

Current level of consensus on probiotic science

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The present paper summarizes the consensus views of a group of 9 European clinicians and scientists on the current state of scientific knowledge on probiotics, covering those areas where there is substantial evidence for beneficial effects and those where the evidence base is poor or inconsistent. There was general agreement that probiotic effects were species and often strain specific. The experts agreed that some probiotics were effective in reducing the incidence and duration of rotavirus diarrhea in infants, antibiotic-associated diarrhea in adults and, for certain probiotics, *Clostridium difficile* infections. Some probiotics are associated with symptomatic improvements in irritable bowel syndrome and alleviation of digestive discomfort. Probiotics can reduce the frequency and severity of necrotizing enterocolitis in premature infants and have been shown to regulate intestinal immunity. Several other clinical effects of probiotics, including their role in inflammatory bowel disease, atopic dermatitis, respiratory or genito-urinary infections or *H. pylori* adjuvant treatment were thought promising but inconsistent.

Commentary

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 favorable in relation to health claims proposed for some probiotics.¹ More than 95% of these unfavorable opinions were due to a lack of adequate characterisation of the probiotic strains in the submitted dossiers, and the EFSA panel concluded that "As the data available are insufficient to characterize the microorganisms/combination of microorganisms ...and that owing to the strain-specificity of the effects, the evidence obtained for one strain can not be extrapolated to another, [...] a cause and effect relationship has not been established between the consumption of the microorganisms/combination of microorganisms addressed in this opinion and their claimed effects".² Furthermore, the scientific dossiers of the most documented probiotic strains have not been evaluated yet. Although these product-specific opinions were justified and understood by experts in the field, 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 formalize 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 pediatricians, each involved in clinical and/or experimental research. Although the experts were European, we have no reason to believe that the opinions expressed in this document are not common to probiotics researchers in other parts of the world.

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 summarized 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, it is necessary to characterize adequately the strain.

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This characterisation should be performed at the strain level, a rule that is not always replicated 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 bacteria, 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, 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 bacteria 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, among which for example not all prevent scurvy or increase calcium absorption, which does not imply that vitamins are ineffective in health maintenance. Probiotics cannot be properly evaluated as a class but need to be judged on single strain basis. 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.

Clinical effects of probiotics. It is a reflection of the high level of research activity in probiotics that there are sufficient randomized placebo controlled trials in many areas to allow meta-analyses to be performed. Some of these show the consistency of evidence for efficacy across a range of bacterial strains although in many cases, the meta-analyses do not distinguish between strains and often not even between species or genus. Because of the issue of species/strain specificity discussed above such analyses they may lead to inappropriate conclusions and they often do not identify the strains or species with different levels of efficacy.

Probiotics and diarrhea. Diarrhea is one of the most studied of clinical benefits of probiotics. Consideration needs to be given in distinguishing between the different types of diarrhea, 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 diarrhea,³ including *Clostridium difficile*-infections⁴ and that probiotics are effective in the treatment of infectious diarrheas in children,⁵ especially in western countries where rotavirus is the main cause and shortening the diarrheal episode by one day is meaningful. The current level of evidence for prevention or treatment of adult infectious diarrhea by probiotics is more limited and data on travellers' diarrhea are very heterogeneous and inconsistent in terms of prevention by probiotic strains.

Probiotics, immunity and infections. There is extensive evidence that the gut microbiota can modulate the intestinal immune system⁶ and there was a reasonable consensus within the group that several probiotic strains have been shown as able to engage the immune system and in some cases regulate intestinal immunity.⁷ However, the clinical consequences of this engagement are less well established and, for example, the evidence concerning beneficial effects of probiotic strains on atopic dermatitis or asthma in children was evaluated as inconclusive.⁸ 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.⁹

There is evidence from prevention studies that certain probiotics can shorten respiratory tract infections and reduce the severity of symptoms, although they do not appear to influence the incidence of infections.¹⁰ More trials in this area should be encouraged.

Probiotics and irritable bowel syndrome (IBS). Discussion led to a general agreement that some probiotic strains are associated with improvements in global IBS symptoms, including bloating and abdominal pain. Because of the subjective nature of the endpoints, studies in this area need to be well controlled and double blinded. A recent systematic review and meta-analysis of randomized controlled trials¹¹ reported significant though modest benefit of the tested probiotic strains over placebo (RR = 0.71, 95% CI 0.57–0.88) with significant heterogeneity. Relief from symptoms of this functional gastrointestinal disorder could be considered as 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 origin of pleasant sensations and well-being (for instance, eating or drinking induce pleasant sensations in hungry or thirsty subjects). Recently the European Food Safety Agency has stated that "for claims on reducing gastro-intestinal discomfort in the general population evidence in patients with irritable bowel syndrome may be accepted". A similar position was taken by the US FDA, on January 2009.

The consensus was weaker when it came to specific symptoms such as constipation.¹² 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 certain probiotic strains,¹³ and childhood constipation, which has a different etiology and where it seems that the tested probiotic strains are not clinically effective.¹⁴

Probiotics and inflammatory bowel diseases and necrotizing enterocolitis. On the basis of 2 recent meta-analyses, the group agreed that several probiotics strains reduce the frequency and severity of attacks of necrotizing enterocolitis in premature infants and reduce mortality from the disease.^{15,16}

The beneficial effect of probiotics in the prevention of pouchitis was not thought to be adequately demonstrated. Only a single probiotic mixture (8 different strains) has been shown to prevent pouchitis, and although two different research groups have shown an effect with this same probiotic mixture in several clinical studies,^{17,18} this should be confirmed more widely.

The evidence for the role of some probiotic strains 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.¹⁹

Conversely, probiotics do not seem effective when applied to Crohn disease patients.²⁰

Probiotics in miscellaneous clinical conditions. Various probiotic strains have been studied in relation to a wide range of biological or clinical effects. Although recognizing 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 the concerned probiotic strains.

- Some probiotic strains have shown some promising effects as an adjuvant in the treatment of *H. pylori* infections²¹
- There is biological plausibility that some probiotic strains have effects in the prevention of vaginal infections²² and, to a lesser extent, infections of the urinary tract
- Certain probiotic strains might have beneficial effects on colon cancer risk.²³

The recently explored impact of the microbiota on energy metabolism,²⁴ gut hormone regulation²⁵ and on the gut-brain axis²⁶ 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.

Studies investigating the effects of probiotics on dyslipidaemia and on autism have been too limited so far to be conclusive.

By which Mechanisms can Probiotics be Clinically Effective?

The group members were in agreement that some effects of specific probiotic strains may be mediated by direct interaction with intestinal cells, for example via effects on intestinal barrier function,²⁷ and through interactions with immune intestinal cells, triggering higher IgA or altering cytokine production,^{28,29} especially in the upper part of the gut where probiotics may dominate, transiently. Other effects may be mediated indirectly via modulation of gut microbiota,³⁰ by changing the gut microenvironment (through competition for nutrients or other metabolic pathway outcomes). Indeed, there is a wealth of very strong evidence that some probiotic strains may suppress intestinal pathogens or potential pathogens by direct antagonism, e.g., through bacteriocin production, defensins or competitive exclusion. This has been demonstrated in experimental models and it is highly plausible that such direct and indirect mechanisms exist in humans.

Overall however there are several in vitro actions of probiotics which do not translate into clinical effects and clinical observations which can not 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.³¹ 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,^{32,33} which may be described as a characterized imbalance between the major groups of organisms in the gut. Such conditions include GI infections, antibiotic treatment, IBS, IBD and allergy, and these may help in clarifying what defines an unhealthy gut microbiota. This is also true in other instances, such as in obesity or in older populations, where the concept that an altered microbiota can be relevant to health has been suggested. Nevertheless, a dysbiosis definition is not straightforward either 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.³⁴ 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 (balance between several phylogenetic groups, enzymatic activities, metabolic profile) might appear interesting, current knowledge is not yet strong enough to reach distinctive criteria; research should thus be funded to develop tools and criteria allowing the characterization of a meaningful concept of what constitutes a ‘healthy gut microbiota’

Safety

The extensive and safe use of commercial probiotics worldwide over several decades alongside clinical trials to assess potential adverse effects, provide the most compelling evidence for safety of probiotics for the general population.³⁵ Nevertheless, there are reported instances of adverse effects of some probiotic strains in individuals in particular high risk groups. For example, in premature infants with short gut syndrome, cases of bacteremia related to specific probiotic lactobacilli use have been reported³⁶ and several cases of fungemia in subjects taking *S. boulardii* supplements have been described.³⁵ There have also been occasional reports of endocarditis in post-operative patients.³⁵ The most severe adverse event associated with treatment with a mixture of lactobacilli, lactococci and bifidobacteria was fatal bowel ischemia in patients with high risk, acute pancreatitis—a severe, often fatal, condition. Mortality was significantly higher in the lactic acid bacteria group.³⁷ The reason for the increased mortality is not clear, it may have been a consequence of the route of administration (introduction of large numbers of bacteria directly into the small intestine by naso-gastric tube) or even to problems in randomization or

design but such studies do highlight the importance of conducting thorough safety evaluations and risk-benefit analyses when probiotics are being considered for treatment of very high risk groups. Nevertheless it should be pointed out that specific probiotics have also been fed to high-risk populations without significant adverse effects including HIV patients, low birthweight infants, the elderly and critically ill children (reviewed in ref. 35).

Practical Aspects

The group agreed that probiotic survival in the gastrointestinal tract as determined by viable counts in feces, 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 produce an effect. There

are very few dose-response studies that would provide an answer to this question and the consensus is that there is no standardized 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 be studied 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 if the probiotic is provided in a food this could have an important effect. As probiotics are living organisms, whose physiology and metabolism can be affected by the characteristics of the food environment. 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.

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