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Inhaled antibiotics for treatment and prevention of ventilator-associated pneumonia. Narrative review

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Abstract

Background
Ventilator-associated pneumonia (VAP) remains a common and serious complication among patients receiving invasive mechanical ventilation. Inhaled antibiotics have been proposed as a strategy to either prevent or treat VAP by achieving high local concentrations in the lung with minimal systemic toxicity. However, their clinical benefit and optimal use remain uncertain.
Objective
This review aims to summarize current evidence on the use of inhaled antibiotics for both the prevention and treatment of VAP, identify existing knowledge gaps, and suggest directions for future research.
Methods
A narrative synthesis was conducted based on a comprehensive review of randomized controlled trials, meta-analyses, and observational studies published up to 2024. Particular attention is given to antibiotic class, delivery method, patient outcomes, safety, and microbial resistance.
Findings
Several high-quality studies suggest that prophylactic inhaled antibiotics, especially Aminoglycosides such as Amikacin, significantly reduce the incidence of VAP without increasing adverse events or multidrug resistance. Nonetheless, consistent improvements in mortality, ICU length of stay, or duration of mechanical ventilation have not been demonstrated. In the treatment context, inhaled antibiotics are frequently used as adjunctive therapy for multidrug-resistant Gram-negative pathogens, although robust RCT evidence remains limited. Key challenges include heterogeneity in study design, delivery devices, antibiotic regimens, and diagnostic definitions of VAP.
Conclusions
Inhaled antibiotics appear effective in preventing VAP, particularly when delivered via modern nebulization systems. However, their role in improving patient-centered outcomes and in the treatment of established VAP requires further clarification. Future research should focus on standardized protocols, long-term safety monitoring, and identifying patient subgroups most likely to benefit. Well-designed trials powered for clinical outcomes are essential to support the broader integration of inhaled antibiotics into VAP management strategies.

Keywords: Ventilator associated pneumonia, inhaled antibiotics, mechanical ventilation.

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Introduction

Ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) are significant challenges in the critical care setting, and their management is complicated by the fact that the success rate of conventional systemic antibiotic therapy is often below 70%. [1] The difficulty is compounded by the increasing prevalence of multidrug-resistant (MDR) pathogens, which raises the crucial question of whether alternative strategies are needed for these infections. [2] Consequently, inhaled antimicrobial therapy has seen a resurgence of interest as a compelling approach that delivers high drug concentrations directly to the site of infection while minimizing the systemic toxicity associated with intravenous administration. [3]

Despite a sound theoretical rationale, the routine use of inhaled antibiotics for preventing VAP is constrained by limited clinical trial data and a lack of regulatory approval from agencies such as the Food and Drug Administration (FDA) or European Medicines Agency (EMA). [4] The current evidence base presents a nuanced picture; while meta-analyses consistently show a significant reduction in the incidence of VAP, [5] they concurrently fail to demonstrate a significant benefit in key secondary outcomes like patient mortality. [6] This disconnect between preventing the complication and improving overall patient survival is the central challenge complicating the widespread adoption of this therapy.

Beyond its clinical implications, VAP also carries significant financial and quality consequences for hospitals. VAP prolongs ICU and hospital length of stay, leading to higher healthcare costs and reduced institutional performance metrics. [7] These factors further underscore the importance of effective prevention strategies and justify continued investigation into both prophylactic and therapeutic inhaled antibiotic approaches.

Given the established disconnect between the reduction in VAP incidence and the lack of mortality benefit, an updated evidence synthesis is required. Therefore, the primary objective of this review is to provide a more definitive assessment of the role of inhaled antibiotics in both treatment and prophylaxis. This review will evaluate the impact of the therapy on both VAP incidence and critical patient-centered outcomes, including overall mortality, to address the gaps in the current literature.

Mechanism of action (delivery and pharmacokinetics)

The primary advantage of inhaled antimicrobial therapy lies in its ability to achieve high drug concentrations directly at the site of infection within the lung. This targeted approach circumvents pharmacokinetic limitations observed with systemic administration, particularly in critically ill patients who often exhibit altered drug distribution and organ perfusion. Inhaled antibiotics such as Aminoglycosides and Colistin reach the epithelial lining fluid (ELF) in concentrations that are manyfold higher than those attainable by intravenous (IV) routes, with minimal systemic absorption and toxicity. [8,9] For instance, nebulized amikacin achieves superior pulmonary concentrations and is associated with a lower incidence of nephrotoxicity compared to IV administration. [10] Similarly, aerosolized Colistin results in markedly higher ELF concentrations than IV Colistin, as shown in pharmacokinetic studies using bronchoalveolar lavage sampling in ventilated patients. [11] This pharmacokinetic profile makes inhaled antibiotics particularly suitable for infections localized to the lung, especially in the context of multidrug-resistant Gram-negative pathogens where systemic therapy may be inadequate.

Among antibiotics utilized for inhalation, Aminoglycosides (Amikacin, Tobramycin, Gentamicin) and Polymyxins (Colistin) are the most commonly employed agents in the Intensive Care Unit (ICU) setting. Their concentration-dependent bactericidal activity and limited pulmonary penetration when administered systemically make them well suited for inhaled administration. Aminoglycosides such as amikacin have been extensively studied, demonstrating high intrapulmonary concentrations and clinical efficacy in VAP caused by MDR organisms. [8,10] Colistin, administered as Colistimethate sodium (CMS), also shows potent activity against MDR Gram-negative bacilli including PSEUDOMOnas Aeruginosa and Acinetobacter Baumannii. Aerosolized Colistin achieves ELF concentrations markedly above the minimum inhibitory concentrations (MICs) of target pathogens, while maintaining minimal systemic levels. [11,12] Other agents such as Aztreonam and ceftazidime have been investigated, but data on their aerosolized use remain limited to selected settings such as cystic fibrosis or compassionate use in resistant infections. [9]

The effectiveness of inhaled antibiotic therapy depends significantly on the delivery system and administration technique. Vibrating mesh nebulizers are preferred over jet and ultrasonic types due to their ability to generate fine, uniform particles (1–5 μm) with minimal residual volume and without heat-induced drug degradation. 13 Jet nebulizers, while inexpensive, often exhibit inconsistent delivery efficiency and substantial drug loss in the ventilator circuit. Ultrasonic nebulizers can heat the solution, risking drug inactivation, particularly for thermolabile antibiotics.

In addition to device selection, delivery timing plays a critical role: inspiratory phase synchronization has been shown to enhance distal lung deposition and reduce waste, especially in mechanically ventilated patients. [9] Guidelines

recommend placing the nebulizer in the inspiratory limb of the ventilator circuit, ideally 10–15 cm from the Y-piece, and temporarily pausing heated humidification to prevent aerosol condensation. [13] Without attention to these technical factors, therapeutic failure and increased adverse effects may occur despite the use of effective agents.

Inhaled antibiotic therapy offers a pharmacokinetic advantage by delivering high concentrations of active agents directly to the pulmonary infection site while minimizing systemic toxicity. Aminoglycosides and polymyxins remain the principal agents supported by both clinical experience and pharmacological rationale for adjunctive inhalation use in ICU settings. However, the success of this approach is highly dependent on optimal drug selection, appropriate formulation, and delivery techniques that maximize deposition in the lower respiratory tract. While current evidence supports their use primarily in salvage therapy or when systemic therapy is insufficient, standardization of administration protocols and further data from rigorously designed trials are needed to better define their role in routine clinical practice. [9]

Inhaled antibiotic treatment for VAP in the ICU

Among the various antimicrobial agents, Aminoglycosides (such as Tobramycin and Amikacin) and Colistin are the most extensively studied and frequently utilized inhaled antimicrobials for the management of VAP/HAP. While certain inhaled antibiotic formulations have received FDA approval for specific conditions like cystic fibrosis (CF) (Tobramycin, Aztreonam), for Mycobacterium avium complex lung disease (Amikacin liposome inhalation suspension), none currently hold specific FDA approval for the treatment or prevention of VAP/HAP. Despite this, inhaled Colistin is commonly employed as off label in clinical practice for VAP, particularly in cases involving MDR pathogens.

The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) weakly recommend inhaled antibiotics as adjunctive therapy in addition to standard systemic antibiotics for patients with VAP due to Gram-negative bacilli susceptible to Aminoglycosides or polymyxins. Inhaled antibiotics can be considered as a last-resort treatment for patients with VAP refractory to intravenous antibiotics based on very low-quality evidence. [14]

Recent systematic reviews and meta-analyses (SRMAs) investigating inhaled antimicrobials as a treatment for established VAP/HAP presents a nuanced picture. An SRMA published in 2024 included 11 RCTs (1472 patients) comparing nebulized antimicrobial therapy (as an adjuvant to IV antibiotics) with IV therapy alone. [15] This study concluded that adjuvant inhaled antibiotics were associated with a greater rate of microbiological eradication (Odds Ratio (OR) 2.63, 95% CI: 1.36–5.09). However, this finding was accompanied by a low certainty of evidence and a high risk of publication bias. Critically, the study found no significant difference in clinical recovery, ICU or hospital survival, or nephrotoxicity. It identified an increased risk of bronchospasm (OR 3.15, 95% CI 1.33–7.47) with high certainty of evidence. Similarly, another SRMA published in 2024, focusing on adjunctive inhaled tobramycin or Colistin for VAP treatment, [16] reported a higher likelihood of achieving both clinical cure (OR 1.47, 95% CI: 0.82–2.66) and microbiological cure (OR 7.00, 95% CI: 0.95–51.71) in the inhaled groups compared to control. However, consistent with other reviews, no significant differences were observed in mortality or the incidence of adverse events between the groups, and the overall quality of evidence was assessed as low. The latest studies are listed in Table 1.

Inhaled antibiotics prophylaxis for VAP in ICU

Current guidelines from IDSA and ATS do not recommend inhaled antibiotic prophylaxis for preventing VAP in the ICU. [14] Nonetheless, several recent randomized controlled trials (RCTs) and SRMAs have investigated the prophylactic effect of inhaled antibiotics on VAP.

A recent SRMA, published in 2025, focused on prophylactic nebulized antibiotic inhalation for VAP prevention in critically ill patients. [6] It included four RCTs involving a total of 1160 patients. The meta-analysis concluded that nebulized antibiotics significantly reduced the incidence of VAP (Relative Risk (RR) 0.70, 95% CI: 0.52–0.93). However, this finding was associated with low certainty of evidence. Crucially, the review found no statistically significant differences in secondary outcomes such as ICU mortality (RR 0.89, 95% CI: 0.73–1.09) or hospital mortality (RR 0.93, 95% CI: 0.78–1.11).

Another SRMA, published in 2024, included seven RCTs involving 1465 patients. [18] This review also reported a significant reduction in VAP occurrence (RR 0.69, 95% CI: 0.51–0.92) with inhaled antibiotics but found no significant differences in mortality (RR 0.90, 95% CI: 0.74–1.09), ICU or hospital length of stay, or mechanical ventilation duration.

A significant recent contribution to the evidence base for VAP prophylaxis is the multicenter RCT by Ehrmann et al. published 2023. [19] This study investigated the efficacy of inhaled Amikacin (20 mg/kg daily for three days) in preventing VAP among 850 mechanically ventilated patients. It demonstrated a significant reduction in VAP incidence, decreasing from 22% in the control group to 15% in the inhaled Amikacin group between randomization and day 28, representing a 32% relative reduction. Ventilator-associated events were also significantly reduced, and the intervention was very well tolerated, with less than 2% of patients experiencing serious adverse effects. However, consistent with findings from earlier studies and SRMAs, no significant differences were observed in mortality, duration of mechanical ventilation, or length of stay, though the trial was not statistically powered to conclusively evaluate these broader patient outcomes.

Although recent studies suggest that inhaled antibiotics may reduce the incidence of VAP, the lack of evidence regarding key ICU outcomes, along with the overall low quality of available data, indicates that prophylactic use of inhaled antibiotics is not currently recommended. The latest studies are listed in Table 2.

Table1. Summary and characteristics of latest studies for treatment

Author/year	Types of studies	Antibiotics tested	Main outcomes	
			Clinical cure	Microbiological eradication
Nicolò et al /2024 [15]	RCTs	Inhaled antimicrobials through nebulizer	OR 1.40, 95% CI: 0.49–4.00	OR 2.63, 95% CI: 1.36–5.09
Zengzeng et al /2024 [16]	RCTs and observational studies	Inhaled antimicrobials	OR 1.47, 95% CI: 0.82–2.66	OR 7.00, 95% CI: 0.95–51.71
Buendía et al /2024 [17]	SRMA	Inhaled Colistin and Tobramycin	RR 1.23, 95% CI: 1.04–1.45	RR 1.64, 95% CI: 1.31–2.06

RCT: randomized controlled trials, SRMA: Systemic review and meta-analysis, OR: odds ratio, RR: relative risk, CI: confidence interval

Table 2. Summary and characteristics of latest studies for prophylaxis

Author/year	Types of studies	Antibiotics tested	Main outcomes			
			Incidence of VAP	ICU-acquired pneumonia	ICU mortality	Hospital mortality
Yuan et al /2025 [6]	RCTs	Inhaled antibiotics through nebulizer	RR 0.70, 95% CI: 0.52–0.93	NA	RR 0.89, 95% CI 0.73–1.09	RR 0.93, 95% CI: 0.78–1.11
Hsu et al /2024 [18]	RCTs	Inhaled antibiotics	RR 0.69, 95% CI: 0.51–0.92	NA	NA	RR 0.90, 95% CI: 0.74–1.09
Gao et al /2024 [20]	RCTs	Inhaled antibiotics	NA	OR 0.57, 95% CI: 0.43–0.74	NA	OR 0.86, 95% CI: 0.68–1.10

RCT: randomized controlled trials, OR: odds ratio, RR: relative risk, CI: confidence interval, NA: not available

Emergence of resistant organisms

The emergence of antimicrobial resistance is a considerable concern with any antibiotic use; however, this risk is still being elucidated in studies of inhaled antibiotics. [21] Most evidence to date comes from studies of inhaled antibiotics used as monotherapy or as adjunctive therapy against Pseudomonas Aeruginosa in VAP and CF. The significance of Pseudomonas Aeruginosa lies in its ubiquity as a hospital-acquired pathogen, where resistance has been associated with increased mortality and prolonged hospitalization. [22] Studies in VAP and CF suggest a potentially protective effect of inhaled antibiotics against resistance, though continued surveillance is warranted given the limited evidence and small study populations. Among these trials, the MIC which quantifies the lowest concentration of an antibiotic that inhibits visible bacterial growth is frequently reported as a secondary microbiologic endpoint to track potential shifts in susceptibility over time or across treatment cycles.

In a comparative trial of 40 patients with VAP, nebulized Amikacin and ceftazidime demonstrated similar antipseudomonal efficacy as intravenous ceftazidime and Amikacin after 8 days of treatment. However, the nebulized group showed earlier clearance of Pseudomonas Aeruginosa in BAL cultures, with no observed shift in Amikacin or ceftazidime susceptibility. In contrast, the intravenous group demonstrated more gradual clearance and the emergence of ceftazidime-intermediate and -resistant strains from initially susceptible isolates by day 5. [23] In a double-blind, randomized, placebo-controlled trial of 47 intubated patients at high risk for MDR pathogen respiratory infection, treatment with IV antibiotics plus adjunct aerosolized Vancomycin, Gentamicin, or Amikacin resulted in eradication of 96% of bacterial isolates, compared with 9% in the IV-only group ($P < 0.0001$). Notably, 88% of MDR pathogens were eradicated in the aerosolized group compared with 9% in the IV-only group ($P < 0.0001$). Furthermore, new resistant strains were isolated in only 2 of 16 patients treated with aerosolized antibiotics, versus 6 of 11 patients treated with systemic antibiotics alone ($P = 0.03$). [24]

In the context of CF, earlier studies on 28-day on/off cycles of inhaled Tobramycin and Aztreonam were associated with significantly diminishing antimicrobial efficacy and slight increases in MIC over time. In an open-label trial by Ramsey et al., the reduction in Pseudomonas Aeruginosa sputum density declined from 1.9 $\log_{10}$ CFU/g in the first cycle to 0.8 $\log_{10}$ by the third, with the proportion of isolates with Tobramycin MIC ≥ 8 μg/mL increasing from 25% to 32%. [25] The EVOLVE trial similarly reported diminishing sputum clearance and rising Tobramycin MICs, with 10% of mucoid Pseudomonas Aeruginosa isolates having MIC > 8 μg/mL at baseline, increasing to 18.5% by the end of cycle 3. [26] In a comparative trial on inhaled Aztreonam and Tobramycin, no changes were observed in the proportion of multidrug-resistant Pseudomonas Aeruginosa or in susceptibility to other Aminoglycosides, Quinolones, or β-lactams across six 28-day treatment cycles, including the extension period. Notably, in patients treated with Aztreonam, the proportion of isolates shifting to MIC ≥ 8 μg/mL was similar regardless of treatment duration: 15% after three cycles versus 14.8% after six. [27] In contrast, the more recent CLEAR-108 trial demonstrated sustained microbiologic efficacy and no significant MIC shift with Amikacin liposomal inhalation suspension (ALIS) or Tobramycin, potentially reflecting improved baseline CF management and reduced selective pressure for resistance. [28]

It is important to note that while MIC is a standard in vitro measure of antibiotic susceptibility, it does not capture the complex tolerance mechanisms that occur in vivo. Classical antibiotic resistance involves stable, heritable genetic changes such as efflux pump overexpression, target site modification, or enzymatic degradation that raise MICs and confer survival against specific antibiotics at clinically relevant concentrations. [29] Selection of resistant strains is typically driven by pathogen exposure to subtherapeutic antibiotic levels, particularly those falling below the mutant prevention concentration (MPC). [30,31] In contrast, antibiotic tolerance mechanisms such as biofilm-mediated metabolic dormancy, persister cell survival, and stress-induced adaptive pathways allow bacteria to persist at antibiotic concentrations exceeding the MIC, independent of genetic resistance. [32,33]

While inhaled antibiotics have been shown to accumulate in target tissues at concentrations sufficient to overcome these tolerance mechanisms, effective penetration into diseased or under-ventilated regions must also be considered. In a 2023 porcine model of heterogeneous pneumonia, adjunctive inhaled Amikacin suppressed the emergence of resistant Pseudomonas Aeruginosa compared to systemic therapy alone; however, resistant isolates still emerged in poorly ventilated lung regions where drug delivery was insufficient to exceed the MPC. [34] These findings underscore the importance of optimizing local drug concentrations and accounting for both resistance and tolerance when evaluating the long-term impact of inhaled antibiotics.

Evidence gap

Inhaled antibiotics have been evaluated as both prophylactic and therapeutic strategies for preventing and managing VAP in critically ill patients.

Despite promising reductions in VAP incidence, several key uncertainties limit the clinical adoption of inhaled antibiotics. First, the impact of inhaled antibiotic prophylaxis on patient-centered outcomes such as mortality, duration of mechanical ventilation, and ICU length of stay remains inconclusive. Across multiple meta-analyses, no significant differences were observed in mortality (e.g., RR 0.89, 95% CI: 0.73–1.09 in Yuan et al. and RR 0.86, 95% CI: 0.68–1.10 in Gao et al.), [6,20] suggesting that while VAP episodes may be prevented, this does not consistently translate into improved survival or faster recovery. Second, the optimal regimen including agent, dose, duration, and timing has not been established. Trials varied widely in their use of antibiotics (e.g., Amikacin, Colistin, Tobramycin), nebulizer types, and treatment durations, introducing heterogeneity that precludes firm recommendations. [16] Third, concerns remain regarding potential long-term effects on microbial ecology, particularly the selection for resistant pathogens. Although recent trials did not observe a significant increase in multidrug-resistant organisms, earlier studies especially those using continuous administration reported adverse microbial shifts. Finally, evidence is sparse regarding the comparative efficacy of prophylaxis versus early treatment strategies, and there is a lack of robust data in specific populations (e.g., immunocompromised patients or those with prolonged ventilation > 14 days). [3]

Future research should prioritize well-powered, multicenter randomized trials that focus on clinically meaningful outcomes beyond VAP incidence specifically in mortality, ventilator-free days, and ICU/hospital length of stay. Comparative effectiveness studies are needed to determine whether inhaled antibiotics offer advantages over early intravenous therapy or biomarker-guided strategies in high-risk subgroups. Standardization in trial design including consistent definitions of VAP, uniform antibiotic delivery protocols (e.g., vibrating mesh nebulizers), and harmonized endpoints will be essential to reduce heterogeneity and improve generalizability. Mechanistic studies exploring the interaction between inhaled antibiotics, airway microbiota, and biofilm formation may help explain differential responses across patient phenotypes. Finally, longer-term surveillance of resistance patterns is warranted to assess ecological risks, particularly in ICUs with high baseline antimicrobial use pressure. As the field moves forward, precision in identifying the optimal timing, patient selection, and antibiotic combinations will be critical for integrating inhaled antibiotic prophylaxis into evidence-based VAP prevention bundles.

Conclusion and further directions

The current body of evidence on inhaled antimicrobials for VAP/HAP demonstrates their potential in reducing VAP incidence and achieving microbiological eradication, particularly against MDR pathogens. However, a consistent and statistically significant benefit on crucial patient-centered outcomes such as overall mortality, ICU length of stay, or duration of mechanical ventilation remains largely unproven. [6] This finding suggests a complex interplay between VAP/HAP as a complication and the overall severity of critical illness, where preventing or treating the pneumonia alone may not be sufficient to alter the ultimate patient trajectory in terms of survival.

The most pressing evidence gap is the immediate need for an updated systematic review and meta-analysis that incorporates the pivotal Ehrmann et al. RCT, [19] which significantly strengthens the evidence base for VAP prevention. Such a review is crucial to provide a more definitive understanding of the role of inhaled antimicrobials in VAP prophylaxis.

Beyond this immediate need, future research should focus on:

1. Patient-Centered Outcomes: Designing large-scale RCTs powered to detect differences in mortality, ventilator-free days, and ICU-free days, rather than solely relying on VAP incidence or microbiological eradication.
2. Specific Patient Populations: Investigating the efficacy and safety of inhaled antimicrobials in carefully defined high-risk patient subgroups, where the impact on hard clinical outcomes might be more pronounced.
3. Optimization of Delivery: Conducting trials that compare different inhaled antimicrobial agents, dosing regimens, and delivery devices (e.g., nebulizer types, inspiratory synchronization) to establish optimal administration protocols.
4. Antimicrobial Stewardship: Rigorously evaluating the long-term impact of inhaled antimicrobials on overall systemic antibiotic consumption and the emergence of antimicrobial resistance.
5. Standardization: Advocating for standardized definitions of clinical and microbiological outcomes in future trials to enhance the comparability and robustness of meta-analyses.

In conclusion, while inhaled antimicrobials offer a promising targeted approach to address the challenges of VAP/HAP,

particularly with MDR pathogens, their precise role in routine clinical practice requires further high-quality, patient-centered research. New and updated SRMAs, integrating the latest robust RCTs and addressing the identified evidence gaps, are indispensable for informing evidence-based guidelines and optimizing patient care in critical care settings.

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