

***Current level of consensus on probiotic science-
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Attendees:

Prof. Ian Rowland (Chair)
Department of Food and Nutritional Sciences
University of Reading, UK

Prof. Lucio Capurso
Dipartimento di Gastroenterologia
Gastroenterologo Direttore UOC S. Filippo Neri di Roma
Italy

Prof. Kevin Collins
Departments of Microbiology and Medicine,
University College Cork, Ireland

Prof. John Cummings
Emeritus Professor of Experimental Gastroenterology
Ninewells Hospital and Medical School
Dundee, UK

Prof. Nathalie Delzenne
Unité Pharmacocinétiques, Métabolisme, Nutrition & Toxicologie
Université Catholique de Louvain, Brussels, Belgium

Prof. Olivier Goulet
Head of Pediatric Hepato-gastroenterology & Nutrition Department
Hôpital Necker, Paris, France

Prof. Francisco Guarner
Digestive System Research Unit,
University Hospital Vall d'Hebron, Ciberehd, Barcelona, Spain

Prof. Philippe Marteau,
Head of Medico-surgical Hepatogastroenterology Department
Hôpital Lariboisière - Fernand Widal,
Paris France

Prof. Rémy Meier
Head Gastroenterology, Hepatology
and Nutrition Department
University Hospital
Liestal, Switzerland

Introduction

In recent months, the increased level of press information about probiotics has led to confusion among the general public. This can be attributed, at least partly, to misunderstandings following the announcement of the European Food Safety Agency's (EFSA) scientific opinions, which were not favourable in relation to health claims proposed for some probiotics. Although these product-specific opinions were justified and understood by experts, they have led non-specialist media to deliver confused, generic and subsequently, false statements to the general consumer. It was thus thought useful to gather together a group of European experts in probiotics research to formalise today's scientific knowledge about probiotics, that is to say what has been clearly shown, is promising, or is unsubstantiated.

The group of nine scientists, emanating from seven European countries, was composed of gastroenterologists, microbiologists, nutritionists and paediatricians, each involved in clinical and/or experimental research. Topics for discussion concerned the clinical effects of probiotics, their mechanisms of action, with specific attention given to the interaction with gut microbiota, as well as some practical aspects relevant for probiotic consumption. For each topic, some statements were proposed for a short discussion, followed by an evaluation of the consensus level. This discussion and the consensus points are summarised in this report. This report does not intend to be a scientific review, yet rather a position paper about the existing 'state of the art' of probiotic science.

Strain specificity

'Probiotic' is a very generic term that includes a large number of species of microorganisms, particularly lactobacilli and bifidobacteria. To be subject to a consumer health claim, the need to adequately characterise the probiotic bacteria tested in a study is mandatory, as requested by the EFSA. This characterisation should be performed at the strain level, a rule that is not always adhered to in scientific publications. Indeed, the group agreed, with a high degree of consensus, that clinical effects of probiotics, in treatment or prevention, depend on the specific strain of bacteria or yeast, which should be defined not only by its genus and species, but also at the strain level. Although there are few clinical studies that directly compare effects of various strains within a single species (for example various strains of *Bifidobacterium longum*), available evidence - including preclinical data - show that some effects of probiotics are strain specific while others may be only species-specific. In any case, a clinical effect of a probiotic should be attributed only to the strains which have demonstrated it. Conversely, when a strain is not eliciting a given clinical effect, this does not mean that no other strain can produce it. A comparison was given with vitamins; for example not all prevent scurvy or increase calcium absorption, which does not imply that vitamins which don't have these properties are ineffective in general. Probiotics cannot be properly evaluated as a class but need to be judged on single strain basis.

In most cases, meta-analyses of health benefits of probiotics do not distinguish among strains, and often not even among species or genera. Depending on the characteristics of included studies, and on the strength of data, such analyses may lead to inappropriate conclusions that do not differentiate efficacy effects for different strains. However, even though meta-analyses with different probiotic strains do not increase the level of evidence, they provide valuable proof of a concept.

Consequently, all the statements which are discussed later in this report should be understood as relating to a given strain or a limited number of strains. The word “probiotics” should therefore be read as “some probiotic strains”.

Clinical effects of probiotics

Probiotics and diarrhoea.

Diarrhoea is one of the most studied of clinical benefits of probiotics. Consideration needs to be given in distinguishing between the different types of diarrhoea, and their causes. However, there was a high level of agreement among members of the group that certain probiotics contribute to the prevention of antibiotic-associated diarrhoea, including *Clostridium difficile*-infections. Furthermore, probiotics are effective in the treatment of infectious diarrhoeas in children, especially in Western countries where rotavirus is the main cause and shortening the diarrhoeal episode by one day is meaningful. The current level of evidence for prevention or treatment of adult infectious diarrhoea by probiotics is limited and data on travellers’ diarrhoea are very heterogeneous and inconsistent in terms of prevention by probiotics.

Probiotics, immunity and infections.

There is extensive evidence that the gut microbiota can modulate the intestinal immune system and there was a reasonable consensus within the group that probiotics can engage the immune system and in some cases regulate intestinal immunity, especially as probiotics can become the dominant microbiota in the upper intestine. However, the clinical consequences of this engagement are less well established. There is evidence from prevention studies that certain probiotics can shorten respiratory tract infections and reduce the severity of symptoms such as fever, rhinitis and diarrhea, although they do not appear as able to influence the incidence of infections. More trials in this area should be encouraged. Furthermore,, the evidence concerning beneficial effects of probiotic strains on atopic dermatitis or asthma in children was evaluated as inconclusive. Research should however be pursued in this area, both because allergy is an increasing concern and because evidence is probably more difficult to reach here than in other clinical areas; it is indeed likely that the potential effect can vary according to the target, timing of probiotic intake, dose and other features.

Probiotics and irritable bowel syndrome (IBS).

Discussion led to a general agreement that probiotics are associated with improvements in global IBS symptoms, relief from symptoms of functional gastrointestinal disorders (e.g. bloating, abdominal pain) and thus confer an improvement in digestive discomfort. Digestive discomfort was here understood as a situation during which symptoms lead the subject to ‘feel’ negative or unpleasant sensations from his/her gastrointestinal tract, which is generally a silent organ, or may even be the origin of pleasant sensations and well-being (for instance, eating or drinking induce pleasant sensations in hungry or thirsty subjects). It was emphasized that the relief of symptoms in IBS-suffering populations is a valuable method to demonstrate the efficacy of probiotics and that these effects can be extrapolated to subjects who are symptomatic without being diagnosed as IBS-sufferers.

The consensus was weaker when it came to specific symptoms such as constipation. This appears to be linked mainly to the lack of clear definitions of constipation or what constitutes a ‘normal’ transit time, leading to wide variations in inclusion criteria and outcome measures; this prevents accurate evaluations of studies involving probiotics. Furthermore, the situation is

quite different between adult constipation, where some studies have shown beneficial effects of probiotics, and childhood constipation, which has a different etiology and where it seems probiotics are not clinically effective.

Probiotics and inflammatory bowel diseases.

The group agreed that probiotics reduce the frequency and severity of attacks of necrotizing enterocolitis in premature infants and reduce mortality from the disease. The beneficial effect of probiotics in the prevention of pouchitis was not thought to be adequately demonstrated, as a single probiotic mixture (8 different strains) has been shown to prevent pouchitis. Although two different research groups have shown an effect with the same probiotic mixture in 3 clinical studies, this should be confirmed more widely. The evidence for the role of probiotics in prolonging remission in ulcerative colitis patients is promising and deserves further investigation. Indeed, some recent trials have shown additional efficacy when administered with conventional therapy. Conversely, probiotics do not seem effective when applied to Crohn's disease patients.

Probiotics in other clinical conditions

Probiotics have been studied in relation to a wide range of biological or clinical effects. Although recognising a lack of necessary expertise on every topic, the group briefly discussed each of them in relation to the current scientific support existing for a clinical effect. For most of these 'indications' there are interesting hypotheses, biological plausibility and positive results obtained on pertinent experimental (animal or *in vitro*) models; the group's debate was however restricted to dealing with the evidence for beneficial effects in humans.

Among the statements that can be made in these areas, the most consensual ones appear to be the following, while acknowledging that a significant amount of research is still needed to demonstrate the clinical effects of probiotics.

- Probiotics have shown some promising effects as an adjuvant in the treatment of *H. pylori* infections
- There is biological plausibility that probiotics have effects in the prevention of vaginal infections and, to a lesser extent, infections of the urinary tract
- Probiotics might have beneficial effects on colon cancer risk

The recently explored impact of the microbiota on energy metabolism, gut hormone regulation and on the gut-brain axis was judged to be a fascinating topic and the extremely promising areas that this opens have been acknowledged. However, the current limited human data does not allow the suggestion that probiotics can have a clinical role in the management of obesity or diabetes.

Effects of probiotics on dyslipidaemia and on autism currently are not supported by scientific data.

By which mechanisms can probiotics can be clinically effective?

The group members were in agreement that some effects of probiotics may be mediated by direct interaction with intestinal cells, for example via effects on intestinal barrier function, and through interactions with immune intestinal cells, triggering higher IgA or cytokine production, especially in the upper part of the gut where probiotics may dominate, albeit transiently. Other effects may be mediated indirectly via modulation of gut microbiota, by

changing the gut microenvironment (through competition for nutrients or other metabolic pathway outcomes). This has been demonstrated in experimental models and it is highly plausible that such direct and indirect mechanisms exist in humans.

Indeed, there is a wealth of very strong evidence that probiotics may suppress intestinal pathogens or potential pathogens by direct antagonism, e.g. through bacteriocin production, defensins or competitive exclusion.

Overall however there are several *in vitro* actions of probiotics which do not translate into clinical effects and clinical observations that cannot be satisfactorily explained at the cellular level. There is thus a wide range of possible mechanisms which are only just beginning to be unravelled and need further investigations. Interestingly, it has been suggested that a large number of these mechanisms cannot easily be measured in humans for ethical or feasibility reasons.

Gut microbiota

There is a very strong consensus that a commensal gut microbiota is essential to human health and development. It appears difficult however to define a “healthy” microbiota, in part because the gut microbiota varies widely from one individual to another depending on their geographical origin, the location within the gut and not least because there is no agreement about what constitutes the characteristics of a healthy gut microbiota.

However it is agreed that several clinical conditions have been associated with dysbiosis of the gut microbiota, for example GI infections, antibiotic treatment, IBS, IBD, and allergy, which may help in clarifying what defines an unhealthy gut microbiota. This is also true in other instances, such as in obese people or in older populations, where the concept that an altered microbiota has a role in disease appears relevant. Nevertheless, a dysbiosis definition is not straightforward and depends on the specific reference.

In attempting to define a healthy microbiota, one should take into account its functionalities (metabolic characteristics) as well as its composition. Furthermore, as well as identifying several types of dysbiosis, there are also likely to be different states of a “healthy” microbiota or eubiosis. Although some parameters (such as balance between several phylogenetic groups or enzymatic activities) might appear interesting, current knowledge is not yet strong enough to reach distinctive criteria; research is warranted to develop tools and criteria allowing the characterisation of a meaningful concept of what constitutes a ‘healthy gut microbiota.’

Practical aspects

The group agreed that probiotic survival in the gastrointestinal tract as determined by viable counts in faeces, is not necessarily a pre-requisite for efficacy and absence of survival does not mean an absence of efficacy. It depends on the clinical effect or on the mechanism involved. Indeed, cell walls or other bacterial components may be the effective agents. The need for probiotic bacteria to be alive at ingestion is however clear.

A frequently asked question relates to the number of probiotic bacteria needed to be ingested to trigger an effect. There are very few dose-response studies that would provide answer to this question and the consensus is that there is no standardised number of probiotic bacteria that would ensure an effect. The effective quantity, for a given effect and a given strain, is the quantity which has demonstrated an effect in the relevant human intervention trial.

A combination of probiotic strains in a product does not necessarily add to the benefits of each strain. A combination of strains needs to prove its efficacy. A high number of different strains is not in itself indicative of greater efficacy than a lower number of strains.

The group agreed that the matrix of a probiotic product is important for effect and consequently a probiotic product should be tested as such and any claim should relate to the finished product. It is indeed possible that bacteria in different physiological states exhibit different effects. However, direct evidence for matrix-specific effects in humans is lacking.

Finally, there was a good consensus between experts of the group that probiotic food products have shown their safety in the general population as well as in patients.

Box 1: Consensual facts about probiotics.

Clinical effects of probiotics in treatment or prevention depend on the specific bacteria, which should be defined not only by its genus and species, but also at the strain level

Some probiotics contribute to the prevention of diarrhoea caused by antibiotics

Some probiotics reduce the risk of *C. difficile* infection

Some probiotics are effective in the treatment of infectious diarrhoeas in children

Some probiotics can engage the immune system

Some probiotics can regulate intestinal immunity

Some probiotics are associated with improvements in global IBS symptoms

Some probiotics relieve symptoms of functional gastrointestinal disorders (e.g. bloating, abdominal pain) and thus alleviate digestive discomfort

Some probiotics reduce the frequency and severity of attacks of necrotizing enterocolitis in premature infants

Survival of probiotic bacteria in the gut is not essential for efficacy

Box 2: Consensual facts about gut microbiota.

Some probiotics may suppress intestinal pathogens or potential pathogens by direct antagonism, e.g. through bacteriocin production, defensins, or competitive exclusion

A commensal gut microbiota is essential to human health and development. Several clinical conditions have been associated with dysbiosis, including GI infections, antibiotic treatment, IBS, IBD, and allergy, which may help to define what constitutes an unhealthy gut microbiota

Defining a healthy gut microbiota should take into account its functionalities (metabolic characteristics) as well as its composition.

There is no standardised number of probiotic bacteria to ensure an effect. The effective quantity, for a given effect and a given strain, is the quantity which has demonstrated an effect

A combination of probiotic strains in a product does not necessarily increase the benefits of each strain

Probiotic food products are safe for the general population as well as in some patients

Box 3: Promising areas for clinical effects of probiotics

In prevention studies, some probiotics are efficient in shortening infections of the respiratory tract

Some probiotics can regulate systemic immunity

Some probiotics have beneficial effects on constipation

Some probiotics have beneficial effects on longer than average transit times

Some probiotics can prevent pouchitis

Some probiotics have been shown to prolong remission in ulcerative colitis patients

There is biological plausibility that probiotics have effects in the prevention of vaginal tract infections

Some probiotics are efficient in the prevention of atopic dermatitis in infants and children

Some probiotics have shown promising effects as an adjuvant in the treatment of *H. pylori* infections

Some probiotics might have beneficial effects on colon cancer risk

Some probiotics are effective in the treatment of infectious diarrhoeas in adults

Box 4: Unsupported areas

Prevention of HIV infections

Management of obesity and diabetes

Management of dyslipidemia and autism

Prevention of recurrence of Crohn's disease

Prevention of infections of the urinary tract