ISOLATION AND CHARACTERIZATION OF BACTERIOPHAGES INFECTING *Pseudomonas aeruginosa* AND ENHANCING BACTERIAL ANTIBIOTIC SUSCEPTIBILITY

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ABSTRACT

Pseudomonas aeruginosa is an opportunistic Gram-negative pathogen in plants and animals, including humans. It causes considerable challenges due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Bacteriophage therapy, which utilizes specialized viruses to target and eliminate bacteria, has emerged as a potential approach to overcome the burden of antibiotic resistance. This study focused on the isolation and characterization of bacteriophages capable of infecting *P. aeruginosa* and evaluated their enhanced inhibition effect with antibiotics to enhance bacterial susceptibility. This combination increased antibiotic suseptibility of MDR *P. aeruginosa* strain. Our results indicated that 6 bacteriophages isolated from samples collected from the To Lich River and West Lake exhibited the ability to eradicate *P. aeruginosa* ATCC9027. Further experiments in collaboration with Ha Dong Hospital aimed to evaluate the lytic efficacy of these phages against antibiotic-resistant *P. aeruginosa* strains isolated from clinical samples. Among them, two novel lytic phages, provisional designation as bvB_Pae_BK5 and vB_Pae_BK6, were successfully isolated. Lytic phages are generally preferred for therapeutic applications due to their ability to directly kill bacterial cells, unlike lysogenic phages. Despite challenges such as bacteriophage specificity, host immune responses, and regulatory barriers, this integrated approach represents a promising strategy for treating *P. aeruginosa* infections.

Keywords: Antibiotic resistance, bacteriophage, infection, *Pseudomonas aeruginosa.*

1. INTRODUCTION

Pseudomonas aeruginosa is an opportunistic Gram-negative bacterium that causes a wide range of infections in both plants and animals, including humans. It is a leading cause of hospital-acquired infections such as urinary tract infections, pneumonia, bloodstream infections, and wound infections, particularly in burn patients. Notably, mortality rates associated with *P. aeruginosa*-related ventilator-associated pneumonia range from 32% to 42.8%, while bloodstream infections can result in mortality rates as high as 43.2% to 58.8% [1-3].

Since the discovery of antibiotics in 1929, these agents have played a pivotal role in controlling bacterial infections [4]. However, the widespread and often indiscriminate use of antibiotics in clinical settings, veterinary medicine, agriculture, and prophylaxis has accelerated the emergence and dissemination of antimicrobial resistance (AMR), particularly in low- and middle-income countries such as Vietnam, Sri Lanka, and Indonesia. Among the most concerning multidrug-resistant pathogens are the so-called ESKAPE organisms: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. These bacteria are capable of "escaping" the effects of conventional antibiotics and have been categorized by the World Health Organization (WHO) as "critical priority" pathogens for the development of new antimicrobial agents [5].

Emerging evidence also suggests that food may serve as a reservoir for multidrug-resistant strains of *P. aeruginosa*. A recent study by Bloomfield et al. (2024) revealed that while the majority of *Pseudomonas* spp. isolated from retail food samples were non-pathogenic and lacked antimicrobial resistance genes (ARGs), *P. aeruginosa* was identified in 11% of samples using a selective enrichment method. These isolates harbored between four and seven ARGs and were classified into 16 sequence types (STs), four of which overlapped with STs previously identified in clinical settings. Comparative genomic analysis demonstrated high genetic similarity between food-derived and clinical isolates, indicating that food products may represent a significant source of transmission for multidrug-resistant *P. aeruginosa* [6].

Bacteriophages are viruses that kill disease-causing bacteria, discovered by Frederick Twort and later by Félix d'Hérelle. Like any promising alternative treatment, phages existed long before the discovery of penicillin. Between the 1920s and 1940s, phages were commercially available and used in several countries to treat infectious diseases (cholera, respiratory infections, dysentery, and many others). However, their effectiveness was questioned for several reasons: the inability to reproduce the results, inadequate information on phage concentrations, control groups, and host range. Furthermore, most scientists were skeptical about phage therapy against infectious diseases. As a result, phage therapy was immediately abandoned when penicillin and other antibiotics were discovered in the 1940s, especially in Western countries [7]. In the rising antibiotic resistance among serious pathogens, bacteriophages are emerging as a potential alternative. Bacteriophages have several advantages over antibiotics, including their specificity for bacteria and their ability to rapidly evolve to target new strains of bacteria [8, 9]. Several clinical trials have demonstrated the safety and efficacy of bacteriophages in treating *Pseudomonas aeruginosa* infections [9-11].

This research aimed to isolate and characterize bacteriophages targeting *Pseudomonas aeruginosa* and to assess their potential synergistic effects when combined with antibiotics. Given the rising concern over multidrug-resistant *P. aeruginosa* infections in Vietnam and other countries, phage-antibiotic combination therapy offers a novel strategy to enhance treatment efficacy. By increasing bacterial membrane permeability and applying dual selective pressure, this approach may reduce resistance development and improve antibiotic susceptibility.

2. MATERIALS AND METHODS

2.1 Materials

The host bacterial strain of phages was *P. aeruginosa* ATCC9027. Mueller–Hinton medium, Brain Heart Infusion medium (Himedia, India) were used for the identification and

amplification of *P. aeruginosa.* The grown culture of *P. aeruginosa* ATCC9027 was used for further experiments including phage isolation, purification, and titration.

The sewage samples were collected from West Lake and To Lich River in Hanoi, Vietnam. The samples were packed in 50 mL plastic centrifugation tubes, sealed, and placed in a foam box with ice at 0–4 °C. The samples were processed immediately upon arrival after reaching the laboratory.

2.2 Methods

2.2.1. Isolation, identification of P. aeruginosa and antibiotic suseptibility testing

Clinical *P. aeruginosa* isolates were provided by the Microbiology Department of Ha Dong General Hospital, Hanoi, Vietnam. In addition to clinical isolates, *P. aeruginosa* reference strains; ATCC 9027 were included in this study. Bacterial strains were stored in Brain Heart Infusion broth (Himedia, India) containing 15% glycerol and kept at − 80 °C. Identification and the susceptibility of *P. aeruginosa* strains to different antibiotics was determined by the VITEK® 2 COMPACT system (bioMérieux, France). Bacterial susceptibility to antibiotics was interpreted as resistant (R), intermediate (I) and susceptible (S) according to guidelines recommended by CLSI (2018) [12].

2.2.2. Phage isolation and purification

Bacteriophages were isolated from polluted water in West Lake and To Lich River (Hanoi, Vietnam) by the enrichment technique [13]. The sample was clarified through centrifugation at 8000×*g* for 15 min and filtered through a 0.22 µm membrane filter (Satorius AG, Germany). In particular, 10 mL of filtrate was mixed with 10 mL of *P. aeruginosa* ATCC9027 culture grown (OD_{600nm}= 0.2- 0.3). The mixture was incubated for 24 h at 150 rpm and 37 °C on a rotary shaker. After incubation, the solution is filtered through a 0.22 µm membrane filter, and the presence of plaques was observed by the spot test method [14]. The phage purification step was repeated three times by a double-layer plate. Finally, the purified phages were stored in SM buffer (100 mM NaCl, 8 mM $MgSO_4.7H2O$, 50 mM Tris-Cl 1M) at 4 °C.

2.2.3. Host-range determination and selective of broad-spectrum phages

A total of twelve multidrug-resistant *Pseudomonas aeruginosa* clinical isolates obtained from Ha Dong General Hospital were employed to evaluate the host range of the isolated bacteriophages**.** For each assay, 100 µL of bacterial culture at mid-log phase (OD_{600} = 0.5–0.6) was mixed with 5 mL of LB semisolid medium (0.5% agar) and overlaid onto solid LB agar plates. Subsequently, 10 µL of purified phage suspension, adjusted to a titer of 10^9 PFU/mL, was spotted onto the surface of the double-layer agar. The plates were incubated overnight at 37°C. Following incubation, lytic activity was assessed based on the presence and morphology of inhibition zones, which were categorized as clear (complete lysis), turbid (partial lysis), or absent (no lysis). Phages demonstrating the broadest and most potent lytic activity across the tested strains were selected for subsequent analyses.

2.2.4. Phage-Antibiotic enhanced inhibition testing

For combined disk testing of antibiotics and phages, ready-to-use disks of levofloxacin (2.5 µg) and gentamicin (5 µg) were placed onto the inoculated agar. Then, 10 µL of phage suspension (BK5, BK6) was immediately spotted onto the disks. Controls were performed by commercial disks (Oxoid, UK).

2.2.5. Isolation of phage-resistant mutants and anti-biotic suseptibility testing

Aliquots of 1 mL of overnight culture of multi-drug resistance clinical strain (OD_{600}nm = 0.3 - 0.5) were incubated with 100 µL of phage (10^7 PFU/mL) overnight at 37 °C. After that, the mixture was diluted before spreading on BHI plates. After 24 h of incubation, the colonies were selected and purified at least three times. The phage resistance of the candidates was confirmed by the spot test method.

Antibiotic susceptibilities of *P. aeruginosa* phage-resistant mutants were performed following Vitek 2 (bioMérieux, France) instructions. Phage-resistant mutants were isolated as described above. A Vitek susceptibility card (AST-N240 for Gram-negative bacteria) was used for each isolate, including 13 commonly used antibiotics (ticarcillin-clavulanic acid, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, gentamicin, tobramycin, ciprofloxacin, levofloxacin, and colistin), according to the manufacturer's instructions.

3. RESULTS AND DISCUSSION

3.1.1. P. aeruginosa isolation and antibiotic suseptibility testing

A total of 12 *P. aeruginosa* isolates obtained from different clinical sources were included in this study. The susceptibility profile of *P. aeruginosa* isolates against different antibiotics was determined by Vitek 2 system according to CLSI (2018) guidelines (Table 1). All *P. aeruginosa* isolates were sensitive to colistin while high bacterial resistance was observed towards gentamicin (100%), imipenem (100%), ticarcillin/clavulanic acid (100%). The antibiotic susceptibility results reveal that about of 100% of *P. aeruginosa* isolates were multidrug-resistant (MDR).

Table 1. Antibiotics susceptibility profile of *P. aeruginosa* isolates *: ticarcillin (TIC), ticarcillin/clavunic acid (TIM), gentamycin (CN), ciprofloxacin (CIP), meropenem (MEM), piperacillin (PIP), piperacillin/tazobactam (TZP), cefepime (FEP), ceftazidime (CAZ), colistin (CT), tobramycin (TOB), imipenem (IMP), levofloxacin (LEV). S: Susceptible, I: Intermerdiate, R: Resistant

Isolate	TIC	TIM	PIP	TZP	CAZ	FEP	IMP	MEM	CN	TOB	CIP	LEV	CT
DK3	R	R	R	R	R	R	R	R	R	R	R	R	S
DK4	R	R	R	R	R	R	R	R	R	R	R	R	S
DK5	R	R	R	R	R	R	R	R	R	R	R	R	S
DK6	R	R	R	R	R	R	R	R	R	R	R	R	I
DK7	R	R	R	R	R	R	R	R	R	R	R	R	S
DK9	R	R	R	R	R	R	R	R	R	R	R	R	S
DK10	R	R	R	R	R	R	R	R	R	R	R	R	S
DK13	R	R	R	R	R	R	R	R	R	R	R	R	S
DK16	R	R	R	R	R	R	R	R	R	R	R	R	S
DK17	R	R	R	R	R	R	R	R	R	R	R	R	S
DK18	R	R	R	R	R	R	R	R	R	R	R	R	S
DCE3	R	R	R	R	R	R	R	R	R	R	R	R	S

3.1.2. Phage isolation and purification

In total, 4 samples of water were screened using *P. aeruginosa* ATCC9027 strains for the presence of phages. Using the host strains, 6 phages were isolated by the double agar overlay method. Lytic phages were isolated from all the sampling sites. These phages produced clear and centered plaques of different sizes, one phage produced clear plaque with halo (Figure 1). All positive results were denoted as lytic bacteriophages due to the clear zone plaques on the agar. Isolated phages were named according to the *P. aeruginosa* host according to the recommended nomenclature procedure: vB_Pae_BK1, vB_Pae_BK2, vB_Pae_BK3, vB_Pae_BK4, vB_Pae_BK5, vB_Pae_BK6Bấm hoặc gõ nhẹ vào đây để nhập văn bản..

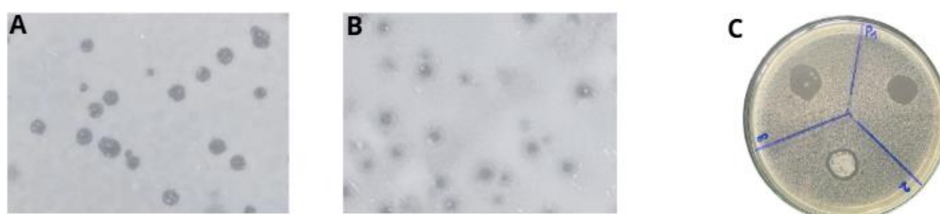

Figure 1. Representative bacteriophage plaque images during isolation and purification
(A) Clear plaque (B) Halo plaque (C) Spot test result for enrichment sample

3.1.3. Host-range determination and selective of broad-spectrum phages

A total of 6 bacteriophages were isolated from water samples. Host range tests were then conducted on these bacteriophages, using 12 isolated *P. aeruginosa* strains as target bacteria. Based on the results, the two bacteriophages with the highest lytic activity were selected: BK5, BK6. A comparison of the six capacities of these five bacteriophages is presented in Table. 2, indicating that BK5 and BK6 had the highest lytic capacity, lysing 12 *P. aeruginosa* strains with a lysis rate of 100%.

Table 2. Host range spectrum of six isolated bacteriophages.
+: clear zone (lysis), *: turbid zone (weak lysis efficiency), -: no lysis

Host bacteria	Bacteriophage						Origin
	BK1	BK2	BK 3	BK 4	BK 5	BK 6	
P.aeruginosa ATCC 9027	+	+	+	+	+	+	Commercial bacterial strain
P.aeruginosa DK3	-	*	-	+	+	+	Human sputum
P.aeruginosa DK4	+	+	+	+	+	+	Human sputum
P.aeruginosa DK5	-	-	-	-	*	*	Human sputum
P.aeruginosa DK6	-	-	-	*	+	+	Human sputum
P.aeruginosa DK7	*	+	*	+	+	+	Human sputum
P.aeruginosa DK9	-	*	-	+	+	+	Human sputum
P.aeruginosa DK10	*	+	*	+	+	+	Purulent surgical site
P.aeruginosa DK13	+	+	+	+	+	+	Surgical drainage
P.aeruginosa DK16	-	*	-	*	+	+	Human sputum
P.aeruginosa DK17	-	+	-	+	+	+	Human sputum
P.aeruginosa DK18	+	+	+	+	+	+	Purulent surgical site
P.aeruginosa DCE3	-	*	-	+	+	+	Endocrine

3.1.4. Phage-Antibiotic enhanced inhibition testing

Potential additive or enhanced inhibition effects of phages and antibiotics were tested by adding 10μL of phage suspension to antibiotic disks. For combined testing of phages and antibiotics, the marked increase in the diameter of the inhibition zone was observed (Fig. 2; Fig. 3). Compared to the CLSI standard, the combination with bacteriophage makes the phage-antibiotic cocktail highly effective in inhibition, with the zone of inhibition within the susceptible range. This integration of bacteriophage significantly enhanced the efficacy of the phage-antibiotic cocktail in inhibiting bacterial growth, resulting in an inhibition zone that remains within the susceptible range, despite the antibiotic concentration being less than fifty percent of the standard.

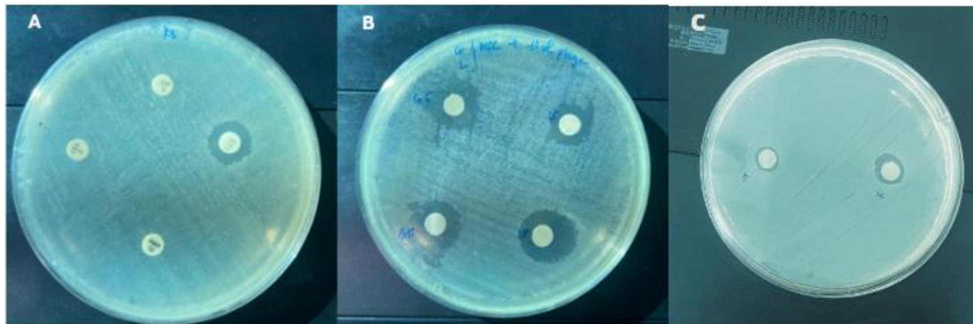

Figure 2. Phage – antibiotics enhanced inhibition testing.
A. Antibiotics susceptibility testing of P. aeruginosa DK7. B. Phage -antibiotics combinations; C. Phage–only control

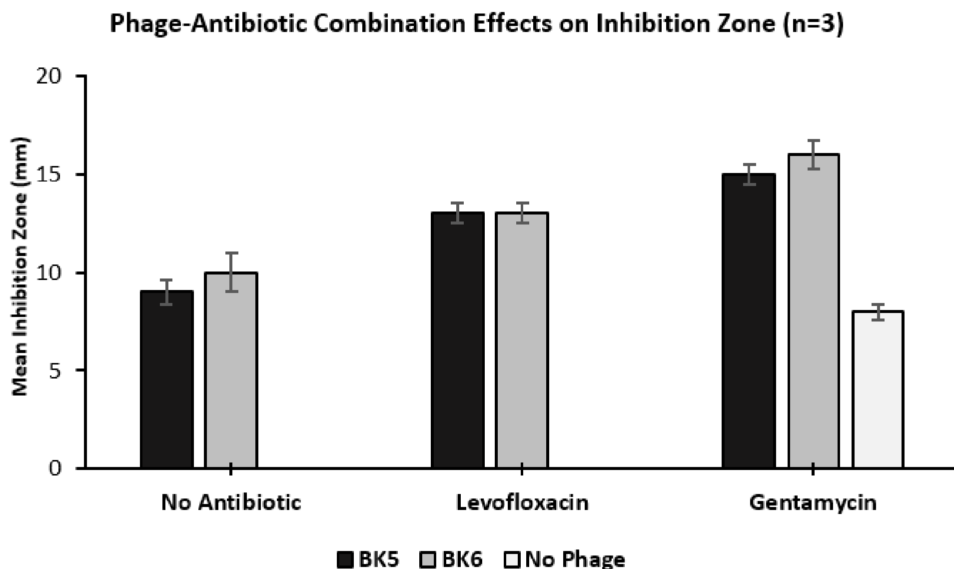

Figure 3. Combined testing of lytic phage and antibiotic activities using ready-to-use antibiotic disks

3.1.5. The trade-off between bacteriophage resistance and antibiotics susceptibility

The changes in antibiotic resistance of *Pseudomonas aeruginosa* DK13 were compared according to CLSI standards. Details of the antibiotic resistance of the DK13 and DK13 mutant strain are shown in Table 3.

Table 3. Antibiotics susceptibility profile of *P. aeruginosa* DK13 and DK13 mutant strain. S: Susceptible, I: Intermediate, R: Resistant

Antibiotics	*P. aeruginosa* DK13	*P. aeruginosa* DK13 mutant
Ceftazidime	R	I
Imipenem	R	S
Meropenem	R	S
Levofloxacin	R	R
Piperacillin/tazobactam	R	I
Cefepime	R	I
Colistin	S	S

The antibiotic resistance of bacteria decreased significantly to ceftazidime, imipenem, meropenem, piperacillin/tazobactam. According to CLSI standards, phage-resistant mutants of strain DK13 were sensitive to commonly used antibiotics in the treatment of *Pseudomonas aeruginosa* infections. These results indicate that the evolution of bacterial resistance to phages significantly affected the changes in antibiotic resistance, highlighting potential in phage-antibiotic synergistic therapy.

4. CONCLUSION

The antibiotic resistance of *Pseudomonas aeruginosa* is escalating significantly in Vietnam. The strains isolated from hospital settings in Vietnam exhibit resistance rates ranging from 40% to 60% against ciprofloxacin, meropenem, and imipenem [15]. In this study, 12 isolates of *P. aeruginosa* were collected and assessed for their susceptibility to various antibiotics. The isolates demonstrated high levels of resistance to several antibiotics, including betalactams, fluoroquinolones, and monobactam, indicating that 100% of the isolated *P. aeruginosa* strains were multidrug-resistant (MDR). Consequently, phage therapy may serve as a viable alternative approach to address the concerning rise in antibiotic resistance among *P. aeruginosa*. Phage therapy offers numerous benefits compared to antibiotics, such as its high specificity for targeted bacterial strains, its capacity to infiltrate biofilms, and a reduced likelihood of developing resistance. However, research on bacteriophages targeting *P. aeruginosa* in Vietnam remains limited, highlighting the need for further investigation and development in this area [16].

In the present research, two novel lytic phages, designated vB_Pae_BK5 and vB_Pae_BK6, which targets *Pseudomonas aeruginosa*, was successfully isolated and characterized. Lytic phages are typically favored for therapeutic applications over lysogenic phages. Lysogenic phages could be vehicles for horizontal gene transfer, results in the development of antibiotic resistance in bacteria, and in certain instances, converts non-

pathogenic bacteria into pathogenic strains [17]. The results of host range are very important parameters that should be determined when selecting bacteriophages for the useful of therapeutic applications [18]. Bacteriophages with a broad host range present significant opportunities for clinical applications and can also serve as biosensors for the detection of pathogenic bacteria in food, environmental [19].

The studies described here show that using *P. aeruginosa* phages BK5, BK6 in combination with different classes of antibiotics was synergistic in the reduction of bacterial populations and resulted in the re-sensitization of MDR *P. aeruginosa* to antibiotics. The diameter of the inhibition zone of the antibiotic disc increased upon phage supplementation, indicating that the bacteria regained sensitivity to the antibiotic according to CLSI standards. This is also consistent with previous studies, which have shown that the use of *P. aeruginosa* phage in combination with various antibiotics is not only effective but also has a synergistic effect in reducing bacterial populations and leading to *P. aeruginosa* MDR becoming resensitized to antibiotics [20].

In conclusion, two lytic phages vB_Pae_BK5 and vB_Pae_BK5, were isolated from water samples that targets *P. aeruginosa*. The isolated phages were capable of lysing12 strains of multidrug-resistant bacteria. The addition of phages made the bacteria susceptible to antibiotics again. The isolated phages could be applied to synergize the action of traditionally used antibiotics targeting *P. aeruginosa* infections.

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TÓM TẮT

PHÂN LẬP VÀ NGHIÊN CỨU ĐẶC ĐIỂM CỦA CÁC THỰC KHUẨN THỂ ĐẶC HIỆU CHO *Pseudomonas aeruginosa* VÀ CẢI THIỆN ĐỘ NHẠY KHÁNG SINH CỦA VẬT CHỦ

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Pseudomonas aeruginosa là một loại vi khuẩn Gram âm cơ hội gây bệnh ở cả thực vật và động vật, bao gồm cả con người. Loài vi khuẩn này đặt ra nhiều thách thức nghiêm trọng trong điều trị do sự xuất hiện ngày càng nhiều của các chủng đa kháng thuốc (MDR) và siêu kháng thuốc (XDR). Liệu pháp sử dụng thực khuẩn thể - các virus chuyên biệt có khả năng tiêu diệt vi khuẩn - đang nổi lên như một hướng tiếp cận đầy hứa hẹn nhằm đối phó với gánh nặng của tình trạng kháng kháng sinh. Nghiên cứu này tập trung vào việc phân lập và đặc trưng các thực khuẩn thể có khả năng nhiễm *P. aeruginosa*, đồng thời đánh giá hiệu quả tăng cường ức chế vi khuẩn khi kết hợp với kháng sinh, từ đó nâng cao độ nhạy của vi khuẩn với thuốc. Kết quả cho thấy sự kết hợp này đã làm tăng khả năng nhạy cảm với kháng sinh của chủng *P. aeruginosa* kháng thuốc đa dòng. Cụ thể, sáu thực khuẩn thể được phân lập từ mẫu nước thu thập tại sông Tô Lịch và hồ Tây đã cho thấy khả năng tiêu diệt chủng *P. aeruginosa* ATCC9027. Các thí nghiệm tiếp theo, phối hợp với Bệnh viện Hà Đông, được thực hiện nhằm đánh giá hiệu lực tiêu diệt của các thực khuẩn thể này đối với các chủng *P. aeruginosa* kháng thuốc được phân lập từ mẫu bệnh phẩm lâm sàng. Trong số đó, hai thực khuẩn thể ly giải mới, có tên tạm thời là vB_Pae_BK5 và vB_Pae_BK6, đã được phân lập thành công. Các thực khuẩn thể thuộc nhóm ly giải thường được ưu tiên sử dụng trong điều trị do khả năng tiêu diệt tế bào vi khuẩn trực tiếp, khác với các thể ôn hòa (lysogenic). Mặc dù còn tồn tại một số thách thức như tính chuyên biệt của thực khuẩn thể, phản ứng miễn dịch của vật chủ và các rào cản pháp lý, phương pháp kết hợp này vẫn là một chiến lược đầy triển vọng trong điều trị các bệnh nhiễm trùng do *P. aeruginosa* gây ra.

Từ khóa: Kháng kháng sinh, MDR, XDR, nhiễm trùng, *Pseudomonas aeruginosa*, PAS, thực khuẩn thể.