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Prophylactic Post-Lung Transplant Bacteriophage Therapy against XDR Pseudomonas aeruginosa in Cystic Fibrosis: a case report

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Case Report

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Abstract

Lung transplant recipients (LTRs) with cystic fibrosis (CF) are frequently colonized with multidrug-resistant pathogens, including extensively drug-resistant (XDR) *Pseudomonas aeruginosa* (PA), which increase peri-transplant morbidity. Bacteriophage therapy (BT) has shown efficacy against MDR bacteria, but its prophylactic use post-transplant has rarely been reported.

A 46-year-old woman with CF and chronic lung allograft dysfunction (bronchiolitis obliterans syndrome III) after bilateral transplantation in 2005 underwent retransplantation in 2024. She was colonized with XDR PA and *Aspergillus* spp. Peri-transplant prophylaxis included ceftolozane/tazobactam, intravenous and inhaled colistin, amoxicillin/clavulanic acid, and intravenous liposomal amphotericin B. BT was personalized based on phage susceptibility testing (PST) and initiated immediately post-transplant via combined intravenous and endobronchial administration for three weeks. Pulmonary cultures remained negative for XDR PA during this period. The patient ultimately developed multiorgan failure unrelated to XDR PA and died 88 days post-transplant.

This is one of the first reported case of prophylactic BT in lung transplantation, achieving pulmonary microbiologic suppression of XDR PA. While the patient's outcome was determined by other complications. Prospective studies are needed to define its efficacy, safety, and optimal administration.

Introduction

Cystic fibrosis (CF) patients undergoing lung transplantation or retransplantation are frequently colonized with multidrug-resistant (MDR) bacteria and fungi, including *Aspergillus* species and Gram-negative pathogens such as *Pseudomonas aeruginosa* (PA)[1,2]. Infectious complications remain the leading early cause of death among lung transplant recipients (LTRs) [3]. Effective antimicrobial therapy is required in patients colonized with such organisms to achieve survival outcomes comparable to those of non-colonized recipients [1].

Lytic bacteriophages are viruses that infect and lyse bacteria. Bacteriophage therapy (BT) has emerged as a potential therapeutic option against antimicrobial-resistant bacteria [4]. In vitro data demonstrates activity of bacteriophages against PA [5], and several case reports have described successful treatment of MDR bacterial infections, including bronchopulmonary infections caused by PA in LTRs [6,7]. However, BT has not previously been reported as a prophylactic strategy in the immediate post-transplant period.

We report on of the first case of prophylactic BT in a CF patient colonized with extensively drug-resistant (XDR) PA who underwent a second bilateral lung transplantation, resulting in complete microbiological clearance.

Case Presentation

Patient background

A 46-year-old woman with advanced CF underwent bilateral lung transplantation in 2005. Since 2013, she developed chronic lung allograft dysfunction with bronchiolitis obliterans syndrome stage III. Progressive decline in lung function prompted listing for retransplantation in June 2024.

Pre-transplant evaluation showed end-stage obstruction with forced expiratory volume at 1st second of 0.37 L (12% predicted). Echocardiography demonstrated preserved biventricular function and no pulmonary hypertension. Serologies were positive for CMV, EBV, *Toxoplasma*, and *Aspergillus*. Bronchial cultures showed chronic colonization with two PA strains and XDR *Aspergillus* spp. The first was an XDR PA strain (Table 1), the second was a MDR PA strain, retaining susceptibility to ceftolozane/tazobactam, ceftazidime/avibactam, and cefiderocol, both were last identified 4 months prior to transplantation. No evidence of extra-pulmonary colonization was found. There were no preformed anti-HLA antibodies. Maintenance therapy included tacrolimus, corticosteroids, and azithromycin, with inhaled colistin for antimicrobial prophylaxis.

Table 1

Antibiogram and Phage susceptibility testing of Pseudomonas aeruginosa isolated from respiratory samples prior to re-transplantation.

Antibiogram		
Antibiotics	***P. aeruginosa***	**Minimum Inhibitory Concentration (mg/L)**
ceftazidime/avibactam	R	256
ceftozolane/tazobactam	R	8
cefiderocol	R	> 32
colistin	**Susceptible**	**0.5**
ticarcilline	R	> 512
ticarcillin/clavulanate	R	> 512
piperacillin/tazobactam	R	> 512
ceftazidime	R	> 128
cefepime	R	> 512
imipenem	R	> 32
meropenem	R	> 64
aztreonam	R	> 512
amikacin	R	> 16
tobramycin	R	
ciprofloxacin	R	> 64
fosfomycin	R	> 128
doxycycline	R	
minocycline	R	
trimethoprim-sulfamethoxazole	R	
Phage susceptibility testing		
Phages	**Susceptibility**	
PP1450	S	
PP1777	I	

"S" = Susceptible bacterial strain to standard dosing regimen; "I" = Susceptible bacterial strain to increased dose exposures; "R" = Resistant bacterial strain.

Antibiogram		
Antibiotics	***P. aeruginosa***	**Minimum Inhibitory Concentration (mg/L)**
PP1792	S	
PP1797	I	
"S" = Susceptible bacterial strain to standard dosing regimen; "I" = Susceptible bacterial strain to increased dose exposures; "R" = Resistant bacterial strain.		

Based on the pre-existing colonizing strains and covering potential donor-derived pneumonia due to Gram-positive cocci such as *Staphylococcus* or *Streptococcus* species, peri-transplant antimicrobial prophylaxis consisted of ceftolozane/tazobactam, intravenous and inhaled colistin, amoxicillin/clavulanic acid, and intravenous liposomal amphotericin B. Immunosuppression included basiliximab induction followed by mycophenolate mofetil, cyclosporine, and corticosteroids. Given the high risk of early post-transplant recurrence of XDR PA, a multidisciplinary team decision was made to administer prophylactic BT.

Bacteriophage therapy

Bacteriophages were provided by PHAGENIX Therapeutics (Lyon, France, https://phagenix.com/). Patient PA isolates obtained before retransplantation were sent for phage susceptibility testing (PST). PST confirmed susceptibility to four Good Manufacturing Practices -grade phages (PP1450, PP1777, PP1792, PP1797) **(**Table 1**).**

Following institutional and French health authorities' approval and informed consent, compassionate use of BT was initiated immediately post-transplant. Based on prior report of BT in LTRs [8] and following multidisciplinary discussion, the protocol consisted of: Intravenous therapy; 10 mL per dose (1 mL each of PP1450, PP1777, PP1792, PP1797, plus 6 mL 0.9% NaCl), administered twice daily for 7 days, associated with Endobronchial instillation; 10 mL per main bronchus (1 mL each of PP1450, PP1777, PP1792, PP1797, plus 6 mL 0.9% NaCl), administered via bronchoscopy on postoperative days 1, 3, 7, 14 and 21. Hospital pharmacist mixed the active phages (initial concentration 1 ml of 10^{10} PFU (plaque forming unit)) in aseptic conditions under a laminar air flow hood to obtain these cocktail of four phages diluted with 0.9% NaCl in 10 ml syringes.

Post-transplant course

On December 4, 2024, the patient underwent bilateral lung retransplantation using intraoperative central ECMO. The procedure required massive transfusion and large-volume resuscitation. The ECMO was weaned off at the end of the procedure. Chest closure was delayed because of pulmonary edema and primary graft dysfunction.

On postoperative day 1, BAL revealed 10^5 copies of PA by multiplex PCR (FilmArrayPneumonia Panel®, Biomérieux, Marcy L'Etoile, France). BT was initiated as described above. By day 8, all BAL cultures performed within 1 week were negative for PA but positive for *Aspergillus nomius*; BT continued till day 21. The bacterium was no more detected in subsequent pulmonary samples.

Six weeks later, XDR PA was isolated from blood cultures and peritoneal fluid in the setting multiple intra-abdominal abscesses. At that time, pulmonary samples remained negative for PA. A new PST was performed on the 23rd of January and showed resistance to all available anti-*Pseudomonas* phages, precluding further BT. The therapeutic regimen consisting of intravenous colistin in combination with cefiderocol and peritoneal lavage resulted in successful clinical management of the patient. The genomes of the PA strains from the respiratory and abdominal abscesses were sequenced using Illumina technology. The first strain belongs to Sequence Type (ST) 654, while the second strain belongs to ST5036, confirming that the first strain was not responsible for the second infection.

Despite microbiological clearance of PA in the lungs, the patient developed invasive pulmonary aspergillosis, *Enterococcus faecium* and *Corynebacterium tuberculostearicum* ventilator-associated pneumonia. Antifungal and broad-spectrum antibiotics were administered, but her course was complicated by persistent sepsis, ARDS requiring prolonged mechanical ventilation, acute kidney injury (KDIGO stage 3), hepatic dysfunction, and hematologic complications.

Given refractory multiorgan failure, the patient died on February 27, 88 days post-transplant.

Discussion

This report describes one of the first documented case of prophylactic BT in LTR. Targeted BT achieved complete microbiological clearance of XDR PA from the lungs within one week despite retransplantation in context of frailty.

Clinical BT use has been reported for a range of infections, including bacteremia, osteomyelitis, and advanced pulmonary disease [9]. In LTRs, BT has been used exclusively for treatment of established MDR infections [6,8], with rare reports of prophylactic administration. In our case, it is reasonable to consider that BT, associated with conventional antimicrobial therapy, could have helped to achieve PA eradication.

BT can be administered intravenously, via inhalation, or endobronchially. Intravenous administration achieves measurable phage concentrations in the lung [6], while inhaled therapy may be limited by variability in deposition and phage viability [10]. Based on our center's experience [11], we chose combined intravenous and bronchoscopic instillation. We did not administer BT orally or via a nasogastric tube because, unlike in our previous case [11], PA was not detected during pre-transplant bacterial screening of stool or rectal samples.

Safety data for BT are generally reassuring [12], with few adverse events reported in LTRs [13,14]. Nevertheless, the high host specificity of phages may theoretically alter the respiratory microbiome or

exert selective pressure favoring resistant strains. In our patient, the phage-resistant PA strain identified at extrapulmonary sites was genetically distinct from the pre-transplant pulmonary isolate, suggesting that BT did not promote resistance in the colonizing XDR PA strain.

Although this single case cannot establish efficacy, it supports the feasibility and microbiological potential of prophylactic BT in the peri-transplant setting.

Conclusion

This case demonstrates the feasibility and microbiological efficacy of prophylactic BT in a LTR colonized with XDR PA. BT and antibiotics, initiated immediately post-transplant, resulted in complete pulmonary clearance within one week — a result unlikely achievable with conventional antimicrobials alone. While the patient's death was due to unrelated infections and multiorgan failure, the observed microbiological success supports further investigation of prophylactic BT as a strategy to reduce infection-related morbidity in high-risk transplant candidates. Future prospective studies are warranted to determine its impact on clinical outcomes and transplant eligibility for patients colonized with multidrug-resistant organisms.

Abbreviations

BAL
Bronchoalveolar lavage
BT
Bacteriophage therapy
CF
cystic fibrosis
PA
Pseudomonas aeruginosa
LTRs
Lung Transplant recipients
XDR
extensively drug-resistant
PST
phage susceptibility testing

Declarations

Ethics approval

All procedures in this study were carried out in accordance with the 1964 Helsinki declaration.

Consent for publication

Patient’s family received oral information regarding this case report.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Clinical data were provided by JM, CE, GB, DB, XD, SH, BC. JM wrote the original draft. SB, CE, FM, FP, KJ, AB, GB, DB, XD, SH, BC reviewed and edited the manuscript. Tables were created by JM. Supervision by CE, SH, BC. All authors read and approved the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Lay C, Law N, Holm AM, Benden C, Aslam S. Outcomes in cystic fibrosis lung transplant recipients infected with organisms labeled as pan-resistant: An ISHLT Registry–based analysis. J Heart Lung Transpl. 2019;38(5):545–52. 10.1016/j.healun.2019.01.1306.
2. Holm AE, Schultz HHL, Johansen HK, et al. Bacterial Re-Colonization Occurs Early after Lung Transplantation in Cystic Fibrosis Patients. J Clin Med. 2021;10(6):1275. 10.3390/jcm10061275.
3. Chambers DC, Perch M, Zuckermann A, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report – 2021; Focus on recipient characteristics. J Heart Lung Transpl. 2021;40(10):1060–72. 10.1016/j.healun.2021.07.021.
4. Aranaga C, Pantoja LD, Martínez EA, Falco A. Phage Therapy in the Era of Multidrug Resistance in Bacteria: A Systematic Review. Int J Mol Sci. 2022;23(9):4577. 10.3390/ijms23094577.

5. Nordstrom HR, Evans DR, Finney AG, et al. Genomic characterization of lytic bacteriophages targeting genetically diverse Pseudomonas aeruginosa clinical isolates. iScience. 2022;25(6):104372. 10.1016/j.isci.2022.104372.
6. Aslam S, Courtwright AM, Koval C, et al. Early clinical experience of bacteriophage therapy in 3 lung transplant recipients. Am J Transpl. 2019;19(9):2631–9. 10.1111/ajt.15503.
7. Haidar G, Chan BK, Cho ST, et al. Phage therapy in a lung transplant recipient with cystic fibrosis infected with multidrug-resistant Burkholderia multivorans. Transpl Infect Dis. 2023;25(2):e14041. 10.1111/tid.14041.
8. Aslam S. Phage Therapy in Lung Transplantation: Current Status and Future Possibilities. Clin Infect Dis. 2023;77(Suppl 5):S416–22. 10.1093/cid/ciad528.
9. Marongiu L, Burkard M, Lauer UM, Hoelzle LE, Venturelli S. Reassessment of Historical Clinical Trials Supports the Effectiveness of Phage Therapy. Clin Microbiol Rev. 2022;35(4):e0006222. 10.1128/cmr.00062-22.
10. Leung SSY, Carrigy NB, Vehring R, et al. Jet nebulization of bacteriophages with different tail morphologies - Structural effects. Int J Pharm. 2019;554:322–6. 10.1016/j.ijpharm.2018.11.026.
11. Levêque M, Cassir N, Mathias F, et al. Refractory Pseudomonas aeruginosa Bronchopulmonary Infection After Lung Transplantation for Common Variable Immunodeficiency Despite Maximal Treatment Including IgM/IgA-Enriched Immunoglobulins and Bacteriophage Therapy. Infect Drug Resist. 2023;16:4265–71. 10.2147/IDR.S413900.
12. Uyttebroek S, Chen B, Onsea J, et al. Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review. Lancet Infect Dis. 2022;22(8):e208–20. 10.1016/S1473-3099(21)00612-5.
13. Aslam S. Bacteriophage therapy as a treatment option for transplant infections. Curr Opin Infect Dis. 2020;33(4):298–303. 10.1097/QCO.0000000000000658.
14. Nicholls P, Aslam S. Role of bacteriophage therapy for resistant infections in transplant recipients. Curr Opin Organ Transpl. 2022;27(6):546–53. 10.1097/MOT.0000000000001029.