



WHAT ARE POOP TRANSPLANTS AND HOW DO THEY WORK?

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JADA

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Microbes are tiny creatures that live in and on our bodies. Many of them, especially those in the gut, help to keep us healthy. Sometimes, when we eat spoiled food or take antibiotics, we wipe out many of these good microbes. Usually, our good microbes recover from these disturbances, but sometimes harmful microbes can take their place and cause disease. *Clostridioides difficile* is a harmful microbe that causes severe diarrhea. Usually, antibiotics can kill *C. difficile* and return the gut to a healthy state, but in some cases, this microbe can come back again and again. Some people end up dying from these recurrent, antibiotic-resistant *C. difficile* infections. Recently, scientists have found that recurrent *C. difficile* can be cured by transplanting poop from a healthy person into a sick person. This process is called fecal microbiota transplantation (FMT) and it saves thousands of lives in the U.S. each year.

Figure 1

More than half of the cells in and on our bodies are microbial and they account for ½–1 pound of our body weight. These microbes can be found all over the exposed surfaces of our bodies, with most of them inside the gut.

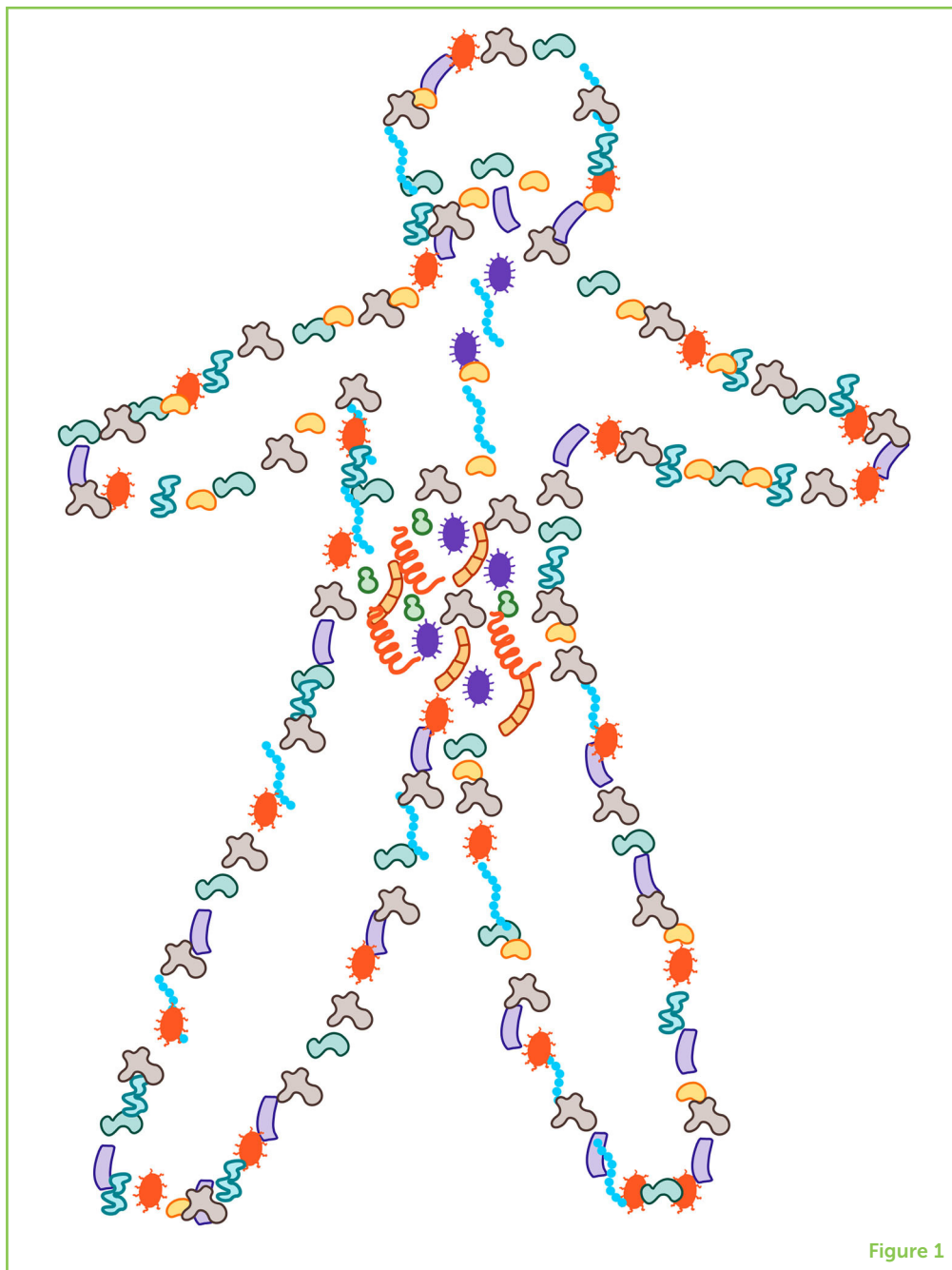


Figure 1

MICROBES—FRIENDS NOT ENEMIES!

You may have heard of **microbes**, or maybe you have heard them referred to as “germs” or “bugs.” Despite these rather scary terms that remind us of disease, many of these organisms are actually good for you and play an important role in keeping you healthy. Although you cannot see these tiny creatures with your eyes, they are present all around you—in the air, on the wall, in the soil, and in and on your body (Figure 1). The vast majority of microbes are harmless or even beneficial. They consist of bacteria, archaea, protists, fungi, and viruses, collectively known as your **microbiota**, which outnumber the

MICROBE

A microscopic organism.

MICROBIOTA

All the microbes that live in and on your body.

Figure 2

The gut is an ecosystem, like a forest or a coral reef. Often, a disturbed ecosystem, like a forest after a fire (A) or the gut microbiota after antibiotic treatment (B), recovers back to a healthy state. Occasionally, however, weedy species (such as *C. difficile* in the gut) can invade and take over after a disturbance, leading to a collapse of the normal ecology of the system.

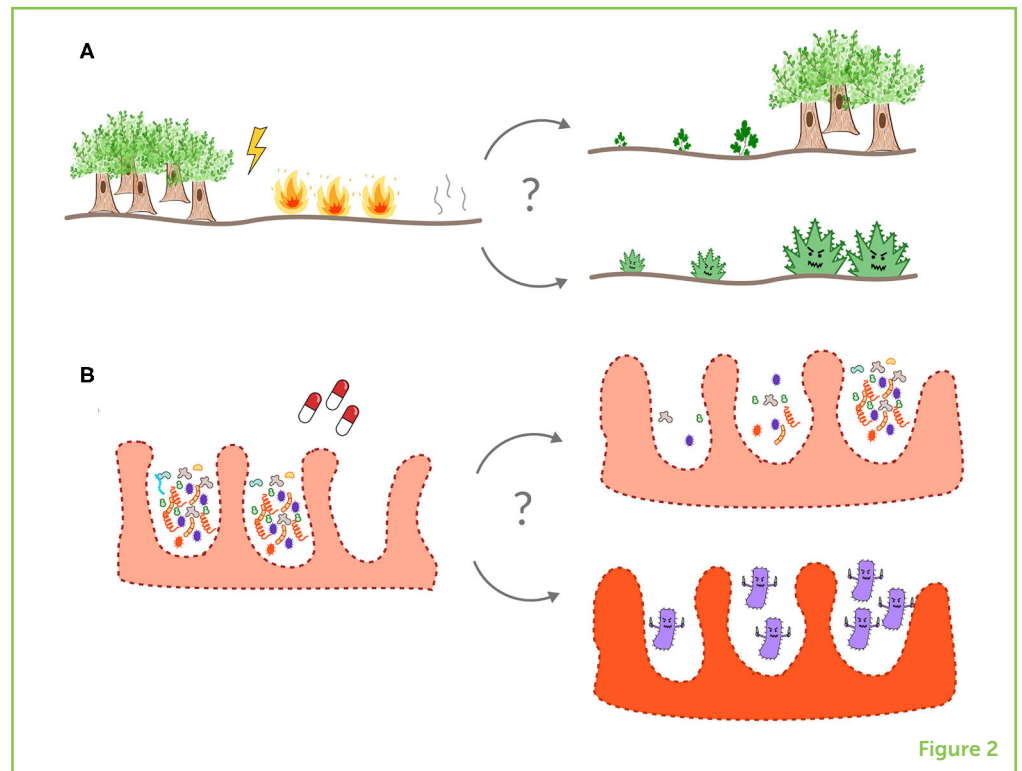


Figure 2

human cells in our bodies and make up between $\frac{1}{2}$ and 1 pound of your body weight.

We start out microbe-free in the womb [1], and begin to collect our microbiota at birth [2]. Humans are seeded with microbes from their moms and from their surrounding environments following birth. Over the course of a lifetime, we are colonized by different varieties of microbes depending on what foods we eat, where we live, how much we exercise, even whether or not we have a cat or a dog [2]. Thus, our bodies are complex ecosystems. We give our microbiota a home and in return they help to keep us safe and healthy.

The gut is where most of our microbiota live. And the most abundant component of the gut microbiota are the bacteria. Gut bacteria help us digest our food, absorb vitamins and nutrients, protect our bodies from harmful microbes known as pathogens, and train our immune systems to prevent allergies, asthma, and other immune dysfunctions. Gut bacteria can even send signals to our brains, altering our moods and behaviors [3]. We need a balance of the right kinds of bacteria in our guts to stay healthy.

HEALTHY VS. UNHEALTHY MICROBIOTA

What is a healthy gut microbiota? Each person has a unique microbiota and there is no one-size-fits-all definition for what comprises a healthy gut ecosystem [4]. Even if we do not know exactly what a healthy

Figure 3

(A) Usually, the gut microbiota can recover from antibiotics. (B) However, sometimes a pathogen, like *C. difficile* can invade a damaged gut ecosystem. Usually, another dose of antibiotics can return the gut back to health. (C) Occasionally, *C. difficile* comes back again and again after antibiotics and becomes a recurring infection. Recurrent *C. difficile* causes thousands of deaths in the United States each year. (D) The most effective cure for recurrent *C. difficile* is a fecal microbiota transplant (FMT) from a healthy poop donor, otherwise known as a poop transplant.

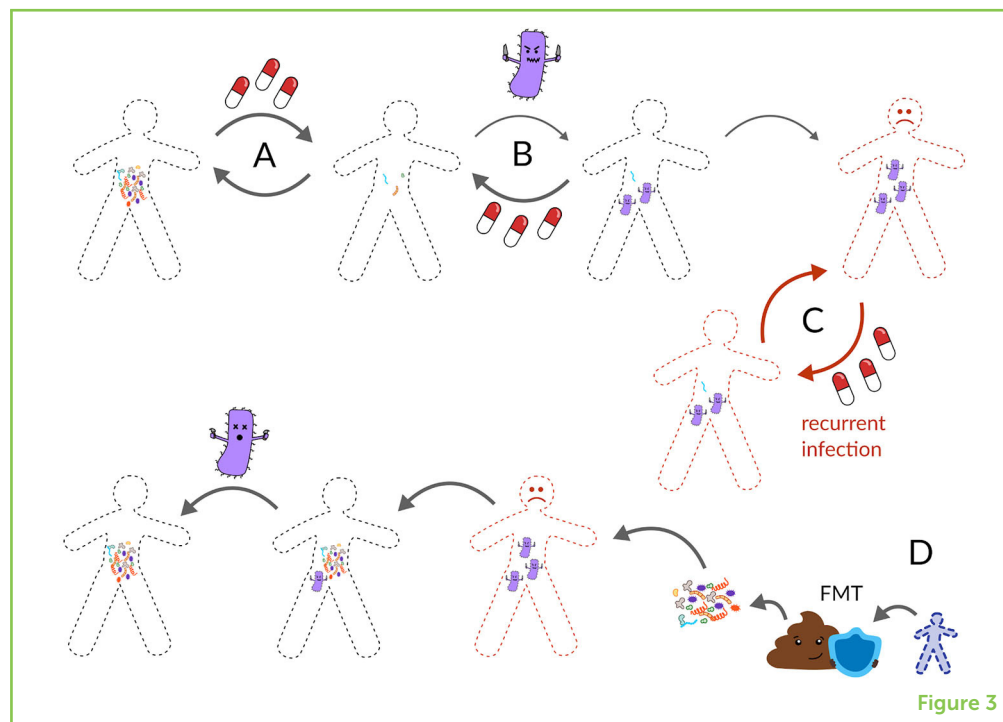


Figure 3

microbiota looks like, we can often recognize an unhealthy microbiota when we see one. For example, eating spoiled food can introduce pathogens into the gut, leading to an upset stomach and diarrhea. Most of us have taken **antibiotics** at some point in our lives to get rid of the bacteria that make us sick. However, antibiotics cannot tell the difference between “good” and “bad” microbes. Each time we take antibiotics, it is like having a fire burn through our gut, damaging our internal ecology. Just like a forest after a fire, the gut ecosystem usually bounces back from antibiotic treatment. But sometimes, instead of bouncing back, weed-like microbes can take over, causing disease and preventing the good microbes from returning (Figure 2).

DEADLY *CLOSTRIDIODES DIFFICILE* INFECTIONS

Clostridioides difficile is a weed-like microbe known as an **opportunistic pathogen**. Opportunistic gut pathogens are microbes that do not normally cause harm, but when the gut ecosystem is damaged these bacteria can invade and cause a problem. For example, *C. difficile* can sometimes live in a healthy person’s gut without causing trouble—the resident gut microbiota prevents it from producing toxins and causing an infection. However, when the gut ecology is damaged, like after taking a round of antibiotics, this weed-like pathogen can take over and cause severe diarrhea (Figure 3A) [5]. According to a report by the Center for Disease Control (CDC) in 2011, *C. difficile* causes about 500,000 infections and kills around 15,000 people each year in the United States, making it one of the most important diseases on the CDC’s prevention list [5]. *C. difficile* tends to infect older

ANTIBIOTICS

Medicines that kill or inhibit the growth of bacteria.

CLOSTRIDIODES DIFFICILE

An opportunistic bacterial pathogen that causes severe diarrhea in nearly 500,000 people and is responsible for over 10,000 deaths each year in the U.S.

OPPORTUNISTIC PATHOGEN

A microbe that is usually harmless but can cause disease when the immune system is depleted or when the normal ecology of the microbiota is damaged.

adults with weakened immunity or people who have recently been sick or taken antibiotics. About 70% of *C. difficile* infections can be successfully treated with the antibiotic vancomycin (Figure 3B). However, in 20–35% of cases, the infection returns after vancomycin treatment [6]. These recurrent *C. difficile* infections are highly resistant to further antibiotic treatment, leading to endless cycles of antibiotic treatment and infection recurrence, which can eventually result in patient death (Figure 3C) [7].

POOP TRANSPLANTS

Thinking back to our forest metaphor, imagine the ecosystem has burned down, been stripped of its native vegetation, and is now overgrown by weeds. One way to return the forest to its original state would be to cut down all the weeds and transplant flora and fauna from a nearby patch of unburned forest. Poop transplants, known as **fecal microbiota transplants** (FMTs), work in a similar way. First, a patient is given a dose of antibiotics to reduce the abundance of *C. difficile* and then the patient is given a dose of healthy poop from a poop donor (Figure 3D). Traditionally, poop transplants were administered by enema or through a tube going through the nose, down the throat, and into the gut, but now patients can swallow pills containing frozen or freeze-dried poop.

While the exact mechanisms are not completely understood, transplanted microbiota from a healthy person's gut regain control of the ecosystem and push *C. difficile* out. FMTs can be either **autologous** (healthy poop from yourself, collected before you were sick) or **heterologous** (healthy poop from another person). As gross as they sound, these poop transplants have been shown to be 80–90% effective in resolving recurrent *C. difficile* infections¹ and have been used to cure tens-of-thousands of patients in the U.S. Thus, FMT is a life-saving option for people with recurrent *C. difficile*.

SAFETY FIRST

FMTs are highly effective and the Food and Drug Administration (FDA) has temporarily approved them as treatments for recurrent *C. difficile* infections. However, it is important to be extremely careful when choosing healthy poop donors. Currently, companies that make FMT material must test poop donors for most known human pathogens and for antibiotic-resistant bacteria. Poop donors are also subject to strict screening based on their lifestyle, travel, and medical history. Only the very best poop is acceptable, and approved donors can make up to \$40 per poop donation². Most healthy people carry one or more opportunistic pathogens in their gut, which are harmless when the gut ecosystem is healthy, but these organisms could cause trouble if they were transferred into a sick patient.

FECAL MICROBIOTA TRANSPLANT (FMT)

A procedure in which poop from a healthy donor is transplanted into the colon of a sick patient.

AUTOLOGOUS

Obtained from the same individual.

HETEROLOGOUS

Obtained from a different individual.

¹ <https://www.openbio.me.org/about-fmt>

² <https://www.openbio.me.org/stool-donation>

³ <http://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-about-potential-risk-serious-infections-caused-multi-drug-resistant-organisms>

⁴ <https://www.openbiome.org/press-releases/2020/3/12/openbiome-announces-enhanced-donor-screening-protocols-following-fda-alert>

Recent events have shown how important donor screening is. Over the last couple years, eight patients have developed infections from pathogens that were passed to them through FMT, leading to the deaths of three patients³. Some of these patients had undergone bone marrow transplants, and their immune systems were extremely weak, making them especially susceptible to opportunistic pathogens. In one case, the poop donors were not screened using the most up-to-date regulations [8]. In another case, proper screening was done but this screening was still not sufficient to catch certain pathogens that caused problems in six patients, leading to updated screening criteria⁴. Thus, it is crucial that FMT material be prepared in an FDA-regulated lab with strict procedures in place. Screening should be continuously updated in response to new pathogens like SARS-CoV-2, and FMT procedures should always be performed by certified doctors. FMTs should never be performed at home! Furthermore, long-term risks from FMTs are not well-known yet, because these procedures have not been in use for very long. Despite the potential risks of FMT, properly-screened donor material is currently the most effective treatment for recurrent *C. difficile* infections, with very few adverse effects after tens-of-thousands of treatments across the U.S.

FMT: THE CURRENT BEST OPTION FOR RECURRENT *C. DIFFICILE*

Despite FMT's success, it remains a controversial treatment. Poop is highly variable between donors and cannot be controlled or regulated under the same rigorous standards that the FDA applies to other drugs. To solve this problem, many biotechnology companies are in a race to assemble artificial microbial communities that can be reproducibly manufactured under strict conditions, and which mimic the effects of natural human poop in treating recurrent *C. difficile* infections. So far, none of these synthetic FMT alternatives have proven to be as effective as FMTs. The major difficulty with developing an alternative to FMTs is our lack of detailed understanding of exactly how FMTs work. While there is hope that someday soon a simpler treatment will be available, for now, FMTs are still the best option for fighting the deadly scourge of recurrent *C. difficile* infections.

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YOUNG REVIEWERS



JADA, AGE: 14

Hi! My name is Jada from Atlanta, GA. In my free time, I like to draw/sketch, listen to music, write short stories, and watch an array of movies. I play lacrosse, and I swam for about 5 years. When I become older, I want to be a Cosmetic Plastic Surgeon because I want to make all of my patients proud of their bodies and not insecure about themselves. Helping others is one of my motivations in life!!!



JOSHUA, AGE: 14

I am a rising ninth grader and I live in Atlanta, Georgia. During the academic school year I participate in many programs including the Academic team and the Lacrosse team. When I am not studying or at school I love to read books and play lacrosse. I am happy to be a part of this program because I enjoy science, and I am happy that my feedback is so important in helping people publish their articles.



REEYA, AGE: 15

My name is Reeya and I am a soon-to-be A-level student who is passionate about Biology. In my spare time, I love to read crime novels, a particular favorite is James Patterson's "Along Came a Spider." Furthermore, I like to watch TED Talks and listen to podcasts, such as the BBC's Law in Action podcast. I really like to travel, especially to countries in Europe. In the future, I aspire to study law or economics as I have an interest in social sciences.

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