

An Effective Treatment with a PR Challenge

By Tyler Smith

It was Valentine's Day 2012 and Stephen Freeman, MD, a gastroenterologist at University of Colorado Hospital, was preparing to perform a decidedly unromantic procedure.

His patient, Charmayne Casal, 71, of Cheyenne, Wyo., was suffering from a long-running infection caused by a toxin-producing bacterium called *Clostridium difficile*, or C-diff. She'd spent the past two years on an on-again, off-again regimen of expensive antibiotics that had failed to quell the C-diff infection, which produces bouts of diarrhea, persistent watery stools and abdominal pain.



UCH gastroenterologist Stephen Freeman, MD, says fecal transplant offers important advantages over antibiotics in treating stubborn C-diff infections.

Now Freeman was trying another approach. He would deliver roughly 12 fluid ounces of fecal material collected from her donor husband to Casal's upper large intestine via a colonoscopy. The idea: repopulate her C-diff-ravaged gut with "good" bacteria that help with digestion. In essence, Freeman would deliver the biologic troops needed to battle the bacterial enemy and restore order.

The procedure, known as fecal transplant, worked. Within a day, Casal felt better, and she remains symptom-free (*see sidebar*). Since then, Freeman has performed some three dozen fecal transplants with similarly excellent results. More than 90 percent of his patients recovered after the first transplant. Two suffered a relapse, but recovered after a second procedure.

The success rate, which is mirrored nationally, is especially impressive when it's matched against antibiotic treatment. Metronidazole and vancomycin, the two antibiotics most frequently administered to fight C-diff, are successful only about 60 percent to 70 percent of the time, Freeman said. And the success rate plunges to about 20 to 30 percent if the patient relapses twice.

Name blame. Despite the apparent clinical mismatch, the standard of practice is to use fecal transplant only after two rounds of antibiotic treatment, Freeman said.

Why? The procedure may suffer from an image problem.

"It sounds distasteful and unattractive," Freeman said. "There is a 'yuck factor' involved."

Cost may also play a role, at least in the short run, he added. Currently, most insurers don't cover the cost of screening – \$500 to \$1,000 – necessary to ensure a viable and noninfectious donor stool. Yet a 14-day regimen of vancomycin typically runs \$1,500. Two newer antibiotics proven effective, fidaxomicin and rifixamin, cost about twice that amount, Freeman said.

Furthermore, fecal transplant changes the terms of engagement in the infection fight. Its aim is to rebalance the natural ecosystem of the gut rather than to wipe out the C-diff invaders with antibiotics – an approach that can cause collateral damage to the bacteria the body needs and also spawn increasingly resistant, harmful strains of C-diff.

"There is no question we have had more antibiotic resistance in the past 20 years," Freeman said. "C-diff has not only become more common, its harmful effects have become worse. The increased virulence makes people sicker."

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Losing ground. Indeed, the incidence of C-diff has been on the rise in recent years. The rate of infection per 10,000 patient days **increased fivefold at UCH** between 2005 and 2009. Between 2012 and 2013, the rate of C-diff infections that began within two days of admission at UCH grew nearly 60 percent, from 7.3 to 12.9 per 10,000 patient days, said Teri Hulett, RN, an infection preventionist with the hospital.

Nationally, the rate of increase in C-diff infections 2008 to today is double what it was from 2000 to 2008, Freeman said. In addition, the Centers for Disease Control and Prevention **reports** that the number of deaths related to C-diff infections rose 400 percent between 2000 and 2007. The cost of treating the infections is an estimated \$1.1 billion.

The source of infection is also elusive, Freeman said.

"We used to think that the reservoirs of C-diff infections were hospitals and long-term care facilities," he said. Today evidence increasingly points to person-to-person or possibly animal-to-person contact as a more common means of transmission, he said. Hulett said she was surprised to see the increase in the number of C-diff cases in 2013 that began after patients were admitted to UCH.

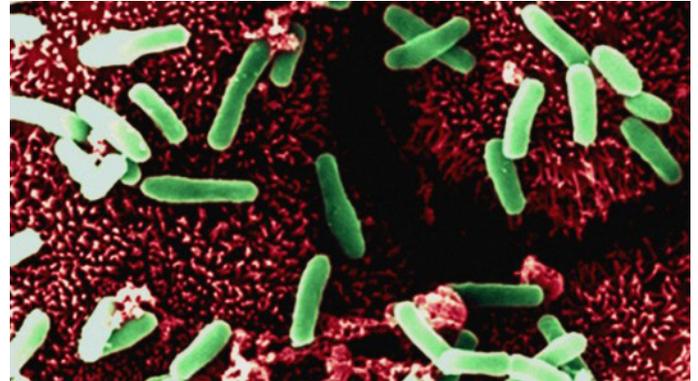
"Years ago, the majority of cases were in our ICUs," she said. "Today we do see much more in the community."

Old idea, new respect. Whatever the source of C-diff, fecal transplant has been available to fight it for a couple of decades, Freeman said. Awareness of the treatment heightened following a series of national meetings in 2011 that addressed its potential benefits. Follow-up articles on the success of the procedure appeared, and Freeman began reading about it. Still, when he began treating Casal as a referral patient, he continued with antibiotics. When they failed to clear up the infection, his patient put her feelings to him bluntly. She'd read about fecal transplants and was ready to give it a try.

"I said to him, 'I can't go on like this. If you can't do this, I have to find someone who will,'" she said.

"It was apparent to me that this was no longer something we could ignore and put off," Freeman said. He called experts in the procedure from around the country and developed a plan and protocol to implement at UCH.

Quick results. Fecal transplant relies first and foremost on a donor, usually, but not always, a member of the patient's household. The hospital screens the potential donor's stool for parasites and harmful bacteria, and administers a blood test to rule out hepatitis, HIV, syphilis and other blood-borne diseases. The donor must also be generally healthy and antibiotic-free for at least three months.



The hospital processes the collected sample with non-bacteriostatic saline – which prevents bacteria from reproducing without harming them – to produce a homogenized solution that is a mixture of solids and liquids. It then filters the solution through gauze to remove the solids. The transplant uses 300 to 350 cubic centimeters of fecal material administered via a nose tube or upper endoscope, enema, or colonoscopy.

The outpatient procedure takes 15 to 30 minutes, Freeman said, but he keeps the patient still and quiet for another couple of hours and gives an anti-diarrheal medication to make sure the donated material stays in the colon as long as possible. After a day patients can generally resume normal activities, he said.

For now, UCH does no special marketing for fecal transplant, said Jenny Maxwell, director of the hospital's Digestive Health Center. "We feature it in fliers, one-pagers and postcards as part of our overall service to patients," she said in an email.

Efforts are afoot to make the fecal transplant less threatening – and more palatable – to patients. For example, a study that includes UCH and Denver Health is testing the safety of a fecal solution, delivered by enema, that could one day be marketed for home use. The trial will involve 40 patients with C-diff infections who have relapsed after taking antibiotics, Freeman said.

Meanwhile, a Canadian study is testing gel capsules containing concentrated fecal material as an alternative treatment. Early results show the pills, taken over a period of time, prevented recurrences of C-diff, and patients tolerated them well.

“Ultimately, we may see commercially available products that contain large numbers and types of bacteria,” Freeman said.

And that troublesome name? Freeman pointed to a slide presentation he delivers about the procedure. An alternate moniker has promise: intestinal microbiota transplant. Stay tuned.

One-Day Procedure Ended 18 Months of Misery

Charmayne Casal still has no idea how or where she contracted her C-diff infection. The 74-year-old homemaker from Cheyenne, Wyo., said she hadn't been in the hospital or any other health care facility when she suddenly became ill in July 2010.

"It's still a mystery," she said.

She awoke that summer morning at 3 a.m. with severe abdominal pain. When she saw a large amount of blood in her stool, she went to her physician's office, whereupon a nurse sent her to the emergency department. She left with a diagnosis of diverticulitis – inflammation of pouches that form in the abdominal wall – and a prescription for antibiotics.



Bacteria from transplanted fecal material help to halt C-diff infections.

When the medicine didn't clear the problem, she spoke up. She'd had diverticulitis and knew this was something different. She landed in the hospital, where a stool test finally identified the C-diff infection.

Antibiotic treadmill. The diagnosis began a long and frustrating round of antibiotic treatment, mainly with vancomycin.

"It controlled the symptoms but I couldn't get off it," she said. She'd begin with four doses a day for a week, then taper down to two daily doses. When she hit that point, though, the symptoms would come back after a few days.

That meant persistent diarrhea that disrupted her life. It was difficult to go to the store or church. And the illness took a

financial toll. Her insurance covered only a portion of the expensive antibiotics.

After she was referred to UCH gastroenterologist Stephen Freeman, MD, Casal read about the fecal transplant procedure and asked for it. Freeman had not performed it at that point, but he read up on it and developed a protocol.

Her husband was tested and approved as the donor. Casal stayed at a motel across from the hospital the night before, preparing for the colonoscopy Freeman would use to deliver the fecal material provided by her husband.

Casal became the first fecal transplant patient at UCH Feb. 14, 2012. She learned only after the pain-free procedure that some 17 people stopped in to view what otherwise appeared to be a routine colonoscopy.

"I just remember seeing a few men with ties," she said.

Within a day of the procedure, Casal felt an improvement, but after 18 months of misery, she was cautious.

"I thought, 'How long is this going to last?'" she said. "I couldn't believe the symptoms were gone. My body said, yes, I was better, but my mind was still saying 'no.'"

Her body was right. Today, Casal is symptom-free.

Casal said she wants more people to know that fecal transplants can stop C-diff infections with a relatively simple procedure.

"I'm very concerned for others who have had to go through what I went through," she said.