Microbiome and Abdominopelvic Radiotherapy Related Chronic Enteritis: A Microbiome-based Mechanistic Role of Probiotics and Antibiotics

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Abstract: Chronic diarrhea and abdominal pain after radiotherapy continue to be a problem in cancer survivors. Gut microbiomes are essential for preventing intestinal inflammation, maintaining intestinal integrity, maintaining enterohepatic circulation, regulating bile acid metabolism, and absorption of nutrients, including fat-soluble vitamins. Gut microbiome dysbiosis is expected to cause inflammation, bile acid malabsorption, malnutrition, and associated symptoms. Post-radiotherapy, Firmicutes and Bacteroidetes phylum are significantly decreased while Fusobacteria and other unclassified bacteria are increased. Available evidence suggests harmful bacteria Veillonella, Erysipelotrichaceae, and Ruminococcus are sensitive to Metronidazole or Ciprofloxacin. Beneficial bacteria lactobacillus and Bifidobacterium are relatively resistant to metronidazole. We hypothesize and provide an evidence-based review that short-course targeted antibiotics followed by specific probiotics may lead to alleviation of radiation enteritis.

Key Words: microbiome, radiation enteritis, antibiotic, probiotic, abdominopelvic radiotherapy

(*Am J Clin Oncol* 2024;47:246–252)

Cancer is the second leading cause of death worldwide (https://www.who.int/health-topics/cancer). Compared with 30 years ago, cancer survival has improved due to multimodality treatment. Notwithstanding improved survival, 20% to 25% of survivors suffer from decreased quality of life due to persisting treatment-related side effects.[1] Patients who receive radiotherapy (RT) form a large cohort of such sufferers. RT is important in managing various pelvic malignancies, including gastrointestinal, gynecologic, and urological cancers. About 20% of patients diagnosed with pelvic malignancy receive RT. Up to 90% of such patients receiving RT develop acute gastrointestinal (GI) symptoms, which often settle after completion of treatment, but ~25% of patients experience chronic GI disturbances reducing the quality of life.[2] Radiation enteritis is mainly characterized by diarrhea with abdominal cramps. In rare instances, it also leads to intestinal fistula, hemorrhage, and obstruction. PORTEC-2 study established that patients receiving pelvic radiation were more likely to experience diarrhea that affected their quality of life, requiring that they remain close to a toilet, resulting in a lower level of social functioning.[3] Results of the PARCER trial also suggest that >20% of patients treated with intensity-modulated radiation therapy continue to have >grade 2 late GI toxicity at 3 years.[4] Despite advances in technology through which radiation oncologists have been able to reduce the physical dose received by the gut, chronic bowel symptoms, that is, diarrhea and abdominal pain after RT, continue to be a problem in many cancer survivors.

No standard guidelines are available regarding preventing or managing these symptoms in patients receiving pelvic RT. The ORBIT trial suggested that an algorithm-based management and targeted intervention rather than treatment as per physician choice significantly improve symptoms post pelvic RT.[5] The algorithm included evaluation for bacterial overgrowth, bile acid, and carbohydrate malabsorption. Targeted interventions based on results were made. Broadly postulated etiology of radiation-induced diarrhea (RID) includes bile acid malabsorption (BAM), small intestinal bacterial overgrowth (SIBO), persisting inflammation, intestinal dysmotility, and decreased intestinal integrity. Which of these factors contribute more to the bowel symptoms is unknown. In a study by Danielsson et al, BAM was diagnosed in 65% of patients with diarrhea after pelvic RT.[6] Interestingly, no direct relation between the severity of diarrhea and the degree of BAM was identified, and not all patients responded to bile acid sequestrants, antibiotics, or both.[6] Preclinical data show that germ-free mice are more resistant to lethal radiation injury with reduced RT-induced epithelial damage than conventional mice with commensal gut microbial flora.[7] Recently, research has focused on variations in gut microbiome with RT and its correlation with the incidence of bowel symptoms. Publications with small patient numbers have shown that fecal microbial transfer (FMT) may effectively improve symptoms.[8,9] FMT involves the administration of a minimally manipulated microbial community from the stool of a healthy donor into the patient's intestinal tract. The process of FMT acknowledges the high degree of complexity and functionality of natural microbiota that is difficult to reproduce at this stage of microbiome science. Clinically, FMT is performed with the intent of restoring normal function of the gut microbiota. Issues with FMT in radiation enteritis include high relapse rates, invasive procedures for microbial transfer, and availability.[8]

Research using antibiotics in rats has shown to improve radiation-induced intestinal injury by remodeling microbiota, reducing inflammation, and inhibiting fibrosis.[10] In humans, antibiotics have been shown to reduce alpha and beta diversity

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ISSN: 0277-3732/24/4705-0246
DOI: 10.1097/COC.0000000000001082

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in the gut.[11] In this narrative review, we intend to discuss the role of the gut microbiome in health and disease and changes in the gut microbiome with RT and attempt to provide a mechanistic role of using antibiotics and probiotics in sequence in improving bowel symptoms.

NORMAL GUT MICROBIOTA

The normal gut microbiota consists primarily of bacteria, along with viruses and a few fungi. The density of bacterial cells in the colon is estimated as 10^{11} to 10^{12} per milliliter, which makes the colon one of the most densely populated microbial habitats known on Earth.[12] The gut microbiota can be identified and quantified by 16S rRNA sequencing (PCR) of nucleic acids directly extracted from stools. Normal gut microbiota plays roles in extracting, synthesizing, and absorbing many nutrients and metabolites, including bile acids, lipids, amino acids, vitamins, and short-chain fatty acids (SCFAs), modulating inflammation in the gut and immune function against pathogenic bacteria colonization. It is important to note that there is a complex interplay between gut cells and microbes and also symbiosis and competition among the gut microbes.[13]

NORMAL COMPOSITION OF GUT MICROBIOME AND FUNCTIONALITY

The dominant phyla in the normal gut include Firmicutes (Bacillota), Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria. Firmicutes and Bacteroidetes constitute close to 90% of gut microbiota. Firmicutes include genera like Ruminococcus, Lactobacillus, Bacillus, Clostridium, and Enterococcus, of which Clostridium constitutes 95% of firmicutes bacteria. In Bacteroidetes, the predominant genera in the gut include Bacteroides and Prevotella, while in Actinobacteria, it is Bifidobacterium.[12]

BILE ACID METABOLISM AND ENTEROHEPATIC CYCLING

Bile acids (BA) are synthesized in the liver from cholesterol through a series of enzymatic reactions. The primary bile acids (PBA) produced are cholic acid (CA) and chenodeoxycholic acid, which undergo conjugation with the amino acids glycine or taurine, forming glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid. Conjugated bile acids (CBA) are transported into the bile ducts, stored in the gallbladder, and, upon food ingestion are released into the small intestine. CBA emulsifies fat globules, breaks them into smaller droplets, and increases the surface area. This helps in lipid digestion by pancreatic enzymes. CBA also forms mixed micelles with fatty acids, cholesterol, and fat-soluble vitamins for absorption. Ninety-five percent of bile acids are absorbed in the ileum. Bacterial enzymes deconjugate and dehydroxylate PBA, converting them into secondary bile acids (SBA) - deoxycholic acid (DCA) and lithocholic acid. SBA and any unconjugated PBA are partly reabsorbed in the distal ileum through active transporters and transported back to the liver through portal circulation. They are taken up by hepatocytes and secreted into bile, completing the enterohepatic circulation. This cycling of BAs between the liver and intestine occurs multiple times during a meal, allowing for the efficient reutilization of bile acids. Primary CBA that escapes metabolism in the distal small bowel is metabolized by gut microbiota in the colon and excreted in feces.[14]

ROLES OF GUT MICROBIOTA

Effect on Cholesterol and Bile Acid Metabolism

Cholesterol oxidation is part of a process leading to coprostanol formation and increased cholesterol excretion. Cholesterol oxidase encoding genes are found in the phylum Bacteroidetes, Proteobacteria, and Actinobacteria but are absent in one of the dominant phyla, that is, Firmicutes.[15]

Cholesterol reduction leads to the direct production of coprostanol. Specific enzymes needed are found in Bacteroides and Eubacterium belonging to phyla Firmicutes.[16] Bile salt hydrolase does deconjugation of PBA in the large intestine, and the enzyme is present in genera *Bacteroides, Clostridium, Lactobacillus, and Bifidobacterium* (more diverse in the phylum Firmicutes). It acts as a bile acid detoxification mechanism for bacteria. The pelvic RT-induced killing of these useful bacteria may lead to an increase in the concentration of conjugated PBAs, causing the killing of both useful and harmful gut bacteria and diarrhea.[17]

7-Dehydroxylation of bile acids, that is, conversion of PBAs to SBAs, is demonstrated by limited bacteria like *Eubacterium, Clostridium scindens, and Clostridium hylemonae* The biological implications of SBA, that is, DCA and lithocholic acid include inhibition of growth of certain pathogenic bacteria while promoting the growth of beneficial bacteria. It also helps maintain the intestinal barrier function; interestingly, though, DCA is also pro-inflammatory and may lead to colonic inflammation.[18]

Oxidation-reduction of BAs by hydroxysteroid dehydrogenase is present in all 4 major phyla, that is, Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes.[19]

Epimerization of BAs is done by Clostridium, Collinsella, Ruminococcus, or Eubacterium.[20]

Short-chain Fatty Acid (SCFA) Production

SCFA production, that is, mainly Butyrate, is produced by Roseburia inulinivorans (under Lachnospiraceae), Faecalibacterium Prausnitzii, Clostridium and Lactobacillus species. Butyrate is the major source of nutrition for colonic epithelial cells. Butyrate causes a shift from glycolysis to fatty acid metabolism and decreases levels of inflammatory markers.[21]

Intestinal Epithelial Barrier Function

Several *Peptostreptococcus* species produce a tryptophan metabolite indole acrylic acid that promotes intestinal epithelial barrier function and mitigates inflammatory responses. Roseburia intestinalis also performs the same functions.[22]

In short, certain types of the gut microbiome are essential for preventing intestinal inflammation, maintaining intestinal integrity, maintaining enterohepatic circulation, regulating BA metabolism, and absorption of nutrients, including fat-soluble vitamins. Hence, gut microbiome dysbiosis is expected to cause inflammation, BA malabsorption, malnutrition, and associated symptoms.

VARIATIONS IN GUT MICROBIOTA IN HEALTH AND CANCER

Variation with Anatomical Regions

The small intestine provides a challenging environment for microbes due to short transit times and high bile concentrations. It predominantly contains Lactobacillus and Enterobacteriaceae, including E. coli.[23] The large intestine harbors the largest microbial community dominated by obligate anaerobic bacteria, including Bacteroides, Prevotella, Lachnospira, and Ruminococcus.[23]

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Variation as per Cancer Subtype

Genomic analyses have identified that gut microbiota is different in different cancers. The gut of patients with colorectal cancer is enriched in Fusobacterium, whereas the Bacteroidetes and Firmicutes phyla are depleted.[24,25] An increase in opportunistic pathogens like Bacteroides fragilis, Enterococcus, Escherichia, Shigella, Klebsiella, Streptococcus, and Peptostreptococcus is also seen. Erysipelotrichaceae belonging to Firmicutes phylum is also increased in colorectal cancer.[24,25] In cervical cancer patients, Ruminococcus decreases with increasing stages of the disease.[26]

Variations with Pelvic RT

On the one hand, the pre-RT composition of intestinal bacteria determines the incidence of post-RT diarrhea. In contrast, the composition of intestinal bacteria changes significantly during and post-RT, which also correlates with the incidence of diarrhea.[27] Though some discordance is found between studies regarding bacterial order/genus analyses, overall, beneficial bacteria are decreased after pelvic RT, and patients with diarrhea have less beneficial gut bacteria before RT than those without diarrhea. Overall, post-RT Firmicutes and Bacteroidetes phylum are significantly decreased while Fusobacteria and other unclassified bacteria are increased. At the general level, pelvic RT preferentially kills Faecalibacterium, Peptostreptococcus, Lactobacillus, and Roseburia.[27] Tables 1, 2, and 3 summarize data regarding changes in gut microbiome with RT, its functional role in the gut, sensitivity to antibiotics, and availability of probiotics. Available evidence suggests that potentially harmful bacteria like Veillonella, Erysipelotrichaceae, and Ruminococcus are sensitive to metronidazole or ciprofloxacin.[32,41] Some beneficial bacteria, like Lactobacillus and Bifidobacterium, are relatively resistant to metronidazole. Interestingly, some beneficial bacteria like Roseburia and Clostridium are also sensitive to metronidazole.[41] We may, therefore, hypothesize that short-course targeted antibiotics to reduce harmful organisms followed by specific probiotics containing beneficial bacteria may improve gut dysbiosis and metabolome, leading to alleviation of symptoms of radiation enteritis. Literature search shows that this approach has not been systematically evaluated in large trials. In the following section, available evidence supporting this approach, its pitfalls, and low-cost trial designs for the future are discussed.

CLINICAL EVIDENCE FOR THE USE OF ANTIBIOTICS FOR BOWEL SYMPTOMS POSTRADIOTHERAPY

In a small randomized controlled trial by Cavic et al, 60 patients with rectal bleeding and diarrhea after RT were randomized to oral metronidazole, oral mesalamine and steroid enema versus only oral mesalamine and steroid enema. Patients who received metronidazole had significantly better diarrhea control at 6 and 12 months.[51] Interestingly, in a recent preclinical study on mice, metronidazole treatment improved the reconstitution ability of the gut microbiota. Further experiments showed that antibiotic treatment effectively reduced the content of lipopolysaccharide and inhibited the toll-like receptor family (TLR)4/MyD88/NF-κB signaling pathway in the ileum. TLR4 is an important component of TLR. It mediates the high reactivity of intestinal epithelial cells and activates NF-κB. These cause effector cells to secrete cytokines such as tumor necrosis factor-α and play an important role in inflammatory response. In addition, antibiotics also caused macrophage cell polarization regulation in the ileum along with downregulation of TGF-β1 and phosphorylation of Smad-3 and α-SMA protein levels. Antibiotics significantly improved mice survival rate and attenuated intestinal injury after radiation by reducing inflammation and preventing intestinal fibrosis.[10] Further, Hyperbaric oxygen treatment (HBOT) has recently been shown to increase partial pressures of Oxygen in the gut lumen, turning the anaerobic gut lumen into mildly aerobic region with the resultant modification in the composition of commensal anaerobic bacteria. An analysis of the bacterial community showed that obligately anaerobic Firmicute was detected in fewer samples after HBOT, consistent with selective loss of an oxygen-intolerant lineage. This change was temporary and moderate.[52] HBOT has also been shown to reduce radiation-related diarrhea and pain.[53] The above findings provide indirect and some direct evidence that antibiotics may be a low-cost and reliable approach to improve radiation enteritis.

CLINICAL EVIDENCE FOR THE USE OF PROBIOTICS

A meta-analysis of 8 trials involving 1116 patients concluded that prophylactic probiotic use along with RT might modestly improve acute RID.[54] Compared with placebo, probiotics were associated with a lower risk of RID (risk ratio [RR] = 0.62, 95% CI = 0.46, 0.83). Interestingly, no statistically significant reduction in RID (RR = 0.52, 95% CI = 0.14, 1.91) was observed in subgroup analysis in patients receiving both RT and chemotherapy. However, those patients receiving only RT demonstrated significant benefit (RR = 0.61, 95% CI = 0.48, 0.78). There was also a significant difference in the antidiarrheal medication use with the use of probiotics. The reason for the modest benefit is most likely multifactorial. The preferential killing of Lactobacillus and Bifidobacterium by RT while supplementation is going on may be an added factor for only modest benefit. Based on the above findings and evidence, we may hypothesize that using probiotics after a short course of targetted antibiotics in chronic radiation enteritis may lead to more beneficial effects.

ISSUES WITH THIS APPROACH

The symptomatic relief may be temporary for a few weeks to months as intestinal dysmotility that occurs due to RT may lead to recurrent dysbiosis and, therefore, recurrent diarrhea and pain.[55] On recurrence, a repeated course of antibiotics may lead, in rare cases, to difficile-related diarrhea, though this is unlikely as clostridium is itself sensitive to metronidazole (Table 1). All beneficial organisms are not yet available commercially as probiotics (Tables 1, 2 and 3). Metronidazole sensitivity for a few organisms like Faecalibacterium is not available (Table 2). Also, as mentioned earlier, the spectrum of symptomatology post-RT, may be due to BAM, SIBO, persisting inflammation, intestinal dysmotility, and decreased intestinal integrity. Though a significant percentage of patients are expected to benefit from the approach, failures are also expected.

Future Directions for Chronic Radiation Enteritis Management Research

Identifying molecular effectors of intestinal dysmotility post-RT is necessary to stimulate drug research in this area. Variations in microbiome occur depending on dietary patterns as well as cancer subtype. Further, as previously elaborated, RID may be due to other added factors like BAM, SIBO, persisting inflammation, intestinal dysmotility, and decreased intestinal integrity. Therefore, any clinical trial that would

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TABLE 1. Gut Microbiome Showing Increase With Radiotherapy, Their Antibiotic Sensitivity and Availability of Probiotics

Genera	Phylum	Functional role in gut	Beneficial or harmful	Sensitivity to Metronidazole/ other antibiotics	Probiotic availability
Lachnospira[28]	Firmicutes	1. Butyrate production 2. Improved fat metabolism 3. Anti-inflammatory[28]	Beneficial	Clinical data shows sensitivity to Vancomycin and Imipenem. No resistance gene to Metronidazole was detected. Expected to be sensitive[29]	Not commercially available. Low animal fat intake may improve numbers in the gut[30]
Veillonella[31]	Firmicutes	1. Induces inflammation in the gut with the promotion of inflammatory cytokines and releases LPS. 2. Impairs tight junction function in colonic epithelial cells. 3. May induce intestinal dysmotility[31]	More harmful than beneficial	Sensitive to Metronidazole. Resistant to penicillin in up to 65% of cases[32]	
Erysipelotrichaceae[33]	Firmicutes	1. Increases inflammation in the gut. 2. May affect lipid metabolism[33]	More harmful than beneficial	Sensitive to Ciprofloxacin. Resistant to Vancomycin. No data on sensitivity to Metronidazole[34]	
Ruminococcus[35]	Firmicutes	1. Polysaccharide breakdown. 2. BA metabolism. 3. Pro and anti-inflammatory effects[35]	Unclear. May be strain-specific. Levels raised in inflammatory bowel disease	Sensitive to Metronidazole[36]	
Phascolarctobacterium[37]	Firmicutes	Acetate and Propionate production alleviates the mood of the host[37]	Beneficial	Resistance to Penicillin identified. No data on sensitivity to Metronidazole[36]	Not commercially available
Clostridium[38]	Firmicutes	BA deconjugation and conversion of primary BAs to secondary BAs, butyrate production; attenuate inflammation[38]	Beneficial with some pathogenic species as well-Clostridium difficile, Clostridium perfringens	Sensitive to Metronidazole and Vancomycin	Not available. Safety concerns are present. Toxin genes should be excluded to avoid vertical and horizontal transmission of virulence factors. Antibiotic resistance genes should also be assessed before probiotic creation.[39]

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TABLE 2. Gut Microbiome Showing Decrease With Radiotherapy, Their Antibiotic Sensitivity, and Availability of Probiotics

Genera	Phylum	Functional role in gut	Beneficial or harmful	Sensitivity to Metronidazole/ other Antibiotics	Probiotic availability
Lactobacilli[40]	Firmicutes	BA deconjugation and Butyrate production. Production of antimicrobials-Hydrogen peroxide, bacteriocins. Intestinal barrier maintenance[40]	Beneficial	Resistant to Metronidazole[41]	Available: L. lactis, L. acidophilus, L. casei, L. rhamnosus, L. plantarum, L. reuteri
Bifidobacterium[42]	Actinobacteria	BA deconjugation and Polysaccharide breakdown. Intestinal epithelial barrier maintenance[42]	Beneficial	Resistant to metronidazole[41]	Available; B. actiregularis, B. lactis, B. bifidum
Faecalibacterium[43]	Firmicutes	Beta-mannan metabolism and Butyrate production.[43]	Beneficial	No data	No
Peptococcus[44]	Firmicutes	Butyrate production[44]	More harmful than beneficial	Sensitive	No
Peptostreptococcus[45]	Firmicutes	Intestinal epithelial barrier maintenance[45]	Beneficial	Sensitive[46]	No

TABLE 3. Gut Microbiome Showing Both Increase and Decrease With Radiotherapy, Their Antibiotic Sensitivity, and Availability of Probiotics

Genera	Phylum	Functional role in gut	Beneficial or harmful	Sensitivity to metronidazole/other antibiotics	Probiotic availability	Studies showing increase	Studies showing decrease
Roseburia[47]	Firmicutes	Butyrate production- main role: 1. Butyrate maintains pro- and anti-inflammatory balance. 2. Inhibits IL 17 production in the gut 3. Intestinal epithelial barrier maintenance[47]	Beneficial	No data on metronidazole	Not available commercially. A comprehensive safety assessment is done. Found not to be cytotoxic and has no safety concerns in vivo[48]	Reis Ferreira M et al[49] (Larger data)	Zhao et al[50]

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evaluate the role of antibiotics and probiotics in radiation enteritis should include 16sRNA sequencing to identify if there is development of dysbiosis with RT and randomize patients after dysbiosis is established. A preliminary study on the type of dysbiosis after RT should be performed in different populations. This may be followed by a placebo-controlled randomized controlled trial of metronidazole followed by probiotics for improvement of radiation enteritis.

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