

MULTIDRUG-RESISTANT AND HIGHLY VIRULENT STRAINS OF *BURKHOLDERIA CEPACIA* COMPLEX – PHAGE THERAPY AS A POTENTIAL TREATMENT OPTION FOR INFECTIONS

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Abstract: The *Burkholderia cepacia* complex (Bcc) consists of multiple opportunistic pathogens capable of causing serious infections, especially in individuals with cystic fibrosis (CF). Some patients may develop “cepacia syndrome,” a rapidly worsening and often deadly complication. Treatment is difficult because Bcc naturally resists many antibiotic classes and can form biofilms, which help it persist and shield bacteria from the immune system. These issues have made traditional antibiotic treatments mostly ineffective, highlighting the urgent need for alternative solutions.

Phage therapy has shown promise as a potential strategy, but its use against Bcc remains limited. Isolating strictly lytic phages is challenging because most available *Burkholderia* phages are temperate and have narrow host ranges. So far, only a few phages with activity against clinically relevant isolates have been identified. Evidence from compassionate use cases indicates that phage therapy can be safe and well-tolerated, but solid clinical data are still missing. Important gaps in knowledge include the limited availability of phages, the need for standardized protocols, and the optimization of delivery methods, such as aerosolization for lung infections. Solving these issues will be crucial for making phage therapy a practical treatment option for multidrug-resistant Bcc infections.

1. Introduction 2. Resistance of Bcc 3. Virulence of Bcc 4. Phage therapy 5. Conclusions.

Keywords: *Burkholderia cepacia* complex; bacteriophage therapy; cystic fibrosis; multidrug resistance; virulence,

1. Introduction

Burkholderia cepacia complex (Bcc) comprises approximately 26 bacterial species that are considered plant pathogens, with *Burkholderia glumae* and *Burkholderia gladioli* being linked explicitly to bacterial panicle blight or leaf strike (Nandakumar et al. 2009; Ham et al. 2011).

Certain *Burkholderia* species can cause disease in plants, animals, and humans. In individuals with a weakened immune system or those with cystic fibrosis, infection with the Bcc may result in “cepacia syndrome” (Eberl and Vandamme 2016). “Cepacia syndrome” is characterized by rapid respiratory deterioration, bacteremia, and necrotizing pneumonia. It is nearly always a fatal complication of Bcc infection,

even with intensive antibiotic treatment (Martina et al. 2018; Velez et al. 2023).

Although less prevalent than *P. aeruginosa* and *S. aureus*, Bcc remains a significant clinical concern for individuals with CF across all age groups (Cystic Fibrosis Foundation 2023). At least five Bcc species—*B. cepacia*, *B. cenocepacia*, *B. multivorans*, *B. dolosa*, and *B. contaminans*—can spread through aerosol droplets, allowing these strains to easily disseminate among susceptible patients through both direct and indirect contact.

A systematic review conducted by Häfliger et al. documented 111 outbreaks of Bcc infections in hospitals across multiple continents between 1971 and 2019, underscoring the global relevance of this opportunistic pathogen. In total, 2,390 patients were affected, with

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240 deaths reported; however, only 28 fatalities (1.2%) were directly attributed to Bcc infection, reflecting both the opportunistic nature of the pathogen and the complex health conditions of affected patients. The analysis revealed that the majority of outbreaks were linked to external contamination sources, which were identified in 73.9% of cases (Häfliger et al. 2020). Several outbreaks of Bcc have been reported in recent years. In India between 2017 and 2018, a large hospital outbreak in a surgical unit resulted in 183 cases of bloodstream infection, with a 47% mortality rate (Fomda et al. 2023). Despite an extensive investigation, the exact source of the outbreak was not identified. In 2019, an outbreak in an intensive care unit in Turkey involved six patients, where the source was successfully traced to a contaminated 2% chlorhexidine mouthwash solution, highlighting the potential for antiseptic products themselves to become vehicles of infection (Bilgin et al. 2021). In a neonatal intensive care unit, researchers investigated an outbreak of New Delhi metallo- β -lactamase (NDM)-producing *Burkholderia cepacia* complex (BCC) that resulted in mortality 55.5% (Batool et al. 2023). In 2021, a quaternary-care children's hospital detected an increase in Bcc infections, specifically *B. contaminans*, resulting in 12 confirmed cases, all of which were linked through respiratory cultures (Teoh et al. 2022). These events illustrate the persistent risk posed by Bcc in hospitals and the importance of stringent infection-control practices and monitoring of medical products.

2. Resistance of Bcc

The clinical outcome of Bcc infections varies significantly and is strain-dependent (Zlosnik et al. 2020). The intrinsic resistance of Bcc strains to most antibiotics makes their eradication even more challenging (Lauman and Dennis 2021). The Bcc species are intrinsically resistant to β -lactams, aminoglycosides, cationic antimicrobial peptides, and polymyxins and have multiple mechanisms of resistance to several other classes of antibiotics, including quinolones, tetracyclines, chloramphenicol, and trimethoprim, which is connected to many resistance mechanisms, such as porins, enzymes, efflux pumps, and the ability to form and grow in biofilms (Mahenthiralingam and Vandamme 2005). The primary mechanism associated with antimicrobial resistance in Bcc species is efflux pump-mediated extrusion. Resistance to β -lactams is due to enzymatic modifications (such as chromosomally encoded β -lactamases) and altered drug targets (altered

penicillin-binding proteins). The outer membrane also contributes to increased resistance to antibiotics. The structure of LPS in this genus is unique, preventing the binding of aminoglycosides and cationic antimicrobial peptides (Vinion-Dubiel and Goldberg 2003). Even the most potent anti-Bcc antibiotics may not be effective against nearly 60% of the isolates, indicating that conventional antibiotic treatments are largely ineffective and highlighting the urgent need for alternative approaches to treat Bcc infections. Multidrug-resistant Bcc strains were reported in 26.1% of the strains isolated from 111 healthcare-associated outbreaks (Häfliger et al. 2020).

Because Bcc is intrinsically resistant to multiple classes of antibiotics and has high virulence, the treatment of Bcc infections is particularly challenging (Kamal and Dennis 2015). Owing to the lack of standardized clinical trial data and eradication strategies, there is no consensus on first-line treatments (Regan and Bhatt 2019). Therapy for Bcc lung infections in people with CF is particularly challenging (Frost et al. 2019; Regan and Bhatt 2019). The use of colistin, a last-resort antibiotic, is also hampered by nephrotoxic and neurotoxic side effects, further complicating treatment. In vitro studies have reported decreased antimicrobial efficacy of aminoglycosides (such as amikacin and tobramycin) against Bcc (Van Dalem et al. 2018).

Additionally, rifampicin is ineffective in preventing Bcc biofilm formation (Sfeir 2018). Despite intensive antibiotic courses, eradication is not always successful and may pose a barrier to lung transplantation in patients with cystic fibrosis (Pilewski 2022). All these challenges highlight the need for alternative treatment strategies for Bcc infections.

3. Virulence of Bcc

Strains belonging to Bcc are also highly pathogenic. Understanding the mechanisms underlying the virulence and persistence of Bcc during infections is crucial, particularly in relation to its antimicrobial resistance capabilities. Bcc utilizes a variety of virulence factors that increase its pathogenicity at different stages of infection, particularly in lung epithelial cells. Among all its virulence factors, the following can be distinguished: pili, which aid in epithelial cell attachment; extracellular proteases, which cause tissue damage; quorum-sensing genes, which enable biofilm formation; T3SSs and T4SSs, which facilitate cellular invasion; and others, such as hemolysin, gelatinase, siderophores, and a protective capsule.

Bcc species utilize quorum sensing to regulate gene expression in response to population density, controlling the production of virulence factors and biofilm formation, which is crucial for persistence in the host (Eberl 2006; Cui et al. 2018). Quorum sensing (QS) is generally mediated by LuxI/LuxR-type systems, which consist of an acyl-homoserine lactone (AHL) synthase (CepI) and its corresponding transcriptional regulator (CepR) (Chapalain et al. 2017).

Biofilms play a central role in chronic infections, such as those found in CF patients' lungs, where they help bacteria evade the immune system and resist antibiotic treatment (Eberl 2006; Sokol et al. 2007). The regulation of biofilm involves multiple genetic pathways, including *rqpSR*, *fixLJ*, and *atsRT* (Schaefer 2020), as well as genes responsible for exopolysaccharide synthesis (*cepA*, *cepB*, *cepC*), which are essential for the structural integrity (Chapalain et al. 2017; Eberl 2006; Huber et al. 2001).

Additionally, quorum-sensing genes, such as *lasI* and *lasR*, play crucial roles in regulating biofilm formation by modulating the expression of these biofilm-associated genes (Huber et al. 2001). Disruption of quorum-sensing pathways has been proposed as a potential strategy to reduce Bcc pathogenicity and antimicrobial resistance.

The unique structure of Bcc LPS reduces the anionic charge on the Bcc cell surface, which prevents the binding of cationic antibiotics and their subsequent effects (Sfeir 2018). It is involved in immune evasion and contributes to the pathogenicity of bacteria by inducing the production of proinflammatory cytokines, which can lead to tissue damage.

Strains within the Bcc have developed numerous strategies to withstand the effects of antibiotics and immune-mediated killing, including the use of Type III (T3SS) and Type VI (T6SS) secretion systems (Chen et al. 2011).

The *cepIR* genes and *cciIR* genes influence the control of extracellular proteases, and the production of extracellular proteases contributes to increased potential for pathogenesis (Ganesh et al. 2020). Bcc secretes the ZmpA and ZmpB proteases, which are responsible for disrupting tissue integrity and host defense mechanisms (Ganesh et al. 2020).

Bcc species are among the most important lipase-producing bacteria, with *B. multivorans* and *B. cenocepacia* exhibiting the highest expression and production of extracellular lipases, which play crucial roles in facilitating the invasion of lung epithelial cells (Mullen et al. 2007).

The virulence of Bcc strains hinders effective therapy by promoting persistence, reducing the efficacy of antibiotics, and limiting the treatment options available.

4. Phage therapy

Owing to the intrinsic resistance of Bcc to multiple classes of antibiotics and its high virulence, treating infections caused by these bacteria is particularly challenging. This highlights the urgent need for alternative therapeutic strategies for Bcc infections.

One alternative may be phage therapy. However, isolating bacteriophages against Bcc is challenging, as they are not as abundant as bacteriophages that target other species and are mainly temperate (Lauman and Dennis 2021). Reports have shown that isolation of the strictly lytic phage is possible (Summer et al. 2006; Lynch et al. 2013). Strictly lytic phages are preferred for therapeutic use because of their ability to kill bacterial cells directly through the lytic cycle, which ensures effective eradication of the infection (Kakasis and Panitsa 2019). In contrast, lysogenic (temperate) phages integrate their genome into bacterial DNA, remaining dormant as prophages and replicating with bacteria, which prevents immediate bacterial cell death (Kakasis and Panitsa 2019). Temperate phages pose a risk of horizontal gene transfer, potentially passing on virulence or antimicrobial resistance genes (Keen et al. 2017). This makes only strictly lytic phages reliable and effective for treating bacterial infections.

Currently, phages are primarily available as treatments under compassionate use protocols in many parts of the world, where special approval allows for their administration to patients who have not responded to antibiotic therapy and have no other treatment options remaining (Patey et al. 2018). One of the primary barriers to translating Bcc phage therapy is the limited availability of phages specifically targeting Bcc, which hinders research progress and impedes clinical application (Semler et al. 2012). According to the published data, approximately 90 *Burkholderia* phage whole-genome sequences have been uploaded to GenBank (GenBank database of the National Center for Biotechnology Information (<https://www.ncbi.nlm.nih.gov/>), Accessed January 2025). The main known phages, along with data such as lifecycle (lytic vs. lysogenic), host, genome size, and family or genus, are summarized in Table 1.

Table 1. *Burkholderia* phages by lifecycle detailing host, morphotype, taxonomy, and genome size.

Phage name	Host	Phage morphotype	Phage taxonomy (Family; Genus)	Genome sipze [bp]	Reference
Lytic lifecycle					
AH2	<i>B. cenocepaica</i> ; <i>B. gladioli</i>	Siphovirus	Casjensviridae; Ahduovirus	58.065	Lauman et al. 2024; Lynch et al. 2012b
Bcep1	<i>B. cenocepaciac</i>	Myovirus	Naesvirus	48.177	Summer et al. 2006
BcepB1A	<i>B. cenocepaciac</i>	Myovirus	n/a	47.399	Lynch et al. 2012a
BcepSauron	<i>B. cenocepaciac</i>	Myovirus	Sarumanvirus	262.653	Park et al. 2014
KP1	<i>B. cenocepaciac</i>	Siphovirus	Siphovirus	52.676	Mankovich et al. 2023
KL1	<i>B. cenocepaciac</i>	Siphovirus	Jondennisvirinae; Kilunavirus	42.832	Lynch et al. 2012b
Bcep43	<i>B. cepaciac</i>	Myovirus	Naesvirus	48.024	Summer et al. 2006
Bcep781	<i>B. cepaciac</i>	Myovirus	Naesvirus	48.247	Summer et al. 2006
BcepNazgul	<i>B. cepaciac</i>	Siphovirus	Casjensviridae; Nazgulvirus	57.455	Ahern et al. 2014
CSP3	<i>B. contaminans</i>	Podovirus	Lessievirus	63.038	Stanton et al. 2023
WTB	<i>B. gladioli</i>	Myovirus	Bglawtbvirus	68.641	Wang et al. 2024
FLC10	<i>B. glumae</i>	Myovirus	Peduoviridae; Kisquattuordecim-virus	32.867	Kanaizuka et al. 2023
NBP1-1	<i>B. glumae</i>	Myovirus	Peduoviridae; Tigrvirus	40.57	Jungkhun et al. 2021
NBP4-7	<i>B. glumae</i>	Myovirus	Peduoviridae; Tigrvirus	40.563	Jungkhun et al. 2021
NBP4-8	<i>B. glumae</i>	Myovirus	Peduoviridae; Tigrvirus	40.568	Jungkhun et al. 2021
FLC6	<i>B. glumae</i> ; <i>B. plantarii</i>	Myovirus	Chimalliviridae; Chingmaivirus	227.105	Sasaki et al. 2021a
FLC8	<i>B. glumae</i> ; <i>B. plantarii</i> ; <i>B. gladioli</i>	Myovirus	Chimalliviridae; Chingmaivirus	225.545	Kanaizuka et al. 2023
S13	<i>B. multivorans</i> ; <i>B. cenocepaciac</i> ; <i>B. dolosa</i> ; <i>B. ambifaria</i>	Myovirus	Chimalliviridae; Chingmaivirus	227.647	Supina et al. 2025
JG068	<i>B. multivorans</i> ; <i>B. cenocepaciac</i> ; <i>B. stabilis</i> ; <i>B. dolosa</i>	Podovirus	Autonotataviridae; Mguuvirus	41.604	Rezene et al. 2022
ST79	<i>B. pseudomallei</i> ; <i>B. mallei</i>	Myovirus	Peduoviridae; Nampongvirus	35.43	Yordpratrum et al. 2011
Temperate lifecycle					
KL3	<i>B. ambifaria</i>	Myovirus	Peduoviridae; Kayeltresvirus	40.555	Lynch et al. 2010a
AP3	<i>B. cepaciac</i>	Myovirus	Peduoviridae; Aptresvirus	~38–40	Roszniowski et al. 2017
BcepIL02	<i>B. cenocepaciac</i>	Podovirus	Lessievirus	62.715	Gill et al. 2011
BcepMu	<i>B. cenocepaciac</i>	Myovirus	Bcepmuvirus	36.748	Semler et al. 2012
Magia	<i>B. cenocepaciac</i>	Myovirus	Magiavirus	44.942	Gafford-Gaby et al. 2021
Mica	<i>B. cenocepaciac</i>	Myovirus	Micavirus	43.707	Garcia et al. 2021
Milagro	<i>B. cenocepaciac</i>	Myovirus	Peduoviridae; Kayeltresvirus	39.088	n/a
Paku	<i>B. cenocepaciac</i>	n/a	Autonotataviridae; Pakuvirus	42.727	Rezene et al. 2022
vb BceM AP3	<i>B. cenocepaciac</i>	Myovirus	Peduoviridae; Aptresvirus	36.499	Roszniowski et al. 2017
Bcep22	<i>B. cenocepciac</i>	Podovirus	Lessievirus	63.882	Gill et al. 2011
KS10	<i>B. cenocepciac</i> ; <i>B. stabilis</i> ; <i>B. ambifaria</i>	Myovirus	n/a	37.635	Goudie et al. 2008
BcepC6B	<i>B. cepaciac</i>	Podovirus	Ryyoungivurs	42.415	Summer et al. 2006
DC1	<i>B. cepaciac</i> ; <i>B. cenocepaica</i> ; <i>B. stabilis</i>	Podovirus	Lessievirus	61.847	Lynch et al. 2012b
Maja	<i>B. gladioli</i>	Myovirus	Lindbergviridae; Gladiolivirus	68.393	Yu et al. 2021

FLC5	<i>B. glumae</i> ; <i>B. plantarii</i>	Myovirus	Peduoviridae; Kisquattuordecimvirus	32.09	Sasaki et al. 2021b
phiE125	<i>B. mallei</i>	Siphovirus	Stanholtvirus	53.373	Woods et al. 2022
phi1026b	<i>B. mallei</i> ; <i>B. pseudomallei</i>	Siphovirus	Stanholtvirus	54.865	DeShazer et al. 2004
phi644_2	<i>B. mallei</i> ; <i>B. pseudomallei</i>	Siphovirus	Stanholtvirus	48.674	Ronning et al. 2010
phiE12_2	<i>B. mallei</i> ; <i>B. pseudomallei</i> ;	Myovirus	Peduoviridae; Duodecimduovirus	36.69	Ronning et al. 2010
phiE202	<i>B. mallei</i> ; <i>B. pseudomallei</i> ;	Myovirus	Peduoviridae; Tigrvirus	35.741	Ronning et al. 2010
phiE058	<i>B. mallei</i> ; <i>B. pseudomallei</i> ; <i>B. thailandensis</i>	Myovirus	n/a	44.121	Hammerl et al. 2020
KS5	<i>B. multivorans</i> ; <i>B. cenocepacia</i>	Myovirus	Peduoviridae; Kisquiquevirus	37.236	Lynch et al. 2010a
KS14	<i>B. multivorans</i> ; <i>B. cenocepacia</i> ; <i>B. dolosa</i> ; <i>B. ambifaria</i>	Myovirus	Peduoviridae; Kisquattuordecimvirus	32.317	Lynch et al. 2010b
Bcep176	<i>B. multivorans</i> ; <i>B. cepacia</i>	Siphovirus	Stanholtvirus	44.856	n/a
phi52237	<i>B. pseudomallei</i>	Myovirus	Peduoviridae; Tigrvirus	37.639	Ronning et al. 2010
PK23	<i>B. pseudomallei</i>	Myovirus	Peduoviridae; Duodecimduovirus	35.343	Khongsee et al. 2024
PE067	<i>B. pseudomallei</i> ; <i>B. thailandensis</i>	Myovirus	n/a	43.649	Hammerl et al. 2020
Bp-AMP1	<i>B. pseudomallei</i> ; <i>B. thaliandensis</i>	Podovirus	Autonotataviridae; Ampunavirus	42.409	Letarov et al. 2022; Shan et al. 2014;
phiX216	<i>B. pseudomalleri</i> ; <i>B. mallei</i>	Myovirus	Peduoviridae; Tigrvirus	37.637	Kvitko et al. 2012
KS9	<i>B. pyrrocinia</i> ; <i>B. cenocepacia</i>	Siphovirus	Stanholtvirus	39.896	Lynch et al. 2010
PhiE255	<i>B. thailandensis</i>	Myovirus	Bcepmyovirus	37.446	Ronning et al. 2010
phiE094	<i>B. thailandensis</i> ; <i>B. pseudomallei</i>	Myovirus	Peduoviridae; Tigrvirus	37.727	Muangsoombut et al. 2021
Lifestyle unclassified					
BcepF1	<i>B. ambifaria</i>	Myovirus	Lindbergviridae; Bcepfunavirus	14.8	Quinones-Olvera et al. 2024
BcepMigl	<i>B. cenocepacia</i>	Podovirus	Lessievirus	72.415	Lynch et al. 2012a
BcepNY3	<i>B. cenocepacia</i>	n/a	Naesvirus	52.414	Lynch et al. 2012a
BcepSaruman	<i>B. cenocepacia</i>	Myovirus	Sarumanvirus	62.952	n/a
BCE1	<i>B. cepacia</i>	n/a	Tectiviridae; Alphatectivirus	47.382	n/a
BcepGomr	<i>B. cepacia</i>	n/a	n/a	263.735	n/a
BCSR129	<i>B. cepacia</i>	Myovirus	n/a	66.147	Ben Porat et al. 2021
BCSR52	<i>B. cepacia</i>	Myovirus	Lindbergviridae; Irusalmivirus	227.351	Ben Porat et al. 2021
BCSR5	<i>B. cepcia</i>	Myovirus	n/a	70.038	n/a
Mana	<i>B. gladioli</i>	Myovirus	Peduoviridae; Aptresvirus	37.631	Roszniewski et al. 2017
FLC9	<i>B. glumae</i> ; <i>B. plantarii</i>	Myovirus	n/a	42.492	Shan et al. 2014
vB BmuP KL4	<i>B. multivorans</i>	n/a	Kelquatovirus	41.882	Shan et al. 2014
BEK	<i>B. pseudomallei</i>	Myovirus	Peduoviridae; Tigrvirus	42.112	Shan et al. 2014
Bp-AMP2	<i>B. pseudomallei</i>	Podovirus	Autonotataviridae; Ampunavirus	321.833	Kanaizuka et al. 2023
Bp-AMP3	<i>B. pseudomallei</i>	Podovirus	Autonotataviridae; Ampunavirus	38.038	Godoy et al. 2021
Bp-AMP4	<i>B. pseudomallei</i>	Podovirus	Autonotataviridae; Ampunavirus	54.921	n/a
phiBP82.1	<i>B. pseudomallei</i>	n/a	Stanholtvirus	56.453	n/a
phiBt	<i>B. pseudomallei</i>	n/a	Stanholtvirus	42.25	n/a

Legend: n/a- data unavailable.

Therapeutic application of *Burkholderia* phages remains constrained by their narrow host ranges and the predominance of temperate phages (Yao et al. 2023; Lauman and Dennis 2021). The population of Bcc phages consists mainly of Myoviridae, while Bcc Siphoviridae and Podoviridae are vastly outnumbered. The host ranges of Bcc phages are diverse - phages such as KL3, Bcep1, and Bcep22 infect a single strain, whereas NS2 is capable of infecting strains among four distinct Bcc species (Lauman and Dennis 2021). Phages belonging to different families, including Podoviridae (BcepIL02) and Myoviridae (KS5, KS12, KS14), can reduce mortality, as demonstrated in *in vivo* studies (Carmody et al. 2010; Seed and Dennis 2009; Semler et al. 2014). According to current data, only five of the known Bcc phages are strictly lytic, whereas more than 50% are temperate. The lifecycles of the remaining ones are uncertain due to a lack of sequencing (Lauman and Dennis 2021).

It has been demonstrated that antibiotics can enhance phage activity by stimulating increased phage production, a phenomenon known as Phage-Antibiotic Synergy (PAS) (Comeau et al. 2007; Semler et al. 2014). Combined phage therapy with doses of antibiotics representing different drug classes has been used for treating a Bcc infection in *G. mellonella* (Kamal and Dennis 2015). Results of this study suggest that antibiotics can be used together with phages to stimulate the production of phages and improve their activity, leading to more efficient bacterial killing. Moreover, PAS remains effective even against bacteria that have developed antibiotic resistance, representing a promising strategy to achieve greater bacterial reduction than either antibiotics or phages alone (Kamal and Dennis 2015).

There are two reports documenting the use of phages against Bcc in humans, highlighting a critical gap in knowledge regarding Bcc phage therapy, with human data remaining scarce (Aslam et al. 2019; Haidar et al. 2023). Both case reports reported no harmful immune responses or adverse events linked to phage therapy.

A patient suffering cystic fibrosis (CF) who had undergone a lung transplant became infected with antimicrobial-resistant *B. dolosa*, resulting in pneumonia and septicemia. Six months post-transplant, the patient received phage therapy with BdPF16phi4281 (produced by Adaptive Phage Therapeutics) together with broad-spectrum antibiotics (minocycline, meropenem, and trimethoprim/sulfamethoxazole).

During phage therapy, a reduction in bacterial load in bronchoalveolar fluid was observed, accompanied by temporary improvements in lung function, fever, and airway secretions. The patient's condition deteriorated due to antibiotic toxicity and CF-related hepatopathy, and both antibiotic and phage therapy were stopped after a 12-week phage course, leading to a rise in *B. dolosa* load. The patient ultimately died from infection-related complications, but no adverse events were reported from phage administration (Aslam et al. 2019).

In the second case, a patient undergoing a bilateral lung transplant with a history of *B. multivorans* infection received nebulized phage therapy with phage Bch7, administered three times daily for 7 days (Haidar et al. 2023). The patient was receiving antibiotics and was intubated prior to therapy. Initial clinical improvements, including reduced oxygen requirements and lower white blood cell counts, were observed on day 1; however, these effects were short-lived, and the bacterial load in sputum remained positive throughout. The patient developed secondary fungal infections and ultimately received intravenous phage therapy. Despite phage DNA being detected in tracheal aspirate and BALF, indicating lung delivery, the patient developed multiple organ failure and acidosis, and subsequently died. Significantly, no adverse events were attributed to phage therapy, and blood cultures after intravenous administration were negative for *B. multivorans*. This case highlights both the potential for safe lung delivery of phages and the challenges in achieving clinical efficacy in severe, multidrug-resistant infections (Haidar et al. 2023).

The preliminary case reports indicate that phage therapy targeting Bcc is generally safe and well-tolerated in humans, with no significant adverse events directly linked to its administration. These observations underscore the importance of closely monitoring immune responses during phage therapy. Despite these encouraging findings, significant, controlled clinical trials are still lacking, and robust evidence is needed to establish the efficacy, optimal dosing, and standardized protocols for Bcc phage therapy.

5. Conclusions

The *Burkholderia cepacia* complex can cause chronic, life-threatening lung infections, particularly in patients with cystic fibrosis, and is challenging to treat due to its high intrinsic antimicrobial resistance and

virulence, underscoring the urgent need for alternative therapies. Phage therapy is safe and effective, with the added advantage of reducing antibiotic-related toxicity when used in combination. Phage–antibiotic combinations have demonstrated efficacy in animal models and show promise in eradicating Bcc species. While compassionate use cases provide valuable insights, the lack of standardized case reporting limits their broader applicability (McCallin et al. 2019). To translate phage therapy successfully, standardized clinical trials and consensus on phage selection and production are crucial (Pires et al. 2020). Guidelines for phage manufacturing, including adherence to good manufacturing practices (GMPs) and the removal of bacterial toxins (such as LPS), are essential for ensuring the safety and efficacy of the prepared formulas (Pires et al. 2020). Delivering phages effectively to the lungs via intravenous administration may be challenging; however, nebulization of bacteriophages has shown promising results (Prazak et al. 2020; Prazak et al. 2022). Studies suggest that phages (including those against Bcc) can be stable and effective in aerosolized formulations, warranting further evaluation for clinical use in respiratory infections (Prazak et al. 2020; Mitropoulou et al. 2022; Prazak et al. 2022). Despite the promising results, several challenges must be considered. Most Bcc phages exhibit a narrow host range, limiting their applicability across diverse clinical isolates.

Additionally, the patient's immune system may neutralize phages, particularly during repeated administrations, reducing therapeutic efficacy. Regulatory issues, including the lack of standardized clinical trial protocols and manufacturing requirements, complicate the translation of phage therapy into routine clinical practice. Addressing these limitations is critical for the safe and effective implementation of phage-based treatments. Future research should focus on standardizing phage selection and production, understanding Bcc phage receptors, targeting efflux pumps and virulence factors, systematically studying phage–antibiotic synergy, and rigorously evaluating delivery routes such as intravenous versus nebulization.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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