Editor-in-Chief's Note

Host–Pathogen Interactions

Richard I. Shader, MD

I first learned about host–pathogen interactions during my medical school years (1956–1960). In microbiology, the major focus was on bacteria and viruses as pathogens, but we also learned about commensal relationships in which humans are hosts of nonpathogenic bacteria and viruses. In addition, we covered intermediary hosts such as the mosquito for malaria and for the filarial worm *Wuchereria bancrofti*. Saying the latter name aloud amused me then. It still does, although I hasten to add that the serious infirmities it causes are not at all amusing. While I have forgotten much that I learned in those years, the curious names for certain parasites still stick with me. Somehow the flowing and alliterative pronunciations of such parasites have kept my knowledge about them intact even after 60 years. Two other parasites prevalent in central Africa are memorable: (1) *Loa loa*, a filaria that causes eye disease and is carried by the deer fly (aka *deer ked*)—the deer fly also is a vector for other diseases such as anthrax, tularemia, and Lyme disease; and (2) *Onchocerca volvulus*, which is carried by blackflies and causes river blindness. I recently learned that the deer fly population on deer, moose, and elk is increasing in the United States and Canada.[1] Fortunately, deer flies rarely bite people, and in North America they are not known to carry *Loa loa*.

We also briefly discussed a relatively recently discovered bacterium that was described as an aerobic gram-negative rod found in onions (*Allium cepa*).[2] A number of years later it was named *Burkholderia cepacia*.[3] *B cepacia* generally does not harm humans. It exists in soil and in water all over the world except in areas of extreme cold, causing disease in vulnerable people (eg, compromised immune systems, cystic fibrosis [CF]) and skin rot in many damaged or weakened plants (eg, tomatoes, potatoes, bananas, soybeans, and garlic).[4,5] The pathology it produces in onions, known as *sour skin rot*, is especially common when onions are stored in warm, moist, dark places and have started to sprout. Because it is resistant to many antibiotics, colonization with *B cepacia* in the lungs of patients with CF has been associated with poor outcomes. It increases their lung congestion and problems with breathing and can produce high fevers and cause death. Although the transmission of *B cepacia* may occur from contact with an infected plant, human-to-human contact and contact with contaminated surfaces (eg, doorknobs) are the more common modes of spread.[6–8]

B cepacia began to have personal significance for me years ago when the daughter of one of my nieces was found to be colonized with it. Mallory Smith was a beautiful, positive, happy child who loved life and sports, including volleyball, swimming, and water polo. For the last 15 years of her life she kept a secret diary; excerpts from it have recently been published posthumously by Random House with the title *Salt in My Soul*.[9] She was a gifted writer and her words tell an informative and poignant story of what it is like to endure a chronic illness with such a poor prognosis. I believe all who read her book will have a moving experience, but I particularly recommend it to health care professionals and students and literature majors, as well as to youth with chronic illnesses and their parents. Some may feel that it is inappropriate for me to recommend and publicize a book written by a family member. Some conflicts of interest are inevitable. My view is that this is mostly a problem when conflicts are not disclosed. Furthermore, the royalties from book sales are going to research on cystic fibrosis.

There is a second part to Mallory's story that is relevant to this Note. Mallory's *B cepacia* were resistant to antimicrobial agents. As Mallory's disease progressed, she was finally able to have a lung transplant. To prepare her for this surgery, she was given a cocktail of specially selected bacteriophages.[10] Although Mallory survived only briefly after the surgery, postmortem examination revealed that the phage therapy had worked; the *B cepacia* were eradicated! This successful result was unfortunately too late but it has laid the foundation for others to follow. After Mallory's story was made public in the press, several dozen patients have received phage therapy.

Phage therapy is another host–pathogen interaction that, when it works, leads to an unhappy outcome for the pathogen. *Bacteriophages* are viruses that can penetrate bacteria. Once inside, the virus's double-stranded DNA genome is deposited into the cytoplasm of the bacterium, where it self-replicates and lyses the bacterium. Effective bacteriophages have an icosahedral head and a tail whose receptor proteins interact with the surface of the targeted bacterium. Bacteriophages have an affinity for prokaryotic organisms (eg, bacteria) and not for eukaryotic organisms (eg, humans, fungi).

During microbiology, we learned that phage therapy was being used in Georgia and Russia (in the former Soviet Union), Poland, and Germany. Because phage cocktails were said to be unstable and their potency was often reduced or even lost during preparation and storage, phage therapy was presented to us as having more theoretic than practical value. Excellent reviews of the history of bacteriophages were recently published by Kakasis and Panitsa[11] and by Salmond and Fineran.[12] Because of increasing concerns with bacterial resistance and the evolution of so-called "superbugs," phage therapy has reemerged as an important and viable option.[13,14]

I am aware of only one modern, completed clinical trial of phage therapy[15]: a small-sample, multicenter, Phase I/II study in patients with burn wounds infected with *Pseudomonas aeruginosa*. Thirteen patients received a cocktail of 12 anti–*P aeruginosa* phages, and the control group (n = 14) was treated with a sulfadiazine silver cream. The results were that the phage-treated patients as a group took over twice as long to achieve a response compared to the antibiotic-treated cohort. There were many limitations of that study, not the least of which were its limited sample size and that the phage treatment was not very potent. Despite the randomization, more of the phage-treated patients had bacteria that were unresponsive, and, in addition, there was no masking of the treatments. I do not consider the findings from that study to be discouraging. They just suggest that more work needs to be done to increase the potency of the treatment cocktails and to use susceptibility as an inclusion criterion.

During my preparation for this Note, I was made aware of a positive single-case report.[16] A 15-year-old girl with CF underwent an apparently successful bilateral lung transplantation. She was found to have skin nodules containing *Mycobacterium abscessus*, a nontuberculosis mycobacterium that is multidrug resistant.[17] She was effectively treated with a 3-phage cocktail of lytic phages developed via genome engineering and forward genetics (a way of determining effective phenotypes)[18] that were specific for her *M abscessus*.

From recent discussions about phages and from my reading of current literature, I am cautiously optimistic about phage therapy. We are not there yet, but the future seems positive.

Our Update this month was generated by Dr. Ravi Jhaveri, our Topic Editor for Infectious Diseases. He has assembled a group of papers under the rubric of The Host Side of Host-Pathogen Interactions to bring attention to host factors that influence susceptibility to various microbes and inform patient care.[19–23]

DISCLOSURES

The late Mallory Smith, the author of *Salt in My Soul,* was my great-niece.

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This month's Infectious Diseases Update is a special feature which is available as FREE ACCESS content on the journal's website. One of the previous Infectious Diseases Updates, entitled "Hot Topics in Viral Diseases" was published in Volume 40, No. 8 of Clinical Therapeutics. To view the previous Update, see the articles below:

Jhaveri R. Hot Topics in Viral Infections

Kapadia SN, Marks KM. Hepatitis C Management Simplification From Test to Cure: A Framework for Primary Care Providers

Jhaveri R. Live Attenuated Influenza Vaccine: Is Past Performance a Guarantee of Future Results?

Dionne-Odom J, Njei B, Tita ATN. Elimination of Vertical Transmission of Hepatitis B in Africa: A Review of Available Tools and New Opportunities

Nicholson EG, Munoz FM. A Review of Therapeutics in Clinical Development for Respiratory Syncytial Virus and Influenza in Children

Poole CL, James SH. Antiviral Therapies for Herpesviruses: Current Agents and New Directions

Espinosa C, Jhaveri R, Barritt IV AS. Unique Challenges of Hepatitis C in Infants, Children, and Adolescents

Bell CE, Shane AL, Pickering LK. Discrepancies Between US Food and Drug Administration Vaccine Licensure Indications and Advisory Committee on Immunization Practices Recommendations: Provider Knowledge and Attitudes