix with greater amounts of the same or different probiotic bacteria might not have had an effect. Designing interventions without considering these and other issues may diminish the number of subjects who respond to treatment.[52] Finally, interventions for severely malnourished children need to consider the effects of the probiotic and prebiotic therapy, compared with the standard nutrient rich food, which itself has a positive benefit.

Another study, involving 317 Malawian twin pairs in the first three years of life, characterized the gut microbiome of twin pairs discordant for kwashiorkor, during and after treatment with RUTF. A model of gnotobiotic mice was used to test the effectiveness of the same nutritional intervention,[53] following transplantation of frozen fecal communities from three twin pairs, with one twin from each pair suffering from kwashiorkor, into germ-free mice.[53] The animals were then fed the low-caloric density and nutrient-deficient diet similar to that of Malawian children. After 3 wk, their diet was switched to the high energy, micronutrient rich RUTF for 2 wk and then switched back to the initial Malawian diet. The authors reported a profound difference in weight change between mice transplanted with healthy and kwashiorkor fecal communities, with a more dramatic change in body weight when switching between diets in kwashiorkor mice than in the healthy control mice.[53] This study would suggest that there are clinically important differences in the gut microbiota of children who develop kwashiorkor, which may determine the response to dietary change. The study also indicates that gnotobiotic mice, transplanted with the fecal communities of different groups, might be a valuable model in devising individualized dietary interventions.

Malnourished Pregnant Women

Pregnant women are among the most nutritionally vulnerable groups due to their increased nutrient requirements.[54] In developing countries, poverty often limits the quantity and quality of available food, placing a further nutritional burden on pregnant women. The seasonal deterioration of nutritional status due to food shortages and an increase in agricultural labor (often coinciding with seasonal endemic diseases) further affects their

Table 1. Composition of discussion group on the topic "How do the microbiota and pro/prebiotics influence poor nutritional status?"

Name	Affiliation	Country
Karen Scott, (chair)	Rowett Institute of Nutrition and Health, University of Aberdeen	UK
Nathalie Delzenne (co-chair)	Université Catholique de Louvain,	Belgium
James Bunn	Alder Hey Childrens NHS Foundation Trust	UK
Laure Bindels	Université catholique de Louvain,	Belgium
Gregor Reid	Lawson Health Research Institute	Canada
Esther Nova	Institute of Food Science, Technology and Nutrition (ICTAN)-CSIC	Spain
Eduardo Schiffrin	Nestle Research Centre	Switzerland
Paul O'Toole	University College Cork	Ireland
Marcus Claesson	University College Cork	Ireland
Connie Weaver	Purdue University	USA
Andrew Serazin	Gates Foundation	USA
Howard Jenkinson	Bristol University	UK
Paul Sheridan	Rowett Institute of Nutrition and Health, University of Aberdeen and University College Cork, Ireland	UK
Delphine Saulnier	NIZO Food Research	Netherlands
Maciej Chichlowski	Mead Johnson Nutrition	USA
Saskia van Hemert	Winclove Probiotics	Netherlands
Kerstin Holmgren	Probi	Sweden
Natalie Lamb	Probiotics International	
Tomoyuki Sako	Yakult Europe	Netherlands
Lori Lathrop Stern	Pfizer Consumer Healthcare	USA
Pramod Gopal	Fonterra Research	New Zealand

nutritional status,[55] with annual cycles of weight gain and loss. A report published by the LINKAGES project revealed that these factors result in 5–20% of women in various African countries being underweight. The report also indicates that micronutrient deficiencies (particularly iron, vitamin A, zinc, folic acid, riboflavin, and iodine) are common in pregnant African women.[56] This can result in increased risk of mortality from severe anemia and eclampsia for the mothers, and premature delivery and low-birth weight babies.[57]

Mechanisms to improve maternal and childhood nutrition in the developing world include initiatives to set up sustainable kitchens to provide fermented milk products to the local community. This provides employment for the mothers, and much-needed nutrient-rich food for the children and adults. A study in Mwanza, Tanzania, evaluated the ability of a probiotic-containing and micronutrient-fortified yogurt that could be locally produced, to improve the nutritional status of pregnant women. The yogurt was produced from locally sourced milk, to which 2% standard yogurt cultures (*Lactobacillus delbrueckii* subsp. *bulgaricus* and *S. thermophilus*) and 4% probiotic culture *Lactobacillus rhamnosus* GR-1 were added. Since the costs of importing the micronutrients supplemented to the yogurt in the two previous studies were too high to be sustainable in Sub-Saharan Africa, a locally available food source (the leaves of the *Moringa oleifera* plant) was added to the yogurt as a source of vitamin A, C, zinc, and iron. This study is a noteworthy example of customizing treatment to suit the target group (Gregor Reid, personal communication). The outcomes of this study have yet to be published, but the development of a probiotic food in a locally sustainable way shows that such interventions are indeed feasible in resource disadvantaged areas like Sub-Saharan Africa.[60] This study was prompted by two previous studies by the same group. The first study involved a micronutrient enriched probiotic yogurt containing various added vitamins and minerals that was found to be safe for use in Tanzanian subjects and improved hemoglobin levels.[58] The second was a Canadian study of HIV infected adults on anti-retroviral therapy, in which the same enriched yogurt improved the CD4 cell count and had no adverse effects.[59]

A recent study involving 91 pregnant women suggests that the gut microbiota is profoundly altered during pregnancy.[61] The microbial composition changed markedly between the first and third trimesters, with an increase in the relative abundances of Proteobacteria and Actinobacteria in 69.5% and 57% of women, respectively. There was also a decrease in the overall bacterial diversity as women progressed from the first to the third trimester.[61] The authors argue that these alterations are a mechanism by which the gut microbiota can promote weight

gain, thus providing energy for fetal growth. If this is the case, then there is a need to define what constitutes a healthy gut microbiota for pregnant women, as the microbial composition by the third trimester resembles a disease-associated dysbiosis in non-pregnant women.[61] None of the pregnant women enrolled in that study were under-nourished, and further work would be required to determine whether the same reduction in bacterial diversity occurs during pregnancy when adequate nutrition is not available.

Malnourished Elderly

By the end of this decade, it is estimated that in many countries for the first time the proportion of people over the age of 65 y will be greater than those under the age of 5 y.[62] As the global population grows older, maintaining the health of elderly individuals becomes increasingly more important, and as medical expenditure is highest during the later years of life, the ability to maintain the health of elderly individuals becomes critical for economic reasons. Older consumers present paradoxical nutrition-related challenges; malnutrition is increasingly prevalent in this age group, even in developed societies such as the European Union.[63] At the same time, obesity in older people in western countries is following the same increasing trend for younger adults.[64] Recent studies have revealed that the composition of the gut microbiota changes markedly with age, and elderly individuals (>65 y) tend to have greater inter-individual variation than younger adults. Additionally, there is a general decrease in species diversity for *Bacteroides*, *Prevotella*, *Bifidobacteria*, and *Lactobacillus* spp., and an increase in species numbers within the *Enterobacteriaceae*, staphylococci, streptococci groups, and *Candida albicans*, relative to healthy young adults.[65-68] This altered microbial community may be pro-inflammatory, and the presence of inflammatory markers correlates to frailty.[69] Changes in the composition of the gut microbiota in elderly individuals have been linked to poorer health and nutritional status, and correlated with habitual diet, particularly comparing older subjects living in their own homes with those living in long-term residential care facilities.[70] Metagenomic analysis showed that these diet-microbiota composition differences between residence location groups were also reflected in the genetic capacity of the microbiota for producing short-chain fatty acids such as butyrate and propionate, which are important energy sources and signaling molecules in the intestine.[70] The gut microbiota may therefore represent an attractive target for improving nutritional status in malnourished elderly individuals. Increasing the diversity of the general diet, and including probiotic and prebiotic products, could be a simple and affordable way of modulating the intestinal microbiota of older people to promote beneficial microbial metabolism. In the last decade, there have been several human studies evaluating the potential of prebiotics and probiotics to improve the health of the elderly, generally by modulating the gut microbiota composition.[71-75] Prebiotic intervention in frail elderly individuals increased the prevalence of bifidobacteria but also reduced the levels of pro-inflammatory cytokines such as IL-6, and improved immune status, even after treatment ended.[76] In this study there was a distinction between responders and non-responders, which needs further investigation, and which may be related to specific populations of gut bacteria in the subjects prior to the intervention. This phenomenon has been demonstrated in a study showing a differential response of the gut microbiota of younger adults to resistant starch, depending on their starting microbiota.[12]

The application of metagenomics elucidates the relationships between different microbiota compositions and genetic capacities, and health statuses in the elderly.[70] This approach circumvents functional redundancy in a way that microbial composition studies cannot. This enables a more logical approach to designing intervention studies, which aim to improve the microbial metabolic output. Physiological changes that occur as individuals become elderly should also be considered: for example, the decline in cutaneous levels of 7-dehydrocholesterol means that there is a reduced synthesis of cholecalciferol (vitamin D) after exposure to the sun. This decline, combined with an increase in body fat, contributes to the high prevalence of vitamin D deficiencies in the elderly. This in turn, lowers calcium and phosphate absorption[77] potentially contributing to osteoporosis. Therefore, the altered requirements of the elderly should be considered when attempting to optimize the microbiota for their health. Reduced diversity of the gut microbiota in older subjects correlates with susceptibility to *Clostridium difficile* infection,[78] and the *Bifidobacterium* element of low-diversity microbiota of older subjects in long-term residential care is also more susceptible to antibiotic therapy.[79] Probiotic administration may therefore be indicated for these subjects.

Undernourishment Associated with Non-Communicable Disease

Malnutrition can also be associated with the presence of a non-communicable disease, such as anorexia nervosa (AN) or cancer, leading to cancer-related cachexia. There have been few studies to date investigating the potential for probiotics or prebiotics in alleviating the symptoms, signs, and complications of these diseases.

AN is a syndrome characterized by an intense fear of fatness, and the individual's refusal to eat with the purpose of losing weight or maintaining it below normal standards. Severe situations of malnutrition can develop over time and high mortality rates are associated with the illness.[80] AN patients exhibit an immunocompromised status that shares some characteristics with typical malnutrition, namely leukopenia and an impaired cell mediated immunity (for example depleted T cell subset counts and altered cytokine production in response to a stimulus).[81] Administration of yoghurt (milk fermented with *L. delbreuckii* subsp. *bulgaricus* and *S. thermophilus*) to AN patients was associated with increased interferon gamma production upon stimulation of isolated peripheral blood mononuclear cells. This enhanced immune response could be relevant in achieving an improved protection against pathogens.[82] Genomic analysis of fecal microbiota in a few individuals with AN (n = 9) has shown a higher proportion of methane producers (*Methanobrevibacter smithii*) than in lean controls, which might represent an adaptive

mechanism allowing for an increase in the efficiency of nutrient utilization.[83]

Cachexia is the term used to describe the weight loss and malnutrition linked to debilitating chronic diseases. The inflammation associated with these is the result of an exaggerated immune response, and the mediators of this inflammatory response may cause the development of cachexia. Cancer cachexia is characterized by a significant reduction in body weight resulting predominantly from loss of adipose tissue and skeletal muscle. Cancer remains a major global health burden, and cachexia affects the majority of the patients with advanced disease.[84,85] There is much evidence that malnourished cancer patients have a reduced survival; however, the corollary hypothesis, that reversal of nutritional deficits should extend survival, remains unproven.[86]

The gut microbiota composition is different between cancer patients under treatment and matched controls, and this is at least partially due to the administration of chemotherapeutic drugs and antibiotics. In pediatric patients with acute myeloid leukemia, van Vliet and colleagues[87] reported a 10 000-fold decrease in anaerobic bacteria and a 100-fold increase in potentially pathogenic enterococci. This disturbance in the gut ecosystem might influence colonization resistance and thereby favor infections by enteric diarrhea-causing pathogens, which can affect nutrient absorption, aggravating malnutrition.

Two studies published in 2012 highlighted that gut microbiome is modified in rodent models of cancer.[88,89] In the first study, the cecal microbiota composition was modified in leukemic mice with cachexia, and lactobacilli levels in the cecal content exhibited a 50-fold decrease. Interestingly, restoring lactobacilli levels using the putative probiotic bacteria *L. reuteri* 100–23 and *L. gasseri* 311476 decreased systemic inflammation and atrophy markers in the muscle, two features of the cachexia syndrome.[88] In the second study, an increase in *Clostridium* clusters I and IX and in *Enterobacteriaceae* was reported in feces of rats subcutaneously implanted with a colon tumor. This study mainly aimed to analyze the impact of irinotecan, a chemotherapeutic drug, on intestinal microbiota. The authors proposed that the presence of the tumor induced greater changes in the microbiota than chemotherapy.[89]

Gastrointestinal complications constitute a major dose-limiting side effect of chemotherapy, promote overall malnutrition, aggravate cancer cachexia, and may contribute to a worsened prognosis. More than 90% of chemotherapeutic drugs induce gastrointestinal toxicity. In this context, probiotics and prebiotics have been proposed as therapeutic factors that could potentially modulate gastrointestinal complications related to cancer treatments. Suggested mechanisms include improving colonization resistance and boosting gut barrier function, through the production of short chain fatty acids and intestinal hormones such as glucagon-like peptide 2.[90]

Recommendations

The workshop discussion reflected the research background of the participants and their knowledge about the current uses of prebiotics and probiotics in the specific areas mentioned above. The following four recommendations are made with the aim of increasing the success of probiotic and prebiotic nutritional interventions in treating malnutrition:

(1) The categories of malnourished individuals need to be differentiated. To improve treatment outcomes, subjects should be categorized based on the cause of malnutrition, additional health-concerns, differences in the gut microbiota, and sociological considerations. The effectiveness of a treatment can be dramatically altered by the cause of malnutrition (lack of intake or lack of absorbance), additional health problems (HIV, other infections), differences in nutritional requirement (pregnancy and old age), differences in the gut microbiota (antibiotic treatment, alternative diet), and sociological considerations (treatment sustainability, seasonality, affordability). Appropriate categorization may allow clarification of the responder and non-responder phenomenon.

(2) Define a baseline "healthy" gut microbiota for each category. There is evidence that the gut microbial composition is different in specific groups of individuals, in different geographical locations, and may even alter to accommodate changes in nutrient requirements, therefore changing what defines a healthy gut microbiota for the individual. This appears to be the case in pregnant women, with the gut microbiota shifting to a composition that accommodates weight gain and the energy requirements essential for fetal growth. This may also be the case in the elderly, but studies investigating the metabolic consequences of the altered elderly microbiota are required.

(3) Perform studies using model systems to test the effectiveness of potential probiotics and prebiotics against these specific categories. The benefit to the host is specific to which pro- or pre-biotic (or combination of these) is used. Probiotics and prebiotics act primarily through modulation of the gut microbiota and by interacting directly with the host. If the gut microbial composition of one population is different from another, then it follows that different probiotics or prebiotics may be required. Therefore, laboratory studies analyzing the efficacy of probiotics and prebiotics must take geographical differences in the human gut microbiota into account.

(4) Perform robust well-designed human studies with probiotics and/or prebiotics, with appropriate, defined primary outcomes and sample size. Ultimately, the knowledge gained from laboratory experimentation must be translated into treatments that improve the health outcomes of individuals suffering from undernourishment. This requires that comparable and high-quality trials be performed, with clinically relevant primary outcomes, rather than proxy laboratory markers. This may be achieved by conducting studies according to CONSORT guidelines.[91] The controversy surrounding the efficacy of probiotics, in general, can be mainly attributed to the lack of clinical trials examining the ability of specific probiotic strains to alleviate the effects of specific diseases. This has resulted in meta-analyses averaging the efficacy results of different probiotics

treatments against a specific disease.[9,92] This can generate misleading conclusions, as depending on the mechanism, the probiotic effect can be highly strain-specific.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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