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Probiotics to prevent gastrointestinal toxicity from cancer therapy: An interpretive review and call to action

Matthew A Ciorba[1], **Christopher L Hallemeier**[2], **William F Stenson**[1], and **Parag J Parikh**[3]

[1]Division of Gastroenterology, Washington University in St. Louis School of Medicine, St Louis, MO

[2]Department of Radiation Oncology, Mayo Clinic, Rochester, MN

[3]Department of Radiation Oncology, Washington University in St. Louis School of Medicine, St Louis, MO

Abstract

Purpose of Review—There is currently an unmet need for agents that can prevent the gastrointestinal toxicity (mucositis, enteritis) associated with chemotherapy and radiation therapy of abdominal and pelvic cancers. Herein we provide an overview of how manipulation of the gut microbiota by probiotic administration affects these gastrointestinal symptoms. We focus this review on published human trials and also provide suggestions on how the field can move forward.

Recent Findings—Several clinical trials of varying design, patient populations and probiotic product have been reported. *Lactobacillus* probiotics of adequate dosage demonstrate a potential to reduce gastrointestinal toxicity when administered prophylactically. Common study limitations prevent the widespread adoption of this practice at this point, but are informative for rational design of future trials.

Summary—No single probiotic strain or product has emerged from human clinical trials for this indication. Further human studies are required to address limitations in the current literature. Preclinical model data should be used to inform the rational design of these new clinical trials to adequately address this important question.

Keywords

microbiota; metabolome; fluorouracil; diarrhea; prebiotic; probiotics

INTRODUCTION

Gastrointestinal (GI) side effects complicate therapy in approximately 50% of patients with an abdominal or pelvic malignancy. Collateral damage to the normal GI epithelium during cytotoxic chemotherapy and radiation therapy leads to acute mucositis (enteritis). The resulting malabsorption and tissue damage can result in acute symptoms of bleeding, pain, diarrhea and malnutrition. These acute toxicities prevent optimal cancer treatment and can

Correspondence: Matthew A Ciorba MD, mciorba[AT]wustl.edu.

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also lead to chronic complications in survivors.[1] There remains an important unmet need for prophylactic agents which can prevent this collateral damage without impacting tumor cytotoxicity and cancer outcomes.

Substantial clinical and preclinical evidence indicate that manipulation of the microbiota can limit damage to the normal GI epithelium in the setting of cytotoxic cancer therapy. Probiotic bacteria prevent GI damage in preclinical models and reduce GI side effects in some human trials.[2–4] Based on these data, experts have opined and society guidelines have suggested that physicians consider recommending probiotics to patients undergoing abdominal or pelvic radiotherapy.[5,6]

Despite the evidence and expert support, probiotic supplementation is not yet universally recommended for these patients. Herein we critically review the evidence supporting probiotics for this condition. Additionally, we make suggestions as to how to fill the gaps in knowledge which currently prevent this practice from being universally accepted by practitioners and adopted by patients.

Mechanisms of mucositis

Epithelial cell dysfunction and death underlie acute mucositis pathophysiology, though a role for endothelial cells has also been identified.[1,7] While the initiating mechanism differs between chemotherapy and radiation, the subsequent steps resulting in mucositis share similarities. The sequence of events involve reactive oxygen species, clonogenic cell death, inflammatory cytokines, epithelial and endothelial apoptosis, ulcer formation, and ultimately healing. Prostaglandin and the NF B signaling pathways play important roles across these phases. It is notable that these signaling pathways both interact intimately with luminal microbiota and their products.[2] Finally, breakdown of mucosal barrier function can lead to bacterial translocation and sepsis with pathogenic bacteria complicating treatment.

Microbiota in pathophysiology of mucositis

The response of the gastrointestinal tissues to injury, including radiation, is influenced by resident intestinal bacteria.[2] Germ-free mice are more resistant to lethal radiation enteritis than conventionally raised mice, in part due to a lack of pathogenic bacteria to breach the compromised epithelial layer and cause fatal sepsis.[8,9] However, certain bacteria and bacterial products are capable of mitigating epithelial cell apoptosis induced by irradiation.[10–12] Furthermore, both chemotherapy and radiation therapy can affect the composition of luminal microbiota. [13,14] These changes have been studied both in humans and in preclinical models and highlighted in recent reviews.[3] In general, cancer therapies appear to be associated with a decrease in *Lactobacillus* and other protective bacterial species and an increase in certain pathogenic bacterial species.

Probiotic bacteria exert many beneficial functions which may be able to counter the underlying pathophysiology of mucositis. For example, they activate cytoprotective pathways in epithelial cells, counteract reactive oxygen species, displace pathogenic bacteria and interact with tight junctions to enhance mucosal integrity.[15,16]

Our group recently demonstrated that the commercially available probiotic *Lactobacillus* rhamnosus GG (LGG) protects the normal intestinal epithelium in a mouse model of radiation injury.[12] A proposed mechanism for this involved TLR2 and migration of Cox2 expressing mesenchymal stem cells. These experiments were conducted with a single dose of 12 Gy irradiation, but might be extrapolated to the epithelial damage associated with cancer therapy. Notably, other single strain bifidobactera probiotics and commercially available multi-strain probiotic preparations (unpublished) were less effective than this single *Lactobacillus* strain. Moreover, among lactobacillus probiotics, LGG offered numerically superior radioprotection verses common L. casei or L. acidophilus stains.

In considering the role of microbiota in mucositis, one should factor into consideration the distinction between the small bowel and colon. The assessment of gut microbiota in most research is based on stool samples from the colon. However, it is small bowel injury rather than colon that accounts for most of the GI symptoms associated with cytotoxic therapy. While the colon is a rich reservoir of diverse microbiota, bacterial counts and diversity in the small intestine are log fold fewer. Thus, relatively small concentrations of probiotic may be able to have a big impact on the small intestinal physiology, while having an almost imperceptible effect on the colon. As demonstration of this principle, administration of LGG protects the murine small intestine from radiation injury, but frequently cannot be recovered from the feces of treated mice even by highly sensitive genomic methods.[12]

HUMAN TRIALS OF PRE- AND PROBIOTICS IN CANCER THERAPY

Several clinical trials of probiotic preparations have been reported. All of these studies were conducted outside of the US, most were small, and in some the primary endpoints were not clearly defined at study outset.[17–21] The trials use both single and multi-strain probiotic bacteria and used various outcome measurements. While some studies showed positive trends towards efficacy, no single study has been convincing enough to change practice.

Though the quality of reporting in these studies is variable, several concepts emerge as contributory limitations. We believe that preclinical data and these studies should serve as a guide for a new rationally designed trials that would be able to overcome limitations and definitively determine the efficacy of this approach. If appropriately executed, the results would be practice changing for this important clinical problem. Hereafter, we summarize these studies, highlight the likely limitations and discuss relevant concepts to consider for moving forward.

Prevention of chemotherapy enteritis

Osterlund et al conducted a prospective open-labeled randomized trial in Sweden investigating the use of probiotics in the *prevention* of chemotherapy-related diarrhea.[22] 150 patients with colorectal cancer receiving postoperative 5FU-based chemotherapy were randomized in a 2:1 ratio to receive either probiotic supplementation with *L. rhamnosus* GG 1×10^{10} (ATCC 53103, Gefilus®, Valio Ltd, Helsinki, Finland) twice daily for 24 weeks during adjuvant treatment or nothing. Of note, 26% of patients also received concurrent pelvic RT. The primary endpoint of NCIC CTCAE version 2 grade 3 or 4 diarrhea occurred in 22% versus 37% of those receiving probiotic versus no probiotic, respectively ($p = 0.027$).

Hospitalization due to bowel toxicity occurred in 8% versus 22% of those who received probiotic versus no probiotic, respectively (p=0.021). Chemotherapy dose reduction due to bowel toxicity was required in 21% versus 47% of those who received probiotic versus no probiotic, respectively (p = 0.0008). Compliance and safety were excellent, with all patients completing scheduled treatment of the probiotic. A major limitation of this study was the lack of blinding and placebo control.

Prevention of radiation enteritis

Salminen et al conducted a small prospective randomized pilot study in Sweden.[17] 24 patients undergoing pelvic RT for gynecologic malignancies were randomized to receive dietary counseling and fermented milk containing at least 2×10^9 of live *L. acidophilus* bacteria daily versus dietary counseling only. The probiotic was started five days prior to RT and stopped ten days after completing RT. Patients who received the probiotic had significant reductions in the incidence of diarrhea and usage of anti-diarrheal agents but experienced greater flatulence. The overall details of this study's results were limited.

Delia et al conducted a large prospective, double-blinded, placebo-controlled randomized trial at a single institution in Italy investigating the role of probiotics in the prevention of RT-induced acute diarrhea. This trial was published twice.[18,19] 490 patients undergoing postoperative RT for colorectal or cervical cancer were randomized to sachets containing VSL#3® or placebo three times per day during RT. The VSL#3® sachet contained 4.5×10^{11}/gram of viable lyophilized bacteria including four strains of *Lactobacilli*, three strains of *Bifidobacteria*, and one strain of *Streptococcus*. Significant improvements were noted in diarrhea, WHO grade 3 or 4 diarrhea, daily bowel movement count and time to loperamide use. It was reported that 99.1% of patients in the probiotic group completed therapy. Despite the robust number of patients reported in this trial, the overall methodology and results are very sparse in detail limiting the reader's ability to assess the data quality for application to their own patient population. This is especially important as some of the reported measures were confusing. For example, Grade 3 or 4 diarrhea was reported to occur in a higher number of patients then those reported as having any diarrhea. Additionally, the time to loperamide use was less than four days in the placebo group, though in typical practice patients tend to develop diarrhea symptoms only in the late second or third week of therapy. Furthermore, it is not clear whether any patients received concurrent chemotherapy with RT.

Giralt et al conducted a multicenter, prospective randomized, placebo-controlled trial in Spain.[20] 85 patients undergoing pelvic RT with or without chemotherapy for cervical or endometrial cancer were randomized to a liquid yogurt containing 10^8 CFU/g of *L. casei* or placebo three times per day starting one week prior to RT. There was no significant difference between the two groups in the composite primary endpoint of NCI CTCAE version 2 diarrhea or need for loperamide (p = 0.6). It has been postulated that the negative results of this trial may have been due to the specific probiotics formula used, the yogurt carrier and/or the relatively small dose of probiotics administered.[23]

Chitipanarux et al conducted a prospective, double-blinded, placebo-controlled randomized trial in Thailand.[21] 63 patients with cervical cancer undergoing pelvic RT and weekly cisplatin were randomized to 2 capsules of Infloran (Laboratio Farmaceutico SIT, Mede,

Italy) containing a total of 2×10^9 units each of *L. acidophilus* and *B. bifidum*, or placebo twice per day during RT.[21] Stool samples were collected weekly and the stool consistency was objectively determined by a laboratory technician. The primary endpoint of NCI-CTCAE version 2.0 grade 2 or 3 diarrhea was observed in 45% versus 9% of patients who received placebo versus the probiotics, respectively ($p = 0.002$). Need for anti-diarrheal medication was seen in 32% versus 9% of patients who received placebo versus probiotics, respectively ($p = 0.03$). At weekly assessment, the prevalence of liquid stool was 65% versus 19% in patients who received placebo versus the probiotics, respectively ($p < 0.001$).

Most recently, Demers and colleagues from Canada reported a randomized double-blind control trial of 229 patients receiving probiotics as prophylaxis during pelvic radiation. The probiotic used was the commercially available combination probiotic product Bifilact (*L.* acidophilus-361 and *B.* longum). Three groups were compared, placebo, standard-dose (1.3 billion CFU; 1 billion *Bifido*, 0.3 billion *lacto*) and high dose (10 billion CFU) both taken twice daily. Therapy was started on the first day of radiation and the primary endpoint was the ability to prevent or delay moderate to severe diarrhea. While the study did not meet its primary endpoint, some significant differences were noted on subgroup and secondary analysis. Moderate to severe diarrhea was significantly lower at day 60 in the standard-dose, but not high dose group compared to placebo. The standard dose was also associated with a reduction in grade 4 diarrhea in patients who had surgery before radiation.

Though this was a large placebo controlled trial, several limitations exist. The justification for using the Bifilact probiotic product is not made clear and does not appear to be supported by efficacy in preclinical models. Notably this product favored *bifidobacteria* over *lactobacillus* by 4:1 ratio. Whether these organisms would work in synergy or compete against each other in the small bowel is not known. The study also enrolled a heterogeneous population with a mixture of cancers including prostate, endometrial, cervical, rectal and other cancers. This inclusion criteria is likely to confound results and interpretation at these cancers have distinct therapeutic approaches including timing and type of chemotherapy, radiation therapy, and surgery. For example, in this study 50% of patients received concurrent chemotherapy and one third had undergone surgery prior to therapy. They also have different rates of small bowel radiation. Beyond that, the details are not provided but it may be difficult to identify differences in toxicity profiles in such a mixed population.

Treatment of radiation enteritis

Urbancsek et al conducted a prospective, double-blinded, placebo-controlled randomized trial in Hungary investigating the use of probiotics as a rescue *treatment* of acute RT enteritis.[24] 206 patients with mild to moderate diarrhea within 4 weeks of completion of RT to the pelvis were randomized to sachets of placebo or a probiotic containing *L. rhamnosus* 1.5×10^9 CFU (Antibiophilus®, Germania Pharmazeutika GmbH, Vienna, Australia) given three times per day. Treatment was continued for up to one week. The primary endpoint of need for rescue medication for diarrhea was observed in 48% versus 35% in those receiving placebo versus probiotic, respectively ($p = 0.064$). Additional endpoints including number of bowel movements per day and the not-validated end point of

investigator assessed “fecal consistency rating” trended positively toward the probiotic group.

Clinical Safety of Probiotics in Proposed Patient Population

All of the studies described reported that the probiotic preparations are well-tolerated and that no safety signal was identified. In particular, no cases of bacteremia have been reported in cancer patients receiving probiotics during therapy. While this is encouraging, the level of reporting on some of these studies leave doubt as to how well probiotic related adverse events may have been tracked. Finally, it would be advantageous to eventually harness the power of probiotics by extracting and administering the active cytoprotective components or metabolic products rather than the live bug.[10,12]

SUMMARY AND SUGGESTIONS FOR FUTURE STUDIES

Existing preclinical and clinical data support the possibility that certain probiotic strains might serve as a safe and effective prophylactic therapy to limit radiation and chemotherapy induced mucositis. In light of our findings in preclinical models,[12] our group has interest in translating our findings to human disease. Hereafter, we offer an interpretation of the current literature and provide perspective on how this information can be contextually integrated into further studies poised to move this strategy from plausible to practice changing.

Probiotic selection

It is clear that not all probiotics are equivalent and that species effective in one disorder may be ineffective in another.[16] In cytotoxic therapy associated mucositis, both clinical and preclinical studies support efficacy for *Lactobacillus* probiotics. *Bifidobacteria* have not been tested in isolation, but products containing predominantly *bifidobacteria* have not met endpoints in human trials.[25] In a preclinical study, a common *bifidobacteria* probiotic was not radioprotective.[12] It remains unclear as to whether adding *bifidobacteria* to an adequately dosed *Lactobacillus* containing probiotic offers therapeutic synergy or antagonism.[16] From a safety monitoring standpoint, there are clear advantages to single strain products. In our opinion, *Lactobacillus* rhamnosus GG is an attractive target probiotic for next stage studies for several reasons. It has wide commercial availability, a proven safety record, superior efficacy in preclinical models and reasonable support in human studies. With regard to dosing of *Lactobacillus* probiotics, 1×10^9 to 2×10^{10} CFU appears to be a target range, and more is not necessarily better.[12,25]

Probiotic delivery and dosage

A pill appears to be adequate and preferred. In one study where the probiotic was administered in a yogurt format, it was interpreted as detrimental due to potentially causing flatulence.[17] However, it may be that a synbiotic (probiotic plus a prebiotic substance which fosters the growth of the probiotic) approach is also reasonable. For example, a synbiotic preparation containing *L*. reuteri and soluble fiber was reported to reduce proctitis symptoms and improve the quality of life in a small cohort of prostate cancer patients.[26]

Notably, therapy for prostate cancer typically does not typically lead to small bowel mucositis and thus this may be a different mechanism.

Regulatory and funding logistics

Issues of support and regulation can complicate the development and initiation of a probiotic clinical trial. Probiotics fall under the category of dietary supplements, and thus are not normally regulated by the Food and Drug Administration (FDA) in the United States. However, if a study plans to examine whether a probiotic can prevent or treat a disease, then the FDA requires successful completion of an investigational new drug (IND) application. This can be a long and arduous process and typically requires collaborative input from the probiotic producer as well as the investigator independently testing the product for identity, purity, and potency. These approvals must be in hand before the investigator team can work to get approval from the institutional review board (IRB). We have crossed these hurdles for LGG.

Funding of probiotic trials can be challenging. The companies that market and produce probiotics are not traditional pharmaceutical companies and are not necessarily interested in having their product approved for a specific medical indication as this would draw closer oversight from regulatory agencies. These companies also may not have the resources to sponsor well-conducted clinical trials even if they did want to seek a clinical indication. While federal funding for clinical trials in probiotics exist, is still highly competitive.

Study design considerations

An appropriately powered, double-blind placebo-controlled trial will be necessary to change practice. A preventative approach rather than treatment-based approach for probiotic administration is recommended.[4,12] Focus the trial on an individual or specific set of abdominal or pelvic malignancies is recommended so that heterogeneity of the cancer regimen does not conceal the potential effect of the probiotic. Appropriate endpoints should include a standard symptomatic assessment of mucositis/enteritis like the common toxicity criteria for adverse events (CTCAE). However, additional assessment tools measuring patient-reported symptom assessment and quality of life should be included. Secondary endpoints should also include surrogate biomarkers such as serum citrulline and fecal calprotectin even if limitations exist for each of these.[2,27] Moreover, such a study would provide an excellent opportunity for further assessment of novel biomarkers and the impact of shifts in microbiota or metabolomic profiles. Finally, safety must be closely monitored during the study and long-term follow-up on delayed GI consequences of cancer therapy should be incorporated.[1]

CONCLUSION

The role for microbiota in protecting against cytotoxic cancer therapy associated mucositis is robust in principle. Clinical studies and preclinical models suggest that *Lactobacillus* containing probiotics of an adequate dosage may reduce symptoms of acute mucositis. Further studies are needed to delineate the specific probiotic and patient population which will benefit from this intervention. Additional investigations into the mechanisms that

mediate this protection will also give a leg up on interpreting current studies and designing future trials.

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Key Points

- The role for microbiota in protecting against cytotoxic cancer therapy associated mucositis is robust in principle.
- Clinical studies and preclinical models suggest that *Lactobacillus* containing probiotics of an adequate dosage may reduce symptoms of acute mucositis.
- Further studies are needed to delineate the most effective probiotic (or probiotic product) and patient population that will benefit from this intervention. These should be rationally guided by existing human trial and preclinical data.
- Additional investigations into the mechanisms that mediate this protection will also give a leg up on interpreting current studies and designing future trials.