INTERNATIONAL PROBIOTICS ASSOCIATION EUROPE[1]

IPA Europe Q&A on the publication of the American Gastroenterological Association (AGA) - 2020 Clinical Practice Guidelines of Probiotics in the Management of Gastrointestinal Disorders

IPA Europe welcomes AGA's new analysis of the role of specific probiotics in the management of digestive diagnoses. In particular, IPA Europe welcomes the approach of analysing probiotic interventions individually and not grouping different probiotic strains and combinations of strains into one meta-analysis.

The overwhelming current body of evidence points towards strain-specific effects for probiotics. All studies indicate that the probiotic family is not a single uniform block: if several different probiotics have shown similar effects in different studies, their action depends on the strain, or the combination of strains used.

It is also important to note that, according to an IPA study, the analysis of the geography of clinical trials on probiotics published on ClinicalTrials.gov indicates that a large majority of trials are conducted in Europe (420 in Europe compared to 270 in North America in 2018). Excluding studies solely because they were not conducted in North America, as AGA states, could therefore reduce the relevance of AGA's recommendations.

Do these microorganisms have a positive effect on some gastrointestinal conditions?

In the end, AGA analyses a limited number of digestive diseases, such as IBS, and among this limited number, AGA identifies three specific clinical areas where selected probiotics can be recommended. These include the treatment and prevention of pouchitis (a common complication following surgery for ulcerative colitis), the prevention of necrotizing enterocolitis (NEC) in premature infants, were AGA recommends that probiotics can prevent mortality and necrotizing enterocolitis (necrosis of the intestinal mucosa), and for the management of diarrhoea with Clostridium (CID) associated with antibiotic use. For these serious diseases, conventional treatment options are few, can have serious side effects, and are costly.

Probiotics are an appropriate complement, often used in combination with traditional therapy and not as a replacement.

It thus appears that AGA recommends probiotics for some gastrointestinal conditions as a drug; to prevent, cure and treat the disease. A wide evidence for probiotics substantiates their use to support health and in preventing and mitigating disease and in a wider scope of conditions. The effects of probiotics have been

[1] IPA Europe is the European chapter of IPA, the International Probiotics Association; it was established in Brussels in 2015. The members of IPA Europe are Companies directly engaged in the manufacture of probiotic cultures or probiotic foods, supplements, nutritionals or therapeutic products: BioGaia, Chr. Hansen, Danone, DuPont, IPA, Lallemand, Lesaffre, Probi and Yakult. The IPA Europe mission is: to gain acceptance of the term "probiotic" throughout Europe as a defined category and to create a favourable environment for probiotics in Europe. For additional information on IPA Europe's activities see: http://ipaeurope.org

studied on other aspects of digestive health and well-being, such as comfort, digestion of lactose, etc. In this respect, some probiotics are recommended by medical and scientific organizations other than AGA, such as WGO, ESPGHAN, ESCMID. These recommendations are also based on evidence from several clinical trials in various countries and with different strains. For example, the effect of yogurt symbiosis on lactose mismanagement has been studied extensively, and EFSA has given a positive opinion on the use of this claim on the basis of over ten clinical studies.

Other international organizations, such as the World Gastroenterology Organization (WGO), have recently issued evidence-based Guidelines on a number of gastrointestinal conditions, for which there is evidence of efficacy, from at least one well-designed and conclusive clinical trial, that oral administration of a specific probiotic strain has good evidence of efficacity for the given dietary and clinical setting.

https://www.worldgastroenterology.org/UserFiles/file/guidelines/probiotics-and-prebiotics-french-2017.pdf

Moreover, another scientific society recognised worldwide, the European Society for Paediatric Gastroenterology Hepatology and Nutrition, (ESPGHAN) published in 2014 an evidence-based guidance, providing indications for the use of probiotics in the management of children with acute gastroenteritis. This document is based on a systematic review of randomized controlled trials (RCTs) published on the subject; the administration of probiotics should be considered in the management of children with acute gastroenteritis, to reduce the duration and severity of diarrhoea.

http://www.espghan.org/guidelines/gastroenterology/

http://www.espghan.org/fileadmin/user_upload/guidelines_pdf/Guidelines_2404/European_Society_for_Pediatric_Gastroenterology_.26.pdf

Can we talk of probiotics as a "drug in disease management"?

The AGA report recommends probiotics as a drug for the treatment of certain gastrointestinal diseases, to solve a medical problem. It is important to remember that much evidence for probiotics substantiates their use to support health and in preventing and mitigating disease, and in a wider range of situations. Probiotics thus appear as a treatment solution but also a preventive one.

Probiotics are generally not prescribed as an exclusive therapy in disease management, but most often suggested as part of the diet, in prevention, or as a complement to standard treatment. Probiotics are defined by the World Health Organization as, "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". This 2001 definition includes many types of products for different uses, including food, food supplements or medicines, which are available worldwide. To produce these products and to communicate their effects, manufacturers are required to comply with the regulations and the rules for the scientific assessments for these different uses.

How do probiotics work?

As described above, probiotics are microorganisms that have been highly studied in recent decades and recommended by several international health organizations. The relevant scientific progress in the last decade suggests that the gut microbiota can also affect several non-gastrointestinal conditions, making a clear link between these conditions and the gastrointestinal tract. The analogy between the microbial nature of the gut microbiota and that of probiotics, some of which are usually located in the colon, may suggest that some of the effects observed during controlled administration of these microorganisms are related to an interaction between the flora of the microbiota and these orally administered bacteria.

Joint Research Centre (JRC), the EU Science Hub JRC F7 - Knowledge for Health and Consumer Safety, The Human Gut Microbiota: Overview and analysis of the current scientific knowledge and possible impact on healthcare and well-being, EUR 29240 EN, Publications Office of the European Union, Luxembourg, 2018,

ISBN 978-92-79-86471-1, doi:10.2760/17381, JRC112042 - https://publications.jrc.ec.europa.eu/repository/bitstream/JRC112042/hum an_gut_microbiota_online.pdf

How can probiotics be beneficial for premature infants or in the prevention of some infections?

The AGA recommends under certain conditions probiotics for the prevention of NECs: “For premature (born before 37 weeks), low birthweight (<2500 g) infants, specific probiotics can prevent mortality and necrotizing enterocolitis, reduce the number of days required to reach full feeds, and decrease the duration of hospitalization”.
Given the scarcity of therapeutic options available for this disease and its severity, and on the basis of these clinical recommendations, each hospital should assess the value of certain probiotics recognized for having an impact on the NEC as part of their treatment plans.

Can probiotics be effective for the prevention of CID associated with antibiotic use?

The AGA also recommends, under certain conditions, probiotics for the prevention of CIDs associated with the use of antibiotics.
The contribution of probiotics to the prevention of diarrhoea associated with Clostridium remains significant and is recognized by the WTO.
Information and education are essential to respond to consumer questions and concerns. This means that health professionals should be educated in order to be able to handle questions, and must be informed about what probiotics they should be co-prescribing or recommending to patients.

Can probiotics help to relieve other digestive diseases?

The AGA's recommendations deviate from the recommendations of other international medical societies. For example, the AGA states that, in the case of IBS, given the lack of evidence to make a recommendation, patients should consider stopping probiotics. However, according to the World Gastroenterology Organization (WGO) Guidelines on Probiotics and Prebiotics, "a reduction in abdominal proliferation and flatulence as a result of probiotic treatments is a constant finding in published studies."

Other evidence-based medical and scientific organizations, such as the European Society for Hepatology and Nutrition of Paediatric Gastroenterology and the European Society for Paediatric Infectious Diseases, recommend the use of probiotics in acute gastroenteritis in children. The existence of clinical evidence is confirmed by the International Scientific Association for Probiotics and Prebiotics (ISAPP), for example in the case of IBS, and also for other recognised effects of probiotics.

https://isappscience.org/isapp-take-home-points-from-american-gastroenterological-association-guidelines-on-probiotic-use-for-gastrointestinal-disorders/

The logical approach would be to recommend probiotics that have good evidence of efficacy. For the prevention of acute diarrhea, the AGA argues that the studies were conducted primarily outside of North America, which should not be a valid reason to exclude them, as there is no regional specificity for these diseases.

Are there any side effects of probiotics?

Side effects of probiotics are very rare in healthy population, while it is the opposite for drugs. It is generally recommended to take probiotics with caution in vulnerable individuals, with severely compromised immune systems.

According to the National Institute of Health (NIH), Office of Dietary Supplements (ODS), "many probiotic strains originate from long-safe food species or microorganisms that colonize healthy gastrointestinal

leaflets," and "given the large quantities of probiotics consumed worldwide, the number of opportunistic infections resulting from currently marketed probiotics is negligible."

The safety profile of probiotics is excellent in healthy individuals and for a very large part of the population, and can be safely combined with most known drugs without adverse consequences.

The AGA is rightly concerned about the cost-benefit ratio.

In the case of IBS, it is worth pointing out that the effectiveness of the treatments with drugs are not very significant, in specially when comparing the possible side effects and high cost of a medication against its benefits. By comparison, a recent meta-analysis shows that probiotics have conclusive results for the same indication, without adverse side effects.

In conclusion, for IBS an initial trial of appropriate strains of probiotics seems reasonable, rather than immediately embarking on an expensive drug that has known common side effects.

Probiotic consumption helps with keeping the cost of the healthcare system under control.

A healthy behaviour and products able to enhance health, wellbeing and quality of life can play an important role and will have a positive impact in keeping the cost of the healthcare system of the EU Countries under control.

A health-economic analysis was undertaken to estimate the public health and budget consequences of a generalized probiotic consumption in France. The conclusions indicated that the Public Health and the costs reduction are substantial. Another study on the general population in Canada and USA also shows the potential positive impact of probiotics on the management of health care costs.

Lenoir-Wijnkoop I, Gerlier L, Bresson J-L, Le Pen C, Berdeaux G (2015) Public Health and Budget Impact of Probiotics on Common Respiratory Tract Infections: A Modelling Study. PLoS ONE 10(4): e0122765. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122765

Lenoir-Wijnkoop I, Gerlier L, Roy D, Reid G (2016) The Clinical and Economic Impact of Probiotics Consumption on Respiratory Tract Infections: Projections for Canada. PLoS ONE 11(11): e0166232. https://doi.org/10.1371/journal.pone.0166232

Lenoir-Wijnkoop I, Merenstein D, Korchagina D, Broholm D, Sanders ME, Tancredi D (2019) Probiotics Reduce Health Care Cost and Societal Impact of Flu-Like Respiratory Tract Infections in the USA: An Economic Modeling Study. Frontiers in Pharmacology 28 August doi:10.3389/fphar.2019.00980

Heath claims and EFSA (European Food Safety Authority)

All studies indicate that the probiotic family cannot be considered as a single homogeneous block: on one hand, their action depends on the strain, or the combination of strains used, and on the other hand the efficacy of individual probiotic or combinations of probiotics in different studies can show close effects.

Having said that, it should be noted that only a small number of health claims received a favourable opinion by EFSA.

Only 12 health claims on food products based on new scientific evidence have been formally approved by the European Commission, which corresponds to a very low rate of 6% of the total number of cases submitted.

These are discouraging results, and several experts are of the opinion that the European Food Safety Authority has set the bar far too high by requiring that probiotic foods and food supplements demonstrate an efficacy close to those required to medicinal products, that they are not, while some probiotics dossier have a have a better evidence of efficacy than certain minerals and vitamins which are authorized as health claims.

Science exists around probiotics. The implementation of significant pre-submission consultations between the companies and the European Food Safety Authority (EFSA), as is currently the case with the European Medicines Agency (EMA), would certainly facilitate the evaluation of a health claim request.

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Rosanna Pecere
Executive Director IPA Europe

r.pecere@ipaeurope.org

IPA Europe

Avenue d'Auderghem 22-28, B-1040 Brussels

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