To
Editor-in-Chief
Journal of Bangladesh College of physicians and surgeons
Subject: Letter to editor on the review article ‘Probiotics and their role in GI Diseases’

Dear Sir,

I would like to thank Colonel Dr Shaila Parveen and Colonel Dr Mir Azimuddin Ahmed through you for the well articulated and informative review article on the role of Probiotics in medical practice.

This is a hot topic in the field of medical research. The article started with amazing fact that trillions of bacteria and yeasts live within our GI. They outnumber total number of human cells and genome. This beneficial symbiosis coevolve through generations and ages. Its impact on immune system and gut homeostasis has opened a new horizon of knowledge of healing different gastrointestinal diseases. In the later part of the indications and precautions on usage of probiotics has been detailed in a nice and descriptive way. Use of probiotics in recurrent Clostridium difficile associated diarrhea and necrotizing enterocolitis is life saving. It is praiseworthy that the authors mentioned the side effects of probiotics as well. I would be obliged if some of my confusions are addressed.

(a) It is mentioned that in the USA Probiotics are medical food and must be used under medical supervision. Would you please clarify the kind of supervision and recommendations of regulatory bodies like US FDA and European Food Safety Authority? Is there any recommendation of Bangladesh Pharmacy Council or food safety authority?

(b) Whether the level of evidence is available for use in maintenance of remission of Ulcerative Colitis and Crohn’s disease?

(c) Can we predict the group of persons who are vulnerable to the side effects?

(d) What are the effect of different human gut microbiome of babies born through normal delivery and cesarean section?

(e) Is there any impact of commercially available household water filters and hand wash campaign on human gut microbiome?

At last I must thank the authors again for the hard work and trouble taken by them to write the thoughtful review article at right time.

With regards

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Author’s reply
To
The Editor-in-Chief
Journal of BCPS.

Sir,

The gut microbiome has now been linked to an ever increasing number of clinical fields beyond gastroenterology like immunology, rheumatology, diabetes and neurology. More so for gastroenterology as the GI system is the seat of the microbiome. The link between Helicobacter pylori and GI diseases like peptic ulcer disease and gastric cancer is considered by some to be the most significant discovery yet to have arisen from this new field of research. I shall try to address the five queries raised by the readers one by one.

a. US FDA

Probiotics face challenges similar to other areas of development where there is a lack of conclusive findings as to the safety of an evolving product. The FDA regulates products by category. Each category is
regulated by a center that evaluates and monitors many aspects of the life cycle of a product. These may include research, manufacture, safety, efficacy, transportation, labeling and claims.

Probiotics have traditionally appeared in foods which along with cosmetics are the least regulated products consumers use in or on their bodies. The earliest probiotic products were fermented products such as kefir (a fermented milk drink), yogurts and present day products like Redness Solutions Makeup SPF 15 with Probiotic Technology made by Clinique company. Probiotics are regulated based on the product category into which they fall i.e., food, food additive, cosmetic, medical devices, dietary supplement or drug. When questions arise regarding into which category a probiotic belongs, the answer is determined on a case-by-case basis. Many Working Group members expressed concern that because probiotics fall into multiple categories, expertise about them is spread unevenly across multiple centers at the FDA. Finally, although no probiotic drug have yet been approved by the FDA, several clinical trials are under way that are studying the safety and efficacy of probiotic formulas.

b. Crohn’s disease and Ulcerative colitis
Crohn’s disease, ulcerative colitis and pouchitis after ileal pouch anal anastomosis in ulcerative colitis patients are often refractory to standard therapy. So the rational to use probiotics and its beneficial efficacy in the treatment of chronic inflammatory bowel disease (IBD) is increasingly under scrutiny. Most of relevant data derived from studies on probiotics report some efficacy in ulcerative colitis and in pouchitis while disappointing results are available for Crohn’s disease.1 There is emerging interest on the role of selective modulation of microflora in inducing benefits in inflammatory intestinal disorders, by as probiotics, prebiotics, synbiotics, antibiotics and fecal microbiota transplantation (FMT). Recent developments in gene-sequencing technologies and potent bioinformatic tools have enabled new insights into the effects of microbial communities on various pathological conditions. Analysis of the microbiome using 16S rRNA sequencing confirmed that microbiota in IBD patients significantly differs from the one present in healthy individuals.2 With its diversity and bacterial load decreased assembles the characteristics of the status known as “dysbiosis”. It still remains unknown whether dysbiosis is a cause or consequence of intestinal inflammatory response in IBD.

The most convincing data for using probiotics in IBD comes from studies on commercial probiotic supplement VSL#3, a highly concentrated (450 billion bacteria/sachet) freeze-dried cocktail containing eight different bacterial species. VSL#3 cocktail, given in combination with standard UC therapy, results in higher rates of response and remission when compared to standard therapy alone. VSL#3 was also found effective in maintenance of chronic pouchitis and in prevention of pouchitis after ileal pouch anal anastomosis. Recently, researchers have taken probiotics to the next level, genetically modifying bacterial species to produce specific immunosuppressive mediators, i.e., IL-10 and antioxidant enzymes, i.e., superoxide dismutase (SOD). This is an interesting approach for mucosal delivery of selected proteins and could prove a feasible strategy for down regulating gut inflammation in IBD. It ultimately led to European Crohn’s and Colitis Organisation (ECCO) guidelines suggesting the use of this particular probiotic mixture both for maintenance of antibiotic-induced remission and for prevention of pouchitis. E. coli Nissle 1917 and VSL#3 both received a very strong “A” recommendations in American Recommendations for probiotic use for the maintenance of remission in UC. ECCO guidelines also recognized the role of VSL#3 probiotic mixture for treating relapsing, mild-to-moderate UC. The reports on the use of probiotics in Crohn’s Disease do not suggest any disease improvement, so probiotics are not advocated for this patient population.

c. Safety
In people who are generally healthy, probiotics have a good safety record. On the other hand, there have been reports linking probiotics to severe side effects, such as dangerous infections in people with serious underlying medical problems. The people who are at risk of severe side effects include critically ill patients, those who have had surgery, very sick infants and people at extremes of age with weakened immune system. Even for healthy people, there isn’t enough information right now to answer some safety questions. Most of our knowledge about safety comes from studies of Lactobacillus and Bifidobacterium; less
is known about other probiotics. Information on the long-term safety of probiotics is limited and safety may differ from one type of probiotic to another. For example, even though a study showed that a particular kind of *Lactobacillus* appears safe in healthy adults of age 65 and older this does not mean that all probiotics would necessarily be safe for people in this age group.

d. NVD and C/S

It has become clear that the gut microbiota not only plays a major role in priming and regulating mucosal and systemic immunity but the immune system also contributes to host control over microbiota composition. These two ways of mutual communication between the microbiota and the immune system were coined as “outside-in” and “inside-out” respectively.

In comparisons with other mammals, scientists have noted that human mothers produce a much more varied number of complex sugars called oligosaccharides (more than 200 have been identified to date). These sugars cannot be digested by babies and are more likely to be food for the microbiome as they selectively provide nourishment to one bacterial subspecies that in turn produces adhesive proteins with immunoprotective and anti-inflammatory qualities. A recent study showed that the microbiome of children who were exclusively breastfed differed significantly from those who were given formula and even from those who alternated between the two. Same is the case with babies born by NVD who are exposed to mothers birth passage commensal microbiota than with those born in aseptic condition by C/S.

e. Handwash Campaign

The microbiome’s delicate ecologic balance has given rise to the theory that modern hygienic practices (overuse of antibiotics, improved sanitation, too much hand washing, non-touch way of living) have actually weakened aspects of our health by reducing exposure to the bacteria on which we thrived for thousands of years. Kids today don’t play with mud. They just stay inside and text. They are not exposed to anything or anybody. Isolated hunter-gatherer tribes in South America have been shown to have considerably more diverse microbiomes than those from industrialized populations. The same progress that may be hurting us has also given us the means to unravel the reasons potentially to intervene and correct it.

Regards,

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