Phage therapy: A promising weapon in the global superbug crisis

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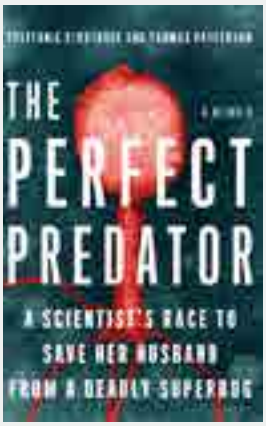
Although phage therapy has been used to treat bacterial infections for over 100 years, it remains an experimental treatment in most Western countries. This article describes a case report where intravenous phage therapy was used to treat a systemic multidrug-resistant ESKAPE pathogen in a critically ill patient in the United States. Lessons learned from this case and others who have since been treated with intravenous phage therapy offers hope that phage therapy may be considered a promising alternative and/or adjunct to classic antibiotic treatment. Given the growing global crisis of antimicrobial resistance, rigorously designed clinical trials are urgently needed to evaluate its efficacy.



As an infectious disease epidemiologist and a professor with academic appointments in both the United States and Canada, I never imagined that some bacteria I used to steak on my petri plates back in the 1980s would evolve to become "superbugs" that had become increasingly resistant to antibiotics. However, in November 2015, during a holiday to Egypt with my husband, Tom, I got a first-hand look at how serious the global antimicrobial resistance (AMR) crisis really was. Tom, suffered a gallstone attack and a superbug moved into the giant abscess that had formed inside his abdomen. It wasn't a garden variety bacterium, but *Acinetobacter baumannii*, which the World Health Organization considers number 1 on its list of the most dangerous superbugs to human health *(1)*. Since I had last met *A.baumannii* as an undergraduate, it had essentially evolved into a bacterial kleptomaniac that collects plasmids laden with antibiotic-resistance genes from other bacteria. By the time Tom was medevacked back to our home to San Diego, his bacterial isolate had become pan-resistant. Despite receiving top medical care, my husband was dying.

When I realized that my husband was about to become a statistic – one of the estimated 1.5 million people who die from superbug infections every year – I took matters into my own hands. Although I was not an MD, I knew how to conduct a literature review and turned to PubMed, a publicly available database made available by the National Library of Medicine. Buried in the scientific literature was something that rang a bell from my virology class decades ago at the University of Toronto: bacteriophages.

Bacteriophages (phages) are the natural predators of bacteria. They were discovered over one hundred years ago by Felix d'Herelle, a self-taught microbiologist who hailed from Canada. D'Herelle initially became famous after the turn of the twentieth century when he discovered a strain of bacteria that killed locusts and developed it into the first organic pesticide. But when he plated the bacteria on a petri dish, his keen eye observed clear zones surrounding some colonies where no bacteria grew. After moving to Paris years later, d'Herelle hypothesized that these clear zones were caused by viruses that preyed upon the bacteria, which he called "bacteriophage" (derived from Greek, meaning "bacteria eater") *(2)*. After dosing himself, his family and staff with a purified suspension of bacteriophages with no ill effects, d'Herelle used phages to treat a boy suffering from dysentery during an outbreak in Paris in 1919; the child was miraculously cured within 24 hours and, subsequently, so were many others.

Phage therapy became popular in the 1920s and 1930s, especially in the former Soviet Union, where d'Herelle helped a bacteriologist named Giorgi Eliava launch the first phage therapy centre in what is now Tbilisi, Georgia. Meanwhile, in the West, phage therapy came under fire after several attempts at commercialization. No one knew at the time that phages needed to be matched to the specific bacteria they

infected, and if they weren't handled properly they could be rendered useless. Some companies over-promised and under-delivered. After the first antibiotic, penicillin, was introduced in 1942, phage therapy was largely abandoned in the West *(2)*. Since d'Herelle was considered an egotist with a tendency to infuriate his peers, and anything resembling Russian was shunned during WWII, phage therapy was essentially forgotten for decades outside of the Republic of Georgia and Poland.

Penicillin and other antibiotics were considered wonder drugs and they certainly were for a while. But the more antibiotics were used and misused, it was clear by the end of the twentieth century that AMR was spreading faster than anyone imagined. In November 2015, the same month my husband fell ill, the mcr-1 gene that confers resistance to colistin, considered an antibiotic of last resort, was discovered in China, where it had been routinely given to pigs as a growth promoter *(3)*. By the time the report was published in *The Lancet*, mcr-1 had spread to 30 countries. Tom's bacterial isolate had it, along with 50 other AMR genes.

When I proposed treating Tom with phage therapy in early 2016, most of his physicians had never heard of it. They were understandably sceptical. Although phage therapy was standard of care in Poland, the Republic of Georgia, and other regions in the former Soviet Union, it was considered experimental by the Food and Drug Administration and similar agencies in many Western countries. But faced with a dying man who had no antibiotic options left, they were willing to give it a chance.

With the help of the internet, I managed to find phage researchers – a global village of total strangers from the USA, Belgium, Switzerland, India and even the Unted Sates Navy Medical Research Center – who undertook a phage hunt to see if they could find some to match Tom's bacterial strain. Phage researchers from Texas A&M University (TAMU) turned their lab into a command centre. They tested not only characterized phages from established libraries but environmental samples from sewage, the ship bilges, barnyard waste and garbage dumps, since phages are best sourced from locations where there are vast quantities of bacteria.

Within three weeks, TAMU and the navy team had each prepared a phage cocktail active against Tom's bacterial strain that was purified and re-purified to enable us to administer the phages intravenously. We obtained emergency approval from the FDA for compassionate use of phage therapy. Three days after phages were injected into Tom's bloodstream, he woke from a deep coma and began his long recovery. Our experience prompted us to write a book which we hope will encourage global awareness of AMR and phage therapy *(4)*.

Immediately after Tom's case was presented at the Pasteur Institute's 100th anniversary of the discovery of bacteriophages in Paris in 2017, and again following publication of his case report *(5)*, I began receiving requests from all over the world from family members asking for phage therapy to save their loved ones from superbug infections. We were able to help some. Others sought treatment from Georgia, Poland or Belgium. Some died before phages could reach them. In response to the growing number of requests, my colleagues and I founded the non-profit Center for Innovative Phage Applications and Therapeutics (IPATH) at UC San Diego (UCSD) in 2018. Our goal is to move phage therapy into clinical trials, and to assist with emergency requests for patients with superbug infections that are no longer responding to antibiotics. To date, IPATH has treated six patients at UCSD and several others in the USA and internationally.

Until recently, the pharmaceutical industry has viewed phage therapy with scepticism. However, in Tom's case and in several others, phage-antibiotic combinations were synergistic *(5-7)*. In other words, the selective pressure that phage and antibiotics exert on a bacterial pathogen can cause it to mutate and suffer a genetic penalty, rendering it more susceptible to antibiotics and/or the immune system. More research is needed to enable clinicians to rapidly identify and exploit these relationships. Looking ahead, the advent of genetically modified and synthetic phage cocktails that can be patented is likely to usher in a new era of antimicrobial treatment.

While it is unlikely that phage therapy will ever replace antibiotics, it is a promising alternative and/or adjunct therapy that deserves to be rigorously evaluated in clinical trials. Given that the global AMR crisis is worsening and is considered to be a more immediate threat to human health than climate change, we cannot afford to allow a promising alternative to be forgotten for another hundred years *(5, 8)*. ■

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