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# Nutrition and the Gut Microbiome: General Recommendations for the Microbiota Enrichment Program Website

Karen Riggs

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# General Recommendations for the Microbiota Enrichment Program website

by

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**Introduction**

The gut microbiome represents trillions of microbes found in the gastrointestinal (GI) tract and has been the subject of much research and exploration, especially over the last 10 years. Researchers around the world seek to define a healthy microbiome and to determine the impact these bacteria have on long-term health and disease. In 2008, the National Institutes of Health Common Fund Human Microbiome Project helped identify the microorganisms associated with the human body. This project has since expanded to the Integrative Human Microbiome Project which furthers the research to determine the microbiota's role in health and disease. Research thus far has credited the gut microbiome with a wide range of important functions such as maintaining the epithelial structure of our GI system, supporting our immune system, facilitating the absorption of needed nutrients, and many others.[1-7] The exact balance of the bacteria of "good vs. bad" bacteria has not been determined definitively. However, many lifestyle factors including antibiotic use and diet have been shown to disrupt the balance and provide a pathway for the growth of aggressive pathogens such as *Clostridium difficile* (*c. diff*).

Under the direction of Dr. Colleen Kraft, physicians and researchers with Emory University's Microbiota Enrichment Project (MEP) currently use Fecal Microbiota Transplant (FMT) as a microbiome restorative technique and treatment for patients with *Clostridium difficile* Infection (CDI). As an alternative to repetitive antibiotic use, FMT has been shown as an effective treatment, ending recurring CDI. However, not all of Dr. Kraft's patients with debilitating GI symptoms qualify for FMT. The MEP would like to create online content with a nutrition component as it influences the gut microbiome and bacterial diversity and balance. This literature review seeks to explore current research and information available which connect gut microbiome with diet and nutrition. The ultimate goal of this capstone project is to create nutrition education materials for MEP, so that participants and those interested in maintaining a "healthy gut" have evidence-based information available.

**Definition of the gut microbiome**

Some refer to the gut microbiome as an organ and a bacterial ecosystem as it contains the highest density of microbes of anywhere on the human body.[1,8] The majority of these microbes are found in the large intestine[1,9] and include over 400 different types of bacteria which synthesize vitamins and essential amino acids, as well as ferment sugar alcohols, fiber, and resistant starch to create short chain fatty acids (SCFA) such as butyrate, propionate and acetate.[1.] These SCFA in turn provide needed energy for the epithelial cells of the GI tract and help maintain a strong mucosal barrier.[1,5]

Although the exact composition of a healthy microbiome has yet to be defined, determining the ideal function of the microbiome within an individual plays an important role in a patient's resiliency to stress and immune function.[8.] Multiple researchers report that the most common bacteria in the gut consist of four main phyla: *Firmicutes, Bacteroidetes, Actinobacteria,* and *Proteobacteria.*[2,8-10] with *Firmicutes and Bacteroidetes*[1] being the most prevalent. However, according to the Human Microbiome Project, the composition of those bacteria within the gut vary widely between individuals.[2]

Multiple lifestyle factors influence the bacterial flora including age and health status, diet, alcohol intake, antibiotic use, transit time through the GI tract, mode of birth (vaginal vs. cesarean section), stress, genetic and environmental factors such as geography.[2,8,11.] These factors – especially antibiotic use[8,12] and age[12] - matter because dominant bacteria and the bacterial diversity affect the strength of the gut mucosal barrier and determine whether or not pathogenic bacteria such as *Clostridium difficile* thrive.[2] Gram positive bacteria such as *Bifidobacteria*[2] protect intestinal epithelial cells as they form a barrier to protect the tight junctions between the cells and the mucosal immune system from the microbial community inside the lumen.[3.] Infants tend to have a greater proportion of *Bifidobacteria* and young adults have a greater proportion of *Bacteroidetes* and *Firmicutes*.[2.] Individuals who have taken antibiotics and those who are older show less microbial diversity and a different proportion of bacteria: increased *Proteobacteria* and decreased *Firmicutes* and *Bacteroidetes*.[12] This dysbiosis has been suggested to be part of the reason *c. diff* bacteria can grow, although this cannot be used as a diagnostic tool yet for those at risk for CDI.

Dysbiosis has also been linked with many other diseases including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease and slow transit constipation.[8,13.] Alteration of the microbiome has also been associated with obesity and metabolic syndrome,[9,14] neuropsychiatric disorders, multiple sclerosis, atherosclerotic cardiovascular disease, autism, fibromyalgia, and chronic fatigue syndrome.[8]

**Fecal Microbiota Transplants as a technique for *Clostridium difficile***

*C. diff* is one of the most infectious bacterium causing CDI – one of the most prevalent complications from hospitals stays worldwide.[15-18] Having CDI extends hospital stays and has an estimated economic impact on the healthcare system of $4.7 billion in 2014 alone.[19.] Often patients develop drug resistant CDI and enter a cycle of antibiotics to kill the infectious bacteria which also kills the good bacteria thus allowing *c. diff* either to proliferate or to cause a reinfection.[16-17,20.] Patients with CDI who have used antibiotics typically have fecal microbiota with decreased *Bacteroidetes* and *Firmicutes* and increased *Proteobacteria* and Verrumicrobia.[21] Antibiotic treatment of CDI is often seen as ineffective with 15-35% of patients having at least one recurrence,[22] and 60% of patients with one recurrence are likely to have another.[17,22] However, the use of Fecal Microbiota Transplant (FMT) has been an effective tool for treating CDI and repopulating the gut microbiome. Studies have shown that the cure rate of treating CDI with FMT to be at least 90%.[16-17, 22] In 2018, infectious disease clinical guidelines included FMT as a recommended course of treatment for recurring CDI which have not responded to antibiotics.[18]

First used as a treatment for colitis in 1958,[21.] FMT uses stool from a healthy donor which is then transplanted into another patient's colon or treatment of a disease.[10,23.] Several studies showed that the composition of the healthy donor stool included higher abundance of the *Bacteroidetes* and *Firmicutes* bacteria,[21.] whereas in a review of several studies, Samarkos et al found that the patient pre-FMT had a stool composition of reduced *Bacteroidetes* and *Firmicutes,* with increased *Proteobacteria.*[24]

The form and administration of the FMT stool sample can include via enema, a colonoscopy, a nasogastric tube, or swallowed in pill form.[17.] The sample can be fresh or frozen-and-thawed.[17.] These samples not only must be viable but also administration must be acceptable to the patient. One meta-analysis reported that "fresh FMT through enema had no advantage compared to antibiotic therapy or frozen FMT"[25] which calls for the need to standardize the method of administration.[25] Research results in FMT appear promising in that patients have found relief from recurring CDI. Other research has shown a reduction in inflammatory markers after FMT,[16] the transfer of 'healthy' bacterial communities,[16] and increased diversity of the microbiome.[16, 22, 25] As for patient satisfaction, one retrospective study found that 95% of patients who had been treated with FMT would do it again, with 70% saying they would use FMT as a first round of treatment.[15]

Questions still remain, however, around regulating stool donors and their samples. The FDA has proposed that stool samples should be regulated much like a drug which is complicated by the variability of each individual's microbiome.[20] Rather than trying to manufacture a commercial alternative for FMT, some researchers have argued that stool donations should be screened and treated like blood banking, with using a screening method similar to blood donor screening to include detailed medical history excluding for high risk behaviors, chronic health conditions, GI symptoms, history of autoimmune diseases, diabetes, and many other conditions.[20]

Post FMT, studies indicate that the proliferation of two bacteria have repopulated the colon and give less room to the germination and proliferation of *c. diff,* such as the increase in *Firmicutes* and *Bacteroidetes*[21, 26] and a decrease in *Proteobacteriae*[10, 26] and *Actinobacteria.*[21.] Weingarden et al examined fecal microbiota of four patients with CDI pre and post-FMT in comparison with fecal samples from the FMT donor and from healthy individuals included in the Human Microbiome Project. Researchers found that fecal microbiota communities post-FMT more closely resembled those of healthy individuals.[26] Follow-up 26 days post FMT suggested that although the microbial community changed from that of the donor, however, the composition still remained similar to a healthy individual.[26] Weingarden further proposes that the "dynamic behavior" of microbiota with time needs to be considered in future research; diet plays a role in this behavior.[26]

**Diet and the microbiome**

Maintaining microbiome diversity appears to be important for healthy individuals[4] to help protect them from pathogen colonization and to maintain a healthy mucosal barrier.[4] Yet the microbiome composition and diversity are highly adaptable to diet.[1, 14, 26-29] According to a feeding study with ten participants randomized to either a high fat/low-fiber or high-fiber/low-fat diet, the composition of the gut microbiota can change within 24 hours; however, after following the controlled diet for 10 days, the individual's microbiota composition had not changed much from their long-term diet.[30] Adopting a diet that is animal-based can also alter the composition of the microbiome within 24 hours, but those changes revert back to the individual's baseline microbiome composition within 48 hours of stopping the diet.[14] In a dietary intervention of obese individuals, researchers found that the composition or proportion of the microbiota can change within 3-4 days with alterations in diet, especially with the introduction of non-digestible carbohydrates.[31] However, dietary changes and the shift in microbiota are highly individualized.[31]

Currently no dietary recommendations exist for a patient post-FMT other than potentially a high fiber diet. However, given that the risk for recurrent CDI increases with decreased *Firmicutes* and *Bacteroidetes,* supporting this bacterial composition and diversity could potentially decrease the risk for *c. diff* infection. Butyrate-producing bacteria may be important as they help maintain homeostasis of intestinal cells, reduce permeability, and enhance defense barriers within the intestinal wall.[4-5] If the gut microbial diversity or composition can respond to diet, especially an animal-based diet within 24 hours,[14] what dietary factors and bacterial components could influence microbiome health?

**Agrarian vs. Western Diet**

Dietary habits are considered one of the main factors contributing to the human microbial richness and diversity.[27, 31, 33] Initial studies within communities with an Agrarian, plant-based diet versus an Industrialized, Western diet indicated a difference in microbiome bacterial composition. In 2010, researchers compared the gut microbiota between two groups of children:

one in rural Burkino Faso and one in Italy. The Burkino Faso group followed a Neolithic diet characterized by a mainly vegetarian diet which was low in fat and animal protein and high in starch, fiber and plant polysaccharides.[27] The European children followed a more typical Western diet for developed countries which was high in animal protein, sugar, starch, and fat and low in fiber.[27] Results from their study showed that the Burkino Faso children had a higher diversity and microbial richness of microbiota with a difference in ratio of *Firmicutes* to *Bacteroidetes* between the two groups. Those following the Western diet had twice more *Firmicutes:Bacteroidetes* compared to those following the high fiber, low animal protein diet. The African group also showed fewer calories consumed with a more efficient microbial activity to extract calories from complex carbohydrates/plant polysaccharides and produced more abundant short chain fatty acids (SCFAs).[27] These SCFAs include 1) butyrate which provides 60-70% of energy needed by the epithelial cells of the colon; 2) propionate which the liver uses for gluconeogenesis, liponeogenesis and protein synthesis; and 3) acetate which is used in peripheral tissues and serves as a substrate for cholesterol synthesis.[27] Mills et al suggested that butyrate is produced by *Firmicutes;* propionate, produced by *Bacteroidetes;* and acetate, produced mainly by gut anaerobes.[4]

These researchers further extrapolated that given the African community's fewer incidences of obesity, inflammation of the gastrointestinal tract, and of chronic diseases such as heart disease and diabetes, this proportion of bacteria could be important in preventing chronic and gastrointestinal diseases.[27] Their results provided the basis for future studies of exploring the impact of diet on the microbiota, and speculation that microbiota play a role in disease.

A 2018 study followed groups of Hmong and Karen immigrants while in Thailand and after settling in the United States adopting a Western diet.[34] The longer the immigrant resided in the United States, the more the microbiome decreased in diversity, increased in *Bacteroides* which replaced the *Prevotella* strain, and an increase in BMI.[34] David et al's feeding study showed that when a participant decreased their usual long-term fiber consumption, *Prevotella* strain decreased.[14] Also, those fed an entirely animal-based diet saw a greater shift in microbiota composition such as an increase in *Bacteroides* and a decrease in *Firmicutes* than those adapting to an entirely plant-based diet.[14]

**Prebiotics**

As being able to breakdown carbohydrates is significant in microbiome diversity, prebiotics represent one of the primary themes emerging in the nutritional impact on the microbiome. Defined as food components that feed the gut microbiota in the large intestine,[11] these prebiotics include non-digestible carbohydrates, including dietary fiber, resistant starch, inulin, and oligosaccharides that are not digested enzymatically in the small intestine; instead they travel to the large intestine where they feed the microbiota that reside in the colon or result in fermentation[1, 4, 35] which produces short-chain fatty acids (SCFAs).[27] Researchers Sonnenburg and Sonnenburg define these food sources as "Microbiota-Accessible Carbohydrates" (MACs) and include those plant or animal tissues that are metabolized by the gut microbes.[35]

Study results of the Agrarian diet studies showed a much higher consumption of fiber, about 7 times greater than that in typical Western diets.[36] Recommended dietary fiber intakes for Americans for men ages 19-50, are 38 grams per day; over 51, 31 grams per day. For women ages 19-50, the recommendation is 25 grams per day and over 51, 21 grams per day.[37] However, intakes typically fall around 18 grams of fiber per day. In order to increase intake of fermentable soluble dietary fibers, recommendations should be made around increasing consumption of fruits, vegetables and whole grains in particular the following:

Pectins: Citrus fruits, strawberries, apples, raspberries, legumes, nuts, some vegetables (such as carrots), and oat products.[37]
Fructans: Chicory, asparagus, onion, garlic, artichoke, tomatoes, bananas, rye and barley[37]
Beta-glucans: Oat products and barley[37]
Gums: Oatmeal, barley, and legumes[37]
Resistant Starches: partially milled grains and seeds, unripe (green) bananas, legumes, raw and cooked potato, and high-amylose corn, rice, and pasta[11]

Inulin-type fructans are naturally found in agave, artichokes, asparagus, bananas, chicory root, garlic, onions, leeks and wheat.[38]

Within the microbiome product development industry, the search for a prebiotic supplement or a way to enrich foods with fiber is the fastest growing segment of the industry.[39] Some of the research focuses on the creation of an inulin supplement, of which many can be found available online. However, consumers should exercise caution due to the lack of federal regulation of the supplement industry as well as due to animal research that links the use of supplemental form of inulin to liver cancer. Sing V et al found that when mice with microbiota dysbiosis were fed a diet with inulin supplements, the mice had an increased risk for liver cancer.[40]

**Protein**

When it comes to protein, amount consumed and digestibility matters to the gut microbiome's quantity and diversity.[1, 32, 41-42] The Western diet is typically higher in protein.[2, 32] Studies have shown that the consumption of high levels of protein can lead to the fermentation of protein in the large intestine.[32, 42] This fermentation process, especially with animal protein, releases nitrogenous compounds[42] and can alter the pH of the colon,[28, 32, 42] providing an environment conducive to the proliferation of pathogenic bacteria and the reduction of butyrate and Bifidobacterium.[28, 32, 41-42] Rats fed a 45% protein/20% carbohydrate diet had increased pathogenic bacteria such as *Esherichia coli* within 1 week and decreased beneficial bacteria such as *Bifidobacterium, Prevotella*, and *Roseburia/Eubacterium rectale.*[28] Concentration of fecal

SCFAs were also reduced and positively correlated with carbohydrate intake.[28] Russell et al. conducted a diet intervention study in obese men to determine the effects on microbiota when following a high protein/low carbohydrate diet for weight loss. When comparing a maintenance diet of 13% protein, 50% carbohydrates, 37% fat diet to a high protein diet of 28% protein, 35% carbohydrate and 37% fat diet, researchers found a two-fold decrease in butyrate production (*Roseburia/Eubacterium rectale)* between the two groups.[41] Although a 28% protein, 35% carbohydrate, 37% fat diet did not show a significant decrease in butyrate production, a decrease was noted with a shift toward protein fermentation in the colon.[41] However, greater carbohydrate intake appeared protective of butyrate production.[41] Participants only followed these high protein diets for 4 weeks, additional changes could have happened over a longer period of time.

Duncan et al supported these findings with a similar dietary intervention comparing a 13% protein, 52% carbohydrate, 35% fat diet to two high protein arms: 1) high protein, low carbohydrate intervention 30% protein, 4% carbohydrate, 66% fat and 2) high protein, moderate carbohydrate intervention of 30% protein, 35% carbohydrate, 35% fat.[42] Overall SCFA production fell, with butyrate concentrations lowest in the high protein, low carbohydrate arm and showing a linear relationship with the amount of carbohydrates consumed.[42] In addition, they also reported a reduction in *Bifidobacterium*.[42]

Studies of plant-based proteins ingestion in hamsters have shown an increase in microbial diversity and quantity with soy-based protein compared to a milk-based protein.[43] Singh et al reports that studies comparing animal versus plant-based proteins such as whey or pea protein extracts found a reduction in butyrate and fecal SCFA in those that consumed primarily animal protein.[1, 27] In addition, plant-based protein studies reported an increase in *Bifidobacteria* and *Lactobacilli.*[1]

**Food Products**

The industrialization of food over the last sixty years has led to the increase in Western-style food products that are highly-processed, calorically dense with high amounts of saturated fat, salt, sugar and low amounts of fiber.[44] The use of convenient, ready to eat, shelf-stable and inexpensive foods coupled with a more sedentary lifestyle have contributed to this categorization that a Western-lifestyle is associated with an increased risk of chronic diseases and obesity.[44] These foods tend to have less micronutrient value, more calories, and additives such as artificial sweeteners and emulsifiers.[44] Although the exact role in metabolic disorders has not been definitively defined, emulsifiers and sweeteners in highly processed foods have been implicated in impacting the gut microbiota.[44-47]

Additives such as emulsifiers and some non-caloric sweeteners interact with the microbiota in the large intestine.[45-47] Emulsifiers represent a widely used additive in processed foods.[45] Generally recognized as safe, emulsifiers such as polysorbate-80 or Tween 80 and carboxymethylcellulose (CMC) are be used in food products to extend shelf-life, improve mouth feel, as an emulsion stabilizer, and as a thickener.[48] However, according to Chassaing et al., when researchers fed mice these two emulsifiers as part of their drinking water or as part of their chow, a change in microbiota, an increase in inflammation, and alteration in mucus thickness were observed.[45] Specifically, results showed a decrease in butyrate and in SCFAs which in turn increases the risk for inflammation and metabolic disorders.[45]

Polysorbate 80 can be found in many items such as ice cream, frozen custard, ice milk, fruit sherbet, pickles, pickle products, fat-soluble vitamins, canned green beans, shortenings and oils, gelatin disserts and dessert mixes, cottage cheese, barbecue sauces.[49] CMC or cellulose gum can be found in frozen dairy foods, diet soft drinks, white and sparkling wines, and tortillas.[48] Polysorbate-80, if used, should be noted on the food label.[49] Currently, use of Polysorbate-80 is deemed safe up to 1.0% and up to 2.0% for CMC.[45]

Non-caloric sweeteners provide consumers food products with a reduced calorie benefit and a heightened sweet taste.[46-47] In particular these products include diet sodas, desserts, and cereals for those that may want to lose weight or need to control type 2 diabetes.[46] However, over the years some research indicates that those that consume these artificial sweeteners could be at increased risk for metabolic disorders, cardiovascular diseases, type 2 diabetes, and weight gain.[46-47] In particular, both animal and human studies indicate that saccharin can alter the microbiota causing dysbiosis and increase glucose intolerance.[46-47] Other studies suggest that sucralose impacts gut microbiota negatively and that polyols potentially could provide prebiotic, beneficial impact to microbiota.[47] Stevia may change the microbiota composition; however, further studies are needed to determine how this translates to gut health.[47] Researchers do suggest the need for continued research to determine whether or not animal studies translate to humans.[47]

**Probiotics**

Microbiota research and sales in conjunction with product development, promotion, and consumer use of probiotics has grown to a $35 billion industry in the United States alone.[50] This area includes foods or supplements as a way to restore the microbiome naturally or synthetically.[11] Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.”[51-52] *Bifidobacteria* and *Lactobacilli* have traditionally been generally recognized as safe for human consumption[53] and are important within the gut to maintain immunity and gut health[1, 37, 53] such as manipulation of microbiota, suppression of pathogens, impact on immune response, support epithelial cell growth, and strengthening intestinal barrier.[54] *Bifidobacteria* in particular has been associated with butyrate-producing microbiota which help protect against gut permeability and inflammatory conditions.[55] With aging the presence of *Bifidobacteria* decreases from around 90% of the gut microbiota in a vaginally-delivered, breastfed baby to <5% in an adult.[55] *Lactobacillus* strains of probiotics have been associated with lactic acid production[53] and regarded as important in maintenance of a healthy intestinal barrier and immunity.[54] To date, pharmaceutical forms of probiotics have been studied and used for a variety of gastrointestinal illnesses such as Inflammatory Bowel Disease, Irritable Bowel Syndrome, diarrhea (especially antibiotic-associated diarrhea), immune responses and certain liver diseases.[52, 55] However, caution must be exercised in probiotic use because of their many strain-specific characteristics[51] and results have been mixed into whether probiotics change an individual's microbiota with clinical benefits.[54] Disease benefit might be tied to a particular strain of these two probiotic groups[52] and research is still developing. In addition, in the United States, probiotics are considered "over-the counter" dietary supplements and are not regulated by the FDA.[50] As such, specific health claims cannot be made by manufacturers.[50]

Given the complexity of determining most beneficial strain for disease and lack of regulation, probiotics might be best consumed as natural foods. Natural food sources for probiotics include cultured milk products and yogurt[1, 56] as well as human breastmilk, fermented cheeses, water kefir,[55] kimchi, sauerkraut, miso, tempeh, and cultured non-dairy yogurts.[56]

**Conclusion**

Identifying the exact bacteria which populate a healthy microbiome has yet to be definitively determined. However, research does suggest that diet can play an integral role in supporting or changing the microbiome. To protect the GI tract and colonocytes, production of the SCFA butyrate appears to be one of the most important protectors. Research does show that a diet rich in plants appears to be more beneficial to gut health, compared to the typical Western high protein, high fat, high sugar, and low complex carbohydrates diet. A plant-focused diet with increased non-digestible carbohydrates such as fruits, vegetables, and whole grains, limited animal-protein and including plant-based protein can support butyrate-production. In addition, focusing on whole foods and limiting ultra-processed foods (especially those with polysorbate 80, saccharin, sucralose, and carboxymethylcellulose) also seems to support intestinal barrier function and could help prevent dysbiosis. Prebiotics and probiotics have been heavily marketed as supplements that both feed and reintroduce bacteria into the gut. However, the benefits of these supplements still appear to be controversial and inconclusive. Recommendations for these dietary components should focus instead on their form through whole, fermentable foods. Given the role of FMT in repopulating the gut and the role of bacteria crowding out the proliferation of *c.diff,* helping support the bacteria through healthy food choices could be beneficial.

# *Proposed Website Content*

**A Healthy Gut Microbiome**

Everyone is talking about a healthy gut microbiome. And for good reason. Found in your lower intestine (your colon), the gut microbiome contains trillions of active bacteria working for your health. This microbiome has been described as an organ and ecosystem with over 400 different types of bacteria. Everyone has their own unique microbiome made up of different types and amounts of bacteria. Depending on the bacterial diversity and composition, the microbiome could influence someone's health.

But what makes a gut microbiome healthy? Isn't bacteria bad?

Some bacteria can make you really sick – like *Clostridium difficile (c.diff)* or *Escherichia coli (E. coli*). But not all bacteria cause you to feel miserable. You want some of your bacteria to be active and thrive. Although, no one knows for sure yet which bacteria you need in your gut to be the healthiest, we do know a few things about how the bacteria function. Which bacteria are thriving seems to depend on which bacteria are being fed.

First of all, the protective bacteria help keep your gastrointestinal (GI) tract intact and help you digest fiber and absorb needed nutrients. Cells called epithelial cells line the GI tract and serve as an important barrier. In an ideal world these cells rest tightly next to each other, creating tight junctions. These tight junctions provide a barrier protecting your body from outside bacteria, much like your skin does on the outside of your body. Researchers think that bacteria called *Firmicutes* and *Bacteroidetes* help protect and strengthen these cells. When this balance gets disturbed (called dysbiosis), the junctions between the cells can loosen causing bacteria to travel from the intestines into the body. This loosening of junctions causes what is called gut permeability.

(Sidebar/Photo of GI tract: Your GI tract goes from your mouth to your anus and is a complex digestive system as you get the energy, vitamins, minerals, fats, proteins, and water that your body needs. Whatever food parts not broken down through the stomach and the small intestine then come to the large intestine. Your gut microbiome found in your large intestine goes to town on these nondigested food parts. Bacteria get the energy they need and help the body absorb more water and nutrients. Whatever is left over becomes poop.)

(Sidebar/Photo of epithelial cells: loose and tight junction)

Secondly, some researchers believe that whatever bacteria survive depends on what nondigested food parts or fiber make it to the colon. This fiber or non-digestible carbohydrates is often referred to as prebiotics. It seems that a bacteria's growth and strength in the gut depend on whether or not they have competition for food. An important thing to remember is that you want protective bacteria to be fed with foods that you eat. If you do not supply them with the food they need, some protective bacteria could die and some of the aggressive bacteria could begin eating from your own cells found in the gut. This could cause dysbiosis as well as gut permeability.

Currently, the relationship between the gut microbiome and diseases is being explored. Some connection has been shown with certain illnesses, however, exactly what this means for the bacteria make-up of the microbiome is not yet known. Those illnesses and diseases include:

*Clostridium difficile (c.diff)*
Inflammatory Bowel Disease
Irritable Bowel Syndrome
Auto-immune Diseases
Obesity
Inflammation
Cardiovascular disease
Chronic Fatigue
Metabolic Syndrome

To make this even more complicated, the amounts and types of bacteria that you have in your gut make you unique. Yours will look different from your neighbor and from your family and from someone in another part of the world. And the bacteria numbers and diversity can change because of some things that happened when you were born and are beyond your control. But other influences on microbiome are due to lifestyle. Factors that influence the gut bacteria survival and composition include:

Your environment
How you were born – vaginally or by c-Section
As an infant, were you breastfed or formula fed?
Genetics
Age
Diet
Antibiotic Use
Stress
Alcohol intake
Exercise
Disease status

Although no one can say for sure exactly what your gut microbiome should be, you can do a few things to help give yourself the best possible scenario for your microbiome.

- Limit antibiotic use, if possible.\
- Reduce stress.
- Exercise regularly.
- Limit alcohol intake.

However, your diet choices can make a huge difference in giving your gut bacteria what they need. Although many companies have products such as probiotics and prebiotics, food seems to be the best starting source for these components.

**Sources:**


1. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, and Laio W. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* (2017) 15: 73.
2. Cresci GA, Bawden E. The gut microbiome: What we do and don't know. *Nutr Clin Pract.* 2015 December; 30(6): 734-746.
3. Mills S, Stanton C, Lane AJ, Smith GJ, Ross RP. Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients*. 2019; 11(4).
4. Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut microbiota in host health and disease. *Cell Host Microbe.* 2018;23(6):705-715.
5. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet and diseases. *Microorganisms.* 2019;7(1).
6. Malikowski T, Khanna S, Pardi DS. Fecal microbiota transplantation for gastrointestinal disorders. *Curr Opin Gastroenterol.* 2017; 33(1):8-13.
7. Lazar V, Ditu LM, Pircalabioru GG, Picu A, Petcu L, Cucu N, Chifiriuc MC. Gut microbiota host organism, and diet trialogue in diabetes and obesity. *Front Nutr.* 2019; 6:21.
8. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: The deleterious consequences of a diet deficient in Microbiota-Accessible Carbohydrates. *Cell Metab.* 2014;20(5):779-786.

**Diet Overall Page**

The old saying "you are what you eat" has never seemed truer than with the bacteria in the gut microbiome. A healthy gut microbiome protects our bodies and our GI tract from infection, inflammation, and diseases. What researchers have found is which bacteria thrive depends on what you eat. These bacteria can change very quickly within 24 hours for some. This could be great news if we could identify exactly which bacteria were the most important. However, no precise way of eating fits all. We are all unique individuals with a unique microbiome.

So, what do we know? The microbiome is very changeable to diet. Research does suggest that there are some general guidelines that could help provide the best environment to protect the gut. These guidelines may sound familiar as they represent an overall healthful way of eating. Research studies have been conducted in the following areas and have found disturbance in the microbiota when not following these recommendations. Therefore, you can create the best environment possible for your gut microbiome through the food you eat. These general guidelines include

- Eat mostly plants such as colorful fruits and vegetables, and whole grains. These provide much needed fiber and non-digestible carbohydrates.
- Choose low fat animal proteins and plant proteins
- Choose whole foods, limit processed foods
- Limit artificial sweeteners, polysorbate 80 and carboxymethylcellulose (CMC)
- Choose unsaturated fats over saturated fats
- Choose food over supplemental prebiotics and probiotics

One of the first studies in microbiome and diet analyzed the gut bacteria in an African population that had low rates of diseases like heart disease, cancer, and Inflammatory Bowel Disease. This African population ate mainly vegetables high in fiber and resistant starch and had a diet limited in animal protein and fat. They compared this microbiome with the microbiome in an Italian population who ate a more traditional Western Diet – low in fiber, higher in animal protein, fat, salt and sugar. The bacteria composition and diversity were very different between those two groups.

Those eating higher amounts of fiber (plants) showed more microbial diversity and activity, producing short chain fatty acids (SCFAs). These SCFAs include butyrate, propionate, and acetate. Butyrate, in particular, helps keep our cells in our colon healthy. Some research has since focused on the butyrate and SCFA activity of our gut bacteria *Firmicutes* and *Bacteroidetes.*

When you eat lots of plants (fruits, vegetables, whole grains), you are eating different types of fiber. This fiber is not broken down in the stomach and small intestine. When it gets to the colon, it feeds the bacteria that produce SCFAs and protect the cells in your GI tract.

Being vegetarian is not a requirement for a healthy gut. However, focusing on plant-based eating is recommended. The balance of carbohydrates to protein is important as well as the type of food - whole vs processed. See links for more info.

**Sources:**

1. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, and Laio W. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* (2017) 15: 73.
2. Mills S, Stanton C, Lane AJ, Smith GJ, Ross RP. Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients*. 2019; 11(4).
3. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484): 559-63.
4. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci USA.* 2010;107(33):14691-6.
5. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: The deleterious consequences of a diet deficient in Microbiota-Accessible Carbohydrates. *Cell Metab.* 2014;20(5):779-786.

**Fiber/Prebiotics – Food first. – Suggested photos for this section: Colorful fruits, vegetables. Plate method**

One of the fastest growing segments of the microbiome market is the creation of supplemental prebiotics and the enrichment of highly refined food products with added fiber. We would argue that eating foods that naturally contain fiber - fresh fruits, vegetables, whole grains, nuts, and legumes - should be the first choice. These carbohydrates are GOOD! They provide important vitamins, minerals, energy, and the many forms of fiber needed by your body.

Carbohydrates contain multiple types of fiber. Fiber helps move food through the digestive system, can make you feel full, and control cholesterol and blood glucose levels. Those carbohydrates left undigested by the body's enzymes become important food for the gut microbiome in the colon. When in the colon, fermentable fibers called microbiota accessible carbohydrates (MACs) feed the bacteria and stimulate the bacteria's growth. The bacteria through fermentation create short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. Butyrate is especially important as it helps protect the cells in the colon.

Eating a variety of plant-based foods helps support a diverse microbiome. A diverse microbiome helps prevent dysbiosis and gut permeability as it maintains a healthy balance in the bacteria. Making sure you eat a variety of fruits, vegetable, whole grains, nuts, and legumes every day is the best way to make sure you get the different fibers you need. The typical Western diet of fast food, processed foods, or food products is typically low in fiber, low in fruits, vegetables, whole grains and high in meat, sugar and salt.

Current dietary recommendations suggest that adult women ages 19-50 should aim for about 25 grams of fiber per day and men, 38 grams. Once over 51 years old, recommended intake for women is 21 grams and for men 31 grams per day. The average American gets about 18 grams of fiber per day. (Photo of low fiber meal – meat, potatoes, mac n cheese, white roll)

Making sure that your plate has colorful fruits and vegetables (Photo) at each meal and whole grains can help increase your fiber intake. Eating plant-based proteins like lentils and beans instead of meat can also increase your fiber. Those foods that have fermentable dietary fibers include:

- Citrus fruits
- Strawberries
- Apples
- Raspberries
- Legumes
- Nuts
- Asparagus
- Onion
- Garlic
- Artichoke
- Tomatoes
- Bananas

Rye
Barley
Oat products
Potatoes
Rice
Pasta
Whole wheat

[Info could be presented as a table] How much fiber is in a serving? (Photos of serving sizes) Depends on the item, but some fruits have about 3-4 grams per serving. These include an orange, tangerine, an apple or pear with skin, 1 cup of blueberries, 1 cup of strawberries. Raspberries have about twice that fiber amount with 8 grams per cup. For vegetables, 10 spears of asparagus have about 3 grams, ½ cup of lentils have 8 grams, ½ cup of black beans have 14 grams. For breads and grains, you will need to read the nutrition label to see how much fiber is in each serving. The fiber content can vary widely between brands and products, but ingredients should include whole grains. (Photo of a nutrition label)

And another thing…Eating a raw piece of fruit like an apple with the peel will have more fiber than eating applesauce. Although juicing whole fruits can give you great nutrients, juices do not contain the fiber that your gut needs.

Because different foods provide different types of fiber, focusing on just one form of fiber is not recommended. It is really important to include as many grains, vegetables, legumes and fruits as possible, even if they aren't listed above. Although prebiotic products or fiber-enriched products are on the market, whole foods should be your first choice.

**Sources:**


1. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, and Laio W. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* (2017) 15: 73.
2. Mills S, Stanton C, Lane AJ, Smith GJ, Ross RP. Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients*. 2019; 11(4).
3. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes.* 2017;8(2):172-184.
4. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: The deleterious consequences of a diet deficient in Microbiota-Accessible Carbohydrates. *Cell Metab.* 2014;20(5):779-786.
5. Gropper SS, Smith JL, Carr TP. *Advanced Nutrition and Human Metabolism*. Boston, MA: Cengage Learning.

**Processed Foods vs Whole Foods**

In industrialized countries like the United States, our diet has changed over the years. All you have to do is go to the grocery store and see that the fresh foods are on the outside aisles and the center of the store is filled with food products. Products you did not even know you wanted. Frozen foods, ready-to-eat foods, drinks of all colors of the rainbow, desserts that could stay on the shelf for a very long time – which seem convenient and cheap. (Photo of processed foods) But caution! Some of these food products can have artificial sweeteners and emulsifiers added to them.

Some research has suggested that emulsifiers and non-caloric sweeteners affect the microbiota in the large intestine. Emulsifiers like polysorbate-80 and carboxymethylcellulose (CMC) can be used to increase shelf-life, improve mouth feel, or thicken foods. However, initial animal studies show that eating these in a similar amount to a human diet could cause a decrease in butyrate. Butyrate is produced by bacteria in the gut and serves to protect the colon. A decrease in butyrate can increase the risk of inflammation. Artificial, non-caloric sweeteners such as saccharin and sucralose have also shown a negative impact to gut microbiota in animal studies. However, more research needs to be done to know exactly how these translate to humans.

What should you do? Read the list of ingredients looking for polysorbate-80, carboxymethylcellulose, saccharin, and/or sucralose. (Photo of food label) Find another product that does not have these ingredients or limit the number of servings you have of these per day. Some items where you might find these ingredients include the following:

Frozen desserts: ice cream, frozen custard, ice milk, fruit sherbet
Pickles
Fat-soluble vitamins
Shortenings and oils
Gelatin desserts and dessert mixes
Cottage cheese
Barbecue sauces
Soft drinks – regular and diet
White and sparkling wines
Tortillas
Ready-to-eat cereals

We also spend less time cooking our own foods. We eat out, or we pick something up on the go from fast food. These habits are spreading around the world. The added sugar, fat, and salt that often comes with these foods can make these items tasty, leaving us craving more. These foods are often low in fiber and needed nutrients. As countries adopt a Western diet, chronic diseases such as heart disease, cancer, obesity, diabetes, inflammation, and Inflammatory Bowel Disease begin to appear. Some believe that the microbiome is disturbed with this Western diet.

Additives for foods are considered safe according to food industry studies but we still are learning what the impact these foods could be for the long-term. Choosing whole foods – buying and cooking foods close to their original state is what is recommended to maximize your health.

**Sources:**


1. Miclotte L, Van de Wiele T. Food processing, gut microbiota, and the globesity problem. *Crit Rev Food Sci Nutr.* 2019 Apr 4:1-14.
2. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature.* 2015;519(7541):92-96.
3. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature.* 2014;514(7521):181-6.
4. Ruiz-Ojeda FJ, Plaza-Diaz J, Sáez-Lara M, Gil A. Effects of sweeteners on the gut microbiota: A review of experimental studies and clinical trials. *Adv Nutr.* 2019;10:S31-S48.

**Protein**

The typical Western diet is high in protein, especially animal protein (beef, chicken, pork, eggs). The trend right now seems to be to eat a high protein, low carbohydrate, high fat diet to lose weight. However, diet studies that looked at the gut microbiome for this diet showed that the bacteria in the gut changed. The bacteria that help the gut remain healthy decreased, and the bacteria that can lead to inflammation grew.

What happens is that when you eat high amounts of animal protein and low carbohydrates, you are starving the bacteria that keep your gut healthy. The high amounts of animal protein travel to the colon and are fermented there. When this happens, the environment for the bacteria changes. The pH of the colon increases which causes a reduction in the healthful bacteria that produce butyrate.

Can I still eat protein? You should always eat some type of protein. Your body needs it for muscles and to function. But you should balance it with complex carbohydrates too. Your plate should be ¼ protein such as a lean meat, ¼ whole grain like brown rice or a potato, and ½ vegetables like broccoli, tomatoes, peppers, cauliflower, carrots. Think of a colorful plate – like a rainbow.

Plant-proteins are always a good option as well such as from soy (tofu), beans (black beans, pintos), legumes (lentils, chickpeas), nuts, and grains like quinoa. Avocado even can be a good source of protein. Eating plant-based meals a few times per week is always a good idea for your gut and overall health. An added bonus, these plant proteins feed the bacteria that are best for our gut.

**Sources:**


1. Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, Duncan G, Johnstone AM, et al. High protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr.* 2011;93(5):1062-72.
2. Duncan SH, Belenguer Al, Holtrop G, Jonhstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol.* 2007;73(4): 1073-1078.
3. Ma N, Tian Y, Wu Y, Ma X. Contributions of the interaction between dietary protein and gut microbiota to intestinal health. *Curr Protein Pept Sci*. 2017;18(8):795-808.

**Repopulating the gut - Probiotics**

As with most areas of health, companies are always trying to find a quick fix to sell. The gut microbiome is no different. One supplement that seems to be everywhere is probiotics. We do not know yet exactly which bacteria we need. *Lactobacillus and bifidobacteria* have generally been recognized as beneficial; however, we do not know yet which strain(s) we need for which condition.

Marketed as "nutraceuticals", probiotics cannot make health claims nor does the FDA regulate them. That makes it hard to regulate quality and quantity of bacterial strains. Everyone's gut microbiome is unique; therefore, we do not know yet which probiotic would be best for your gut health.

The best thing you can do is to continue to eat lots of complex carbohydrates, especially when given antibiotics. Choose whole food sources of naturally occurring probiotics like yogurt, kefir, sauerkraut, and kimchi.

**Sources:**


1. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanism of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol.* 2013;6(1):39-51.
2. Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for the stimulation in the human gut. *Front Microbiol.* 2016;7(979).
3. Wolfram, T. Prebiotics and probiotics: Creating a healthier you. Academy of Nutrition and Dietetics. February 27, 2018. https://www.eatright.org/food/vitamins-and-supplements/nutrient-rich-foods/prebiotics-and-probiotics-creating-a-healthier-you. Accessed May 27, 2019.

**References**


1. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, and Laio W. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* (2017) 15: 73.
2. Cresci GA, Bawden E. The gut microbiome: What we do and don't know. *Nutr Clin Pract.* 2015 December; 30(6): 734-746.
3. Cheng RY, Li M, Li SS, He M, Yu XH, Shi L, He F. Vancomycin and ceftriaxone can damage intestinal microbiota and affect the development of the intestinal tract and immune system to different degrees in neonatal mice. *Pathog Dis*. 2017;75(8).
4. Mills S, Stanton C, Lane AJ, Smith GJ, Ross RP. Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients*. 2019; 11(4).
5. Zhang L, Dong D, Jiang C, Li Z, Wang X, Peng Y. Insight into alteration of gut microbiota in *Clostridium difficile* infection and asymptomatic *C. difficile* colonization. *Anaerobe.* 2015;34:1-7.
6. Krezalek MA, Yeh A, Alverdy JC, Morowitz M. Influence of nutrition therapy on the intestinal microbiome. *Curr Opin Clin Nutr Metab Care.* 2017;20(2): 131-137.
7. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet and diseases. *Microorganisms.* 2019;7(1).
8. Malikowski T, Khanna S, Pardi DS. Fecal microbiota transplantation for gastrointestinal disorders. *Curr Opin Gastroenterol.* 2017; 33(1):8-13.
9. Lazar V, Ditu LM, Pircalabioru GG, Picu A, Petcu L, Cucu N, Chifiriuc MC. Gut microbiota host organism, and diet trialogue in diabetes and obesity. *Front Nutr.* 2019; 6:21.
10. Konturek PC, Haziri D, Brzozowski T, Hess T, Heyman S, et al. Emerging role of fecal microbiota therapy in the treatment of gastrointestinal and extra-gastrointestinal diseases. *Jl of Physiol Pharmacol.* 2015; 66(4):483-491.
11. Nelms M, Sucher KP, Lacey K. *Nutrition Therapy and Pathophysiology*. Boston, MA: Cengage Learning.
12. Ross CL, Spinler JK, Savidge TC. Structural and functional changes within the gut microbiota and susceptibility to *Clostridium difficile* infection. *Anaerobe.* 2016; 41:37-43.
13. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature*. 2012;488(7410):178–184.
14. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484): 559-63.
15. Mamo Y, Woodworth MH, Wang T, Dhere T, Kraft CS. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent *clostridium difficile* infection. *Clin Infect Dis*. 2018; 66(11): 1705-11.
16. Konturek PC, Koziel J, Dieterich W, et al. Successful therapy of *clostridium difficile* infection with fecal microbiota transplantation. *J Physiol Pharmacol*. 2016; 67(6): 859-866.

17. Lee CH, Steiner T, Petrol EO, et al. Frozen vs fresh fecal mictobiota transplantation and clinical resolution of diarrhea in patients with recurrent *clostridium difficile* infection: A randomized clinical trial. *JAMA*. 2016; 315(2): 142-149.
18. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018; 66(7): e1-e48. https://doi.org/10.1093/cid/cix1085.
19. Mollard S, Lurienne L, Heimann SM, Bandinelli P-A. Burden of *Clostridium (Clostridioides) difficile* infection during inpatient stays in the USA between 2012 and 2016. *J Hosp Infect.* 2019;102(2):135-140.
20. Woodworth MH, Carpentieri C, Sitchenko KL, Kraft CS. Challenges in fecal donor selection and screening for fecal microbiota transplantation: A review. *Gut Microbes*. 2017;8(3):225-237.
21. Hamilton MJ, Weingarden AR, Unno T, Khoruts A, Sadowsky MJ. High-throughput DNA sequence analysis reveals stable engraftment of gut microbiota following transplantation of previously frozen fecal bacteria. *Gut Microbes.* 2013;4(2):125-135.
22. Kelly CR, Khoruts, A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *clostridium difficile* infection: A randomized control trial. *Ann Intern Med*. 2016;165(9):609-616.
23. The American Gastroenterological Association. Patient info: Fecal Microbiota Transplantation (FMT). https://aga-cms-assets.s3.amazonaws.com/2018121921556---FMT_PatientEdPage_Combined.pdf. Accessed February 23, 2019.
24. Samarkos M, Mastrogianni E, Olga K. The role of gut microbiota in *Clostridium difficile* infection. *Eur J Intern Med.* 2018;50:28-32.
25. Hui W, Li T, Liu W, Zhou C, Gao F. Fecal microbiota transplantation for treatment of recurrent *c. difficile* infection: An updated randomized control trial meta-analysis. *PLoS One*. 2019; 14(1):1-14.
26. Weingarden A, Gozalez A, Vazques-Baeza Y, Weiss S, Humphry G, et al. Dynamic changes in short- and long-term bacterial composition following fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Microbiome.* 2015;3:10.
27. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci USA.* 2010;107(33):14691-6.
28. Mu C, Yang Y, Luo Z, Zhu W. Temporal microbiota changes of high-protein diet intake in a rat model. *Anaerobe.* 2017;47: 218-225.
29. Zimmer J, Lange B, Frick J-S, Sauer H, Zimmermann K, Schwiertz A, Rusch K, Klosterhalfen S, Enck P. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *Eur J Clin Nutr.* 2012;66(1):53-60.
30. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-108.
31. Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, Brown D, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J*. 2011;5(2): 220-230.
32. Ma N, Tian Y, Wu Y, Ma X. Contributions of the interaction between dietary protein and gut microbiota to intestinal health. *Curr Protein Pept Sci*. 2017;18(8):795-808.

33. Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut microbiota in host health and disease. *Cell Host Microbe.* 2018;23(6):705-715.
34. Vangay P, Johnson AJ, Ward TL, Kashyap PC, Culhane-Pera KA, Knights D. US immigration westernizes the human gut microbiome. *Cell.* 2018;175(4):962-972.
35. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: The deleterious consequences of a diet deficient in Microbiota-Accessible Carbohydrates. *Cell Metab.* 2014;20(5):779-786.
36. Han M, Wang C, Liu P, Li D, Li Y, Ma X. Dietary fiber gap and host gut microbiota. *Protein Pept Lett.* 2017;24(5): 388-396.
37. Gropper SS, Smith JL, Carr TP. *Advanced Nutrition and Human Metabolism*. Boston, MA: Cengage Learning.
38. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes.* 2017;8(2):172-184.
39. APnews.com. Human Microbiome Market to 2025 – Global Analysis & Forecast Product, Disease, Application, and Geography – ResearchAnd Markets.com. April 3, 2019. https://www.apnews.com/Business%20Wire/d34086b1117344f897cb5f6382e9faed. Accessed May 24, 2019.
40. Singh V, Yeoh BS, Chassaing B, Xiao X, Saha P, Olvera RA, Lapek Jr. JD, Zhang L, et al. Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. *Cell.* 2018;175(3):679-694.
41. Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, Duncan G, Johnstone AM, et al. High protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr.* 2011;93(5):1062-72.
42. Duncan SH, Belenguer Al, Holtrop G, Jonhstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol.* 2007;73(4): 1073-1078.
43. Butteiger DN, Hibberd AA, McGraw NJ, Napawan N, Hall-Porter HM, Krul ES. Soy protein compared with milk protein in a Western diet increases microbial diversity and reduces serum lipids in Golden Syrian hamsters. *J Nutr.* 2016;146(4):697-705.
44. Miclotte L, Van de Wiele T. Food processing, gut microbiota, and the globesity problem. *Crit Rev Food Sci Nutr.* 2019 Apr 4:1-14.
45. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature.* 2015;519(7541):92-96.
46. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature.* 2014;514(7521):181-6.
47. Ruiz-Ojeda FJ, Plaza-Diaz J, Sáez-Lara M, Gil A. Effects of sweeteners on the gut microbiota: A review of experimental studies and clinical trials. *Adv Nutr.* 2019;10:S31-S48.
48. Glade MJ, Meguid MM. A glance at…dietary emulsifiers, the human intestinal mucus and microbiome, and dietary fiber. *Nutrition.* 2016;32(5):609-614.
49. Accessdatafda.gov. Food additives permitted for direct addition to food for human consumption: Sec. 172.840 Polysorbate 80. Code of Federal Regulations database.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.840. Accessed June 3, 2019.
50. Sniffen JC, McFarland LV, Evans CT, Goldstein EJC. Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. *PLoS One.* 2018;13(12):e0209205.
51. Sáncehz B, Delgado S, Blanco-Míguel A, Lourenço A, Gueimonde M, Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. *Mol Nutr Food Res.* 2017;61(1).
52. Floch MH. The role of prebiotics and probiotics in gastrointestinal disease. *Gastroenterol Clin North Am.* 2018;47(1):179-191.
53. Luo G, Li B, Yang C, Wang Y, Bian X, Li W, Liu F, Huo G. Major traditional probiotics: Comparative genomic analyses and roles in gut microbiome of eight cohorts. *Front Microbiol.* 2019;10:712.
54. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanism of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol.* 2013;6(1):39-51.
55. Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for the stimulation in the human gut. *Front Microbiol.* 2016;7(979).
56. Wolfram, T. Prebiotics and probiotics: Creating a healthier you. Academy of Nutrition and Dietetics. February 27, 2018. https://www.eatright.org/food/vitamins-and-supplements/nutrient-rich-foods/prebiotics-and-probiotics-creating-a-healthier-you. Accessed May 27, 2019.