One for the Phages: Kidney Transplant Patient with Recurring Infections Gets Viral Help

By Yadira Galindo | December 01, 2020

Maria Madrigal was born with polycystic kidney disease, though she would not know she had the inherited disorder until adulthood when growing cysts caused the organs to begin to fail. At first, dialysis helped, but eventually Madrigal would require a donor kidney, which she received in 2017.

Before her kidney transplant, recurrent infections had been common. After the transplant, they returned, but this time it was worse. The invasive pathogen, a strain of *Escherichia coli*, was multidrug-resistant. It defied treatment, even with the most powerful antibiotics available.

"My health was deteriorating. The more antibiotics, the worse it got. I felt like I was dying," Madrigal said.

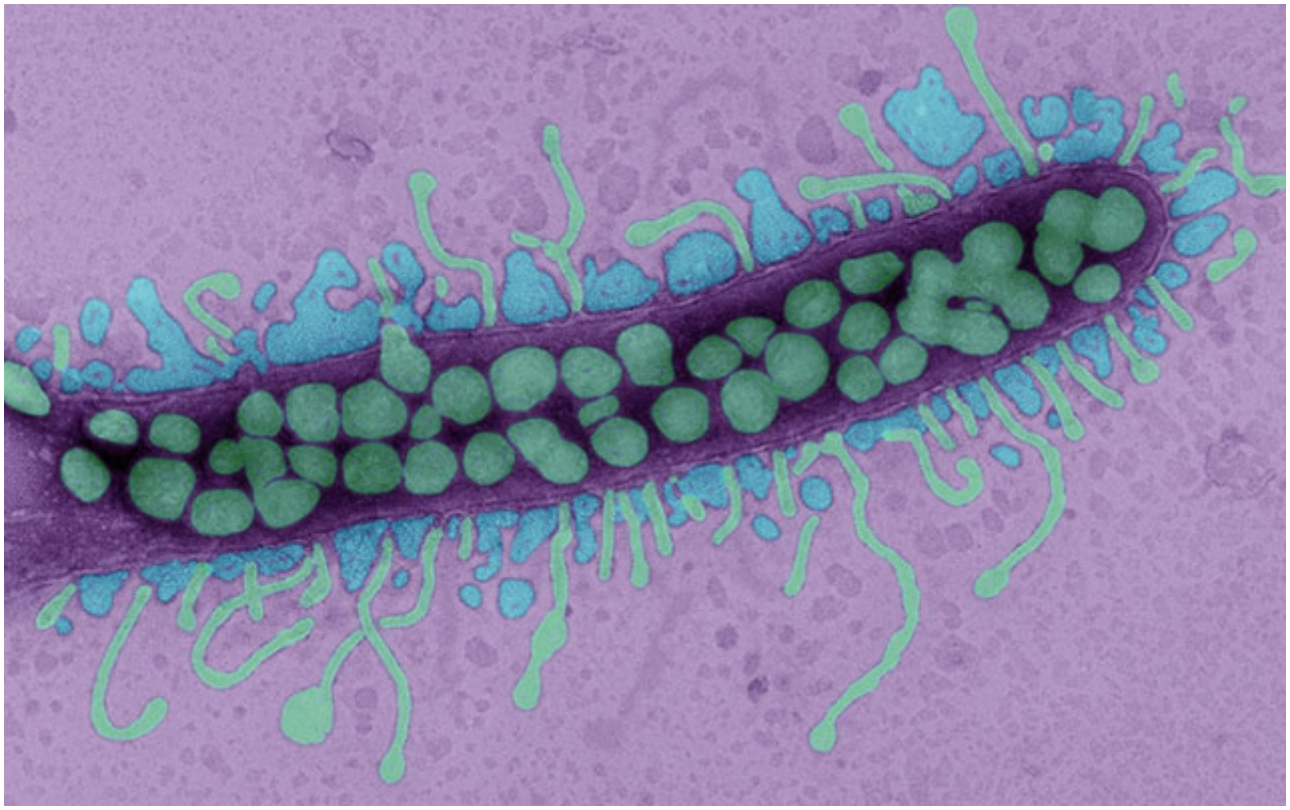
"I first met (Maria) in November 2018 when she was admitted for sepsis and then multiple times after that with recurrent infection," said Saima Aslam, MBBS, director of the Solid Organ Transplant Infectious Disease Service at UC San Diego Health and an associate professor of medicine in the UC San Diego School of Medicine.

"Prognosis in terms of mortality is difficult to judge, but she had multiple hospitalizations for the same issue and has been on almost continuous IV antibiotics — so certainly very poor quality of life and she would eventually run out of treatment options, increasing the risk of dying from the multidrug-resistant infection."

In January 2020, Aslam broached the idea of bacteriophage therapy. Bacteriophages are viruses that specifically attack and kill bacteria. Aslam proposed treating Madrigal's stubborn and life-threatening infections with phages, an emerging treatment that researchers and physicians at UC San Diego have been developing with notable success.

Indeed, the Center for Innovative Phage Applications and Therapeutics (IPATH), the first dedicated phage therapy center in North America, is based at UC San Diego.

"The center arose, in part, out a desperate, life-and-death experience involving my husband," said Steffanie Strathdee, PhD, an infectious disease epidemiologist, professor in the Department of Medicine at UC San Diego School of Medicine and IPATH co-director.



Colorized scanning micrograph of a cell being attacked by phages.

"He was on the brink of death due to a systemic bacterial infection that had defied all other treatments. An experimental phage therapy approved by the FDA on a compassionate basis ended up saving his life. IPATH is about developing and delivering the therapeutic potential of phages to other patients when more traditional approaches don't work."

For every type of bacteria on Earth, there is a phage that targets it. Like other viruses, phages cannot replicate by themselves, but instead commandeer the reproductive machinery of bacteria. They do so by attaching to a bacterium and inserting their genetic material, which begins a process of replication that ultimately splits open the bacterium, spilling out new viral particles in search of new targets.

For Madrigal, the idea would be to find the right combination of phages to treat her specific bacterial infection.

The therapeutic potential of phages is not new. They were explored as a possible medical treatment in the 1920s and 30s, but largely abandoned with the advent of antibiotics. The growing global problem of bacterial antibiotic resistance has fueled their resurgence.

In 2016, a team of UC San Diego Health doctors and scientists used an experimental intravenous phage treatment to save the life of Strathdee's husband: UC San Diego professor Tom Patterson, who had become infected with a multidrug-resistant strain of *Acinetobacter baumannii*, an opportunistic and often deadly bacterium. The treatment worked, with Patterson recovering.

Since the Patterson case, researchers at IPATH, in collaboration with UC San Diego Health physicians, have used phage therapy to treat multiple cases of antibiotic-resistance infections, including patients after organ transplants, with cystic fibrosis or who use implanted medical devices.

In a paper published August 27, 2020 in the journal *Open Forum Infectious Diseases*, Aslam, Strathdee and colleagues describe the first 10 consecutive cases of intravenous phage therapy. In seven of the 10 cases, patients experienced successful outcomes.

Madrigal's is case number 11.

For six weeks, Madrigal received twice-daily infusions of a phage cocktail developed at Baylor College of Medicine in Houston. Her blood count and liver and kidney functions were monitored regularly, and she continued to receive an intravenous antibiotic.

A week into treatment, Madrigal said she began noticing improvement in her health. Her appetite returned. She could walk faster. "I wanted to be active again."

Madrigal's phage therapy ended in August, with blood cultures showing no presence of *E. coli*. She also stopped taking antibiotics. A couple of episodes of fever and increased inflammatory markers have prompted doctors to resume her antibiotics regimen (Aslam is trying to track down the source of the fever) but her blood tests remain negative for the bacterium.

From Madrigal's point of view, phage therapy was an unexpected lifeline: "I saw it as an alternative. I said, 'I'm not going to lose anything if I try. On the contrary, I may benefit.' I did it with all the faith in the world.

"Before phage therapy, I felt my future was uncertain. Actually dialysis too. When one undergoes dialysis, there are always setbacks. There are complications. It has been quite a process to get here. I went through a lot, the removal of both kidneys. But I have always been very optimistic, very confident in myself and very confident in the team behind me. All that has helped me to be well here today."

Aslam said interest in using phages to treat multidrug-resistant organisms is burgeoning. Phage centers have opened elsewhere. From the opening of IPATH in June 2018 to April 2020, physicians and scientists at the center have received 785 phage therapy requests from other doctors, patients and family members of patients. Of these evaluated requests, phage therapy was recommended in 119 cases, with IPATH faculty helping to connect treating physicians with phage labs, therapy plans and logistics. IPATH is also fundraising to develop a phage library of carefully characterized phage that can be used to treat patients faster.

But Aslam cautions that it's still early days: "Clinical trials are being planned to really assess the efficacy in a scientific manner," she said.

Maria Madrigal was born with a kidney disease that ultimately required removal of both organs, and a new donor kidney. But before and after the transplant, she was plagued by a recurring bacterial infection resistant to antibiotic treatment. With assistance from Saima Aslam, MD, and colleagues at UC San Diego Health, Madrigal underwent phage therapy, which involves treating problematic infections with bacteriophages—viruses that specifically target different bacteria.

Clinical trial planned

IPATH is preparing to launch the first National Institutes of Health-funded clinical trial for phage therapy under the auspices of the Antibiotic Resistance Leadership Group.

The single-dose pilot will focus on cystic fibrosis patients who are shedding *Pseudomonas aeruginosa*, an easily transmissible bacterium that can cause infections in the blood, lungs and other parts of the body and which often becomes multidrug-resistant.

Co-principal investigator of the clinical trial is Robert Schooley, MD, professor of medicine and IPATH co-director. There will be multiple trial sites, with the first being UC San Diego and UC San Francisco.

IPATH also received funding from the Cystic Fibrosis Foundation to develop a registry of CF patients with *Burkholderia* (a genus of pathogenic bacteria) and develop a bacteriophage library that can be used in a future clinic trial (Aslam will be the principal investigator Aslam) and from Emily's Entourage to develop a *Staphylococcus aureus* phage library (David Pride, MD, PhD, will be the principal investigator).

To learn more about the featured medical specialties, please visit:

- → Center for Transplantation
- → Infectious Disease
