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Review

Targeting multidrug-resistant pneumonia: The potential of combined antibiotic therapies and non-antimicrobial approaches

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Abstract: As antibiotics are widely used, multidrug-resistant pneumonia has emerged as a grave global health challenge. Multidrug-resistant pneumonia is mainly caused by *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*, among others. Its resistance mechanisms involve various biological processes such as mutations in efflux pump genes, the development of bacterial biofilms, and the secretion of inactivating enzymes. Given the limited effectiveness of traditional single-agent antimicrobial therapy in treating multidrug-resistant pneumonia, the medical community has now shifted towards combination therapy strategies, including precision medication based on drug susceptibility testing, combinations of antibiotics with different mechanisms of action, and phage therapy. Despite the current challenges, such as drug toxicity and the determination of optimal combination regimens, combination therapy offers new hope for overcoming multidrug-resistant pneumonia. This article reviews the current status of multidrug-resistant pneumonia, its resistance mechanisms, and the potential of combination therapy.

Keywords: *Acinetobacter baumannii; Klebsiella pneumonia*; Multidrug-Resistant; Pneumonia; *Pseudomonas aeruginosa*

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INTRODUCTION

Over the past few decades, the prevalence of multidrug-resistant pneumonia has steadily risen due to the extensive and improper use of antibiotics, posing a significant obstacle in clinical treatment (Cillóniz *et al.*, 2021). Multidrug-resistant pneumonia is mainly caused by various Gram-negative bacilli, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, among others (Kim *et al.*, 2022). These pathogenic bacteria exhibit strong drug resistance and are resistant to multiple antibiotics, making traditional treatment methods ineffective (Lai *et al.*, 2021). The resistance mechanisms of multidrug-resistant pneumonia are complex, encompassing biological processes such as drug efflux, target mutation, drug inactivation, biofilm formation, and alterations in metabolic pathways, enabling pathogenic bacteria to persist and multiply despite antibiotic pressure, leading to treatment failure and exacerbation of the disease, posing significant challenges for clinical management (Falcone *et al.*, 2021). Due to the complex and diverse resistance mechanisms of drug-resistant bacteria, traditional single-agent antimicrobial therapy is difficult to effectively inhibit or eradicate the pathogens (Meschiari *et al.*, 2024). Therefore, combination therapy-encompassing both antibiotic combinations and non-antimicrobial strategies-has become an essential strategy for managing multidrug-resistant pneumonia. This review explores two primary approaches: synergistic antibiotic combinations targeting different bacterial pathways, and emerging non-antimicrobial therapies such as probiotics, phage therapy, fecal microbiota transplantation and antibody-based treatments. In combination therapy for multidrug-resistant pneumonia, different drugs can act on different targets of the pathogen or exert antibacterial effects through different mechanisms of action, thereby producing a synergistic effect, enhancing antibacterial activity, and improving the bactericidal effect against drug-resistant bacteria (Gohil *et al.*, 2024). Furthermore, combination therapy can potentially postpone the development of resistance. When a single drug is used alone, bacteria can easily develop adaptive changes and become resistant under the selective pressure of the drug. However, when multiple drugs are used in combination, bacteria need to overcome the mechanisms of action of multiple drugs simultaneously to develop resistance, which greatly increases the difficulty of resistance emergence (Barbier *et al.*, 2024). Therefore, in-depth research on the resistance mechanisms of multidrug-resistant pneumonia and the exploration of effective combination therapy strategies have significant clinical and social value in enhancing the overall prognosis for patients, reducing mortality, and controlling the spread of drug-resistant bacteria.

Etiology of multidrug-resistant pneumonia

The main etiology of multidrug-resistant pneumonia is infection with multidrug-resistant bacteria. These bacteria can gain entry into the human body through diverse routes, such as being inhaled into the respiratory tract, hematogenous dissemination, and spread from adjacent infected sites (Wu *et al.*, 2023). Hospital-acquired pneumonia is the main type of multidrug-resistant pneumonia, often occurring during hospitalization or after

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invasive medical procedures; community-acquired pneumonia may also develop into multidrug-resistant pneumonia due to the spread of drug-resistant bacteria, but it is relatively less common (Campaña-Duel *et al.*, 2024). Chang Y *et al*. (Chang *et al.*, 2021) conducted a study on 381 patients with hospital-acquired pneumonia/ventilator-associated pneumonia in intensive care units of five hospitals in South Korea. They found that most patients had late-onset disease, and a quarter of them had factors that increased their susceptibility to multidrug-resistant pathogens. The findings of the study revealed that Acinetobacter baumannii was the most prevalent bacterial pathogen, with *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* following closely behind. Moreover, the majority of Acinetobacter baumannii (97%) and *Staphylococcus aureus* (88%) isolates exhibited multidrug resistance. The choice of empirical antibiotics had a significant impact on patient outcomes, and appropriate antibiotic use could effectively reduce mortality. However, due to discrepancies between the predominant pathogens and empirical antibiotic therapy, the overall mortality rate among patients with hospital-acquired pneumonia/ventilator-associated pneumonia was considerable.

Resistance mechanisms in multidrug-resistant pneumonia pathogens

Production of β-Lactamases

β-Lactamases, a prevalent resistance mechanism in multidrug-resistant pneumonia bacteria, hydrolyze the β-lactam ring of antibiotics, preventing target binding and inhibiting cell wall synthesis, thereby enabling bacterial growth and multiplication (Veloo *et al.*, 2022). In multidrug-resistant pneumonia, common β-lactamases include extended-spectrum β-lactamases (ESBLs), cephalosporinases (AmpC), and carbapenemases. ESBLs have the capacity to hydrolyze multiple antibiotics, such as third-generation cephalosporins, and their encoding genes are often located on plasmids, facilitating the spread of resistance among bacteria through conjugation, transformation, and other means, leading to the rapid dissemination of resistance among different strains and bacterial species (Al-Sheboul *et al.*, 2023). AmpC enzymes primarily hydrolyze cephalosporin antibiotics, especially exhibiting strong hydrolytic activity against third-generation cephalosporins (El Shamy *et al.*, 2021). Unlike ESBLs, the production of AmpC enzymes in many Gram-negative bacteria can be induced, particularly when exposed to β-lactam antibiotics, and is regulated by chromosomal or plasmid genes, playing a significant role in bacterial resistance mechanisms (Mansouri *et al.*, 2024). Carbapenemases can degrade carbapenem antibiotics, primarily accounting for the reduced susceptibility of bacteria like *Klebsiella pneumoniae* to these drugs (Tumbarello *et al.*, 2021). Carbapenem antibiotics serve as a crucial therapeutic option for severe bacterial infections, yet the emergence of carbapenemases has resulted in bacterial resistance to these potent drugs.

Efflux pump encoding genes

The efflux pump system of bacteria consists of efflux transporters, inner membrane transporters, outer membrane channel proteins, and linker proteins, which work synergistically to actively pump antibiotics that enter the cell out of the cell, thereby reducing intracellular drug concentrations below therapeutic levels and rendering antibiotics ineffective (Yu *et al.*, 2022). These tripartite complexes utilize energy derived from proton motive force or ATP hydrolysis to mediate multidrug resistance (MDR) through three primary mechanisms: direct antibiotic extrusion, prevention of drug accumulation, and reduction of target site exposure. The MexAB-OprM efflux pump in *Pseudomonas aeruginosa*, for instance, recognizes and expels diverse antimicrobial agents including β-lactams, quinolones, and tetracyclines, contributing significantly to its intrinsic and acquired resistance profiles (Lorusso *et al.*, 2022). Recent advances in efflux pump inhibition strategies have identified several promising approaches, including: small-molecule inhibitors (e.g., PAβN and D13-9001) that competitively bind transport proteins, nanoparticle-based delivery systems to bypass efflux mechanisms, and CRISPR-Cas9 mediated suppression of efflux pump gene expression (Ding *et al.*, 2023; Kumar Roy and Patra, 2020). However, clinical translation remains challenging due to issues of bacterial compensatory mechanisms and potential host toxicity.

Biofilm formation

Bacterial biofilm denotes a structured bacterial assemblage adhering to solid surfaces during growth and secreting substances such as polysaccharides, proteins, and DNA. The formation process includes stages of initial bacterial adhesion, microcolony formation, biofilm maturation, and bacterial dispersion (Thi *et al.*, 2020). Biofilms provide a tight environment for bacteria, allowing them to exchange genetic material through transformation, transduction, and conjugation, which promotes the exchange and genetic recombination of bacterial genes, thereby facilitating the acquisition of antibiotic resistance by certain bacteria (Uruén *et al.*, 2020). Studies have shown that biofilms can significantly hinder the diffusion of antibiotics, impeding antibiotic penetration into the biofilm, thereby decreasing the therapeutic concentration of antibiotics against the bacteria enclosed (Shen *et al.*, 2020). In addition, bacteria within biofilms are often in a slow-growing or stationary phase, making them less sensitive to many antibiotics that rely on bacterial metabolic activity.

Acquired resistance genes

Bacteria can acquire resistance genes through various pathways, such as gene mutations, plasmid-mediated mechanisms, and transposon-mediated mechanisms, which constitute an important resistance mechanism in multidrug-resistant pneumonia bacteria (Khare *et al.*, 2021). Acquired resistance genes can encode various resistance enzymes, efflux pumps, membrane protein-modifying enzymes, etc., thereby conferring resistance to multiple antimicrobial agents on bacteria. Currently, multiple acquired resistance

genes have been identified in *Klebsiella pneumoniae*, such as genes encoding KPC-type carbapenemases and genes encoding New Delhi Metallo-β-lactamase-1 (NDM-1) metallo-β-lactamases (Rong *et al.*, 2023). The mecA gene in Staphylococcus aureus encodes PBP2a, which has low affinity for β-lactam antibiotics. When standard penicillin-binding proteins are inhibited by β-lactam antibiotics, PBP2a maintains cell wall synthesis, conferring β-lactam resistance (Zhu *et al.*, 2023).

Antibiotic therapies (See Table 1 and Table 3)

Carbapenems and β-lactamase inhibitors

Carbapenem antibiotics, like imipenem, meropenem, and panipenem, are potent β-lactam antibiotics with a broad spectrum. They bind to penicillin-binding proteins on bacterial cell walls, inhibiting peptidoglycan synthesis, which leads to cell wall defects and bacterial death (Bouza, 2021). Carbapenem antibiotics have a broad antibacterial spectrum and exhibit potent activity against Gram-positive bacteria, Gram-negative bacteria, and anaerobic bacteria. However, they are susceptible to hydrolysis and inactivation by β-lactamases produced by bacteria (Rando *et al.*, 2024). β-Lactamases constitute a class of enzymes that cleave the β-lactam ring, a crucial component within β-lactam antibiotic molecules. This hydrolysis renders the antibiotics inactive, thereby increasing bacterial resistance to these drugs. Importantly, β-lactamase inhibitors can effectively inhibit the β-lactamases produced by bacteria, thereby protecting β-lactam antibiotics from enzymatic hydrolysis and enhancing their antibacterial activity (Kanj *et al.*, 2022). Common β-lactamase inhibitors, such as sulbactam and tazobactam, when combined with β-lactam antibiotics, expand the antibacterial spectrum, enhance efficacy, and mitigate the development of resistance. At the same time, since carbapenem antibiotics themselves have broad-spectrum antibacterial activity and high stability against β-lactamases, their combination with β-lactamase inhibitors not only further broadens the antibacterial spectrum but also improves the stability of antibacterial activity, reducing the risk of bacterial resistance (Mansour *et al.*, 2021). Kaye KS *et al*. (Kaye *et al.*, 2023) compared the efficacy of sulbactam-durlobactam (combined with imipenem-cilastatin) versus polymyxin (also combined with imipenem-cilastatin) in treating patients with nosocomial pneumonia, ventilator-associated pneumonia, and pneumonia related to ventilation caused by carbapenem-resistant Acinetobacter baumannii-Acinetobacter calcoaceticus complex. The findings indicated that sulbactam-durlobactam combined with imipenem-cilastatin had similar 28-day all-cause mortality rates compared to polymyxin combined with imipenem-cilastatin, and had a lower incidence of nephrotoxicity. Furthermore, Deng Y *et al*. (Deng *et al.*, 2022) examined treatment outcomes in 166 patients with hospital-acquired multidrug-resistant *Acinetobacter baumannii* pneumonia and discovered higher mortality among patients aged over 75, those with invasive catheters, and those on mechanical ventilation. The study also indicated that for patients with carbapenem-resistant AB, an antimicrobial treatment regimen combining tigecycline and sulbactam could reduce mortality, and high-dose sulbactam might be more effective. Therefore, reducing the duration of invasive procedures in ICU patients, combined with the aforementioned antimicrobial therapy, could potentially lower mortality rates in critically ill patients with multidrug-resistant *Acinetobacter baumannii* pneumonia. Shields RK *et al*. (Shields *et al.*, 2022) observed that five patients with hospital-acquired pneumonia developed infections with *Pseudomonas aeruginosa* that were nonsusceptible to imipenem-relebactam after 10 to 28 days of treatment. Genomic sequence analysis revealed independent treatment-emergent mutations in the MexAB-OprM and/or MexEF-OprN efflux operons among different *Pseudomonas aeruginosa* sequence types in these patients. However, the use of the efflux inhibitor PAβN restored the susceptibility of these strains to imipenem-relebactam. Carbapenems, the primary therapy for severe Gram-negative infections, face the challenge of carbapenem-resistant Enterobacterales. Shortridge D *et al*. (Shortridge *et al.*, 2023) found in their study that among 1,697 multidrug-resistant Enterobacterales isolates collected between 2016 and 2020, 99.1% were susceptible to meropenem-vaborbactam, with *Klebsiella pneumoniae* carbapenemase (KPC) being the most common carbapenemase. Despite the presence of a few bacteria producing other types of carbapenemases, meropenem-vaborbactam still demonstrated high susceptibility (93.2%) against carbapenem-resistant Enterobacteriaceae, particularly against KPC-producing bacteria (98.9%). This suggests that meropenem-vaborbactam serves as an efficacious alternative for managing multidrug-resistant Gram-negative infections.

Polymyxins and carbapenems

Polymyxins are cationic polypeptide antibiotics which bind to the phospholipid components of bacterial cell membranes, disrupting membrane integrity and causing the leakage of important substances such as proteins and nucleic acids from the cell, ultimately leading to bacterial death (Ray *et al.*, 2022). Polymyxins exhibit good antibacterial activity against Gram-negative bacteria, especially against multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Wang *et al.*, 2024). Zheng JY *et al*. (Zheng *et al.*, 2020) retrospectively analyzed 183 adult patients who received polymyxin therapy for at least 7 days, aiming to assess the clinical and microbiological outcomes, as well as the 30-day mortality rate, associated with polymyxin therapy for pneumonia caused by multidrug-resistant *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex. The results showed that patients who received only inhaled polymyxin exhibited better outcomes in terms of 30-day survival rate, clinical efficacy, and microbiological clearance, while patients who received only intravenous polymyxin had a higher clinical failure rate and a significantly increased incidence of nephrotoxicity.

Table 1: Antibiotic combination therapy

Combination Therapy	Characteristics	Effectiveness	Key Findings
Carbapenems + β-lactamase inhibitors	• Carbapenems (e.g., imipenem, meropenem) target PBPs. • β-lactamase inhibitors (e.g., sulbactam, tazobactam) protect β-lactams from hydrolysis.	• Broadens antibacterial spectrum. • Reduces resistance risk. Effective against carbapenem-resistant strains.	• Sulbactam-durlobactam + imipenem-cilastatin showed similar mortality to polymyxin combinations but lower nephrotoxicity. • High-dose sulbactam + tigecycline reduced mortality in MDR *Acinetobacter baumannii* pneumonia.
Polymyxins + Carbapenems	• Polymyxins disrupt cell membranes. • Carbapenems inhibit cell wall synthesis.	• Synergistic effect against MDR Gram-negative bacteria (e.g., *Acinetobacter baumannii, Pseudomonas aeruginosa*). • Reduces individual drug toxicity.	• Inhaled polymyxin showed better survival and lower nephrotoxicity than IV polymyxin. • Polymyxin-meropenem synergy observed in 60-70% of planktonic *Klebsiella pneumoniae* isolates.
Tigecycline + Carbapenems	• Tigecycline inhibits protein synthesis. • Carbapenems target cell wall synthesis.	• Effective against mixed infections (Gram-positive and Gram-negative). • Delays resistance development.	• High-dose tigecycline (25 mg/kg/day) cured carbapenemase-producing *Klebsiella pneumoniae* in rats. • Tigecycline-based regimens improved clinical outcomes in MDR *Acinetobacter baumannii* pneumonia.
Polymyxin + Amikacin	• Polymyxins target membranes. • Amikacin inhibits protein synthesis.	• Synergy against biofilm-forming MDR *Klebsiella pneumoniae* (70% synergy rate).	• *Polymyxin-amikacin combination was most effective against biofilm-state infections.
Polymyxin + Double Carbapenems	• Dual carbapenems target PBPs with different affinities.	• Salvage therapy for extensively drug-resistant infections.	• Successfully treated an extensively drug-resistant *Klebsiella pneumoniae* ventilator-associated pneumonia case.

Table 2: Non-antimicrobial therapies

Therapy	Characteristics	Effectiveness	Key Findings
Fecal Microbiota Transplantation (FMT)	Restores gut microbiota balance. Reduces antibiotic resistance genes.	Promising for decolonizing carbapenem-resistant *Acinetobacter baumannii*.	FMT recipients showed loss of 95 antibiotic resistance genes, including those for β-lactamases and polymyxins.
Probiotics	Lactobacillus/Bifidobacterium spp. inhibit pathogens via metabolites.	Reduces biofilm formation and virulence in MDR *Klebsiella pneumoniae*.	Probiotic cell-free supernatants (CFS) slowed resistance development and synergized with antibiotics.
Phage Therapy	Lytic phages target specific bacteria (e.g., *Klebsiella pneumoniae*, Acinetobacter).	Effective in early-stage MDR pneumonia. No cross-resistance with antibiotics.	Phages pKp11/pKp383 reduced bacterial load and inflammation in mice. Phage pK4-26 depolymerase disrupted biofilms and virulence.
Antibody Therapy	Monoclonal antibodies (e.g., 65) enhance opsonophagocytosis.	Synergistic with colistin against pan-drug-resistant *Acinetobacter baumannii*.	IgM-enriched immunoglobulin + colistin reduced lung bacterial load in *Pseudomonas aeruginosa* pneumonia.

Table 3: Comparison of Antibiotic Therapies vs. Non Antibiotic Treatments

Treatment Type	Advantages	Limitations
Antibiotic Therapies		
Traditional Antibiotics	• Broadspectrum: Effective against diverse bacteria (e.g., carbapenems for Gramnegative/positive). • Rapid action: Directly kills or inhibits bacterial growth. • Standardized use: Wellestablished dosing and treatment guidelines.	• Resistance development: Overuse leads to resistant strains. • Toxicity: Nephrotoxicity, gut microbiota disruption. • Poor biofilm penetration: Limited efficacy against biofilmembedded bacteria.
Combination Antibiotics	• Synergistic effects. • Delays resistance: Requires simultaneous bacterial mutations. • Expanded coverage: Effective against mixed infections.	• Complexity: Requires susceptibility testing; empirical use carries risks. • Toxicity overlap. • High cost: Novel antibiotics are expensive.
NonAntibiotic Treatments		
Phage Therapy	• Precision targeting: Kills specific pathogens without harming normal flora. • Biofilm disruption: Lysins penetrate biofilms. • No crossresistance: Mechanism differs from antibiotics.	• Narrow host range: Requires strain matching, timeconsuming. • Immune response: Neutralizing antibodies may develop. • Limited clinical data: Mostly case reports or small trials.
Monoclonal Antibodies	• High specificity: Targets virulence factors. • No resistance induction: Bacteria cannot develop resistance. • Low toxicity: Minimal side effects.	• High Research and Development costs: Target screening and optimization are complex. • Limited coverage: Only effective against specific pathogens. • Short halflife: Requires frequent dosing.
Probiotics/FMT	• Restores microbiota: Reduces resistant pathogen colonization. • Preventive potential: Enhances mucosal immunity. • Safety: Few side effects.	• Variable efficacy: High interindividual variability. • Infection risk: FMT may transmit pathogens. • Slow onset: Requires longterm intervention.
Immunomodulators	• Boosts host defense. • Synergy with antibiotics: Reduces antibiotic doses.	• Complex mechanisms: Requires precise immune modulation. • Niche applications: Currently adjunctive only.

In addition, for patients receiving intravenous polymyxin therapy, appropriate dosing is crucial to avoid excessive mortality. This supports inhaled delivery as a safer, targeted approach for lung infections, avoiding systemic toxicity while maintaining efficacy-a paradigm shift for managing critically ill patients with limited treatment options. Monotherapy with colistin is not recommended for critically ill patients in clinical practice due to the development of resistance during treatment. Zhang X *et al*. (Zhang *et al.*, 2023) reviewed relevant literature, includingrandomized controlled trials and observational studies, to evaluate nebulized polymyxin's efficacy and safety for ventilator-associated pneumonia. The results showed that although nebulized polymyxin significantly improved microbial clearance, it did not demonstrate significant differences compared to intravenous antibiotics in improving clinical response, reducing overall mortality, or reducing the duration of mechanical ventilation and ICU stay. However, Cui HM *et al*. (Cui *et al.*, 2021) conducted a comprehensive literature review and meta-analysis to compare the clinical effects of intravenous polymyxin, inhaled polymyxin, or their combination in patients with multidrug-resistant pneumonia. The results showed that patients receiving combination therapy or inhaled polymyxin had higher clinical cure rates and microbiological clearance rates, as well as lower nephrotoxicity and mortality rates, compared to those receiving intravenous therapy alone. These findings provide important references for clinicians to choose the

administration route of polymyxin in managing multidrug-resistant pneumonia.

The combination of carbapenems and polymyxins can produce a synergistic antibacterial effect. For severe multidrug-resistant Gram-negative bacterial pneumonia, especially infections caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, the combined use of polymyxins and carbapenems can increase antibacterial efficacy. Carbapenem drugs inhibit bacteria from the aspect of cell wall synthesis, while polymyxins act by disrupting the cell membrane. This dual mechanism of action can more effectively kill bacteria and also reduce the dosage of individual drugs, thereby lowering drug toxicity (Ardebili *et al.*, 2023). Bayatinejad G *et al*. (Bayatinejad *et al.*, 2023) found in their study that various antibiotic combinations demonstrated synergistic inhibitory effects against different morphological forms (planktonic and biofilm states) of multidrug-resistant *Klebsiella pneumoniae* strains in vitro, particularly for nosocomial infections such as ventilator-associated pneumonia caused by these strains. In the planktonic mode, the combination of polymyxin-meropenem and the combinations of amoxicillin/clavulanate with meropenem, polymyxin, or amikacin exhibited synergistic effects against 60%-70% of the isolates. On the other hand, in the biofilm state, combinations based on polymyxin showed synergistic effects against 50%-70% of the isolates, with the most effective combination being polymyxin-amikacin, which had a synergy rate of up to 70%. These findings serve as a foundation for future research into using these antibiotic combinations to treat carbapenem-resistant *Klebsiella pneumoniae* infections. In addition, Singh M *et al*. (Singh *et al.*, 2021) reported a case of an 8-year-old male patient who suffered from acute respiratory distress syndrome with left-sided tuberculous pleural effusion and subsequently developed ventilator-associated pneumonia caused by multidrug-resistant *Klebsiella pneumoniae*. The patient was successfully treated with a combination therapy of polymyxin and double carbapenems. These studies indicate that polymyxin combination therapy shows clinical benefits of synergistic bactericidal activity against multidrug-resistant Gram-negative bacilli infections, but large-scale randomized controlled trials are still needed to provide high-certainty evidence. When designing these trials, factors such as patient sample size, patient characteristics, pharmacokinetic/pharmacodynamic relationships, rapid detection of drug resistance, minimum inhibitory concentration determination, and therapeutic drug monitoring should be given special attention.

Tigacycline and carbapenems

Tigecycline is a next-generation glycylcycline antibiotic that obstructs bacterial protein synthesis by binding to the 30S subunit of the bacterial ribosome and blocking the entry of aminoacyl-tRNA into the A site of the ribosome (Yaghoubi *et al.*, 2022). Tigecycline exhibits broad-spectrum antibacterial activity and is effective against Gram-positive bacteria, Gram-negative bacteria, and anaerobes. Liu B *et al*. (Liu *et al.*, 2020) performed a retrospective study on patients with hospital-acquired pneumonia caused by a single multidrug-resistant *Acinetobacter baumannii* who were admitted to the intensive care unit of Xiangya Hospital in Changsha, China, between January 2016 and June 2017. They evaluated and compared the effectiveness and prognostic indicators of treatment regimens based on tigecycline versus those utilizing other antibiotics. The findings revealed that while there was no notable disparity in 28-day mortality between the two groups, a greater proportion of patients in the tigecycline group exhibited a favorable clinical outcome, with tigecycline treatment emerging as a protective factor. For some complex multidrug-resistant pneumonias, such as mixed infections (including simultaneous infections with Gram-positive and Gram-negative bacteria) or bacterial infections resistant to a single drug, the combination of tigecycline and carbapenems can improve treatment success rates. This combination can cover a broader range of bacterial species, and due to their different mechanisms of action, it is relatively difficult for bacteria to develop resistance to both drugs simultaneously, which helps to delay the emergence of resistance. In a newly established rat model of lethal lobar pneumonia-sepsis, Van der Weide H *et al*. (Van der Weide *et al.*, 2020) conducted a study to compare the effectiveness of tigecycline monotherapy with meropenem monotherapy. It was found that high-dose tigecycline (25 mg/kg/day) was effective in curing infections caused by Klebsiella pneumoniae producing carbapenemase, while the same dose of meropenem was ineffective. This result supports the recommendation of using high-dose tigecycline as a final treatment alternative for severe multidrug-resistant Gram-negative bacterial infections and provides supporting data for subsequent clinical trials.

Studies on these antibiotic combination regimens have certain limitations due to difficulties in inclusion criteria and design. For example, suboptimal dosing of combined antibiotics, failure to adhere to pharmacokinetic/pharmacodynamic parameters, and the fact that combination therapy has thus far mostly involved two drugs, often selected for extensively drug-resistant Acinetobacter baumannii, have led some scholars to question whether only two drugs may lead to the selection of resistance. Therefore, whether combination therapy should include three or more drugs depends on the specific clinical situation and resistance characteristics. We need to understand that there is no single fixed combination of antibiotics that is effective against every multidrug-resistant or extensively drug-resistant *Acinetobacter baumannii*, due to the multiple resistance mechanisms that form different resistance phenotypes and the inherent genetic heterogeneity among them. Moreover, resistance phenotypes and genetic heterogeneity are significantly

correlated with geographical differences. Clinical practice should reasonably optimize combination therapy regimens by screening known resistance genes using in vitro susceptibility testing, combination susceptibility testing, and whole-genome sequencing technology, and selecting drugs with minimum inhibitory concentrations at or near the upper limit of sensitivity or the susceptibility breakpoint as components of the combination regimen. At the same time, by incorporating pharmacokinetic/pharmacodynamic parameters, optimizing dosing regimens and doses can improve treatment efficacy and reduce the development of resistance.

Non-antimicrobial therapy (See Table 2 and Table 3)

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a therapeutic approach that restores intestinal microbial balance by transplanting fecal microbiota from healthy donors into the intestines of patients. FMT has shown significant potential in the treatment of intestinal and extraintestinal diseases, particularly for patients who are resistant to antibiotics or unresponsive to conventional treatment. To establish an effective FMT pathway, it is necessary to strictly screen healthy donors and consider the immune status of the recipients, while ensuring administration when patients have no active infections and do not require additional antibiotics. Many ICU patients have their intestines colonized by carbapenem-resistant Acinetobacter baumannii, especially those who have previously been exposed to carbapenem drugs (Liu *et al.*, 2022). Leung *et al*. (Leung *et al.*, 2018) identified the loss of 95 antibiotic resistance genes in FMT recipients, including those conferring resistance to broad-spectrum β-lactamases, glycopeptides, quinolones, and polymyxins, through metagenomic sequencing data from 8 pairs of FMT donors and recipients. Although large-scale randomized controlled trials are not yet available, preliminary data suggest that using FMT as a decolonization strategy holds promise for patients colonized with carbapenem-resistant Acinetobacter baumannii in the gastrointestinal tract (Ghani *et al.*, 2022). The key to success lies in preventing invasive diseases, rather than solely pursuing intestinal decolonization. Future research should focus on clinical outcomes, cost-effectiveness, and the identification of markers for successful FMT and functional microbial components.

Probiotics

Probiotics are live microorganisms that can parasitize or colonize the host's gastrointestinal tract for a short period, exerting a positive influence on host health by improving nutrient absorption (Annu *et al*., 2025), enhancing the host's innate immune function, and reducing the relative abundance of potential pathogenic bacteria (Mazziotta *et al.*, 2023). Lactobacilli, Bifidobacteria, Streptococci, Yeasts, Bacilli, and Enterococci are the most common probiotics. Recent studies have shown that probiotics can reduce the risk or duration of respiratory infection symptoms, although the mechanisms are not yet clear (Ray *et al.*, 2023). Abdelhalim MM *et al*. (Abdelhalim *et al.*, 2022) conducted a study to assess the antibacterial activity in vitro of cell-free supernatants (CFS) derived from ten Lactobacillus strains possessing probiotic attributes against 50 clinically isolated OXA-48-producing multidrug-resistant strains of Klebsiella pneumoniae. It was found that the CFS of L. helveticus and L. rhamnosus exhibited significant antibacterial effects when used alone, but showed antagonistic activity when combined with cefoperazone antibiotic. This indicates that the antimicrobial mechanisms of these two probiotics may interfere with the antimicrobial mechanism of cefoperazone, leading to a weakened effect when used in combination. This finding suggests that although probiotics have certain antimicrobial potential, they cannot simply be used as adjuncts to antibiotics. In clinical applications, it is necessary to carefully evaluate the combination of probiotics and antibiotics and further investigate their interaction mechanisms to determine the optimal therapeutic strategy. Similarly, Do AD *et al*. (Do *et al.*, 2024) found that CFS derived from Lactobacillus brevis and *Lactobacillus plantarum* exhibited potent antibacterial activity against *Klebsiella pneumoniae*, inhibiting bacterial growth and virulence gene expression in a dose-dependent manner, reducing biofilm formation, and synergizing with antibiotics to lower their dosage. Furthermore, compared to antibiotics, CFS induced the development of resistance in *Klebsiella pneumoniae* at a significantly slower rate, and strains adapted to CFS exhibited increased sensitivity to antibiotics. No cross-resistance between CFS was observed, highlighting the enormous potential of probiotic-derived CFS as novel antimicrobials in the fight against multidrug-resistant infections. In addition, Savinova OS *et al*. (Savinova *et al.*, 2021) demonstrated the growth inhibitory effects of two lactic acid bacteria, *Lactobacillus reuteri* LR1 and *Lactobacillus rhamnosus* F, on multidrug-resistant *Klebsiella pneumoniae*, and analyzed the mechanism of this inhibition at the level of the extracellular proteome. The results revealed that the extracellular proteomes of these two lactic acid bacteria contained both classical and non-classical secreted proteins. Specifically, Lactobacillus reuteri LR1 exerted its effects primarily through cell wall-degrading enzymes, while only one of the classical secreted proteins in *Lactobacillus rhamnosus* F was a cell wall hydrolase. These findings provide new insights into the antagonistic interactions between lactic acid bacteria and pathogenic microorganisms, and offer a new perspective on utilizing lactic acid bacteria to control microbial transmission.

Phage

Phage therapy, as an alternative or complement to antibiotics, has shown significant potential in recent years for treating multidrug-resistant bacterial infections, with fewer side effects and without causing microbiota

imbalances that lead to various diseases (Mitropoulou *et al.*, 2022). Phages infect and lyse bacteria by binding to specific receptors on the bacterial cell wall, a mechanism that distinguishes them markedly from antimicrobial drugs. The specificity of phages allows them to target specific bacterial species or strains without indiscriminately killing all bacteria, including normal colonizing bacteria, thus avoiding dysbiosis (Dan *et al.*, 2023). Rathor N *et al*. (Rathor *et al.*, 2023) successfully isolated seven phages targeting multidrug-resistant *Acinetobacter baumannii* from the waters of the Ganges River. These phages have a narrow host range, morphologically belong to the order Caudovirales, and have been experimentally proven to effectively reduce bacterial load on plastic surfaces contaminated with multidrug-resistant *Acinetobacter baumannii*, demonstrating potential as potential therapeutic agents and disinfectants. Unlike antimicrobial drugs, the genetic material of phages constantly mutates over time, making this treatment approach fraught with many unknowns, especially as they will continue to mutate after being injected into the human body. Gan L *et al*. (Gan *et al.*, 2022) identified two phages, namely pKp11 and pKp383, which exhibited a broad host range, high lytic activity, and strong environmental adaptability against multidrug-resistant *Klebsiella pneumoniae* strains of sequence types ST11 and ST383. In a mouse model of pneumonia infection, these phages were found to be effective in treating the early stages of the disease. Furthermore, a combination therapy utilizing these two phages was more potent in reducing bacterial load, inflammation, and pathogenic damage, without inducing notable side effects. These findings highlight phages as a promising adjunct to antibiotics, particularly for strains resistant to all conventional drugs, offering a lifeline for patients with otherwise untreatable infections. But further research is needed before phage therapy can be translated into human therapeutic drugs. Furthermore, Cui X *et al*. (Cui *et al.*, 2023) isolated a novel lytic phage (pK4-26) from hospital sewage, which serves as a promising antibiotic alternative and effectively alleviates multidrug-resistant pneumonia caused by Klebsiella species. The capsule depolymerase carried by this phage can remove biofilms, reduce bacterial virulence, and make bacteria susceptible to serum killing, thereby lowering the mortality rate and alleviating pneumonia symptoms in mice with multidrug-resistant *Klebsiella pneumonia*, without causing significant side effects.

Antibody

Compared to antimicrobial drugs, antibacterial antibodies do not affect the normal colonizing bacteria in the human body, are less likely to cause dysbiosis, and do not promote bacterial resistance. They can also be administered as a one-time injection. Monoclonal antibodies can also be used in conjunction with antimicrobial drugs to reduce the use of antimicrobials and associated adverse reactions. Recently, Nielsen TB *et al*. (Nielsen *et al.*, 2021) developed a novel monoclonal antibody, 65, against pan-drug-resistant Acinetobacter baumannii, which has a broader strain coverage compared to the previously developed antibody C8. Monoclonal antibody 65 demonstrated high efficacy in enhancing macrophage opsonophagocytosis, improving survival rates in a mouse infection model, reducing bacterial density in the blood, and improving cytokine production. Additionally, when combined with colistin, it demonstrates a synergistic effect, offering a novel treatment strategy for infections caused by Acinetobacter baumannii. In addition, in an experimental pneumonia model using C57BL/6J male mice, Cebrero-Cangueiro T *et al*. (Cebrero-Cangueiro *et al.*, 2022) evaluated the efficacy of ceftizoxime and colistin, each combined with polyclonal IgM-enriched immunoglobulin (IgM-IG), against two multidrug-resistant Pseudomonas aeruginosa strains (one susceptible to ceftizoxime and the other resistant to colistin). The results showed that ceftizoxime was more effective against both strains than colistin, while the combination of colistin and IgM-IG significantly reduced lung bacterial concentrations for both strains and the incidence of bacteremia for the resistant strain, suggesting that IgM-IG may serve as an adjunctive therapy to colistin and has potential value in the treatment of pneumonia caused by multidrug-resistant Pseudomonas aeruginosa. Despite significant challenges in identifying suitable targets and enhancing their effectiveness, the development of antibacterial antibodies for the treatment of multidrug-resistant pneumonia is a promising prospect.

Mechanisms of combination therapy for multidrug-resistant pneumonia

Currently, the increasing resistance and complexity of resistance mechanisms in pneumonia-causing pathogens have imposed higher demands on the precision of antimicrobial use. Whether in empirical treatment for critical or refractory infections, or in targeted therapy for multidrug-resistant bacterial infections, combination antimicrobial therapy is one of the commonly adopted treatment strategies. Combination therapy requires strict selection of suitable candidates and careful design of treatment regimens, as well as in-depth research into the mechanisms of combination therapy, exploring from multiple dimensions such as drug interactions, pharmacokinetics, and pharmacodynamics, to ensure that the combination therapy can precisely target the pathogen while minimizing side effects and the further development of resistance.

Synergistic mechanism of action on different targets

Different types of antimicrobial agents often act on different targets within bacterial cells or on the cell wall. β-lactam antibiotics (e.g., penicillins, cephalosporins) inhibit penicillin-binding proteins (PBPs), which are enzymes embedded in the bacterial cytoplasmic membrane. PBPs catalyze cross-linking reactions in peptidoglycan synthesis, essential for cell wall stability. By binding to PBPs, β-lactams disrupt cell wall integrity, leading to

osmotic lysis and bacterial death (Kim *et al.*, 2024). Carbapenems also target PBPs but exhibit broader affinity, including PBP2 in Pseudomonas aeruginosa and PBP1/2 in *Acinetobacter baumannii*, making them effective against multidrug-resistant strains (Russo *et al.*, 2023). When combination therapy is used for multidrug-resistant pneumonia, the two drugs attack the bacteria from different targets. Even if the bacteria develop resistance to one of the drugs, causing its target to change or become ineffective, the other drug acting on a different target can still exert antibacterial activity, thereby enhancing the overall bactericidal effect and achieving a synergistic effect.

Mechanism of inhibiting drug-resistant bacteria

The combined use of antimicrobial agents can effectively delay the emergence of drug-resistant bacteria. This is because when a single antimicrobial agent is used, it exerts significant selective pressure on the bacterial population, prompting bacteria to rapidly develop resistance through mutations, among other mechanisms (Reva *et al.*, 2020). When different antimicrobial agents with distinct mechanisms of action are used in combination, the dosage of each drug can be appropriately reduced, thereby distributing the selective pressure. This requires bacteria to simultaneously develop multiple, different, and adaptive resistant mutations corresponding to each drug's mechanism of action in order to survive. The probability of such multiple resistant mutations occurring simultaneously is extremely low, thus significantly delaying the emergence of drug-resistant bacteria. This helps to maintain the antimicrobial activity of the drugs against pathogenic bacteria and improves the treatment of multidrug-resistant pneumonia (Liu *et al.*, 2022). Additionally, the resistance of some bacteria can be transferred among bacteria of the same or different species through mobile genetic elements such as plasmids. Some drugs in combination therapy regimens may interfere with processes related to bacterial gene transfer, such as inhibiting plasmid replication, conjugation, or transformation (Lipszyc *et al.*, 2022). For example, drug combinations that include polymyxin antibiotics, which can affect bacterial cell membrane permeability or interfere with bacterial metabolism, thereby indirectly affecting gene expression regulation, can limit the horizontal spread of resistance genes within bacterial populations through mobile genetic elements and reduce the opportunities for transmission to progeny bacteria (Mousavi *et al.*, 2021). This offers specific benefits when used in combination therapy for multidrug-resistant Gram-negative bacterial pneumonia.

Pharmacokinetic synergistic mechanism

Different antimicrobial agents exhibit distinct distribution characteristics in the body, which are closely related to factors such as the drug's chemical properties, molecular size, liposolubility, and protein binding rate. β-lactam drugs are mainly distributed in the blood and body fluids, with lower concentrations in the lungs, central nervous system, bone joints, and soft tissues. Therefore, to treat pneumonia, the dosing frequency needs to be increased to elevate the drug concentration in the lungs. In contrast, macrolides tend to accumulate in lung tissue, so when treating pulmonary infections, combining them with β-lactam drugs can exert a synergistic effect (Aldhahri *et al.*, 2022). Additionally, when some drugs are used in combination, they can mutually influence each other's pharmacokinetics, thereby prolonging the time during which the drugs maintain effective antibacterial concentrations in the body. For example, macrolide antibiotics like erythromycin can inhibit the Cytochrome P450 3A4 (CYP3A4) enzyme, thereby slowing the metabolism of other drugs, allowing the drug to maintain sufficient concentrations at the site of pulmonary infection for an extended period to continuously inhibit or kill pathogens (Wen *et al.*, 2024).

DISCUSSION

The combination of drugs leverages a synergistic effect that is pivotal in treating multidrug-resistant pneumonia. Utilizing two or more drugs together can result in an overall effectiveness that surpasses the mere sum of their individual impacts. For multidrug-resistant pneumonia, by combining drugs with different mechanisms of action, the antibacterial spectrum can be significantly broadened to cover more potential pathogenic bacteria. The synergistic effect of these drugs not only enhances antibacterial activity but also more effectively clears pathogens from the body. During combination therapy, different routes of administration or drug combination methods may help improve the absorption efficiency of the drugs in the body. Furthermore, combination therapy demonstrates significant advantages in reducing drug toxicity effects. By rationally selecting drugs and optimizing dosages, the adverse reactions of each drug can be minimized. This is particularly important for elderly patients or those with other underlying diseases, who may have poorer drug tolerance. Combination therapy effectively reduces the occurrence of adverse reactions while ensuring efficacy, thereby enhancing the safety of treatment. More importantly, this multi-inhibitory effect lowers the risk of pathogen resistance to single drugs, prolongs the lifespan of existing antimicrobial agents, and delays the onset of new drug-resistant bacteria. As such, combination therapy is regarded as an efficacious approach to postpone or diminish the development of resistance, providing a longer treatment window and higher treatment success rates for patients with multidrug-resistant pneumonia.

CONCLUSION

In summary, multidrug-resistant pneumonia poses a significant challenge to clinicians and often leads to poor outcomes. When selecting targeted treatment regimens, clinicians should strive to combine antimicrobial agents based on their characteristics, opt for individualized and precise treatment plans, and optimize dosing and

administration methods to maximize bactericidal effects while minimizing drug toxicity and side effects. As bacterial resistance becomes increasingly severe, there is an urgent need for new antimicrobial treatment approaches to enter clinical practice. This article introduces some of the most promising combination antimicrobial therapies, which still require a large number of randomized controlled trials to verify their effectiveness. Non-antimicrobial therapies are also promising, and although they hold great potential, there is still a long way to go before these therapies can be widely used in clinical practice. In the future, efforts should be made to combat this challenge from the following aspects: ① Actively develop new effective drugs, and through experimental research, identify effective combination antimicrobial treatment regimens, as well as determine reasonable dosing and dosing intervals to achieve therapeutic effects while delaying the emergence of resistance. ② Restrict the indiscriminate use of broad-spectrum antimicrobials in clinical practice, which is key to preventing the emergence of multidrug-resistant Acinetobacter. ③ Strengthen prevention measures for hospital-acquired multidrug-resistant pneumonia, such as isolating the source of infection, cutting off transmission routes, and protecting susceptible individuals. ④ For hospitalized patients, actively treat the underlying disease, eliminate contributing factors as early as possible, and enhance the patients' physical condition.

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Authors' contributions
[Qinqin Liang]: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.
[Qinqin Liang, Lingbo Liu]: Participated in collecting, assessing, and interpreting the date. Made significant contributions to date interpretation and manuscript preparation.
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