ON THE QUEST OF EUBIOSIS: Statements of an ad-hoc panel following the Romanian-Italian Gastroenterology Meeting of SRNG 9-11 March 2023

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Introduction

During the Romanian-Italian Gastroenterology Meeting organized in Cluj-Napoca by the Romanian Society of Neurogastroenterology, between 9-11 March 2023, a retreat meeting was organized to discuss the current knowledge in the fast-developing field of gut microbiota and its implications in the pathophysiology of a number of digestive diseases. The panel was formed by leaders of opinion from both countries with several publications in this field. Several statements were formulated. All have been accepted by consensus. These are presented below.

Statements

1.Gut microbiota represents an important component of the human body

The human gut hosts more than 100 trillion microorganisms generally called microbiota, all together comprising more than150 fold more genes than the whole human body (1, 2). Thus, gut microbiota represents one of the most important human components. Their implications in the preservation of health and pathophysiology of many digestive, extradigestive and systemic diseases explain the emphasis on its research worldwide (3).

More than 100 years after the first wave of studies on microbiota, launched the belief that probiotics have beneficial effects on health. In the last 20 years, we live in a new wave of scientific progress and knowledge enlargement on gut microbiota and on its modulation by probiotics, prebiotics, symbiotics, synbiotics and antibiotics.

2. Gut microbiota has several benefic functions

Gut microbiota depends on the way of delivery at birth (vaginal or by C-section), on diet, geographical characteristics of living area, even age or body mass index. However, it is rather stable in respect to function and to compositional spectrum. A microbiota is an active organism performing a lot of metabolic reactions, able to induce benefic or pathogenic changes. In order to extract clinically useful conclusions, it is necessary to extrapolate data from those species or strains of microbiota that perform specific metabolic functions (4).

Gut microbiota has local activity (5) and influences the gut-brain axis (6). Among the benefic roles of gut microbiota, one should mention the increase of the intestinal barrier, by reducing the permeability; its anti-inflammatory action via humoral and cellular immune response pathways; the fact that gut microbiota intervenes in the synthesis of liposoluble vitamins and of short-chain fatty acids.

In respect to the gut-brain axis, one should mention the conditions where microbiota from the gut represents a pathophysiologic factor (see below table 2). Indeed, the components of the intestinal microbiota are able to influence intestinal permeability; this process leads to delivery of inflammatory factors and of neuromodulators, i.e., cytokines. The consequence is systemic inflammation and the triggering of the immune reaction. Several neurotransmitters are released

altering the function of the hypothalamic–pituitary–adrenal axis, followed by a decrease of brain trophic factors.

3**. Gut health is related to eubiosis**

Eubiosis has the etymology from two ancient Greek words and means good living. It defines the health standard in the gut lumina. Gut health depends on the abundance of species and strains of microbes (bacteria, fungi, archaea, bacteriophages, viruses) found in the gastrointestinal tract. The healthcare providers try to preserve or to restore eubiosis in the gastrointestinal tract in order to preserve general health or to improve the numerous digestive or extradigestive clinical conditions linked to loss of eubiosis, called dysbiosis.

The limits of our knowledge up today is what really means a true eubiosis, how stable it is, how can it be influenced by diet and lifestyle and how interventions with antibiotics or probiotics can conserve or restore this.

4. Dysbiosis is involved in many pathological conditions

Dysbiosis is defined as the loss of eubiosis, i.e., the rupture of the healthy balance of gut microbiota. Dysbiosis is frequently encountered in many situations, the most common being the acute gastroenteritis following antibiotherapy for an infectious episode, like dental extraction with role of prevention, or therapy of skin infectious, respiratory infections, etc.

Gut microbiota is considered an important pathophysiologic factor in a large series of clinical conditions. (See table 1 and table 2) (7)

Table 1: Digestive conditions where gut microbiota has pathophysiological role

Alcoholic liver disease
Clostridium difficile infection
Colorectal cancer
Diverticular disease
Esophageal cancer
Inflammatory bowel disease
Irritable bowel syndrome
Nonalcoholic liver disease
Pancreatic cancer

Table 2: Extradigestive and systematic conditions where gut microbiota has a pathophysiological role

Allergies
Atherosclerosis
Atopic dermatitis
Autism
Coronary heart disease

Cystic fibrosis
Dental caries
Depression
Diabetes mellitus
Malnutrition
Multiple sclerosis
Obesity (metabolic disease)
Osteoporosis
Parkinson's disease
Rheumatoid arthritis

5. Diet may influence gut microbiota

There are classical data on the modalities diet may influence microbiota and also the health, from the traditional assumptions that yoghurt or kefir is prolonging the life expectancy. Nowadays we know that diverse diets are associated with an abundance of species and strains in the gut microbiota, while unilateral, restrictive diets do not have a benefic effect on gut microbiota. The pathways diet is influencing the microbiota relies on epithelial integrity and absorption from intestinal lumen (8).

The impact of the diet on microbiota depends, of course, on the length of intervention: while short-time dietary interventions produce reversible changes, prolonged interventions can change for long time the profile of gut microbiota, like in malnutrition, as shown in classical reports (9). The changes start just after delivery and are influenced beside diet by associated infections and genetical factors (10).

6. Gut microbiota is altered in irritable bowel syndrome

The irritable bowel syndrome (IBS) is one of the best-known targets of microbiota manipulations in order to obtain symptoms alleviations (11).
There are so many contradictory reports of gut microbiota and IBS, also in respect to IBS subtypes (12) that absolute conclusions cannot yet be decided. However, it is common knowledge that non-absorbable antibiotics like Rifaximin--α and some probiotics improve the IBS symptoms (13).
One of the major players in the regulations of gut microbiota in IBS is the antibiotic with local action Rifaximin-α. This drug has been extensively studied in the TARGET studies (14-16)
All trials have shown the positive effect of Rifaximin-α at the first administration, and, if necessary, the good response to successive administrations. It has been considered and demonstrated that the activity of Rifaximin is due to its action on the compounds forming the entire gut microbiota, having as outcomes the improvement of inflammation and of the epithelial barrier.
The drug is safe and has a very good tolerance. The economic cost of Rifaximin-α administration is considered acceptable (11).
Recently, the American College of Gastroenterology (ACG) has published guidelines for IBS-diarrhea type including Rifaximin-α among the most recommended drugs (17).

Similar recommendations have been formulated also in Europe by the European Society for Neurogastroenterology and Motility (ESNM) in their guidelines, to which some of the present text authors have also contributed (18). Thus, both in Europe and North America, there is a strong recommendation for Rifaximin-α in IBS with diarrhea (IBS-D) and also in chronic functional diarrhea.

7. Gut microbiota is altered in diverticular disease

The diverticula represent an optimal environment for the occurrence of dysbiosis. Therefore, physicians should be aware of this possibility and should prevent the onset of symptoms or complications by correcting dysbiosis. The therapy for symptomatic and complicated diverticular disease requires the quest of eubiosis. Several attempts have been made with non-absorbable antibiotics, probiotics, prebiotics or mesalamine. However, the drug of choice in these conditions is represented by Rifaximin-α which has the most powerful evidences among all the others (19, 20).

There are also contradictory opinions, like a recent one from Australia (21). The conclusion of this systematic review does not bring enough evidence that dysbiosis is linked to symptoms in diverticular disease. However, this paper showed that alpha diversity of gut microbiota was deteriorated in diverticulitis, while alpha and beta diversity was not changed in noncomplicated diverticular disease.

8. Gut microbiota is involved in metabolic and toxic conditions of the liver

In recent decades, a lot of evidence has been gathered in respect to the action of gut microbiota on intestinal permeability. This deterioration of gut barrier is able to allow translocation of bacteria and macromolecules onto the circulation followed by liver and systemic inflammation, systemic. Liver inflammation relates to inflammation of hepatocytes, necrosis, fibrosis and advanced liver disease, including hepatocellular carcinoma (22-24). The main armamentarium for alcoholic liver disease and nonalcoholic fatty liver disease/metabolic associated fatty liver disease or drug induced liver injury or toxic liver disease should be the improvement of the structures of species of microbiota in the gut, in the absence of an etiological therapy. Many studies have recognized the role of dysbiosis as a pathogenic link to the onset of diverse chronic liver diseases and emphasized the need of an appropriate diet change, a potential reset/modulation of gut microbiota, and supplementation with appropriate probiotics (25, 26).

However, another important field for the need to correct dysbiosis is the hepatic encephalopathy of the liver cirrhosis. Rifaximin-α is the main player here. There are several studies proving the role of Rifaximin-α in controlling mental alterations in overt or covert hepatic encephalopathy. In a review, it has been demonstrated the efficacy of rifaximin-α in hepatic encephalopathy, not only in short term administration (up to 6 months), but even in long term administration (up to 5 years or more) (27). Indeed, this drug improved the clinical manifestations of hepatic encephalopathy, and this happened with a simultaneous reduction in blood ammonia. The effect was also superior to other antibiotics. Rifaximin-α also prolonged the survival. The drug was well tolerated, even on a long-term administration. What is not sure, is if the mechanism of

action is only due to the changes on microbiota spectrum, or if there are some other mechanisms which may lay behind (28).

9. Gut microbiota is involved in psychiatric conditions

The role of gut microbiota on the central nervous system functions (neurological and psychiatric) have been considered for many years by healthcare providers and mental health workers. A number of neurological and psychiatric diseases are associated with dysbiosis (see table 2).

We mention in this text two conditions, which are more frequent and relevant for clinical practice: IBS and fatty liver.

In respect to IBS, it is well known that in many psychiatric conditions, there is an association with gastrointestinal disorders and the mechanisms are extensively studied nowadays. Indeed, patients with IBS have frequent psychological symptoms and deteriorated quality of life. Many of these manifestations are supposed to be caused by gut microbiota, but we still need high quality evidence. Till then, we use neuromodulators to treat psychological symptoms in IBS patients as well as in patients with inflammatory bowel disorders. Neuromodulators prescribed in digestive patients target the simultaneous amelioration of both digestive and psychiatric symptoms. Thus, neuromodulators are able to improve the quality of life of these patients (29).

In a similar way, dysbiosis affects the mental state of patients with liver steatosis or non-alcoholic steatohepatitis. There is proof that anxiety and depression of these patients with metabolic syndrome usually, may be improved by changing the gut microbiota composition. Despite some evidence, we do not have strong recommendations for probiotics in liver diseases without encephalopathy (31). However, we may associate probiotics as adjuvant therapy in these conditions.

10. Rifaximin-α restores gut microbiota

In the previous statements we showed that Rifaximin-α is the antibiotic of choice to restore eubiosis, mainly in IBS, in hepatic encephalopathy, but also in symptomatic uncomplicated diverticular disease and early stages of diverticulitis. There are many studies showing its beneficial effects in these conditions (11). In the right way, Rifaximin-α is considered an eubiotic antibiotic. It is a drug with oral administration, but without enteral absorption due to its α polymorphic structure which may limit its activity only in the gut, and therefore without any systemic effect. It has a broad spectrum on many pathogens and is well tolerated as having no systemic effect. Some patients may claim, however, intolerance, but intolerance has to be proven if it is real or only attributed. The property of Rifaximin to be not absorbable, and hence its therapeutic effects, has been investigated and demonstrated only for its α-polymorphic structure. Thus, if ever generics will occur, these should demonstrate a lack of absorption as in case of Rifaximin-α (11, 32), or similar effects in all the cases where Rifaximin-α already proved its efficacy. Rifaximin-α modulates the microbiota in the gut and the gut liver axis. It has also a role of prebiotic because it enhances the growth of some beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli* (33).

11. Probiotics, prebiotics, synbiotics and symbiotics and the gut health

It is obvious that the best way to restore eubiosis is to influence the content of the gut lumina, by eradicating the pathogen factors, like those agents which are always harmful, or only conditionally harmful, and to replace them with beneficial saprophytic microbes, which can act as maintainer of gut health and thus of the whole-body health. The possibilities are either to replace the harmful bacteria with probiotics or prebiotics, synbiotics and symbiotics, or to destroy the harmful microbes with antibiotics (34).

Using probiotics is a very provocative modality to fight for gut microbiota integrity. And many attempts exist in the literature (original trials, reviews, meta-analyses). The attempt to use probiotics and prebiotics is logical and there are some species or strains that have shown their efficacy and good tolerability. However, even though the evidence level is quite good, the level of recommendation is low in most cases, because the difference between active and control group is not always significant. Many errors are produced by indicating the wrong probiotic, or administering it for a too short period of time, or by non-respecting the indications of each probiotic, etc. Another point of view is the quality of the drug: not all probiotics and prebiotics are similar, nor act similarly, but they also may meet in different levels the threshold of quality. Thus, probiotics and prebiotics offer a large field of battle against many diseases, from which the gastrointestinal pathology is very important. But cardiologists, neurologists, psychiatrists, endocrinologists, diabetologists, gynecologists, etc. use probiotics and prebiotics with more or less success in their practice.

Another alternative for restoring intestinal eubiosis is the transplantation of gut microbiota, by fecal material transplantation, but this solution achieved a high level of evidence and recommendation only in very few pathological conditions, like severe pseudomembranous colitis with *Clostridium difficile* (FMT) (35).

The recently developed artificial intelligence opens new pathways toward our knowledge on gut microbiota and its restauration (36).

Conclusions

These statements elaborated and agreed by the retreat group formed by Romanian and Italian specialists represent a synthesis on the role of microbiota in health and disease. Although our knowledge in this field has a tremendous development, we still need more evidence for our practical recommendations. The use of antibiotics as Rifaximin-α is emphasized, in order to improve clinical conditions by restoring eubiosis. The other approach relies on correct selection and prescription of probiotics, prebiotics, symbiotics and synbiotics.

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