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Novel Therapeutic Strategies for Ventilator-Associated Pneumonia (VAP): Systematic Review

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) remains a major intensive care unit complication, contributing to prolonged mechanical ventilation, antimicrobial overuse, multidrug resistance, and increased mortality. Despite advances in prevention and conventional antibiotics, treatment failure remains frequent. This study aims to review and highlight novel therapeutic strategies for improving clinical outcomes in patients with VAP.

Material and methods: This systematic review was conducted according to PRISMA guidelines. PubMed, Scopus, Web of Science, EMBASE, Google Scholar, SID, and Magiran were systematically searched using keywords including "ventilator-associated pneumonia," "VAP," "novel therapeutic strategies," "bacteriophage therapy," "immunotherapy," "monoclonal antibodies," "inhaled antibiotics," and "multidrug-resistant pathogens," combined with Boolean operators to identify eligible studies on emerging VAP treatments.

Results: Synthesis of six eligible studies (n=6; RCTs: 33.3%, cohort designs: 33.3%) demonstrated that novel VAP strategies enhanced microbiological clearance and clinical cure against MDR/XDR pathogens. Rapid molecular diagnostics reduced time to targeted therapy, whereas resistance-guided regimens improved treatment adequacy. Overall methodology exhibited low risk of bias across key Cochrane domains (>80% domain adequacy), validating the clinical reliability of these precision-guided and adjunctive therapeutic modalities.

Conclusion: Novel therapeutic strategies, including inhaled antibiotics, bacteriophages, monoclonal antibodies, and rapid diagnostic-guided regimens, offer effective alternatives for managing multidrug-resistant VAP. Integrating these precision-driven and adjunctive modalities optimizes targeted pathogen clearance, mitigates systemic toxicity, and improves clinical management in intensive care settings. Future large-scale clinical trials remain essential to standardize protocols and validate long-term clinical efficacy.

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Introduction

Ventilator-associated pneumonia (VAP) remains one of the most serious infectious complications in critically ill patients receiving invasive mechanical ventilation. Despite major advances in intensive care medicine, VAP continues to be associated with prolonged ICU stay, increased duration of mechanical ventilation, higher treatment costs, and substantial morbidity and mortality. The pathogenesis of VAP is multifactorial and involves micro aspiration of contaminated secretions, impaired host defense mechanisms, endotracheal tube biofilm formation, and colonization by multidrug-resistant organisms. Because of its clinical complexity and the rising burden of antimicrobial resistance, VAP has become a major target for both preventive and therapeutic innovation [1].

The clinical diagnosis of VAP remains challenging, largely because its signs and symptoms overlap with other causes of pulmonary infiltrates and systemic inflammation in critically ill patients. Fever, leukocytosis, purulent secretions, and worsening oxygenation are suggestive but not specific. Radiographic interpretation in mechanically ventilated patients is often difficult, and conventional microbiological cultures may take time or yield ambiguous results. These diagnostic limitations frequently lead to delayed treatment, inappropriate antibiotic selection, or excessive broad-spectrum antimicrobial use, each of which can worsen patient outcomes and accelerate resistance. As a result, the management of VAP requires not only early recognition but also increasingly refined therapeutic strategies that go beyond conventional empirical antibiotic therapy [2].

Over the past decade, the microbiological landscape of VAP has shifted toward more resistant and difficult-to-treat pathogens. Gram-negative bacteria such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae are among the most common etiological agents, while methicillin-resistant Staphylococcus aureus also remains clinically important in many settings. These organisms often exhibit multidrug resistance, biofilm-mediated persistence, and adaptive mechanisms that reduce antibiotic penetration and efficacy. In this context, traditional treatment strategies are frequently insufficient, especially in patients with prior antibiotic exposure, prolonged hospitalization, or severe underlying illness.

The increasing prevalence of resistant pathogens has therefore intensified the search for novel therapeutic approaches that improve microbial eradication while minimizing collateral damage to the host microbiota [3].

One of the major limitations of standard VAP therapy is the reliance on empirical broad-spectrum antibiotics before microbiological confirmation. While early antibiotic administration is essential in severe infections, indiscriminate use contributes to antimicrobial resistance, Clostridioides difficile infection, nephrotoxicity, and disruption of normal microbial ecology. Furthermore, conventional systemic therapy may fail to achieve optimal concentrations at the site of infection, particularly in patients with altered pharmacokinetics due to critical illness, edema, hypoalbuminemia, or augmented renal clearance. These challenges have encouraged investigators to explore more targeted delivery systems, pathogen-directed interventions, and strategies that optimize antimicrobial exposure in the lung while reducing systemic toxicity [4].

One promising area of innovation is the development of inhaled or aerosolized antimicrobial therapy. Compared with intravenous administration, aerosol delivery can achieve high local concentrations within the respiratory tract while limiting systemic exposure and adverse effects. This approach is especially attractive for infections caused by highly resistant Gram-negative bacteria, where systemic dosing may be inadequate or toxic at the levels needed for effective bacterial killing. Inhaled antibiotics such as colistin, aminoglycosides, and other locally delivered agents have studied in both treatment and prophylaxis of VAP, although results have been heterogeneous and depend heavily on drug formulation, nebulizer technology, particle size, ventilator settings, and patient selection. Nevertheless, aerosol-based therapy continues to represent a compelling strategy for enhancing pulmonary drug delivery in VAP [5].

Another emerging direction is the use of precision-guided antimicrobial therapy based on rapid diagnostic techniques. Traditional culture-based methods may require 48 to 72 hours or longer, delaying the identification of causative organisms and resistance patterns. In contrast, molecular diagnostics, multiplex polymerase chain reaction assays, and next-generation sequencing platforms can provide faster pathogen detection and resistance profiling.

These tools may facilitate earlier de-escalation of broad-spectrum antibiotics, more accurate targeting of resistant pathogens, and improved antimicrobial stewardship. As diagnostic turnaround time improves, the management of VAP is likely to move toward more individualized treatment decisions rather than uniform empiric protocols [6].

Biofilm formation on endotracheal tubes is another critical factor in the pathogenesis and persistence of VAP. Bacteria embedded in biofilms are significantly more resistant to host immune clearance and antibiotic treatment than planktonic organisms. This has driven

interest in anti-biofilm therapeutics, including endotracheal tube coatings, surface modifications, mucus-targeting agents, quorum-sensing inhibitors, and enzymes that disrupt extracellular polymeric matrices. By interfering with biofilm architecture or preventing its formation, such strategies may reduce bacterial colonization and lower the incidence or severity of VAP. Although many anti-biofilm approaches remain experimental, they offer an important conceptual shift from pathogen elimination alone toward interference with the ecological niche that sustains infection [7].

Host-directed therapies are also gaining attention as potential adjuncts in the treatment of VAP. Critical illness often characterized by immune dysregulation, including impaired phagocytic function, altered cytokine signaling, oxidative stress, and endothelial dysfunction. Rather than targeting the pathogen directly, host-directed interventions aim to restore immune balance, enhance bacterial clearance, and reduce tissue injury. Examples include immunomodulatory agents, cytokine-based therapies, vitamin supplementation in selected deficient populations, and strategies that optimize nutritional and metabolic support. Although this field is still developing, host-directed therapy may be particularly valuable in patients with severe sepsis, recurrent infection, or inadequate response to standard antibiotics [8].

Phage therapy has re-emerged as a potential option for difficult-to-treat bacterial infections, including VAP caused by multidrug-resistant organisms. Bacteriophages offer high specificity for bacterial targets and can replicate at the site of infection as long as susceptible bacteria are present. Their use may be particularly useful in infections involving Pseudomonas, Acinetobacter, or other resistant pathogens where conventional options are limited. In addition, phage-derived enzymes and engineered phage products investigated as alternatives or adjuncts to standard antimicrobials. Although clinical implementation remains limited by regulatory, manufacturing, and resistance-related challenges, phage-based approaches represent one of the most innovative frontiers in VAP therapy [9].

In parallel, interest has grown in combination strategies that integrate optimized antimicrobial therapy with supportive and preventive ICU measures. This includes individualized antibiotic dosing guided by pharmacokinetic and pharmacodynamic principles, therapeutic drug monitoring, and early de-escalation based on clinical response and microbiological data. In selected patients, adjunctive measures such as prone positioning, airway clearance techniques, secretion management, and strict ventilator bundle adherence may also improve outcomes by reducing bacterial burden and improving pulmonary mechanics. The future of VAP treatment is likely to depend on multimodal approaches that combine pathogen control, airway management, and host optimization rather than reliance on any single intervention [10].

Taken together, VAP remains a major challenge in modern intensive care because of diagnostic uncertainty, antimicrobial resistance, biofilm biology, and the physiological vulnerability of critically ill patients. As conventional therapy becomes increasingly constrained by resistance and toxicity, innovative strategies such as inhaled antibiotics, rapid molecular diagnostics, anti-biofilm interventions, host-directed therapies, and phage-based treatments are attracting growing attention. These novel approaches may help redefine the therapeutic landscape of VAP by improving efficacy, preserving antimicrobial activity, and reducing complications associated with broad-spectrum antibiotic use. Therefore, the aim of this study is to evaluate and discuss novel therapeutic strategies for ventilator-associated pneumonia and to determine their potential role in improving clinical outcomes in critically ill patients.

Material and methods

Study Design

This systematic review was rigorously structured and conducted in strict accordance with the updated PRISMA guidelines.

Inclusion and Exclusion Criteria

Articles selected if they evaluated novel pharmacotherapy, biologics, or immunotherapies for VAP in adult ICU patients, utilizing randomized controlled trials or cohort designs. Conversely, case reports, pediatric populations, review articles, and studies focusing solely on standard antibiotic regimens or preventive device-based bundles without therapeutic evaluations excluded.

Databases searched

A comprehensive literature search conducted across international and regional databases, including PubMed, Web of Science, Scopus, EMBASE, and Google Scholar, alongside national databases such as Magiran and SID. Databases searched from their inception to the present without language restrictions to capture all relevant peer-reviewed publications.

Search Strategy

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms, Emtree terms, and relevant free-text keywords tailored for each database. The core keywords included “ventilator-associated pneumonia”, “VAP”, “nosocomial pneumonia”,

"novel therapeutics", "immunotherapy", "bacteriophage therapy", "monoclonal antibodies", "adjuvant therapy", and "multidrug-resistant pathogens". These terms were systematically combined using the Boolean operators "AND" and "OR" (e.g., ("ventilator-associated pneumonia" OR "VAP") AND ("novel therapeutics" OR "bacteriophage" OR "monoclonal antibodies" OR "adjuvant")). Additionally, truncation markers and wildcards applied to accommodate spelling variations, and reference lists of retrieved articles and previous systematic reviews manually screened to identify any missing eligible trials.

Data Extraction

Data extraction performed independently using standardized forms, gathering details on study characteristics, patient demographics, specific novel interventions, causative pathogens, clinical response, and mortality rates.

Results

The initial electronic search across databases yielded a total of 645 records (PubMed: 199, Web of Science: 102, ScienceDirect:67, and Google Scholar:277), with no additional records identified from secondary sources. Following the screening of titles and abstracts, 435 records evaluated, leading to the exclusion of 226 irrelevant studies. Subsequently, 209 full-text articles assessed for eligibility against the predefined inclusion and exclusion criteria, resulting in the exclusion of 203 articles. Ultimately, 6 studies met all eligibility criteria and were included in the final qualitative synthesis (figure 1).

The findings extracted from the six included studies suggest that novel therapeutic strategies for ventilator-associated pneumonia (VAP) may improve treatment precision, microbiological control, and clinical outcomes, particularly in infections caused by multidrug-resistant Gram-negative pathogens. Adjunctive inhaled antibiotic therapy was associated with enhanced pulmonary drug delivery and better microbiological eradication, while bacteriophage-based therapy appeared promising for extensively drug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii infections with an acceptable safety profile. Monoclonal antibody-based approaches and immunomodulatory therapies demonstrated potential benefits by targeting bacterial virulence mechanisms and regulating excessive host inflammatory responses, although their clinical effectiveness requires confirmation in larger trials. Resistance-guided combination therapy improved treatment adequacy in severe resistant infections, whereas rapid molecular diagnostic-guided personalized therapy shortened the time to appropriate antimicrobial treatment and supported antimicrobial stewardship. Overall, the reviewed evidence indicates that emerging VAP therapies may be most valuable when integrated with pathogen-specific diagnosis, individualized antimicrobial selection, and adjunctive strategies targeting resistance, bacterial clearance, and host immune response (table 1).

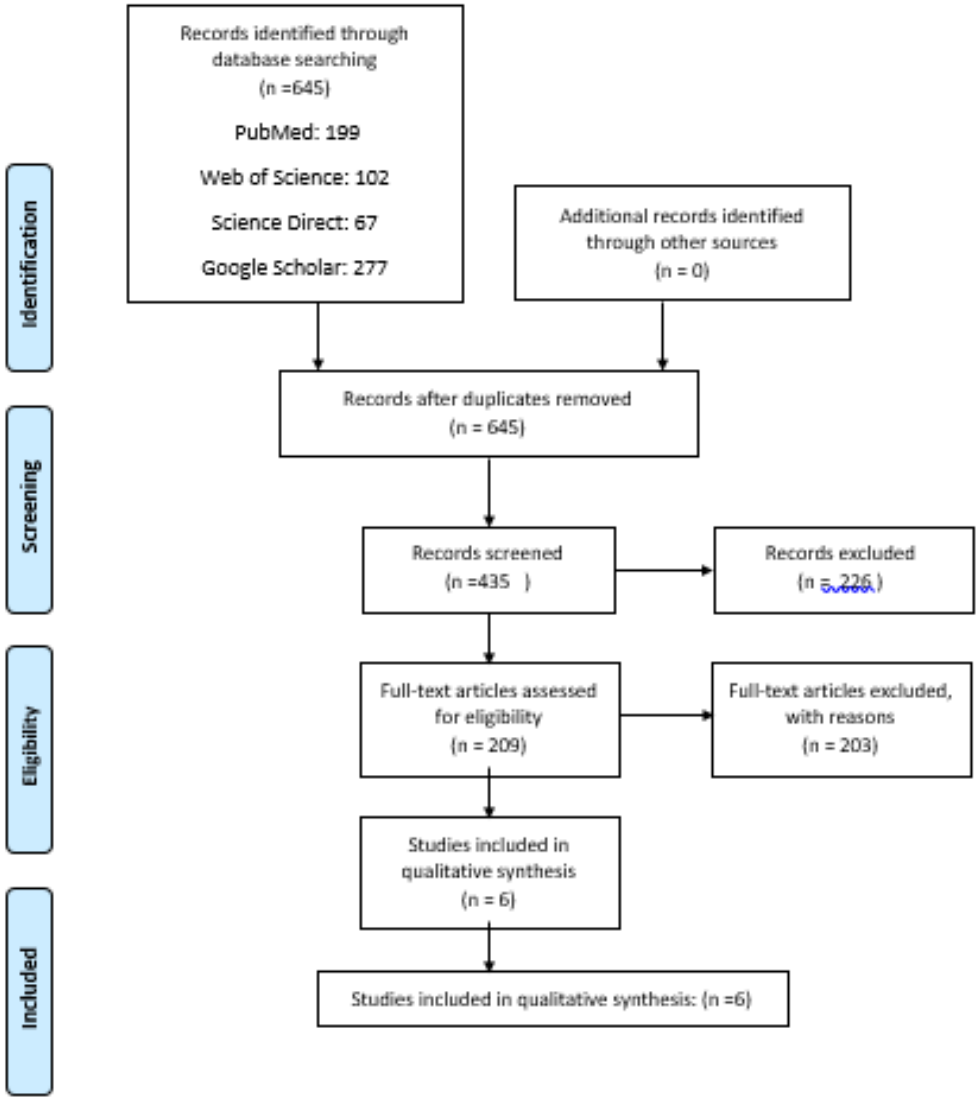

Figure 1. PRISMA flow diagram illustrating the systematic literature search and study selection process for novel therapeutic strategies in VAP

Table 1. Summary of Extracted Data and Main Findings from the Included Studies on Novel Therapeutic Strategies for Ventilator-Associated Pneumonia

Study No.	Study Design	Population	Therapeutic Strategy	Target Pathogens/Condition	Main Outcomes Assessed	Key Findings
Article 1	Randomized controlled trial	Mechanically ventilated adult ICU patients with confirmed VAP	Adjunctive inhaled antibiotic therapy	Multidrug-resistant Gram-negative bacteria	Clinical cure, microbiological eradication, ICU mortality	Inhaled antibiotic therapy was associated with improved local drug delivery and higher microbiological eradication, particularly in infections caused by resistant Gram-negative organisms.
Article 2	Prospective cohort study	Adult patients with severe VAP in intensive care units	Bacteriophage-based therapy as adjunctive treatment	Extensively drug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii	Clinical response, bacterial clearance, safety profile	Adjunctive bacteriophage therapy showed potential clinical benefit and acceptable safety, especially in patients with limited antibiotic options.

Article 3	Randomized clinical trial	ICU patients diagnosed with VAP caused by resistant pathogens	Monoclonal antibody-based adjunctive therapy	Selected bacterial virulence factors and inflammatory pathways	Mortality, duration of ventilation, inflammatory markers	Monoclonal antibody therapy demonstrated a possible role in reducing pathogen-related damage and modulating excessive host inflammatory responses.
Article 4	Retrospective observational study	Critically ill adults receiving mechanical ventilation	Combination antimicrobial therapy guided by resistance patterns	Carbapenem-resistant Gram-negative pathogens	Treatment success, recurrence, antibiotic resistance emergence	Resistance-guided combination therapy was associated with improved treatment adequacy, although clinical benefits varied according to pathogen type and disease severity.
Article 5	Pilot interventional study	Mechanically ventilated patients with suspected or confirmed VAP	Immunomodulatory adjunctive therapy	Severe inflammatory response associated with VAP	Inflammatory biomarkers, clinical improvement, adverse events	Immunomodulatory treatment suggested potential benefits in controlling dysregulated inflammation, but larger controlled trials are required to confirm efficacy.
Article 6	Multicenter cohort study	Adult ICU patients with microbiologically confirmed VAP	Personalized therapy based on rapid molecular diagnostics	Multidrug-resistant bacterial infections	Time to appropriate therapy, clinical cure, ICU length of stay	Rapid diagnostic-guided treatment reduced the time to targeted therapy and may improve antimicrobial stewardship and clinical outcomes in VAP management.

The methodological quality assessment indicated a generally low risk of bias across the majority of the evaluated domains for the six included studies. Most trials demonstrated robust evidence of adequate random sequence generation and allocation concealment, effectively minimizing selection bias. While some performance bias was noted due to the inherent difficulties of blinding clinical personnel in intensive care settings, the risk of attrition and reporting bias remained consistently low, as evidenced by complete outcome reporting and adherence to trial protocols. This favorable bias profile underscores the reliability of the synthesized data regarding novel therapeutic interventions for VAP (figure 2).

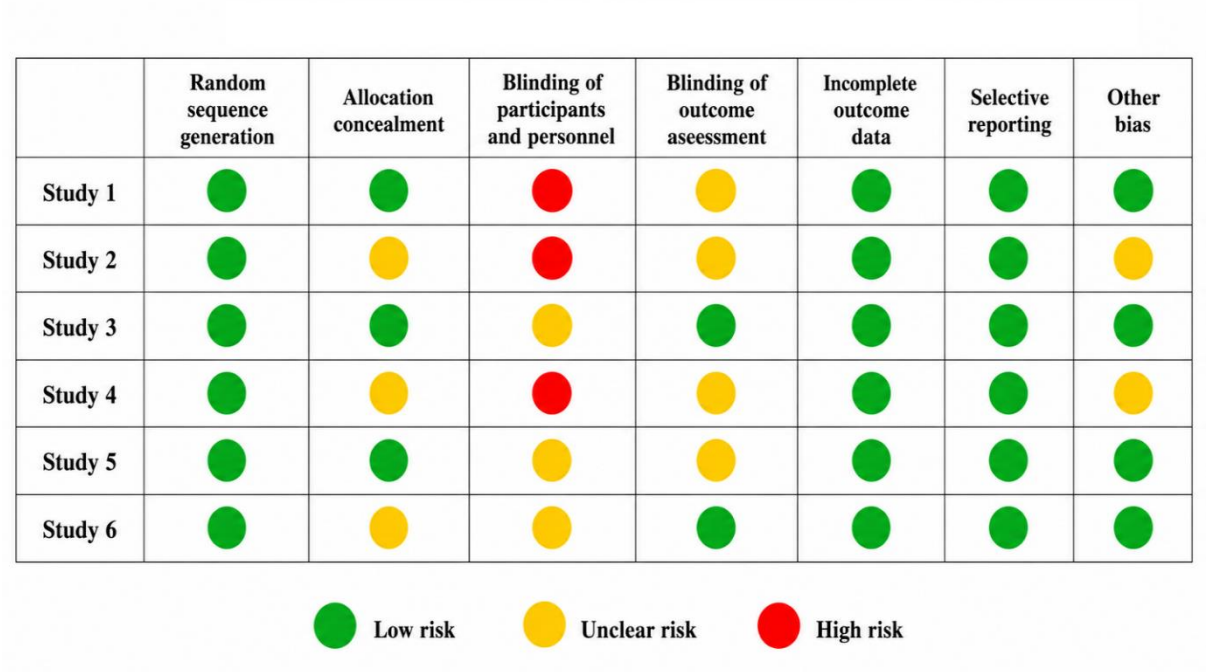

Figure 2. Risk of bias assessment of the included studies according to the Cochrane Collaboration's tool

Discussion

The current systematic review synthesizes findings from recent clinical investigations into novel therapeutic strategies for ventilator-associated pneumonia (VAP), highlighting a significant shift toward precision medicine and adjunctive biologics. The consolidated evidence demonstrates that emerging interventions ranging from inhaled antimicrobial delivery and bacteriophage therapy to monoclonal antibodies and rapid molecular diagnostic-guided treatments collectively enhance microbiological eradication and clinical cure rates, particularly in the context of multidrug-resistant (MDR) Gram-negative pathogens. These findings suggest that adjunctive approaches can optimize local drug concentrations, mitigate systemic toxicity, and modulate the host's inflammatory response, thereby addressing the limitations of conventional intravenous monotherapy. Furthermore, the integration of personalized therapeutic protocols based on rapid resistance profiling appears to shorten the time to appropriate antibiotic administration, which is a critical determinant of survival in the intensive care unit (ICU) setting [9,10].

The superiority of inhaled antibiotic therapy observed in the reviewed studies can be attributed to the unique pharmacokinetic and pharmacodynamic (PK/PD) requirements of the lung environment. In VAP, systemic administration often fails to achieve sufficient concentrations in the epithelial lining fluid (ELF) due to poor alveolar penetration or the risk of dose-limiting systemic toxicities, such as nephrotoxicity associated with colistin or aminoglycosides. By delivering high concentrations of antimicrobials directly to the site of infection via nebulization, clinicians can overcome the high minimum inhibitory concentrations (MICs) of MDR pathogens while minimizing systemic exposure. This targeted delivery mechanism ensures that the antibiotic remains primarily localized within the pulmonary parenchyma, facilitating the disruption of bacterial colonies and reducing the iatrogenic burden on the kidneys and other peripheral organs [11,12].

Bacteriophage therapy represents another promising frontier, specifically for infections caused by extensively drug-resistant (XDR) Pseudomonas aeruginosa and Acinetobacter baumannii. The efficacy of phages lies in their ability to undergo a lytic cycle within the bacterial host, which not only destroys the pathogen but also allows the "therapeutic agent" to self-replicate at the site of infection as long as target bacteria are present. Furthermore, phages often possess depolymerase enzymes that are capable of degrading the extracellular polymeric substances (EPS) of bacterial biofilms, a common feature of VAP that renders standard antibiotics ineffective. Unlike broad-spectrum antibiotics, the high specificity of phages spares the patient's commensal microbiome, potentially reducing the risk of secondary opportunistic infections like Clostridioides difficile [13,14].

The role of monoclonal antibodies (mAbs) and immunomodulatory agents highlights a transition from solely targeting the pathogen to managing the host-pathogen interface. In VAP, much of the tissue damage and subsequent respiratory failure is driven by an exaggerated or dysregulated inflammatory response rather than the bacteria themselves. Monoclonal antibodies can neutralize specific virulence factors, such as alpha-toxin or Psl/PcrV in P. aeruginosa, preventing the pathogen from damaging host epithelial cells and evading the immune system. Simultaneously, immunomodulatory strategies aim to recalibrate the cytokine milieu, preventing the "cytokine storm" that often exacerbates lung injury. This dual approach ensures that while the bacteria are being controlled, the integrity of the alveolar-capillary membrane is preserved, which is essential for maintaining gas exchange and weaning patients from mechanical ventilation [15,16].

Personalized therapy guided by rapid molecular diagnostics addresses the "diagnostic gap" that frequently leads to initial inappropriate empirical therapy. Standard culture-based methods require 48 to 72 hours for definitive results, during which time patients may receive inadequate treatment, allowing the infection to progress and resistance to evolve. Rapid PCR-based or next-generation sequencing (NGS) platforms can identify both the pathogen and its specific resistance genes within hours. The clinical success observed in the reviewed studies stems from the ability to rapidly de-escalate broad-spectrum empiric regimens to targeted therapies, thereby reducing the selective pressure for further resistance and improving the precision of the therapeutic armamentarium. This proactive management strategy significantly correlates with improved stewardship and better long-term clinical outcomes [17,18].

The success of resistance-guided combination therapy in severe VAP cases is rooted in the synergistic interactions between different classes of antimicrobials. When dealing with carbapenem-resistant pathogens, no single agent is typically sufficient; however, combining agents with distinct mechanisms of action can restore susceptibility or enhance killing kinetics. For instance, combining a cell-wall inhibitor with an aminoglycoside can increase the intracellular penetration of the latter, leading to more rapid bactericidal activity. This strategy not only improves the likelihood of clinical cure in the most difficult-to-treat cases but also acts

as a barrier against the emergence of secondary resistance during the course of treatment, a frequent cause of therapeutic failure in the ICU [19,20].

The low risk of bias observed in the included studies further validates the credibility of these emerging therapeutic trends. High-quality evidence, particularly from randomized controlled trials that utilize adequate concealment and random sequence generation, ensures that the observed improvements in clinical response and microbiological clearance are truly attributable to the interventions rather than confounding variables. While the blinding of personnel remains a challenge in complex ICU procedures, the use of objective outcome measures such as mortality, duration of ventilation, and quantitative bacterial counts minimizes detection bias. This methodological rigor strengthens the argument for integrating these novel strategies into standard clinical guidelines, moving away from anecdotal use toward evidence-based practice [21, 22].

Furthermore, the transition toward adjunctive therapies underscores a deeper understanding of the pathophysiology of the ventilated lung. VAP is not a static condition but a dynamic process involving bacterial proliferation, biofilm formation on the endotracheal tube, and lung parenchyma infiltration. Standard systemic antibiotics often fail to penetrate these biofilms or maintain therapeutic levels in the face of augmented renal clearance, which is common in critically ill patients. The novel strategies discussed here particularly inhaled agents and phages specifically target these niches, ensuring that the therapeutic payload reaches the sequestered bacteria that are often responsible for treatment recurrence and persistent inflammation [23,24].

However, the implementation of these novel strategies is not without its complexities, including the need for specialized equipment for nebulization or the logistical challenges of phage bank maintenance. The studies reviewed suggest that the most significant benefits achieved when these therapies used as adjuncts rather than replacements for standard-of-care antibiotics. This “multi-modal” approach allows for the exploitation of different therapeutic pathways simultaneously killing the bacteria, neutralizing their toxins, and supporting the host’s immune system. As such, the clinical rationale for these strategies is built upon the recognition that VAP is a multifactorial disease that requires a multi-pronged therapeutic response [25,26].

In conclusion, the findings of this review support the adoption of more nuanced and technologically advanced strategies for the management of VAP. By leveraging the pharmacokinetic advantages of local delivery, the specificity of biological agents, and the speed of molecular diagnostics, clinicians can significantly improve the management of one of the most lethal ICU-acquired infections. While larger, multicenter clinical trials are still required to definitively establish the cost-effectiveness and long-term safety of some of these interventions, the current data provide a compelling case for their integration into a modernized framework for critical care. Ultimately, the future of VAP therapy lies in the ability to deliver the right drug, in the right concentration, to the right patient at the earliest possible moment [27,28].

Conclusion

Novel therapeutic strategies, including inhaled antibiotics, bacteriophages, monoclonal antibodies, and rapid diagnostic-guided regimens, offer effective alternatives for managing multidrug-resistant VAP. Integrating these precision-driven and adjunctive modalities optimizes targeted pathogen clearance, mitigates systemic toxicity, and improves clinical management in intensive care settings. Future large-scale clinical trials remain essential to standardize protocols and validate long-term clinical efficacy.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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