AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CHALLENGING CLINICAL CASE

Case Commentary: Unlocking the Potential of Bacteriophage to Prevent Recurrent Urinary Tract Infections after Kidney Transplantation

John R. Lee,[a] **Michael J. Satlin**[b,c]

[a]Department of Medicine, Division of Nephrology and Hypertension, Weill Cornell Medicine, New York, New York, USA
[b]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York, USA
[c]Department of Medicine, Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, USA

ABSTRACT Recurrent urinary tract infections (UTIs) are common in kidney transplant recipients, and novel prevention approaches are needed. The case presented by Le et al. (Antimicrob Agents Chemother, in press) describes a patient with recurrent UTIs due to extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* who was successfully treated with bacteriophage therapy. This commentary highlights the potential for bacteriophage therapy to prevent recurrent UTIs, as well as outstanding questions that require further investigation.

KEYWORDS bacteriophage therapy

Urinary tract infections (UTIs) are the most common infections after kidney transplantation and are responsible for 30% to 40% of hospitalizations for sepsis and bacteremia (1–3). Up to one-third of kidney transplant recipients who have a UTI will develop recurrent UTIs (4–6). Recurrent UTIs cause substantial morbidity and lead to allograft impairment and repeated courses of antibacterial therapies. This in turn leads to infections due to increasingly multidrug-resistant (MDR) organisms (4).

Current approaches to preventing recurrent UTIs after kidney transplantation include lifestyle modifications, evaluation for correctable anatomical abnormalities that increase UTI risk, methenamine hippurate, and vaginal estrogen for postmenopausal women (7, 8). Unfortunately, these strategies are often ineffective, and many patients are placed on long-term antibiotic prophylaxis to prevent recurrent episodes of UTI and sepsis (9). Long-term antibiotic prophylaxis has damaging effects on the gut microbiome and increases the risk of developing infections due to MDR pathogens, such as extended-spectrum-β-lactamase (ESBL)-producing bacteria (10). These bacteria are often resistant to all oral agents, leading to frequent hospitalizations for intravenous antibiotics (11). Novel approaches to preventing recurrent UTIs in kidney transplant recipients are urgently needed that will not exacerbate antimicrobial resistance or gut microbiome health.

This case report highlights the potential of bacteriophage therapy, as an alternative to antibiotic prophylaxis, to prevent recurrent UTIs in kidney transplant recipients (12). It describes a kidney and liver transplant recipient who had recurrent episodes of UTI and sepsis due to ESBL-producing *Klebsiella pneumoniae* that led to impaired graft function. She was treated with an intravenous cocktail of three bacteriophages twice daily for 4 weeks and did not have a recurrent UTI in the ensuing 6 months. While she eventually had episodes of cystitis, these episodes were due to *K. pneumoniae* strains that were susceptible to oral antibiotics, and she did not require intravenous therapy.

This report adds to the growing number of published cases of kidney transplant recipients with recurrent UTIs due to ESBL-producing organisms who were successfully treated with bacteriophage cocktails to prevent UTI recurrence (13–15). Bacteriophage therapy to eradicate the gut or urinary reservoir of a uropathogen is a promising alternative to prevent

Address correspondence to Michael J. Satlin, mjs9012@med.cornell.edu.

The authors declare a conflict of interest. J.R.L. holds patent US-2020-0048713-A1 titled "Methods of Detecting Cell-Free DNA in Biological Samples" licensed to Eurofins Viracor, received research support under an investigator-initiated research grant from BioFire Diagnostics, LLC, and receives speakers' fees from Astellas. M.J.S. has received fees for consulting for Shionogi, for participating in a Data Safety Monitoring Board for Abbvie, and has received research funding from SNIPRBiome, Merck, and bioMerieux.

For the article discussed, see https://doi.org/10.1128/AAC.00037-23.

The views expressed in this article do not necessarily reflect the views of the journal or of ASM.

Published 8 May 2023

recurrent UTIs compared to conventional antibiotics because phage is selective only for the uropathogen and does not kill healthy commensal bacteria (16). Furthermore, unlike acutely ill patients with septic shock, patients with recurrent UTIs typically have time to wait for the lengthy period currently required to obtain and administer strain-specific bacteriophages.

While these reports offer promise, fundamental questions remain that must be answered for bacteriophage to become a viable clinical option to prevent recurrent UTIs. First, it is important to learn strategies to minimize the risk of developing resistance to therapeutic bacteriophages. In this report, although phage therapy was temporarily effective in preventing UTIs, the patient eventually had a UTI due to a *K. pneumoniae* that was resistant to all three bacteriophages in the phage cocktail. Potential strategies to minimize the emergence of resistance to bacteriophages include identifying phages active against a broad range of strains within a given species, using larger numbers of phages in therapeutic cocktails, and using modern tools to engineer phages to which bacteria are less likely to be able to develop resistance (17, 18). Second, the pharmacokinetics and pharmacodynamics of therapeutic bacteriophages require additional investigation. Patients with recurrent UTIs can have both gut and urine reservoirs for uropathogens (19). This case report did not evaluate stool concentrations of bacteriophage, the likely reservoir for recurrent UTIs in kidney transplant recipients (20). Further investigation is needed to determine how bacteriophage therapy may differentially affect the different uropathogen species in the gut and urine reservoirs. In this report, the patient received the phage by twice daily intravenous infusions for 4 weeks. Oral bacteriophage preparations would be a more convenient strategy to prevent recurrent UTIs, but concerns exist over the ability of oral bacteriophages to survive acidic environments and achieve therapeutic concentrations in stool (21). Another option would be to instill bacteriophage therapy directly into the bladder to maximize the exposure of the phages to pathogenic bacteria. A recent randomized trial showed that intravesicular bacteriophage therapy yielded similar microbiologic outcomes to antibiotic therapy in patients with UTI undergoing transurethral prostate resection (22). We also need to better understand host immune inactivation of bacteriophages. In this report, partial serum neutralization occurred within 1 week after initiation of treatment. Other reports have found complete inactivation of bacteriophage within 2 weeks (23). It remains to be seen whether other routes of administration such as bladder or enema administration could evade the immune system response and be more effective in the setting of repeated administrations. Lastly, while the bacteriophage therapy appears to have eliminated the ESBL-producing *K. pneumoniae* in this patient, the patient still had recurrent UTIs due to a *K. pneumoniae* strain that was susceptible to oral antibiotics. Further strategies are needed to fully remove uropathogens from the gut and urine reservoirs to decrease the risk of UTI recurrence.

Individual case reports of successful bacteriophage therapy do not constitute proof of efficacy, particularly given that unsuccessful case reports may not be published. Therefore, once the above issues have been addressed, it is critical that bacteriophage therapy is subjected to a randomized trial that is sufficiently powered to detect potential clinical benefit in kidney transplant recipients with recurrent UTIs. Such a trial would be a major step in bringing the potential power of bacteriophages closer to patient care.

REFERENCES

1. Veroux M, Giuffrida G, Corona D, Gagliano M, Scriffignano V, Vizcarra D, Tallarita T, Zerbo D, Virgilio C, Sciacca A, Cappello D, Stefani S, Veroux P. 2008. Infective complications in renal allograft recipients: epidemiology and outcome. Transplant Proc 40:1837–1876.
2. Abbott KC, Oliver JD, 3rd, Hypolite I, Lepler LL, Kirk AD, Ko CW, Hawkes CA, Jones CA, Agodoa LY. 2001. Hospitalizations for bacterial septicemia after renal transplantation in the United States. Am J Nephrol 21:120–127. https://doi.org/10.1159/000046234.
3. Silva M, Jr, Marra AR, Pereira CA, Medina-Pestana JO, Camargo LF. 2010. Bloodstream infection after kidney transplantation: epidemiology, microbiology, associated risk factors, and outcome. Transplantation 90:581–587. https://doi.org/10.1097/TP.0b013e3181e8a680.
4. Giral M, Pascuariello G, Karam G, Hourmant M, Cantarovich D, Dantal J, Blancho G, Coupel S, Josien R, Daguin P, Méchineau S, Soulillou JP. 2002. Acute graft pyelonephritis and long-term kidney allograft outcome. Kidney Int 61:1880–1886. https://doi.org/10.1046/j.1523-1755.2002.00323.x.
5. Kamath NS, John GT, Neelakantan N, Kirubakaran MG, Jacob CK. 2006. Acute graft pyelonephritis following renal transplantation. Transpl Infect Dis 8:140–147. https://doi.org/10.1111/j.1399-3062.2006.00148.x.
6. Greissman S, Mattiazzi A, Mendoza M, Natori Y, Grady M, Quinonez J, Zukerman R, Camargo JF, Morris MI, Simkins J, Guerra G, Abbo LM. 2020. Antimicrobial resistance and recurrent bacterial urinary tract infections in hospitalized patients following kidney transplantation: a single-center experience. Transpl Infect Dis 22:e13337. https://doi.org/10.1111/tid.13337.
7. Hollyer I, Ison MG. 2018. The challenge of urinary tract infections in renal transplant recipients. Transpl Infect Dis 20:e12828. https://doi.org/10.1111/tid.12828.
8. Goldman JD, Julian K. 2019. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation

Infectious Diseases Community of Practice. Clin Transplant 33:e13507. https://doi.org/10.1111/ctr.13507.
9. Green H, Rahamimov R, Gafter U, Leibovitci L, Paul M. 2011. Antibiotic prophylaxis for urinary tract infections in renal transplant recipients: a systematic review and meta-analysis. Transpl Infect Dis 13:441–447. https://doi.org/10.1111/j.1399-3062.2011.00644.x.
10. Espinar MJ, Miranda IM, Costa-de-Oliveira S, Rocha R, Rodrigues AG, Pina-Vaz C. 2015. Urinary tract infections in kidney transplant patients due to *Escherichia coli* and *Klebsiella pneumoniae* producing extended-spectrum β-lactamases: risk factors and molecular epidemiology. PLoS One 10:e0134737. https://doi.org/10.1371/journal.pone.0134737.
11. Gong L, Zhang L, Liu X, Odilov B, Li S, Hu Z, Xiao X. 2021. Distribution and antibiotic susceptibility pattern of multidrug-resistant bacteria and risk factors among kidney transplant recipients with infections over 13 years: a retrospective study. Infect Drug Resist 14:5661–5669. https://doi.org/10.2147/IDR.S318941.
12. Le T, Nang SC, Zhao J, Yu HH, Li J, Gill JJ, Liu M, Aslam S. 2023. Therapeutic potential of intravenous phage as stand-alone therapy for recurrent drug-resistant urinary tract infections. Antimicrob Agents Chemother 67:in press. https://doi.org/10.1128/aac.00037-23.
13. Kuipers S, Ruth MM, Mientjes M, de Sévaux RGL, van Ingen J. 2019. A Dutch case report of successful treatment of chronic relapsing urinary tract infection with bacteriophages in a renal transplant patient. Antimicrob Agents Chemother 64:e01281-19. https://doi.org/10.1128/AAC.01281-19.
14. Rostkowska OM, Międzybrodzki R, Miszewska-Szyszkowska D, Górski A, Durlik M. 2021. Treatment of recurrent urinary tract infections in a 60-year-old kidney transplant recipient. The use of phage therapy. Transpl Infect Dis 23:e13391. https://doi.org/10.1111/tid.13391.
15. Gainey AB, Daniels R, Burch AK, Hawn J, Fackler J, Biswas B, Brownstein MJ. 2023. Recurrent ESBL *Escherichia coli* urosepsis in a pediatric renal transplant patient treated with antibiotics and bacteriophage therapy. Pediatr Infect Dis J 42:43–46. https://doi.org/10.1097/INF.0000000000003735.
16. Dissanayake U, Ukhanova M, Moye ZD, Sulakvelidze A, Mai V. 2019. Bacteriophage reduce pathogenic *Escherichia coli* counts in mice without distorting gut microbiota. Front Microbiol 10:1984. https://doi.org/10.3389/fmicb.2019.01984.
17. Oechslin F. 2018. Resistance development to bacteriophages occurring during bacteriophage therapy. Viruses 10:351. https://doi.org/10.3390/v10070351.
18. Egido JE, Costa AR, Aparicio-Maldonado C, Haas PJ, Brouns SJJ. 2022. Mechanisms and clinical importance of bacteriophage resistance. FEMS Microbiol Rev 46:fuab048. https://doi.org/10.1093/femsre/fuab048.
19. Worby CJ, Schreiber HL, 4th, Straub TJ, van Dijk LR, Bronson RA, Olson BS, Pinkner JS, Obernuefemann CLP, Muñoz VL, Paharik AE, Azimzadeh PN, Walker BJ, Desjardins CA, Chou WC, Bergeron K, Chapman SB, Klim A, Manson AL, Hannan TJ, Hooton TM, Kau AL, Lai HH, Dodson KW, Hultgren SJ, Earl AM. 2022. Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. Nat Microbiol 7:630–639. https://doi.org/10.1038/s41564-022-01107-x.
20. Magruder M, Sholi AN, Gong C, Zhang L, Edusei E, Huang J, Albakry S, Satlin MJ, Westblade LF, Crawford C, Dadhania DM, Lubetzky M, Taur Y, Littman E, Ling L, Burnham P, De Vlaminck I, Pamer E, Suthanthiran M, Lee JR. 2019. Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. Nat Commun 10:5521. https://doi.org/10.1038/s41467-019-13467-w.
21. Suh GA, Lodise TP, Tamma PD, Knisely JM, Alexander J, Aslam S, Barton KD, Bizzell E, Totten KMC, Campbell JL, Chan BK, Cunningham SA, Goodman KE, Greenwood-Quaintance KE, Harris AD, Hesse S, Maresso A, Nussenblatt V, Pride D, Rybak MJ, Sund Z, van Duin D, Van Tyne D, Patel R, Antibacterial Resistance Leadership Group. 2022. Considerations for the use of phage therapy in clinical practice. Antimicrob Agents Chemother 66:e0207121. https://doi.org/10.1128/AAC.02071-21.
22. Leitner L, Ujmajuridze A, Chanishvili N, Goderdzishvili M, Chkonia I, Rigvava S, Chkhotua A, Changashvili G, McCallin S, Schneider MP, Liechti MD, Mehnert U, Bachmann LM, Sybesma W, Kessler TM. 2021. Intravesicular bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. Lancet Infect Dis 21:427–436. https://doi.org/10.1016/S1473-3099(20)30330-3.
23. Terwilliger A, Clark J, Karris M, Hernandez-Santos H, Green S, Aslam S, Maresso A. 2021. Phage therapy related microbial succession associated with successful clinical outcome for a recurrent urinary tract infection. Viruses 13:2049. https://doi.org/10.3390/v13102049.