

# We Are Not Alone: The Unseen World of the Human Microb

by

Joan-Beth Gow  
School of Fire and Health Sciences  
Anna Maria College, Paxton, MA



## Prologue

This case study is an introduction to the amazing world of the microbiome, the vast array of microbes that live in and on you. To introduce you to this world, you will watch three videos.

The first video describes the human microbiome in the context of an ecosystem:

- *The Human Ecosystem*. Genetic Science Learning Center, 2014.  
<<http://learn.genetics.utah.edu/content/microbiome/ecosystem/>>

The fictional microbe Heidi Helicobacter, an inhabitant of college freshman Kristen's gut, narrates the second video, which introduces the diversity of the microbial world and our complicated relationship with it:

- *We Are Not Alone: The Unseen World of the Human Microbiome*. Created by Joan-Beth Gow for the National Center for Case Study Teaching in Science, 2017.  
<[https://youtu.be/RX3\\_sRYXdsA](https://youtu.be/RX3_sRYXdsA)>

The third video discusses the use of fecal microbiota transplantation (FMT) as a treatment for an illness known as *Clostridium difficile* infection:

- *Fecal Microbiota Transplantation*. Mayo Clinic, 2014.  
<<http://youtu.be/Awn3haOpfI>>

As you watch the videos, consider the following questions. Come to class prepared to discuss answers to these questions with your group.

## Questions

1. The terms *germ* and *microbe* are often used interchangeably. What comes to mind when you hear the word *germ*?
2. What exactly is meant by the microbiome? The word *biome* can be defined as a major ecological community type such as a grassland or desert. Why is the term *microbiome* used to describe the microbes that live in or on the human body?
3. Name and briefly describe the types of microbes to which you were introduced that inhabit the human microbiome.
4. Explain, using Heidi Helicobacter's story as an example, how microbes can be both beneficial and harmful. Provide at least one more example of a benefit obtained from a microbe and an example of harm that can be caused by a microbe. Be as specific as you can.
5. What are some factors that can lead to disruption of a healthy microbiome?
6. What surprised you most about what you learned from the videos?

## Part I – Microbiome Out of Balance

Consider the videos you watched outside of class in preparation for this case study. Recall that in the second video, Heidi Helicobacter was the main character and she introduced you to the vast array of different types of microbes that are part of a human microbiome. Heidi and her friends inhabited Kristen, then a college freshman. The next part of the story takes place a year after the scene in the video.

Kristen, now a college sophomore, was in the hospital again. She couldn't take it anymore. This was her third time with "*C. diff*" and by far the worst yet. The diarrhea was almost uncontrollable, her stomach was killing her, and she had a fever. "*C. diff*" is shorthand for *Clostridium difficile* infection, which results from a bacterium that can be present in our guts naturally, but usually in very low numbers. When it proliferates, it can cause symptoms ranging from mild diarrhea to severe ulcerative colitis. About a half million people in the U.S. are diagnosed with *C. diff* each year, and 29,000 die. *C. diff* generally affects older patients, but unfortunately is becoming more common in the younger population. It is frequently a hospital-acquired infection. Kristen's doctor said she had probably picked it up initially when she was in the hospital with pneumonia and it had just never been adequately treated. Kristen had missed so much school she didn't know how she was ever going to catch up.

Deep inside Kristen's gut things were a lot different than they had been a year ago. Heidi Helicobacter and her friends were nowhere to be found. Heidi was most likely killed by all the antibiotics Kristen had been taking, and her non-bacterial friends, although not susceptible to antibiotics, probably died off from the disruption to their microbial habitat. Carmen Clostridium and her family had taken over and were brewing all sorts of poisons.

"It's a new microbiome now," laughed Carmen Clostridium maniacally.

Up above, Kristen was talking to Dr. O'Halleran.

"Why does this keep happening to me?" moaned Kristen.

"Your pediatrician really did you a disservice by prescribing all those antibiotics to you over the years every time you came down with bronchitis. Those antibiotics killed off the good bacteria in your gut and let some of the stronger, nastier ones grow. Your microbiome has been disrupted and you are in dysbiosis. It may sound disgusting to you, but we have had very good success treating patients who have *C. diff* with fecal transplants where we administer feces from a healthy donor to repopulate the gut with normal flora."

"My what and dysbi ... what?" asked Kristen. "And you want to do what—give me someone else's poop?"

"Kristen, you can't keep going on like this. We can give you another round of antibiotics targeted to the *Clostridium difficile*, but you know every time we do that in the long run it is likely making the problem worse. Look how miserable you are. You are too young to be debilitated like this. Please read this informational sheet and talk it over with your family. I'll come back tonight to answer any questions, and you can let me know what you've decided."

### Questions

1. What is *dysbiosis* and how does it contrast with *symbiosis*?
2. How was Kristen's microbiome disrupted?
3. Why does Dr. O'Halleran tell Kristen that in the long run antibiotic therapy is making her *C. diff* worse?
4. The proper term for fecal transplant is fecal microbiota transplant or FMT. Why would FMT work as a treatment for illnesses such as *C. diff*?
5. Besides what is included in the brief informational flyer, what else would be valuable to you in making your decision? Consider the video you watched on FMT to help formulate your response.
6. If you were Kristen, would you have the fecal transplant? Why or why not?

# Fecal Microbiota Transplant (FMT)

## What Is A Fecal Transplant?

A fecal transplant is the transfer of feces from a healthy donor to a patient suffering from a disease, presumably due to disruption of their gut microbiome. The transplant repopulates the gut with “good” bacteria.

## Who Can Benefit?

Currently the FDA only approves FMT for patients suffering from recurrent bouts of *Clostridium difficile* infection (CDI).

## Where Does The Fecal Matter Come From?

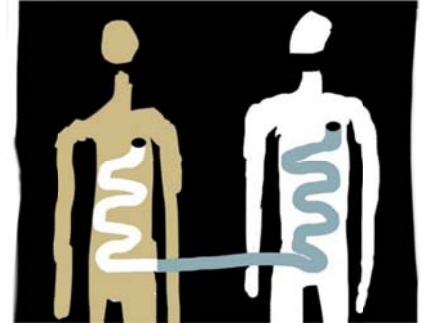
Often a healthy family member or friend will donate the feces, but it may also be obtained from a stool bank. Potential donors are screened for infectious pathogens.

## How Is The Transplant Done?

Donor stool mixed with sterile saline is typically transferred by colonoscopy. Sometimes stool is transferred using a fecal enema or by an infusion via a nasogastric tube.

## How Successful Is It And Are There Any Side Effects?

Common side effects include belching, bloating, and cramping. A success rates of 90% has been reported for treatment of CDI with FMT (see Gough, Shaikh, and Manges, 2011 for additional data).



Credit: Andrea Levy



## Part II – Activity: How Can the Use of Antibiotics Disrupt the Balance of a Healthy Microbiome?

It is very likely that you have taken an antibiotic over the past year, and if you haven't, certainly a friend or family member has. Antibiotics kill bacteria that are making you sick and help you feel better. These drugs, however, target structures common to all bacteria and don't discriminate between bacteria responsible for disease and all the rest of the bacteria that are normal residents of a healthy microbiome.

Over time, overuse or misuse of antibiotics can kill off the normal bacterial residents of the human microbiome and allow the more resistant bacteria to proliferate. *Clostridium difficile* is an example of a bacterium often found in the gut in very low numbers. It is a pathogen and is naturally very resistant to antibiotics. Provided an opportunity it will increase in number until it is a dominant species in the human gut.

Antibiotics do not create resistance, but in a classic example of survival of the fittest, provide the selective pressure for bacteria that are already resistant to propagate. Naturally within any bacterial population, some species will be more sensitive to antibiotics and some will be more resistant. Variation like this is genetic and is normal within any species.

The goal of this activity is to demonstrate how, with use of antibiotics, the microbial balance in our microbiome can be tipped, sometimes in favor of a pathogen. You will observe the response of four hypothetical bacterial species to various antibiotic treatments over time. You will record total bacterial count and the distribution of resistant and non-resistant species.

### Procedure

Four different colors of beads, representing four species of bacteria, all possible residents of the microbiome, will be utilized. The species differ naturally in their resistance to a particular antibiotic. Three different antibiotic treatment regimens will be modeled:

- following doctor's orders
- ending antibiotic treatment early
- skipping Day 3 of treatment

Your initial population of bacteria is represented as follows:

- 40 beads that represent Species 1, the most susceptible to the antibiotic (susceptible on Day 1 of treatment)
- 30 beads that represent Species 2 (susceptible on Day 2), slightly more resistant than Species 1
- 20 beads that represent Species 3 (susceptible on Day 3), slightly more resistant than Species 2
- 10 beads that represent Species 4 (susceptible on Day 4), the most resistant species of all.

Thus the species vary in the concentration of antibiotic and/or the duration of exposure necessary to kill them.

At the beginning of each "day:"

- The antibiotic is taken (except where noted below).
- Ten percent of the total number of bacteria is removed through the action of host immune system defenses (species are assumed to be equally susceptible to these responses). The total number of bacteria to be removed is calculated, and then taken randomly from among the four species. Do this by having one group member close their eyes, touch one of the four cups holding the beads, then remove one from the cup. Continue until the calculated number of bacteria has been removed from the population. On Day 0 and each subsequent day, 10% of the bacteria is removed.
- If the species is susceptible on that particular day, then half of those bacteria are removed. For instance, on Day 1 of the experiment, Species 1 is susceptible and half of those microbes are removed from the population. By Day 4, all the species would be susceptible and half the bacteria from each cup would be removed.
- If a species is not susceptible on a particular day, then the number of bacteria is actually doubled, simulating microbial division. For instance, on Day 1 of the experiment, Species 2, 3, and 4 are not susceptible, so

the number in their respective cups would be doubled. On Day 4, only Species 4 is not susceptible, so that population would be the only one to be doubled.

- Each group should make their calculations and use the data collection sheet to enter the number of each species of bacteria present on each day until 0 bacteria are counted in each species. The number of days necessary to reach 0 will vary according to the antibiotic regimen, and for some regimens will never occur.

### Regimens

- *Following doctor's orders:* Follow the directions above exactly.
- *Ending treatment early:* Discontinue antibiotic use on Day 5. At this point, a patient on antibiotics would begin to feel better and might stop taking their prescribed medication. Once antibiotic use is discontinued, 10% of the total number of microbes is removed randomly at the start of each day. Following that, all species will double in number as antibiotic is no longer present.
- *Skip Day 3 of treatment:* Often, patients think it's no big deal if they skip a day or two of a prescribed antibiotic regimen. Assume that when a day of taking the antibiotic is skipped, the antibiotic concentration will fall to 0 and numbers of all species will double on that day. Following that, the "susceptibility clock" is reset to Day 1. In other words, after the skipped day, only Species 1 is susceptible. Two days after the skipped day, Species 1 and 2 are susceptible, etc.

### Questions

1. Assume Species 1, 2, and 3 are normal gut inhabitants and are not pathogenic. Species 4 represents a pathogen such as *C. difficile*. Explain, using data from this simulation, how *C. diff* can be caused by overuse and misuse of antibiotics.
2. How do the number and distribution of bacteria differ when the prescribed treatment regimen is followed and when antibiotic treatment is stopped prematurely?
3. What are the effects of skipping a day of treatment?
4. Dr. Lita Proctor, Program Director for the Human Microbiome Project, has said this about antibiotic treatment: "We can often cause more problems than we cure in many cases when we take antibiotics, especially when we don't take the full regimen." How would you respond to this statement?
5. Explain why the following statement is incorrect: "Antibiotics have created resistant bacteria."
6. How does this simulation provide support for treatments such as FMT for infections such as *C. diff*?
7. Does this simulation change any thoughts you have on antibiotic use? How?



## Part III – Ten Years Later and the Start of a New Microbiome

Kristen couldn't imagine where the time had gone. It seemed like only yesterday that she was in college and now she was married and expecting her first child. Kristen felt healthy and strong and ready to take on the world.

Deep inside her, her microbes were also healthy and strong and really excited. They were arguing over who would get to leave and colonize the new baby. More and more studies were showing the importance of the microbes that populate a new baby during the trip through the birth canal. Some would be skin flora that could easily jump on board. Others would be swallowed to populate the gut and still others would populate the respiratory system.

"I'm definitely going," stated Bonnie Bacteroidetes. "I'm a descendent of the Bacteroidetes family that helped repopulate Kristen's gut with normal microbial flora after her horrible bout with *C. diff* years ago. My family moved over from Kristen's mom after she donated her feces for Kristen's FMT procedure. I will train the new baby's immune system to keep inflammation down so she doesn't end up with diseases like ulcerative colitis and Crohn's disease. I may even be able to prevent other diseases like type 1 diabetes and multiple sclerosis."

Floyd Firmicutes chimed in, "I want to go too. I don't like living here and I want a new home."

"No way," responded Bonnie Bacteroidetes. "You make people unhealthy."

"Hey, hey," said Lucy Lactobacillus trying to mediate. "There's no proof of any of this. No one knows for sure exactly which of us has to be present to make up a healthy microbiome, and no one knows for sure how the absence of one of us can affect our human host. And no wonder! Apparently there are millions of different species of us that call humans home and every human has a unique microbial fingerprint. Heck, there are some scientists that believe our community is so unique for each person that one day it will be our DNA, and not the human's DNA, that will be used for forensic evidence."

"I do hope Kristen is planning on nursing the new baby," said Bonnie Bacteroidetes. "There are certain sugars in breast milk whose sole role is to nourish particular bacteria. In turn, those bacteria seem to play a major role in protecting the newborn from infection."

Hugo Helicobacter wandered over to insert his two cents. "You know that it's legendary in my family what my great-great grandmother Heidi Helicobacter said about our relationship with our humans. It's complicated, she would say. There are so many factors that play a role in who makes up our community and our community changes as our human does. Age, what they eat, where they work, how they interact with their friends and family—all of that influences our microbial community. And when some key species of us are missing, watch out! Currently, disruptions in the human microbiome have been associated with asthma, colorectal cancer, skin cancer, kidney stones, gum disease, psoriasis, anxiety, depression... There's even a study that some elderly are frail because their microbe mix became too uniform over the years. And it's been shown in mice that the composition of their microbiome affects how likely they are to take risks. We microbes may be small, but we sure are mighty!" Hugo was puffed up with his own self-importance.

"Yes, all true," said Lucy Lactobacillus, "but I think we have to be careful what we take credit for. Scientists are still a ways away from determining the exact relationship the microbiome has to most diseases and even further from determining the mechanism that can lead to these diseases."

All of a sudden the microbes noticed some frantic activity up above. The new baby was coming! Gulping and breathing in Kristen's microbes as the baby moved through the birth canal, her own microbiome would start establishing itself. Being held by the doctor and then her mom and dad would transfer some of their microbes to her skin. Every event that ensued would play a role in establishing the baby's own human microbiome.

### Questions

1. What factors play a role in the development of the microbiome?
2. What role does the microbiome play in human health and disease?

3. Bonnie Bacteroidetes told Floyd Firmicutes that too many of his kind would make people fat. Bacteroidetes and Firmicutes are two of the main phyla that inhabit the human gut. There is evidence from a number of sources that the ratio of Bacteroidetes to Firmicutes plays a role in weight. If the ratio is tipped in favor of Firmicutes, obesity can result. Propose a mechanism (other than that given in the video for *H. pylori*) that would explain how too many of a particular type of microbe could be associated with obesity. *Hint:* Consider that one role of microbes in our gut is to metabolize carbohydrates.
4. Currently FMT can only be used to treat *C. difficile* infections if a hospital is enrolled in a clinical trial. Fecal transplants have been proposed to treat Crohn's disease, multiple sclerosis (an autoimmune disease), obesity, and a host of other diseases. Discuss the appropriateness of this therapy for these diseases.
5. When babies are born by Caesarean section, they do not get exposed to the same microbes as babies delivered by vaginal birth. Research suggests there may be negative consequences to this and studies are now being conducted where babies born by C-section are smeared with gauze incubated in their mother's vagina to pick up the microbes that would colonize a baby born by vaginal birth. What are your thoughts on this? Are there any potential negative consequences to this?
6. Companies such as Ubiome allow you to send in samples from various parts of your body and they will send you an analysis of your microbiome for a fee. Is this information valuable?

