A Randomized Controlled Trial of Bacteriophage Cocktail Therapy for Multidrug-Resistant Gram-Negative Ventilator-Associated Pneumonia

Informed Consent

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Dear Participant:

We invite you to participate in a randomized controlled clinical trial approved by the Eighth Medical Center of PLA General Hospital. This trial evaluates bacteriophage cocktail therapy for drug-resistant Gram-negative bacterial ventilator-associated pneumonia (VAP). This informed consent document provides essential information to help you decide whether to enroll. Please take the time to carefully review the content below. If you have any questions or need clarification regarding specific terms, please discuss them with your attending physician or the study physician.

Why is this study being conducted?

Research Background
Ventilator-associated pneumonia (VAP) caused by multidrug-resistant Gram-negative bacteria—Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa—is associated with high incidence, poor prognosis, and elevated mortality. Even with high-dose combination antibiotic therapy, clinical efficacy remains limited and significant toxic side effects often occur.

Bacteriophages (phages) are viruses that specifically infect and lyse bacteria. Unlike antibiotics, they exhibit high specificity against resistant bacteria while sparing human cells and commensal flora, thereby ensuring good safety. Global studies have demonstrated their efficacy in treating resistant bacterial infections of the lung, bloodstream, abdomen, and urinary tract, with no reports of severe adverse reactions.

This study is conducted under the National Key Research and Development Program of China, "Research on Safe and Effective Phage Preparations and Key Technologies for Clinical Treatment of Drug-Resistant Bacterial Infections." It addresses the urgent clinical challenge of VAP caused by multidrug-resistant Gram-negative bacteria. Using a prospective, multicenter, randomized, double-blind, controlled trial design, the study aims to establish an evidence base for the safety and efficacy of phage therapy and promote its standardized and broader application.

Through this randomized controlled study on phage cocktail therapy for drug-resistant Gram-negative VAP, the research aims to:
1. Establish a standardized clinical efficacy and safety evaluation system for phage treatment in VAP patients.
2. Optimize phage administration strategies.
3. Systematically evaluate adverse reactions during phage therapy.

4. Monitor the development of phage tolerance (including neutralizing antibody levels and mutation rates of phage-tolerant bacteria).
5. Identify key factors influencing phage therapy outcomes.

This will provide high-quality, evidence-based medical support for phage-based treatments.

Research Procedures

This study is a multicenter, prospective, randomized, double-blind, controlled trial. The term "randomized assignment" means you will be randomly assigned by a computer to either the intervention group or the control group. Neither you nor your physician can choose which treatment you receive. This ensures an unbiased evaluation of the investigational product. Your group assignment (intervention or control) does not affect your doctor's standard care for ventilator-associated pneumonia.

Throughout the study, we will collect information about your response to the investigational product and your health through a series of checks and procedures.

(1) Research Overview

a) Efficacy and safety of phage cocktail therapy: For patients with drug-resistant Gram -negative VAP who meet the inclusion criteria, participants will be randomly assigned to either the Intervention Group (phage cocktail combined with conventional VAP treatment) or the Control Group (placebo combined with conventional VAP treatment group) after informed consent is obtained from you or your legal representative. The study will compare clinical improvement rates, bacterial clearance rates, and 28-day mortality rates between the groups. The phage regimen uses a "two-phase" selection strategy:

Phase I: Starts a broad-spectrum phage cocktail based on rapid diagnostic results.

Phase II: Conducts individualized phage typing guided by sensitivity testing to dynamically optimize the treatment plan (if needed).

Case reports will be documented using standardized forms, with detailed records of therapeutic outcomes and any adverse reactions.

b) Establishing a safety and efficacy evaluation system: Building on the validation of clinical efficacy, this research will further investigate the interaction mechanisms within the phage-microecosystem-host system. Key aspects for evaluation include phage resistance development, bacterial adaptation under pressure, and host immune responses. By integrating clinical outcome assessments with multi-omics analyses, the study aims to construct a multidimensional evaluation framework to comprehensively assess the safety and effectiveness of phage therapy.

(2) Study Procedures

Participants will undergo scheduled follow-up visits and laboratory examinations. Please inform the study team of any changes in your health during the trial.

1. Monitoring: During the trial, your clinical infection symptoms and vital signs will be recorded regularly, with close monitoring of disease progression. Any adverse events

will be promptly managed according to the treatment protocol and documented. The total investigational product treatment duration will not exceed 14 days, followed by a 28-day safety follow-up period.
2. Baseline Tests: Before treatment begins, laboratory tests will include: complete blood count (white blood cells, neutrophils, lymphocytes), C-reactive protein (CRP), procalcitonin (PCT), T-lymphocyte subsets, and liver and kidney function tests.
3. Baseline Culture: Bacterial cultures will be performed on sputum, tracheal aspirate, or bronchoalveolar lavage fluid (BALF) specimens obtained before treatment.
4. Phage Administration & Testing:

Starting on the day of enrollment, patients in the intervention group will receive the investigational phage cocktail via nebulization twice daily.

Phage-host specificity validation will be completed within 48-72 hours of enrollment.

On Day 5 (±1 day), another lower respiratory tract sample (sputum, tracheal aspirate, or BALF) will be collected and evaluated by phage spot testing.

If the testing shows the phage is still effective against your bacteria, the original regimen will continue.

If the testing shows reduced effectiveness, you will be switched to a pre-prepared personalized phage formula (if available and suitable). The overall treatment duration with phage will not exceed 14 days.
5. Follow-up Tests: After treatment initiation, sputum or BALF samples will be collected intermittently for pathogen evaluation. Phage concentration and antibiotic resistance gene levels will be monitored in these samples. Phage lysis assays will be repeated weekly to verify activity, and the aerosol formulation may be adjusted if necessary. Concurrently, changes in your blood counts, CRP, PCT, T-cell subsets, and liver/kidney function will be monitored through blood tests.

Other Treatment Options

Participation in this study does not replace the routine standard of care treatments for ventilator-associated pneumonia. You will continue to receive all appropriate standard treatments for VAP regardless of your group assignment.

Potential Inconveniences and Restrictions

You may find the study visits and tests inconvenient and they may require special arrangements. Additionally, some of the tests (like blood draws or sputum collection) may cause you temporary discomfort. If you have any questions about the tests and procedures in this study, please ask your study physician.

Medications: Consult your study physician before taking any new prescription drugs, over-the-counter medications, or herbal supplements during the study.
Contraception: If you are a woman of childbearing potential, you will need to use effective contraception throughout the study. Please consult your study physician to determine an appropriate contraceptive method and duration.
Other Studies: You will not be able to participate in any other clinical studies involving drugs or medical devices during your participation in this study.

Study Risks and Potential Adverse Reactions

You may experience adverse reactions during the study. We will monitor all patients closely for any adverse events throughout the study. If you experience any problems or possible adverse reactions between scheduled visits, please contact your study physician immediately.

Known Risks:
The most common adverse reactions reported with clinical phage therapy delivered by aerosol inhalation include temporary cough, shortness of breath (dyspnea), sweating, and fever. These reactions usually resolve after dose reduction, slowing the inhalation, or discontinuing the treatment.
Unknown Risks: There may be some risks and adverse reactions associated with the investigational phage therapy that are currently unknown or cannot be predicted. Researchers will monitor for any unexpected effects very carefully.

Informing Others:
You should inform your family members or close friends that you are participating in a clinical study and make them aware of the events described above. If they have any questions about your participation, you may tell them how to contact your study physician.
Risks of Blood Drawing:
In this study, additional blood draws beyond those required for your routine care are needed specifically for phage neutralizing antibody detection and single-cell transcriptomics analysis. All other blood draws are part of standard diagnosis and treatment for VAP. No additional blood samples will be sent to other institutions beyond those specified in the protocol for research purposes.
Other Risks:
The diagnosis and treatment of respiratory infections caused by drug-resistant bacteria themselves carry inherent risks (such as side effects from antibiotics, progression of infection, etc.). These risks are part of your underlying condition and its standard treatment, not specifically caused by this research study. Participation in the study does not increase these underlying risks.

Potential Benefits

By participating in this study, you may benefit directly from the investigational phage therapy, though there is also a possibility that you may not receive any direct benefit from it. We hope that the information gathered from your participation will help doctors better understand phage therapy and prove valuable for guiding the treatment of future patients with similar conditions. The insights gained from this research will help determine whether phage therapy can be a safer and more effective treatment option for other patients with drug-resistant Gram-negative VAP like yours.

The relevant research information and results obtained from this study, in aggregate form (without identifying you personally), may be shared with you or made available in due course upon request.

Processing and Use of Biological Specimens and Medical Information

This study requires collecting:

Peripheral blood samples: These will be used for phage neutralization antibody testing and single-cell transcriptome sequencing as part of the research.
Sputum, tracheal aspirates, or bronchoalveolar lavage fluid (BALF): These samples are collected as part of your standard care for VAP diagnosis and treatment. After culturing and confirming the presence of drug-resistant Gram-negative bacteria through antibiotic susceptibility testing (also standard care), these bacterial isolates may be used to match with appropriate phages for the study.

Both the bacterial isolates obtained from your samples and the phages used (if applicable) will be stored securely in duplicate for research purposes. Only the genetic sequence information of the bacterial strains and phages will be retained and potentially used in future research or published; no personally identifiable information (like your name, medical record number, etc.) will be attached to this genetic data or disclosed.

Your Rights and Obligations

Right to Consider and Ask Questions: You have the right to take ample time to consider participation and to ask questions at any time. The final decision to participate in this study is yours.
No Penalty for Declining: If you decide not to participate, it will not affect your entitlement to any other medical care now or in the future.
Obligations if Participating: If you choose to participate, you agree to:
Provide truthful and complete information about your medical history and current physical condition to the study physician.
Disclose any previous or ongoing participation in other research studies.
Sign this written informed consent form.

Right to Withdraw:
You may withdraw your consent and leave the study at any stage, for any reason, after signing this form. Should new, significant information emerge during the study that may impact your willingness to continue participating, your study physician or a research team member will notify you immediately. You may also inquire about the study's progress at any time by contacting the study team.
Withdrawal by the Study Physician: The study physician may withdraw you from the study without your consent if:
You do not comply with the study protocol.
The study physician determines that your continued participation is not in your best medical interest.
You experience significant adverse reactions to the investigational product.
New safety information regarding the investigational product becomes available that warrants your discontinuation.
The study is stopped by the sponsor or regulatory authorities.

Procedures After Withdrawal:
If you withdraw from the study for any reason, the study physician may ask you about your recent use of the study drug. If the study physician deems it necessary for your safety, you may also be asked to undergo some unplanned physical and laboratory tests. The study physician will discuss your ongoing medical care with you after withdrawal.

Costs of Participating in the Study

Provided Free of Charge: The matching of phages (if needed for the intervention group), preparation of the phage investigational product, and the finished phage aerosol preparation will be provided at no cost to you.

Your Responsibility:

All other expenses during your hospitalization related to the routine diagnosis, standard treatment, and monitoring of your ventilator-associated pneumonia (VAP) remain your responsibility (or covered by your insurance as usual). This includes, but is not limited to: hospital room charges, physician fees, routine blood tests (CBC), biochemical tests (liver/kidney function, etc.), imaging studies (lung CT, chest X-ray), bronchoscopy procedures, standard antibiotics, and other supportive care. Participation in the study does not remove your responsibility for these standard medical costs.

Compensation

There is no financial payment or reward for participating in this study.

Compensation for Research-Related Injury

If your health is adversely affected as a direct result of participating in this research study, please inform your study physician immediately. Your study physician will be responsible for arranging appropriate and necessary medical treatment for the research-related injury. The institution/sponsor will cover the costs of such medically necessary treatment related to the research intervention, in accordance with applicable regulations and the study's insurance provisions. This does not imply the institution/sponsor admits fault.

Even if you have signed this Informed Consent form, you still retain all your legal rights.

Confidentiality

If you decide to participate in this study, your personal information and participation will be kept confidential to the extent permitted by law. The physicians and researchers involved will use your coded medical data for research purposes. Your study records will be stored securely and will only be accessible to the authorized research team, the Ethics Review Committee, and regulatory agencies during audits or inspections.

We will use unique code numbers to label your study details and lab test samples. Your identity will be protected; only the attending physician and authorized research team members will have access to the key linking the code numbers to your identity.

To ensure that the research is conducted in accordance with regulations, authorized representatives of government regulatory agencies or the Ethics Review Committee may inspect your original medical records and study data at the research site as required by law. No personally identifiable information about you will be disclosed publicly during this process or in any reports or publications resulting from this research.

We will comply with relevant laws and regulations to ensure that the privacy of your personal medical information is protected.

Voluntary Participation

Participation in this study is completely voluntary. You may refuse to participate in the study initially or withdraw from the study at any time during the study without giving any reason. This decision will not affect your current or future medical care at this institution or elsewhere.

If you decide to withdraw from the study, please inform your research physician in advance. For your safety, you may be asked to undergo relevant tests or a final visit, which are intended to ensure your well-being after stopping the investigational product.

Contact Information

Study Questions: You can learn about information related to this study and its progress at any time. If you have questions related to this study, please contact us at: [Insert Phone Number] and ask for [Insert Name of Lead Researcher or Study Coordinator].
Rights as a Participant: If you need to know about the rights and welfare of participants in this study during the research process, or if you have concerns about the study, you can contact the Ethics Review Committee of the Eighth Medical Center of the PLA General Hospital at: 010-66775212 (or +86-10-66775212 for international calls).
Research-Related Injury: Contact the study physician immediately.

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Subject Declaration:

After carefully reading this entire informed consent form, discussing the study with the research staff, and understanding the risks and potential benefits of participating in this research, I voluntarily agree to participate in this trial and make the following statements:

1. I have read the above informed consent form (or it has been read to me) and I understand the nature, purpose, procedures, potential risks, discomforts, benefits, and alternatives of this study. All my questions have been answered to my satisfaction.
2. I agree to comply with the requirements outlined in the informed consent form. I will fully cooperate with the researchers and provide truthful and objective information about my health status and any relevant information before, during, and at each follow-up period of the study.
3. I understand that I may withdraw my consent and stop participating in this study at any time, for any reason, without penalty or loss of benefits to which I am otherwise entitled. I also understand that the investigator has the right to discontinue my participation at any time based on my medical condition or other valid scientific or administrative reasons.
4. I understand that I will receive a dated and signed copy of this informed consent form.
5. I have been informed that the physicians involved in this study, the heads of relevant administrative departments, the sponsor, representatives of regulatory agencies, and the Ethics Review Committee of PLA General Hospital are authorized to review my research records and original medical case materials for purposes of monitoring the research and ensuring compliance and safety. I agree that these authorized personnel may directly access my confidential research records and medical information related to the study, understanding that such information will be handled with strict confidentiality as described in this document.
6. After full consideration, I freely and voluntarily consent to participate in this clinical research study.

Signature of Subject: _____
Date: _____

Printed Name of Subject: _____
Title (if applicable): _____

Subject's Contact Information:
Phone: _____ Alternate Phone: _____
Email: _____
Address: _____

[If Applicable: Signature of Legally Authorized Representative (LAR)]
Signature of LAR: _____
Date: _____

(Relationship to Subject: Spouse / Parent / Adult Child / Legal Guardian / Other: _____)

Printed Name of LAR: _____
Reason for LAR Signature: _____ (e.g., Subject unable to consent due to...)

Investigator's Statement:

I, or a member of my research team whom I have delegated this responsibility to, have explained the nature, purpose, procedures, potential risks and benefits, and alternatives of this research study to the subject (and their Legally Authorized Representative, if applicable). I have answered all questions to the best of my ability. I confirm that the participant (and LAR) understands the information provided and has voluntarily agreed to participate. A copy of this signed and dated informed consent form has been given to the participant (and LAR).

Signature of Investigator (or Designee): _____
Date: _____

Printed Full Name of Researcher: _____
Title: _____

Researcher's Contact Number: _____