Correspondence

Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema Caused by Pseudomonas aeruginosa

To the Editor:

Pseudomonas aeruginosa is a frequent causative agent of ventilator-associated pneumonia with high attributable mortality (~13%), which may double in patients with multidrug-resistant infection (1).

Bacteriophage therapy was first used as antibacterial therapy in the early 1900s (2). Losing favor in the West with the advent of antibiotics, bacteriophage therapy remained in use in the former Eastern Bloc, and interest in its therapeutic potential has been renewed with the development of increasing antimicrobial resistance globally. Obligately lytic bacteriophages are viruses that destroy specific bacterial cells and are not regarded as harmful to humans, but clinical information regarding their safety and efficacy as therapy remains limited (3). Although there are reports of successful use of antipseudomonal bacteriophage therapy in mouse models of lung disease (4–6) and in in vitro or ex vivo models of respiratory tract infection (7, 8), there are few data regarding use in vivo (9).

Case Report

A 77-year-old woman underwent a right posterolateral mini-thoracotomy for resection of a right lower lobe adenocarcinoma with mediastinal node sampling.

Her past medical history was significant for a 60-pack-year smoking history and hypersensitivity reactions to multiple antibiotics (penicillins, cephalosporins, trimethoprim-sulfamethoxazole, and macrolides).

Tumor excision was macroscopically complete, and an intercostal catheter (ICC) with underwater seal was left in situ. On the second postoperative day, the patient had an elevated white cell count (18.1 x 10^9/L) and C-reactive protein (263 mg/L) and developed severe pleuritic chest pain. Increasing respiratory distress and drowsiness (Glasgow Coma Score of 9) on Day 3 required intubation, and >1.5 L of stomach contents were aspirated via an orogastric tube. A chest X-ray (CXR) showed collapse/consolidation in the right lower lobe, and the patient was commenced on intravenous moxifloxacin and metronidazole for presumed aspiration pneumonia. A procalcitonin level of 25.7 μg/ml and acute kidney injury (nadir estimated glomerular filtration rate, 32 ml/min/1.73 m^2) were noted.

On Day 6, CXR confirmed persisting right lung field consolidation but no pneumothorax, and her ICC was removed. Sputum cultures taken on the day of intubation (Day 3) reported a moderate pure growth of P. aeruginosa susceptible to piperacillin-tazobactam, ciprofloxacin, and meropenem. Fever rose to 38°C on Day 6, and her antibiotic regimen was changed to intravenous meropenem 1 g three times daily.

The patient suffered ongoing fevers and a progressive infiltrate on CXR with evident parenchymal cavitation in the presence of persistent cultures of P. aeruginosa from sputum and BAL samples (Figure 1). Her white cell count remained elevated, and a persistent bronchopleurocutaneous fistula at the ICC site, resulting in further hypoxia and a worsening pneumothorax, required reinsertion of a chest drain on Day 11.

After a week of intravenous meropenem, there was no clinical evidence of other foci of infection, and blood cultures taken almost daily had remained negative. A chest computerized tomogram scan on Day 13 demonstrated patchy consolidation of both lungs (right greater than left), with multiple cavitations and extensive subcutaneous emphysema of the right chest wall with ongoing air leak from a presumed bronchopleural fistula (Figure 2). The patient was assessed as too unwell for further surgery. Her course was further complicated by the development of dense right-sided hemiparesis, with evidence of an acute left posterior cerebral artery ischemic stroke on brain imaging.

On Day 16, the patient remained critically ill, with persisting fevers despite antibiotic therapy. A repeat BAL, ICC-site purulent discharge, and direct swabs of the pleural space cultured P. aeruginosa, which was now resistant to meropenem, imipenem, and piperacillin-tazobactam in vitro (Figure 1). Meropenem was ceased, and she commenced intravenous ciprofloxacin and gentamicin. Infectious Diseases review at this time noted a heavy burden of pulmonary disease with pleural involvement and the development of sequential antibiotic resistance on therapy. AB-PA01 (AmpliPhi Biosciences Corporation), a phage product of four obligately lytic bacteriophages (two Podoviridae and two Myoviridae), each at ~1 x 10^8 plaque-forming units/ml (10), produced in a dedicated Good Manufacturing Practices facility, was shown to be highly active against all of several isolates submitted to AmpliPhi Biosciences for susceptibility testing.

Isolates from five separate samples were sequenced (Paired-End 150 bp; Illumina NextSeq) and identified as ST875 (a rarely reported clonal type that is serotype 6). All five samples differed by 34 SNPs or fewer, with the greatest genetic distance corresponding to the two most temporally distant samples, consistent with a single infecting strain.

With informed consent and under the auspices of our institution’s Human Ethics Research Committee and the Special Access Scheme of the Australian Therapeutic Goods Administration, AB-PA01 was commenced as adjunctive therapy from Day 23. In the absence of data to assure us that either route would suffice to treat airways as well as chest wall, both intravenous (1 ml AB-PA01 in 100 ml of normal saline) and nebulized (4 ml AB-PA01, undiluted) phage were administered twice daily. Within

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Author Contributions: J.R.I. conceived the study and devised the treatment protocol; S. Maddocks and J.R.I. assisted with protocol revision, cowrote the case-report form, and wrote the manuscript; J.H. assisted with primary data collection; A.P.F., J.H., and R.C.Y.L. assisted with protocol revisions, case-report form development, retrospective data collection, and editing of manuscript; C.D. and I.K. managed patients in the ICU and sourced deep pleural cultures; N.L.B.Z. analyzed isolate whole-genome sequencing data; S.B. conducted phage susceptibility testing in vitro and coordinated drug supply; and S. Morales provided the AB-PA01 pharmacy manual, reviewed the patient narrative, and reviewed the manuscript.

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3 days, the patient’s oxygenation had improved and sedation was ceased. On Day 27 (Day 4 of phage therapy), her most recent P. aeruginosa isolate from pleural fluid (collected before phage therapy commencement) demonstrated fluoroquinolone resistance. Ciprofloxacin was ceased and ceftolozane/tazobactam desensitization commenced on Day 28, although it was documented in the patient’s notes at this time that the patient had made “remarkable progress over the last week,” with SaO2 now at 90% on 2 L/min O2 via nasal prongs.

Bacteriophage therapy was ceased after 7 days, and the patient was stepped down from the ICU to a high-dependency unit. She completed 6 weeks of intravenous ceftolozane/tazobactam at 1.5 g three times daily intravenously, which was not increased with improving renal function, and we note that trials are underway to determine whether 3 g three times daily is required in pneumonia (Clinicaltrials.gov NCT02387372). She was discharged from the hospital to an aged care facility 11 weeks after her initial admission, with no sign of infection. Her last positive P. aeruginosa culture was a scanty growth from sputum taken on Day 4 of bacteriophage therapy (1 d before starting ceftolozane/tazobactam), and she remained culture-negative thereafter, including at 6 months after completion of AB-PA01 therapy.

This is the first documented case of bacteriophage therapy being used clinically in the management of extensive, necrotizing, pulmonary pseudomonal infection. Administered as adjunctive therapy to intravenous antibiotics, bacteriophage therapy was well tolerated, with no adverse events detected either during therapy or subsequently. In combination with antimicrobials, bacteriophage therapy was associated with resolution of infection and with apparent eradication of Pseudomonas colonization. Whether successful decolonization would have occurred in the absence of phage treatment is unclear but seems unlikely, given the extent of disease and the sequential development of antimicrobial resistance despite appropriate therapy (including gentamicin-resistant isolates, sputum collected Day 13). Optimal duration of bacteriophage therapy is uncertain; the 7-day duration given in this case, both intravenous and nebulized, was well tolerated, and the evident successful decolonization suggests efficacy with this treatment regimen and duration. Adjunctive bacteriophage therapy could

Figure 1. Clinical course over time. AB-PA01 = anti-Pseudomonas bacteriophage cocktail; CAZ = ceftazidime; CIP = ciprofloxacin; CRP = C-reactive protein (mg/L); CST = colistin; C/T = ceftolozane-tazobactam; Days = postoperative days (D0 = day of initial surgery); FEP = cefepime; GEN = gentamicin; I = intermediate; MXF = moxifloxacin; MEM = meropenem; Mod = moderate growth; MTZ = metronidazole; PA = Pseudomonas aeruginosa; PF = pleural fluid; S = susceptible; R = resistant; Temp = temperature (°C); TZP = piperacillin-tazobactam; WCC = white cell count (×10^9/L); WS = wound swab.

Figure 2. Computed tomography scan of the chest Day 13 postoperatively demonstrating cavitation, consolidation, empyema, and subcutaneous emphysema. A = anterior; L = left; P = posterior; R = right.
be considered in cases of complicated infection, including in the critically ill, where standard antimicrobial therapy is not suitable because of antimicrobial resistance or patient drug allergies.

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In Defense of High-Speed Video Microscopy in Evaluating Patients with Suspected Primary Ciliary Dyskinesia

To the Editor:

The diagnosis of primary ciliary dyskinesia (PCD) is challenging because of the absence of a single gold standard test. As a result, it is arrived at by means of a combination of clinical features and several ancillary diagnostic tests (1, 2). According to the recent American Thoracic Society (ATS) guidelines (1), the diagnosis of PCD in patients with compatible clinical features can be confirmed using nasal nitric oxide (nNO; conditional recommendation; Figure 1). The ATS guidelines include the following tests to be used in conjunction with the nNO test: measurement of the respiratory ciliary beat frequency and its variability, nasal nitric oxide (nNO) measurement, and the determination of the nasal nitric oxide (nNO) concentration. In addition, the ATS guidelines recommend that the diagnosis of PCD should be based on a combination of clinical features and several ancillary diagnostic tests, including measurement of the respiratory ciliary beat frequency and its variability, nasal nitric oxide (nNO) measurement, and the determination of the nasal nitric oxide (nNO) concentration.

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References


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