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An "IBD Passport" Methodology to Assess the Impact of AGA Guidelines on the Behaviors of Gastroenterologists and Patients in Probiotic Use in North-Western Italy

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Abstract

American Gastroenterological Association (AGA), European Crohn's and Colitis Organization (ECCO), and European Society for Clinical Nutrition and Metabolism (ESPEN) currently provide different guidelines for prescribing probiotics in intestinal disorders. These conflicting results cause therapeutic uncertainty in clinicians and an unjustified increase in pharmaceutical spending for the patients, more frequently for patients reporting Inflammatory Bowel Diseases (IBD) in the remission phase. The researchers tried to understand in a group of clinicians and a group of IBD patients whether: a) the indications to prescribe probiotics have to be restricted from clinicians or patients according to recent AGA guidelines, b) the improvement in IBD symptoms during probiotic therapy has to be evaluated based on the opinions of the patient and c) the probiotic to use has to be chosen based on its lower cost. The Authors applied in the general community the Grounded Theory evaluating with the Patients' Outcome Reports (PROs) methodology of investigation. Two reports were addressed twice, in one month, to clinicians and patients selected from those participating in the published educational program "IBD passport", to obtain a critical assessment of the hypotheses. Only 40% of the gastroenterologists adhered to the three assumptions and no patient desired to give up his or her symptomatic treatment with probiotics even when warned that a possible positive result could be due only to a placebo effect. Guidelines for probiotics do not impact the behaviors of clinicians and patients in our area. Clinical trials concerning Live Bio-Therapeutic products (LPBs) could obtain scientifically proven results and clarify when and why to prescribe probiotics in IBD.

Keywords: *Probiotic, IBD, Guidelines*

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1. Introduction

American Gastroenterological Association (AGA) recently published, for the first time to our knowledge, guidelines concerning the role of probiotics in the treatment of gastroenterological disorders, Inflammatory Bowel Diseases (IBD) included [1]. The paper lends itself to some considerations on the originality of the methodology used.

First of all, the usual approach to provide guidelines addressed to a particular disease, gastrointestinal disorders, in this case, is reversed and probiotics are the "core business" of the guidelines. The unusual approach is probably due to the overweight of economic data: the expenses for buying probiotics were considered as not justified in the absence of reliable scientific evidence of their effectiveness (suppl. 1, ref. 29). Furthermore, since the patients can purchase probiotics on their own, their behaviors can become preponderant and be independent of their doctors' recommendations.

Furthermore, the parameters chosen in defining AGA guidelines are different from those chosen in another paper on the same journal issue [2]. In fact, into the paper are considered only statistical and meta-analytical criteria while into the guidelines also ethical criteria, acceptability, and costs are evaluated, undergoing a "patient representative" consensus.

Last but not least AGA guidelines on the use of probiotics in gastrointestinal disorders are, in a counter-intuitive way, restrictive. In particular, the use of probiotics in Inflammatory Bowel Diseases (IBD) is not recommended in daily general practice, without any difference between adult and child nor between Ulcerative Colitis (UC) and Crohn's Disease (CD). Their use is allowed only in clinical trials. These conclusions are conflicting with the indications provided from other outstanding International Scientific Societies such as the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Crohn's and Colitis Organization (ECCO).

ESPEN nowadays promotes the use of probiotics, with grade B evidence, in maintaining therapy in the UC remission phase [3].

ECCO already [4] in 2008 reported Escherichia coli Nissle as an effective alternative to 5-ASA for maintenance in the UC remission phase. Again in 2019 [5], ECCO reports that Escherichia coli Nissle 1917 may be effective in inducing and is effective in maintaining UC remission and suggests that a multi-strain probiotic containing a combination of lactic acid bacteria, streptococcus, and bifidobacterial may be effective in inducing and maintaining remission in UC.

The controversy surrounding the role of probiotics and other strategies for manipulating the microbiota may arise at several steps along the process that translates the original research idea to the marketplace and contributes to poor understanding among consumers of risk-to-benefit appraisal [6].

It is therefore mandatory to determine whether the conflicting indications just mentioned can change the behaviors in prescribing probiotics and how clinicians have to explain these modifications in prescribing probiotics to their patients.

In collaboration with Associazione Malattie Infiammatorie Croniche Intestinali (AMICI) Piedmont and Valle d' Aosta ODV, an IBD patient Association in Turin, we recently developed the project “IBD passport” [7], a cultural pathway for IBD patients, pointing out the different clinical and therapeutical responses and the conflicting evaluations that we found in IBD treatment in our daily gastroenterological practice. Applying this methodology, we demonstrated that the discussion of real clinical cases between clinicians and patients is possible, without generating conflicts. Furthermore, during the meetings on IBD organized both for AMICI and for other Associations from 2015 to 2020 the Author always observed

perplexity and dissent from the audience when they explained that the use of probiotics in IBD could have a placebo effect (suppl. 1, ref. 2). The patient perception about probiotics seemed to be different and conflicting with this opinion and with the guidelines provided by Scientific Societies.

2. Aims

The first aim of the study is to evaluate how the opinions of clinicians differ from AGA guidelines when they evaluate the effectiveness of probiotics similar to that of a placebo. The second aim is to verify the opportunity to modify the indications to the prescription of probiotics. We tried to verify these ideas in a small but homogeneous group of patients and clinicians previously adhering to the "IBD passport" project based on the methodology of PROs [8]. We compared their opinions suggesting to both groups three hypotheses: a) the prescriptions for the treatment with probiotics have to be limited since the absence of sure scientific conclusions, b) the assessment about therapeutic efficacy has to be evaluated from patients based on their individual experience and c) the indication to the right probiotic to use has to be addressed on the criterion of its lower cost (suppl. 1 ref.30-31).

3. Methods

The researchers perform the study in two separate times: A) writing a template document for clinicians and a template document for patients, B) submitting these template documents to clinicians (B1) and patients (B2) with different modalities.

A. Template documents

The three hypotheses were summarized in two different but similar documents.

The first one more complex, in the English language, was mailed to clinicians (suppl. 1).

The second one, simplified in medical terms and Italian language, was sent to IBD patients (suppl. 2).

Both documents required from each component of the two groups a critical evaluation and to agree or to reject the above-mentioned hypotheses. Clinicians and patients were selected between those previously adhering to the "IBD passport" project, held in Piedmont, Northern Italy, during 2018 and 2019. The project consisted of 8 meetings concerning themes of general medicine and discussions on real clinical IBD cases and brought to a strong feeling of shared opinions between clinicians and patients (suppl. 1, ref. 32).

B1. Clinicians template document submission

Since the "clinical" aims of the present study pathologists, epidemiologists, psychologists and psychiatrists were excluded from the 19 clinicians participating in the previous project. Furthermore, one gastroenterologist rejected the participation since his elderly age.

Supplement 1 was mailed twice, in two different moments, to 14 clinicians working in the six major Public Hospitals in Piedmont, Northern Italy. The document in 2175 words and with 33 bibliographic references, pointed out the theoretical hypotheses over mentioned as a), b) and c), reinforced by 21 specific reasons based on literature data (suppl. 1 ref. 4-12, 14-25).

The researchers offered to accept or to reject the participation in the present study as co-Authors whenever they agreed to one, two, or even to all the theoretical hypotheses. In other words, we asked that the responsibility to be co-Authors underwent to the agreement to the expressed hypotheses. Furthermore, we asked for individual comments, if they were considered necessary.

B2. Patients template document submission

Thirteen voluntary patients out of the 29 participating in the IBD passport project were selected based on their involvement in Directive roles in the AMICI Association. All of them had a homogeneous cultural background, with a mean level going from good to high. All the patients experienced almost once the use at least of one probiotic.

Supplement 2 in 1191 words pointed out the same three hypotheses over mentioned reinforced from 17 bibliographic references. It was completed by an invitation letter (Supplement 3) sent from AMICI Piedmont and Valle d'Aosta Association President, to obtain the evaluation about the opportunity to continue, to withdraw or even to amplify during future years two trade agreements with different pharmaceutical companies previously signed in 2010 and 2019 to obtain a lower cost of the probiotics used from the Associates.

The responsibility of maintaining, withdrawing, or even amplifying to other companies these agreements was deserved to these selected IBD patients according to their assessment about the effectiveness of probiotics on their disease The institutional responsibility of each patient could be a reason to adhere to the study similar to the one the researchers offered to clinicians. To maintain or to amplify the existing agreements would signify a positive evaluation from patients about the use of probiotics, independently from the evaluations given by their doctors. Besides this, it was asked to declare whenever the evaluation was due to the experienced effects of the therapy on disease symptoms or to a simple economic relevance of a lower cost for therapy. Also, in this case, free comments were encouraged.

The methodology used in the study was repeatedly reviewed based on the Grounded Theory [9].

Ethical approval was granted from the Ethics Committee of the AMICI Piemonte e Valle D’Aosta and supervised all long the project by the Scientific Director of A.M.I.C.I. Piemonte e Valle d'Aosta OdV.

3. Results

The percentage of clinicians answering to Supplement 1 was 71% (10 out of 14) while it was 69% (9 out of 13) in the group of patients to Supplement 2.

Only 40% of doctors agreed to the hypotheses. Significantly all of them agreed on the absence of scientifically validated evidence for probiotic prescription and accepted to participate as co-Authors to the present study [Table 1].

Table 1. Clinicians

	Answers to Supplement 1 n. (%)	Comments obtained N
Accepting hypotheses	4 (40)	3
Denying hypotheses	1 (10)	1
Without any decision	5 (50)	5

Supplement 1 was sent to 14 clinicians to evaluate their adhesion to hypotheses

Furthermore, the comments from clinicians suggested that they did not agree to devolve to patients the assessment of the effectiveness of probiotics both when prescribed nor when self-managed (hypothesis b). At the same time, the clinicians did not agree to choose the probiotic to be used only based on a lower cost (hypothesis c).

Between the patient's nobody agreed to withdraw the existing trade agreements between AMICI and pharmaceutical companies, indirectly acknowledging the effectiveness of probiotics and rejecting the theoretical hypotheses [Table 2].

Table 2. Patients

	Commercial agreements N. (%)	Comments obtained N
Maintain	9 (100)	3
Withdraw	0	0
Without choice	0	0

Supplement 2 sent to 13 patients with 9 adhesions

In 45% of cases, this positive evaluation for probiotics was justified from their effectiveness on the symptoms of the disease and in 33% of cases only from economic criteria [Table 3].

Table 3. Reasons to maintain agreements

Reasons to maintain agreements	N (%)
Therapeutical reasons	4 (45)
Economical reasons	3 (33)
Undeclared	2 (22)

Answers obtained for maintaining trade agreements

Moreover, 50% of clinicians did not agree on the therapeutical benefit due to probiotics while only 22% (2 out of 9) of IBD patients were doubtful about their effectiveness. The individual comments from each group made the difference more blurred. The patients justified their positive evaluation because of an absent therapeutical risk while also some doctors thinking negatively about probiotic use admitted that they could be helpful in some particular clinical settings. Unexpectedly two comments from gastroenterologists, one with a negative judgment about probiotics and another doubtful about them, suggested that probiotics had to be considered in charge to the National Health System and not only as a supplement also if their therapeutical effect could be due only to a placebo effect.

4. Discussion

This study is an effort to involve IBD patients in therapeutical decisions about their disease and in particular to evaluate the opinions of IBD patients at the same level we do it for the opinions of the clinicians, each one according to their peculiarity [10]. There are many references in literature [11] about the involvement of the patients in medical decisions to obtain the so-called “Patients' Revolution” [12] The patients involved in decisional processes suggest several and sometimes conflicting opinions [13]. The methodology in this study was previously never applied and the adhesion rate of over 65% is a good result for the study itself since the Authors applied this method in a field where the doctor's decision–making process is complex also for experts. A good number of clinicians and all the patients think that the probiotic use in IBD treatment is useful, almost in some clinical conditions, in conflict with the suggestions from AGA guidelines. Patients have a positive assessment of probiotics also when they are warned that the benefits could be due to a placebo effect. It is important to underline that they wanted to use probiotics also when informed of a possible positive effect not surely related to probiotics and also when the economic costs were not covered by National Health Services.

60% of clinicians did not agree with the hypotheses exposed in the document in which, according to AGA guidelines, we suggested limiting the prescription, the use, and even the expenses for probiotics.

Furthermore, the two suggestions to allow reimbursement for probiotics even if they are nowadays labeled as supplements since the supposed placebo effect raised an unsolved and unsolvable problem of sustainability of health spending. In this case, the gratuity of practices

not validated would probably need to be extended also to complementary medicine such as homeopathy, alternative therapies, reimbursement of gluten-free food to non-coeliac patients affected by gluten intolerance. This perspective needs to be discussed. It has to be pointed out by scientific studies and should not be withheld.

This study has limits such as the low numbers of the groups observed and the methodology used but the inclusion of ethical criteria, acceptability, and sustainability in AGA guidelines permit this methodology of evaluation as it was used in the study.

Moreover, the agreement of each clinician to Supplement 1 could be obtained through multiple questions with closed answers but this method was not considered to be practical. The complexity of the problem could determine the number of questions higher than the number of participants with a consequent low value of any statistical evaluation. Besides this, the time required for a reasoned answer could impact the adhesion rate to the study and cause superficial answers.

Since the second aim of the study was to achieve a generic assessment with an important practical decision-making impact, e.g., for clinicians to accept or to reject the theoretical hypotheses exposed and for patients to maintain or to withdraw existing trade agreements, we summarized the hypotheses a), b) and c) in a single document for each group. It is possible that this unification brought doubts in evaluating both Supplement 1 and Supplement 2 and that different evaluations could be made also after having agreed to only one of the hypotheses.

Any statistical analysis or any fragmentation into under-categories is not possible because of the methodology used in the two groups also if they were highly homogeneous. In some clinical situations such as investigating the behaviors of patients, the homogeneity criterion is much more significant than the simple number of subjects undergoing the study [14].

The comments and the adhesion of clinicians working into the 6 major Piedmont Hospitals are widened to the whole Gastroenterology in Piedmont. Our method is therefore not able to understand whether the disagreement of the clinicians to our hypotheses is due mainly to scientific or to economic reasons. Nevertheless, since hypotheses b) and c) constitute a possible practical application of AGA guidelines, it is reasonable to assume that doctors apply a caution induced by direct or indirect economic reasons.

The document mailed to clinicians could be amplified by other published papers. A lot of other data are present in the literature concerning the hypotheses expressed in this work besides the 21 reasons related to 33 bibliographic references. As an example, we did not mention that VSL# 3 can present different mechanisms of action based on the American or Italian site of production [15]: whenever this observation would be repeated for other probiotics the already wide range of confounding factors would widen in evaluating clinical works [16][17].

More generally the recent FDA decision to create a new drug category for Live Bio-Therapeutic Products (LPBs) allows to overcome the term of probiotics [18] The LPBs category will allow future clinical trials on probiotics as real drugs making it possible important scientific acquirement about the use of bacteria in the treatment of diseases. As an example, the SER-287 study reaches good results in the treatment of active moderate to severe UC through the use of spores in association with antibiotics [19] Furthermore a Clostridium cocktail able to work on immunological mechanisms is in phase 1 study [19] some strains of Lactobacillus Salivarius could modify the IL-10/IL-12 ratio [21], some bio-active bacterial products and also the immunization with bacterial products (QBECO) are in experimentation both on UC and CD [22][23]

5. Conclusions

The study suggests that a critical assessment from patients on the scientific conclusions of guidelines also when they conflict with their actual behaviors is useful. The methodology we used shows also that clinicians and patients are similarly conscious that the economic value of the probiotic market is overestimated compared to the results of scientific research. The new guidelines provided by AGA, also when recognized as scientifically correct and pre-eminent, are not able to solve the problem of probiotic prescription for clinicians. The recent acknowledgment of the LPBs category of drugs is the first step to change the methodology of the trials, as we suggested in Supplement 1 and Supplement 2, and to achieve measurable clinical results in the therapeutic strategies based on microbiota or microbiome. Finally, the forthcoming research to overcome the placebo effect of probiotics should adopt the Salerno criteria methodology with a "double-blind placebo-controlled challenge with crossover" (suppl. 1, ref. 18-19).

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