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Phage Therapy for Respiratory Infections: Opportunities and Challenges

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Abstract

We are entering the post-antibiotic era. Antimicrobial resistance (AMR) is a critical problem in chronic lung infections resulting in progressive respiratory failure and increased mortality. In the absence of emerging novel antibiotics to counter AMR infections, bacteriophages (phages), viruses that infect bacteria, have become a promising option for chronic respiratory infections. However, while personalized phage therapy is associated with improved outcomes in individual cases, clinical trials demonstrating treatment efficacy are lacking, limiting the therapeutic potential of this approach for respiratory infections. In this review, we address the current state of phage therapy for managing chronic respiratory diseases. We then discuss how phage therapy may address major microbiologic obstacles which hinder disease resolution of chronic lung infections with current antibiotic-based treatment practices. Finally, we highlight the challenges that must be addressed for successful phage therapy clinical trials. Through this discussion, we hope to expand on the potential of phages as an adjuvant therapy in chronic lung infections, as well as the microbiologic challenges that need to be addressed for phage therapy to expand beyond personalized salvage therapy.

Keywords

Bacteriophage; Phage therapy; Antimicrobial resistance; Chronic infections

Battling Antimicrobial Resistance (AMR) in Chronic Lung Infections

AMR Infections are a rising global threat, with over 4.9 million associated deaths estimated in 2019 [1]. Lower respiratory tract infections, in particular chronic lung infections, have one the highest burden of AMR infections and are a leading cause of death worldwide

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Declarations

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[1, 2]. Individuals with defects in structural airways and/or compromised immunity are at heightened risk for AMR chronic infections. This includes people with cystic fibrosis (PwCF), chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis, and lung transplant recipients with chronic rejection [3-6]. Chronic lung infections are marked by episodes of acute exacerbations, distinguished by increased respiratory distress, eventually resulting in progressive respiratory failure and increased mortality [7, 8].

Antibiotic management strategies for chronic respiratory infections include the recurrent use of prophylactic or suppressive antibiotics to prevent exacerbations and the use of targeted antibiotics when exacerbations occur [9-11]. Despite these measures, once established, chronic infections are difficult, if not impossible, to eradicate [12, 13]. Further, recurrent antibiotic exposure often selects for antimicrobial resistant pathogens, limiting the effectiveness of this intervention. As such, chronic lung infections continue to be a major cause of progressive lung failure and death among patients with underlying pulmonary disease.

Rising AMR has Sparked a Renewed Interest in Bacteriophage (Phage) Therapy

Phage therapy (PT) is a potential alternative or adjuvant therapy to conventional antibiotics for managing AMR infections. Lytic phages are viruses that infect bacteria, hijack their cellular machinery to replicate, and eventually lyse their host bacteria to release newly formed viral progeny [14]. In the pre-antibiotic era, phages were used globally to treat infectious diseases [15]. However, the enthusiasm for PT diminished as concerns grew about inconsistent results and reliance on case studies rather than rigorous standardized trials [16]. The development of antibiotics, which early studies hinted at improved outcomes compared to PT, effectively supplanted phages in treating infectious diseases [17, 18]. Presently, insufficient development of new antimicrobial agents to counter the rise of AMR, as well as preclinical studies that demonstrated phage efficacy against drug-resistant infections, has renewed interest in PT [19, 20].

PT is Associated with Positive Outcomes in Individual Cases

In the US, the use of PT is restricted to compassionate use for patients with progressive or fulminant infections recalcitrant to all other FDA-approved therapies. If these criteria are met, FDA approval for PT under the emergency or expanded access investigational new drug (eIND or eaIND, respectively) pathways may be granted [21]. Despite the restricted use, numerous cases, including international studies, have suggested PT to be a safe and effective intervention [22-24].

A retrospective Belgian case series described 100 consecutive cases of phage therapy for difficult-to-treat pulmonary, bone, skin and soft tissue infections [25]. Those authors reported that 77% of cases demonstrated clinical improvement, and 61% achieved eradication of the pathogen in question. While it seems likely that there is under-reporting of unsuccessful cases, together, these data indicate that individualized PT can be successful.

Respiratory infections are the second most common indication for phage therapy [26]. A recent review evaluated 20 cases of respiratory infections utilizing PT, including two clinical trials involving four participants [27]. These cases included ventilator-associated pneumonia (n = 8, 40%), pulmonary infections following solid organ transplantation (n = 6, 30%), and PwCF (n = 4, 20%). The most common pathogens were *Acinetobacter baumannii* (n = 6, 30%) and *Pseudomonas aeruginosa* (n = 4, 20%). Among those 20 cases, there were 16 instances of infection resolution (4 of which included eradication of the pathogen) and 4 treatment failures [27]. Additional case series have reported positive results of compassionate phage therapy in PwCF, including treatment for non-tuberculous mycobacteria (NTM) and *P. aeruginosa* (Table 1) [28-30]. These cases demonstrate PT is likely safe and potentially effective salvage treatment in patients with advanced pulmonary infections resistant to all other approved therapeutics.

The positive outcomes seen with phage treatment in these studies hint at the potential of PT beyond compassionate use. However, the heterogenicity of cases in these studies, with a range in disease severity, variety of infectious pathogens, lack of standardization or a control group for comparison, and prevalent concomitant use of antibiotics (which is often required for eIND cases), precludes conclusive judgment on the efficacy of PT [25, 31]. To broaden the application of PT beyond compassionate use requires clinical trials to evaluate the safety and effectiveness of PT for respiratory infections. While these trials are currently underway, they have not yet been published.

In the absence of clinical trials to rigorously assess the virtue of PT, we draw insights from in vitro, preclinical, and case studies. By scrutinizing the distinct microbiological challenges to treat chronic lung infections, including AMR, biofilm formation, and polymicrobial disease, we examine how PT addresses these specific obstacles. We also discuss the intrinsic limitations of PT, including widespread phage resistance. Through this framework, we assess the advantages and deficiencies of PT to treat chronic lung infections and pinpoint crucial areas for improvement to expand its application beyond compassionate use.

Widespread Resistance Impedes Pathogen Clearance in Chronic Pulmonary Infections

As discussed above, one of the hallmarks of chronic pulmonary infections is the development of antibiotic resistance. One option may be to substitute antibiotics with PT, which has demonstrated clinical utility [27]. However, phage monotherapy carries the potential of selecting for phage resistance. Another possibility is to combine PT with antibiotics, which, in addition to additive bacterial killing effects, may prevent resistance (antibiotic and phage) through synergistic activity [32]. Indeed, numerous studies have demonstrated in vitro phage-antibiotic synergy (PAS) [33-36]. Evidence of PAS has also been shown in animal models, including evidence that combined therapy re-sensitizes resistant bacteria to antibiotics [37-39]. It has been more challenging to ascertain PAS in clinical cases, as trials comparing phage versus antibiotic monotherapy to combined therapy have not been initiated. However, some clinical reports hint at the potential of PAS. This includes demonstrating that phage-antibiotic combination therapy is associated with the

absence of development of antibiotic resistance as well as re-sensitization of AMR strains to antibiotics [22, 31, 40, 41]. Altogether, these studies encapsulate the potential of adjuvant PT to combat AMR pulmonary infections.

There are several examples by which PAS counters AMR. Co-treatment of bacterial cultures with phages and antibiotics reduces selection for antibiotic resistance, compared to mono-therapy alone [42-44]. Further, phage treatment selects for phage resistance which may re-sensitize antibiotic resistant bacteria through an evolutionary tradeoff. This includes downregulation of phage target receptors involved in drug efflux to prevent phage binding and absorption [45, 46]. While this leads to decreased phage predation, it also results in impaired drug efflux and enhanced antibiotic susceptibility [45, 46]. Phage-mediated bacterial membrane stress, including capsule mutatgenesis, may also re-sensitize resistant bacteria by enhancing antibiotic penetration and killing [35, 46, 47]. Reciprocally, antibiotic-induced membrane stress promotes phage-induced killing by enhancing phage attachment, absorption, and virion production [33, 35, 47]. Although these mechanisms through which PAS enhances antimicrobial susceptibility have been consistently demonstrated in vitro, whether they are observed in patient populations remains a critical question.

A more sobering possible consequence of phage-antibiotic combination therapy, however, is antagonism. Phage-antibiotic antagonism (PAA) was observed as early as the 1940s, when Jones et al. reported specific classes of antibiotics that inhibited phage killing in *Escherichia coli* and *Staphylococcus aureus* [36]. Multiple reports have since reproduced these findings, which show reduced viral production, delayed lysis time, and impaired bacterial killing when phages are combined with antibiotics [48, 49]. Several mechanisms have been proposed to explain the mechanism of PAA. Phages rely on the molecular machinery of its bacterial host for genome replication, virion production, and cell lysis [48]. Consistent with this, antibiotics that inhibit bacterial DNA gyrase and ribosomes, or that reduce bacteria below the phage proliferation threshold, impair phage production [50-53]. Antibiotics may also promote phage resistance. Varied mechanisms have been described, including antibiotic enhancement of Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR), a form of bacterial immunity that protects against phage predation [54-57]. Further, while selection for phage resistance has been associated with a fitness tradeoff leading to enhanced antibiotic susceptibility, Burmeister et al. revealed that some phage-resistant mutants actually demonstrated enhanced resistance to antibiotics [58]. Given the potential of PAA, staggering treatment of phage and antibiotics, rather than co-administration, has been proposed as a method to limit antagonism. However, this approach has had mixed results [59-61].

The final potential consequence of combined therapy is additive or no effect [47]. Here, phages and antibiotics work (or fail) independent of one another. Screening phages with antibiotics largely demonstrates independent activity [62]. Thus, while PT has a promising potential to reverse AMR, this phenomenon is not universally found. The unpredictable phage-antibiotic interactions impede the empiric use of combination therapy. Instead, similar to antibiograms, which delineate antibiotic susceptibility, optimizing PT may require both a “phagogram” and “synogram”, which will reveal phage susceptibility and antibiotic synergy, respectively, for each bacterial isolate [31]. This, however, reveals a new challenge, in that

phage activity demonstrated in vitro may be diminished, if not completely absent, when tested in physiologic conditions [32]. This inconsistency in phage activity recalls Gunther Stent's early observation "just why bacteriophages, so virulent in their antibacterial action in vitro, proved so impotent in vivo has never been adequately explained" [15].

Formation of Bacterial Biofilms in Chronic Lung Infections Promote Persistent Disease

The CYstic Fibrosis bacterioPHage Study at Yale (CYPHY) is a phase 2 study evaluating the use of an inhaled single phage (YPT-01) phage in PwCF (ClinicalTrials.gov ID NCT04684641). YPT-01 was previously shown to kill *P. aeruginosa* and select fitness-defective mutants susceptible to antibiotic killing. Patients selected for the trial were each found to have phage susceptible isolates upon in vitro culture. A preliminary review of the data available on ClinicalTrials.gov suggests that while there were no safety concerns, the primary endpoint was not met as PT did not decrease bacterial titers. While these results and any analyses of them have yet to be published, the difference between in vitro and in vivo outcomes is striking.

One factor relevant to in vivo infections, but is not typically assessed by in vitro phage susceptibility studies, is bacterial biofilms. In contrast to planktonic bacterial growth, which is characterized by free-floating bacteria, biofilms are comprised of densely packed microbial cells contained within a protective matrix of extracellular polymeric substances (EPS) [63]. Biofilm matrix substrates serve as an anchor to the respiratory epithelium, mediating bacterial adherence and resistance to mucociliary clearance [64, 65]. This extracellular matrix also shields bacteria from eradication by host immune cells and antibiotics. Indeed, bacteria grown in biofilms may demonstrate 100–1000-fold increased antibiotic resistance relative to planktonic growth conditions [66, 67]. Several mechanisms by which biofilm promotes antibiotic resistance have been proposed. This includes the EPS matrix serving as a protective sieve, impeding antibiotic penetration and directly sequestering antibiotics through electrostatic interactions [68-70]. The densely packed microbial community within the biofilm also facilitates horizontal gene transfer, which includes the spread of AMR genes [68, 69]. The expansion of persister cells, a subpopulation of bacteria selected due to nutrient scarcity and varying oxygen gradient throughout the biofilm, also contributes to persistent infection despite antibiotic treatment [67, 71]. Displaying altered metabolism and delayed growth rates, these cells essentially remain dormant and unaffected by antibiotics. Once antibiotic levels diminish, persister cells can repopulate the biofilm [71]. Patients with chronic biofilm-forming lung infections thus remain colonized despite frequent, intensive antibiotic and airway clearance treatments [12, 13].

Phages, used independently or in conjunction with antibiotics, may resolve biofilm infections [48, 61, 72]. Clinically, PT has successfully managed biofilms among patients with chronic wounds or prosthetic device infections [73]. PT is also associated with clinical improvement among patients susceptible to biofilm-forming chronic lung infections (Table 1) [24, 74, 75]. Multiple mechanisms by which phages promote biofilm killing have been

ascribed. Similar to AMR strains, the combination of phages and antibiotics demonstrates synergistic activity against biofilms. Some phages express depolymerases, enzymes that degrade polysaccharides including EPS, mediating biofilm breakdown and penetration of both phages and antibiotics [72, 76]. Further, in contrast to antibiotics, phages demonstrate effective activity against persister cells in vitro [77, 78].

Despite the potential of phages to treat biofilm infections, challenges remain. Similar to the uncertainty of phage-antibiotic combinations in addressing AMR, there are concerns regarding which antibiotic classes and treatment order (combined or sequential) that synergize best with phages to dissolve biofilms [79-82]. Phage depolymerases are substrate selective, requiring screening to identify phages capable of penetrating the biofilm matrix [83, 84]. Biofilms may also sequester phages, inhibiting phage diffusion through the biofilm [85]. While matrix-bound phage remain active against surface microbes, bacteria within the biofilm are protected from phage killing [83, 85, 86]. Phages have been shown to kill persister cells in vitro. However, when tested in nutrient-restricted conditions as seen within biofilms, phage activity against persister cells is lost [87, 88]. In nutrient-deplete conditions, phages may actually undergo a hibernation or pseudolysogeny phase within bacteria, during which phage production is halted until growth conditions improve [87-89]. Recently, a study to identify phages capable of killing deep dormant cells in nutrient depleted growth conditions was undertaken. While the majority of phages demonstrated no activity, one phage was isolated capable of killing dormant *P. aeruginosa* [90]. No phages capable of killing dormant *E. coli,* however, were isolated. This finding further emphasizes the need to study phage-antibiotic-biofilm interactions in conditions that reflect the infectious environment. Thus, while there is a promising potential for phages to eradicate persistent lung infections, multiple challenges, including screening phages for anti-biofilm and anti-persister cell activity, remain.

Polymicrobial Lung Infections Pose Significant Challenge to Treatment Approaches

A key obstacle in treating chronic pulmonary infections is its polymicrobial and polyclonal nature. PwCF, in particular, demonstrate diverse airway colonization harboring various species and strains with distinct pathogenicity and antibiotic susceptibility [91, 92]. This diversity complicates both diagnosis and treatment strategies. Antibiotic treatment in these cases is often empiric with broad antimicrobial coverage [8].

Phage specificity to distinct bacterial species, if not strains, limits their empiric use for both mono and polymicrobial infections. Bacterial-phage co-evolution “training” protocols or engineered phages may broaden host range [93, 94]. Unfortunately, these efforts are laborious and time-consuming, resulting in delayed treatment. An alternative approach is using phage cocktails that combine multiple phages to address both polymicrobial infections and limit phage resistance. However, as with phage-antibiotic combinations, phage-phage interactions can either be synergistic or antagonistic, which is difficult to predict [95]. Moreover, the optimum number of phages and whether they should be administered serially or in concert are unclear [96].

Despite these challenges, the use of PT in patients with polymicrobial respiratory infections has demonstrated clinical improvement. In a case series of three patients with polymicrobial MDR pneumonia, a phage cocktail administered by inhalation resulted in clinical improvement and elimination of respiratory pathogens in each case [97]. Moreover, patients with polymicrobial infections who received PT targeting a dominant isolated pathogen also may demonstrate clinical improvement (Table 1) [27, 98]. However, even when targeting a specific pathogen, phage strain selectivity limits empiric use. This includes the treatment of non-tuberculosis mycobacterium (NTM), a major cause of chronic pulmonary infections among susceptible patients. Recent reports have demonstrated success in PT against NTM pulmonary infections, including *M. abscessus* [28, 40]. However, no lytic phages have been identified that target and kill smooth colony variants of *M. abscessus*, which make up over 45% of clinical isolates, constraining PT's therapeutic potential [28]. While there is evidence of PT success in polymicrobial infections, the strain specificity of phages is a potential limiting factor for the treatment of chronic infections.

Phage Therapy: A New Solution Comes with Unique Challenges

There is promising evidence that phages may help address challenges in treating AMR and biofilm infections. Despite strain selectivity, PT has demonstrated clinical improvement among patients with polymicrobial infections. There is also an abundant supply of natural phages that can be bio-prospected to target resistant organisms. This process is exponentially faster and cheaper than generating new antibiotics with minimal side effects and off-target consequences.

While phages offer potential solutions to limitations in treating chronic lung infections with antibiotics, it poses new challenges. Similar to antibiotics, bacteria possess multiple, diverse mechanisms to resist phage killing [27, 55, 99]. Efforts to counter this resistance include combining multiple phages into a treatment cocktail [100]. However, the optimal cocktail design to prevent resistance while also avoiding phage-phage antagonism is unclear. Further, despite the use of phage cocktails, resistance may still occur, requiring additional screening and the inclusion of additional phages [22]. Alternatively, phages can be chosen for their potential to select for resistant mutants that are avirulent or have enhanced antibiotic susceptibility [27, 100]. Unfortunately, both approaches require laborious and time-consuming screening.

It is important to note that phage resistance is not universally seen. Clinical and in vitro selection for phage resistance in NTM appears to be rare, which suggests these infections may be well suited for PT [40, 101]. Further, phage resistance may not always indicate treatment failure as it can be associated with enhanced antibiotic susceptibility or compromised pathogen fitness. In a review of 20 cases of PT for respiratory infections, phage resistance was identified in only 30% of cases [27]. However, among patients in which phage resistance was detected, some continued to demonstrate clinical improvement [27, 102]. As such, the clinical impact of phage resistance remains unclear.

Even in the absence of resistance, other factors may hinder the effectiveness of phage treatment. This includes unpredictable pharmacokinetics and pharmacodynamics,

uncertainty about dosing and delivery, formulation, and storage. In particular, a key challenge in treating pulmonary biofilm infections is drug delivery. Intravenous phage administration is commonly utilized but has poorly predicted biodistribution. Alternatively, nebulized therapy, in which aerosolized droplets containing phages are inhaled, provides targeted delivery. However, the method of nebulization may compromise phage integrity as well as limit the area of distribution throughout the lung [103, 104]. The development of phage-neutralizing antibodies poses another challenge, which may further impede phage activity [105]. However, neutralizing antibodies have also been detected in successful cases of respiratory infections managed by PT, raising questions about their significance [40].

In addition to these distinct limitations, the lack of successful clinical trials compels a sobering pause. Is PT the solution to chronic lung infections? The current enthusiasm is inspired by success in individual cases; however, these studies are heterogeneous and non-standardized. Will PT demonstrate efficacy when tested in rigorous clinical trials, or will inconsistent results continue to stymie this approach? The preliminary review data from the CYPHY, in which PT for treatment of *P. aeruginosa* in PwCF did not meet the primary endpoint, indicates that more work needs to be done to validate PT as a viable therapeutic option for pulmonary infections.

Conclusions

The rise of AMR, particularly in patients with chronic pulmonary infections, has revived interest in PT. Numerous case studies have demonstrated phage effectiveness in treating chronic pulmonary infections. However, as discussed in this review, for PT to be broadly adopted beyond salvage therapy, numerous challenges need to be overcome. Yet, even with these advances, there may be a larger potential challenge ahead. In his Nobel address commemorating the discovery of penicillin, Fleming anticipated the emergence of antimicrobial resistance, which he attributed to antibiotic under dosing and misuse. Chronic lung infections are major sources of AMR, partly due to the nature of the disease requiring repeated antibiotic exposure, potentiating antibiotic resistance. Thus, one possible consequence of increased utilization of PT for persistent pulmonary infections would be phage overuse and misuse, as seen with antibiotics, leading to resistance. While the consequences of phage resistance on clinical outcomes is variable, it is reasonable to assume that rising resistance over time will adversely impact treatment. To ensure PT does not follow the same destiny Fleming predicted for antibiotics, guiding principles to navigate the appropriate use of PT will be necessary. Phages have not yet been shown to be a “magic bullet” for eradicating chronic pulmonary infections, yet there is reason for optimism. The recent development of CF modulator therapy has dramatically altered disease progression in PwCF. By correcting the malfunctioning CFTR protein, modulator therapy has resulted in less accumulation of airway mucus, resulting in improved respiratory function, decreased pulmonary exacerbations, and even reduced pulmonary pathogen burden [106]. *P. aeruginosa* pulmonary infections continue to persist in many of these patients [107, 108]. However, the improved source control achieved by modulator therapy may potentiate pathogen eradication with PT alone or in combination with antibiotics. Finally, if optimized, phage-antibiotic synergy, will fundamentally reshape the potential to effectively and definitively treat chronic pulmonary infections.

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Table 1

Summary of clinical case studies involving phage therapy in patients with pulmonary infections from 2023 to 2019

Article	Pathogen/Indication	Phage treatment	Clinical outcome
Chan 2023 (preprint) [30]	*P. aeruginosa* (MDR *n* = 6, PDR *n* = 3) pulmonary infections in CF patients (*n* = 9)	Inh LPS-5 (*n* = 3) Inh LPS-5, TIVP-H6 (*n* = 4) Inh LPS-5, TIVP-H6, OMKO1 (*n* = 2)	Clinical improvement with increased ppFEV1 and reduction of bacterial burden *n* = 9
Haidar, 2023 PMID: 36864824	*B. multivorans* pneumonia and bacteremia in CF patient (*n* = 1)	Inh Bch7	Clinical failure and death, reduction of bacterial burden
Nick, 2022 PMID:35568033	*M. abscessus, MDR P. aeruginosa and MRSA* pulmonary infection in CF patient with advanced bronchiectasis (*n* = 1)	IV engineered BPsΔ33HTH_HRM10 and D29_HRMGD40 targeting *M. abscessus*	Clinical improvement and listed for lung transplant, reduction of bacterial burden
Winzigh, 2022 PMID: 36568830	*Achromobacter* (MDR and PDR) lung colonization in CF patient (*n* = 1)*	Inh Achr-1 and Achr-2	Clinical improvement, reduction of bacterial burden
Rao, 2022 PMID: 34662188	*A. baumannii* (CRAB) and *P. aeruginosa* ventilation-associated pneumonia (*n* = 1)	Inh and IV AbW4932ø1, AbW4878ø1 targeting *Acinetobacter*	Clinical improvement and bacterial eradication
Dedrick, 2022 PMID: 35676823	NTM pulmonary infection including *M. abscessus* (*n* = 17), *M. avium complex* (*n* = 1), BCG (*n* = 1). Of these patients, 17 had CF.*	Inh and IV Muddy (*n* = 7) Inh and IV BPsΔ33HTH_HRMGD03 (*n* = 3) Inh an IV BPsΔ33HTH_HRM10, Itos (*n* = 2) Inh and IV BPsΔ33HTH_HRMGD03, D29_HRMGD40 (*n* = 1) Inh and IV BPsΔ33HTH_HRM1, D29_HRMGD40 (*n* = 1) Inh and IV BPsΔ33HTH_HRMGD03, Itos (*n* = 1) Inh and IV Muddy, D29, FionnbharthΔ43Δ45, Fred313cpmΔ33 (*n* = 1) Inh and IV BPsΔ33HTH_HRM10, Muddy, ZoeJΔ45 (*n* = 2)	Favorable or partial results, bacterial eradication: *n* = 10 Complex, inconclusive or incomplete responses: *n* = 5 No evident clinical improvement: *n* = 4
Gainey, 2020 PMID: 32662948	*Achromobacter* (MDR and PDR) lung colonization inn pediatric CF patient (*n* = 1)	IV Ax2CJ45ϕ2	Clinical improvement, bacterial eradication
Aslam, 2019 PMID:31207123	*B. dolosa* (MDR) pulmonary colonization in CF patient followed by a bilateral lung transplant and recurrent *B. dolosa* pneumonia (*n* = 1) *P. aeruginosa* pneumonia (MDR) in a bilateral lung transplant patient (*n* = 1) *P. aeruginosa* (MDR), *M. abscessus* lung infection in a post-transplant non CF patient with bronchiectasis (*n* = 1)	IV BdPF16phi4281 IV 4 different cocktails: AB-PA01, AB-PA01 m1, Navy cocktail 1, Navy cocktail 2 IV AB-PA01 targeting *P. aeruginosa*	Initial clinical improvement, but died 11 months after transplantation, no bacterial eradication Clinical improvement and bacterial eradication Clinical improvement and bacterial eradication
Law, 2019 PMID:31102236	*P. aeruginosa* (MDR) pulmonary infection in CF patient on waitlist for lung transplant (*n* = 1)	IV AB-PA01	Clinical improvement, underwent bilateral lung transplant successfully

Cases reported in the USA during this time period

Antibiotic use was not reported in cases with asterisks (*)

All other cases were co-treated with antibiotics

CF cystic fibrosis, *NTM* non tuberculosis mycobacterium, *MDR* multi-drug-resistant, *PDR* pan-drug-resistant, *CRAB* carbapenem resistant *A. baumannii*, *MRSA* Methicillin resistant *Staphylococcus aureus*, *BCG* Bacillus Calmette-Guérin, *PFU* plaque forming units, *N/A* not available, *ppFEV1* percent predicted *FEV1*, *IV* intravenously injected, *Inh* inhaled nebulized therapy, AB-PA01 cocktail: Pa193, Pa204, Pa222 and Pa223, AB-PA01 m1 cocktail: Pa193, Pa204, Pa222, Pa223 and Pa176, Navy cocktail 1: Paφ1, PaSKWφ17, and PaSKWφ22, Navy cocktail 2: PaATFφ1 and PaATFφ3