Pan-Drug-Resistant Acinetobacter baumannii: A Review of Current and Investigational Treatment Options

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Abstract

The rise of pan-drug-resistant Acinetobacter baumannii (PDR-AB) is a growing global health concern, especially in hospital settings. This review provides an overview of current and emerging treatment strategies for managing infections caused by PDR-AB. Several antibiotic combinations such as colistin with rifampicin, fosfomycin with tigecycline or meropenem, and cefepime with Ampicillin/sulbactam, have shown promising results in laboratory and clinical studies. These combinations work by targeting different resistance mechanisms and helping restore the effectiveness of older drugs.

New and experimental approaches, including photodynamic therapy, nanocomposite systems, natural plant-based compounds (e.g., baicalein), and bacteriophage therapy, offer additional treatment options. Furthermore, novel agents like peptide nucleic acids, DHODH inhibitors, and the macrocyclic antibiotic zosurabalpin are under investigation and may play an important role in future therapies. Together, these multi-targeted strategies represent a hopeful path forward for overcoming resistance and improving outcomes for patients with life-threatening PDR-AB infections.

Keywords : Acinetobacter baumannii; Global Health; Anti-Bacterial Agents; pan-drug-resistant.

بكتيريا Acinetobacter baumannii المقاومة الشاملة للأدوية: مراجعة للاستراتيجيات العلاجية الحالية والتجريبية

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الخلاصة:

يُعدّ الانتشار المتزايد لبكتيريا Acinetobacter baumannii المقاومة لجميع فئات المضادات الحيوية (PDR–AB) مصدر قلق صحي عالمي متنامٍ، لا سيما في البيئات الاستشفائية. تهدف هذه المراجعة إلى تقديم نظرة شاملة على الاستراتيجيات العلاجية الحالية والناشئة لمعالجة حالات العدوى الناجمة عن هذه السلالة. وقد أظهرت عدة تراكيب دوائية، مثل الجمع بين colistin و rifampicin ، أو fosfomycin مع tigecycline أو meropenem ، وكذلك cefepime مع Ampicillin/sulbactam، نتائج واعدة في الدراسات المختبرية والسريرية، إذ تعمل هذه التراكيب على استهداف آليات مقاومة مختلفة، مما يُسهم في استعادة فعالية بعض الأدوية القديمة.

كما توفر الأساليب الجديدة والتجريبية، بما في ذلك العلاج الضوئي الديناميكي، وأنظمة النانو المركبة، والمركبات النباتية الطبيعية (مثل baicalein)، والمعالجة بالعاثيات، خيارات علاجية إضافية. إضافة إلى ذلك، يجري حاليًا اختبار عوامل

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جديدة مثل الأحماض النووية الببتيدية، ومثبطات إنزيمDHODH ، والمضاد الحيوي الحلقي zosurabalpin، والتي قد تؤدي دورًا مهمًا في العلاجات المستقبلية. وبمجموعها، تمثل هذه الاستراتيجيات متعددة الأهداف مسارًا واعدًا لتجاوز مقاومة المضادات الحيوية وتحسين نتائج العلاج لدى المرضى المصابين بعدوى PDR–AB المهددة للحياة.

الكلمات المفتاحية: الصحة العالمية، العوامل المضادة للبكتريا, المقاومة الشاملة للأدوية , Acinetobacter baumannii.

Introduction

A. baumannii has become a significant issue in hospital environments, especially in immunocompromised patients in intensive care units (ICUs), burn units, and post-surgical wards, owing to its intrinsic resistance to several antimicrobial drugs and its exceptional capacity to develop resistance via diverse routes [1,2]. The WHO report defines A. baumannii as a priority bacterium for research and development of new therapies. The pathogen is classified among a primary ESKAPE organism, which includes Enterococcus faecium, Staphylococcus aureus, and Klebsiella pneumoniae. baumannii, Pseudomonas aeruginosa, and Enterobacter spp. capable of exhibiting resistance to antimicrobial agents with detrimental effects[3]. A. baumannii demonstrates a notable capacity for resistance development via various and frequently simultaneous mechanisms, such as β-lactamase production, modification of target sites, activation of efflux pumps, biofilm formation, and reduced membrane permeability [4]

Recently, PDR-AB strains characterized by resistance to all existing classes of antimicrobial agents have been increasingly reported, resulting in treatment stalemates and heightened mortality rates, which range from 40% to 60% in bloodstream and ventilator-associated infections[5,6].

This review presents a critical synthesis of current therapeutic options for PDR-AB, encompassing conventional, combination, and last-resort antibiotics, and examines emerging investigational strategies in development. This paper identifies knowledge gaps and ongoing clinical challenges to inform future research priorities and support evidence-based management strategies against a significant threat in contemporary infectious disease medicine.

Mechanisms of Pan-Drug Resistance in A. baumannii

A. baumannii has emerged as a critical nosocomial pathogen due to its remarkable ability to develop resistance against nearly all available classes of antibiotics. The mechanisms underlying PDR in A. baumannii are multifactorial and include enzymatic degradation, target site modifications, active efflux systems, biofilm formation, and horizontal gene transfer (figure 1).

- **Enzymatic Inactivation of Antibiotics**

A. baumannii synthesizes several enzymes that break down or alter antibiotics, so leaving them useless. Beta-lactamases form the main enzymes that confer antibiotic resistance in A. baumannii. These enzymes hydrolyze the beta-lactam ring of beta-lactam antibiotics, hence leaving them useless. Multiple types of beta-lactamases exist, including extended-spectrum beta-lactamases, carbapenem-hydrolyzing class D beta-lactamases, and Metallo-beta-lactamases [7]. Particularly significant for resistance to β-lactam antibiotics, notably carbapenems, which are often regarded as last-resort therapies for MDR Gram-negative infections. OXA-type carbapenemases, classified as molecular class D β-lactamases, are the most abundant among β-lactamases in A. baumannii. The enzymes include OXA-23, OXA-24/40, OXA-58, and the intrinsically encoded OXA-51-like variations. The production of these enzymes, especially when augmented by upstream insertion sequences (e.g., ISAba1), eases significant resistance to carbapenems and other β-lactams [8]. Besides OXA-type enzymes, A. baumannii may synthesize metallo-β-lactamases including IMP, VIM, and NDM, which use

zinc ions to catalyze the hydrolysis of various β-lactams, encompassing carbapenems and cephalosporins. These enzymes are encoded by mobile genetic elements such as integrons and plasmids, which facilitate horizontal gene transfer and rapid dissemination among nosocomial isolates [4].

In addition to producing β-lactamase, A. baumannii has been reported to generate aminoglycoside-modifying enzymes (AMEs). The most prevalent AMEs in A. baumannii include acetyltransferases such as AAC(6')-Ib and AAC(3)-Ia, while phosphotransferases like APH(3')-VIa are also widely distributed among A. baumannii isolates. Nucleotidyltransferases, specifically ANT(2")-Ia, are less common but have been named in certain clinical isolates. These enzymes deactivate aminoglycosides by chemical changes that obstruct drug binding to the bacterial ribosome. These enzymes often occur with β-lactamases in MDR and PDR bacteria, reducing treatment options [9–11].

A. baumannii also produces 16S rRNA methylases, including ArmA, in addition to AMEs. The enzymes methylate the 16S rRNA, changing the aminoglycoside binding site and resulting in high-level resistance to various aminoglycosides, such as amikacin and gentamicin [10,12].

- **Efflux pumps**

Efflux pumps in A. baumannii play a significant role in conferring MDR by actively expelling a broad range of antibiotics out of the cell, thereby reducing intracellular drug concentrations to sub-lethal levels. These pumps are specifically associated with resistance to β-lactams, carbapenems, fluoroquinolones, and aminoglycosides. Mechanistically, efflux systems in A. baumannii include five major families: Resistance-Nodulation-Division (RND), Major Facilitator Superfamily (MFS), Small Multidrug Resistance (SMR), ATP-binding cassette (ABC), and Multidrug and Toxic Compound Extrusion (MATE) transporters, each capable of handling diverse substrates [13]. The most critical efflux systems are part of the RND family, specifically AdeABC, AdeIJK, and AdeFGH, which exhibit high efficacy in exporting various antibiotics, including aminoglycosides, β-lactams, and fluoroquinolones, and are closely linked to MDR phenotypes [14]. The Major Facilitator Superfamily is significant in mediating resistance to drugs such as chloramphenicol and tetracycline [13]. The Multidrug and Toxic Compound Extrusion family eases the efflux of fluoroquinolones and cationic dyes, but with restricted substrate specificity. The Small Multidrug Resistance and ATP-Binding Cassette families are less significant, since they manage narrow-spectrum substrates and contribute less to clinical resistance, although they may function synergistically with other mechanisms [15]. Some pumps, such as MefA and MefE, are encoded within transposons, while others, including OqxAB, qax, qepA, and tet, may exist on plasmids or integrons, facilitating horizontal gene transfer and enhancing the dissemination of resistance traits [16].

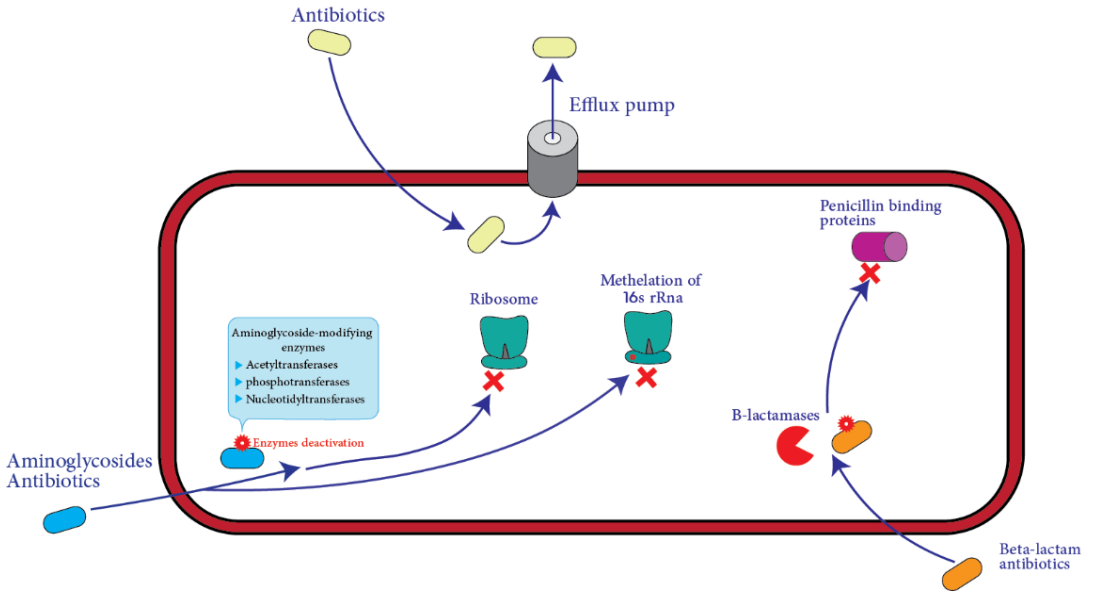

Figure (1). Schematic illustration of the main resistance mechanisms in *A. baumannii*, including enzymatic inactivation, efflux pumps, target modification, and aminoglycoside-modifying enzymes.

- **Biofilm**

The extracellular matrix of biofilms functions as a barrier, diminishing the infiltration of antibiotics. This restricted access leads to elevated minimum inhibitory concentrations (MICs) for antibiotics, making conventional treatment protocols less effective against biofilm-associated illnesses [17]. Moreover, biofilms show increased resistance to antimicrobial drugs owing to the presence of persisted cells and the activation of efflux pumps. The tolerance is further enhanced by the activation of resistance genes in the biofilm environment, resulting in the emergence of PDR [18]. Biofilm creation relates to device-related infections, including ventilator-associated pneumonia and catheter-related bloodstream infections, which are notoriously difficult to manage [19].

Current Treatment Options

➢ **Combination Therapy**

Fosfomycin-Based Combinations

Fosfomycin is a bactericidal antibiotic that exerts its activity by inhibiting MurA (UDP-N-acetylglucosamine enolpyruvyl transferase), an essential enzyme involved in the initial step of peptidoglycan biosynthesis in bacterial cell wall formation. In recent years, it has garnered renewed attention as a therapeutic choice against MDR bacterial pathogens due to its unique mechanism of action and retained activity against various resistant strains [20]. Recent research has demonstrated the potential of fosfomycin when used in combination with other drugs for treating PDR strains of *A. baumannii*. The combination of fosfomycin–meropenem showed strong synergy and lowered fosfomycin MICs from 128 to 32 mg/L and meropenem MICs from 16 to 4 mg/L. Fosfomycin–tigecycline and fosfomycin–colistin displayed partial synergy. However, indifferent interaction was noted with the combination of fosfomycin–amikacin with no notable decrease in MICs [21]. While in earlier studies by Leite *et al.* (2016) showed that fosfomycin-amikacin has the most notable synergistic impact against colistin-susceptible isolates [22].

Fosfomycin-containing regimens have shown encouraging clinical results in critically ill patients with bacteremia caused by PDR-AB. In a case series study, Assimakopoulos *et al.* (2023) reported a significantly higher 28-day survival rate among patients who received fosfomycin-based combinations compared to those who did not. This benefit was seen despite high rates of colistin resistance and underscores

the potential value of fosfomycin as part of synergistic regimens in severe PDR-AB infections [23].

Polymyxin-Based Combinations

Polymyxins, including colistin and polymyxin B, have regained clinical importance due to their bactericidal action against MDR and PDR Gram-negative pathogens. Their mechanism of action involves disruption of the bacterial outer membrane via interaction with lipopolysaccharides [24]. Notably, polymyxins can potentiate the activity of other antimicrobials by increasing membrane permeability, thereby easing the intracellular accumulation of agents that are otherwise ineffective against Gram-negative bacteria, such as glycopeptides and lipopeptides. Galani *et al*. (2024) reported strong in vitro synergy between colistin and apramycin against PDR-AB, with bactericidal activity achieved in 100% of isolates at 2× MIC, despite intrinsic colistin resistance [25]. Similarly, colistin–meropenem combinations reduced meropenem MICs from 32 to 8 mg/L, although colistin MICs remained elevated [21]. In colistin-resistant strains, combinations such as colistin–rifampicin and colistin–vancomycin demonstrated improved efficacy, with rifampicin yielding more potent bactericidal effects [22]. These findings collectively support the clinical evaluation of polymyxin-based regimens, particularly in synergistic frameworks, to overcome resistance in *A. baumannii*.

Tigecycline-Based Combinations

Tigecycline is a glycylcycline-class antibiotic structurally derived from tetracyclines. It functions as a bacteriostatic agent by binding to the 30S ribosomal subunit of bacterial ribosomes, thereby blocking the entry of aminoacyl-tRNA into the A site and ultimately inhibiting protein elongation and synthesis in pathogens such as *A. baumannii* [26].

In an in vitro study by Quraini *et al*. (2023) [21], the combination of fosfomycin and tigecycline was evaluated against eight whole-genome-sequenced *A. baumannii* strains, including one PDR isolate. The checkerboard assay revealed partial synergy in all isolates, with MICs of tigecycline reduced to ≤0.25 mg/L in three cases. Time-kill assays confirmed synergistic action at 24 hours in the PDR strain, although bactericidal activity was not achieved. Complementing these findings, a retrospective clinical case series by Assimakopoulos *et al*. (2019) [27] evaluated a triple combination therapy intravenous colistin, high-dose tigecycline, and high-dose ampicillin/sulbactam—in ten ICU patients suffering from ventilator-associated pneumonia caused by PDR-AB. Despite high tigecycline MICs (>2 μg/mL), 90% of patients exhibited clinical success, and 70% achieved microbiological eradication, with limited nephrotoxicity.

Furthermore, Mohammed *et al*. (2021) [28] investigated tigecycline synergy in 30 *A. baumannii* isolates resistant to carbapenems. Synergy was detected in only 10% of isolates when tigecycline was combined with colistin, and no antagonistic effect was seen. Notably, combinations of tigecycline with meropenem or levofloxacin did not exhibit synergistic activity and even showed antagonism in 66.7% of tigecycline–meropenem pairs. These results emphasize that tigecycline–colistin showed limited result comparing with previous combinations Tigecycline, fosfomycin or Tigecycline, colistin, ampicillin/sulbactam.

Minocycline-Based Combinations

Minocycline, a semi-synthetic tetracycline antibiotic, has re-emerged as a potential therapeutic agent against PDR-AB, especially when used in combination with other antimicrobials. In a systematic review by Fragkou *et al*. (2019), minocycline-containing regimens demonstrated a 72.6% clinical success rate and 60.2% microbiological success in patients with MDR, XDR, and PDR *A. baumannii* infections. Notably, the majority of regimens included combinations with colistin, cefoperazone-sulbactam, or carbapenems. These findings support the inclusion of minocycline as part of combination therapy protocols, particularly in lower respiratory tract infections and ventilator-associated pneumonia, where monotherapy options are limited due to widespread resistance [29].

Cefepime-Based Combinations

Recent investigations have identified cefepime as a potentially valuable agent in combination therapy against XDR and PDR *A. baumannii*. In a study by Halim *et al*. (2024), two cefepime-based regimens were evaluated across 21 clinical isolates, including six PDR strains. The combination of cefepime with ampicillin–sulbactam demonstrated synergistic effects in 76.2% of all isolates and 83.3% of PDR strains, while cefepime with amikacin achieved synergy in 42.9% and additive effects in 38.1% of strains. These findings suggest that cefepime, when paired with either a β-lactamase inhibitor or an aminoglycoside, may restore antimicrobial efficacy through complementary mechanisms, offering a practical and accessible treatment option for infections caused by highly resistant *A. baumannii* strains (Halim *et al*., 2024) [30].

Sulbactam-Durlobactam Combination

Sulbactam–durlobactam (SUL-DUR) is a novel β-lactam/β-lactamase inhibitor combination that has demonstrated strong activity against MDR, XDR, and carbapenem-resistant *A. baumannii* (CRAB). However, its efficacy against PDR isolates remains limited. While durlobactam effectively inhibits class A, C, and D β-lactamases thereby restoring sulbactam's activity PDR strains that harbor metallo-β-lactamases (e.g., NDM) or non-enzymatic resistance mechanisms such as efflux pumps and porin mutations may not respond to treatment. Clinical and surveillance data suggest that although SUL-DUR offers a promising therapeutic option, especially in colistin-resistant cases, its success against PDR strains requires strain-specific susceptibility confirmation prior to clinical use [31].

Table 1: Antibiotic combination therapies used against PDR A. baumannii.

Combination	Synergy Rate (%)	MIC Reduction (Fold)	Bactericidal Effect	Reference
Colistin + Rifampicin	85	≥4-fold	Yes	Galani *et al*., 2024
Tigecycline + Fosfomycin	100	2–4 fold	Partial (no killing)	Quraini *et al*., 2023
Fosfomycin + Meropenem	100	4 fold	Yes	Quraini *et al*., 2023
Cefepime + Ampicillin/Sulbactam	83.3	2–8 fold	Yes	Halim *et al*., 2024
Minocycline + Colistin	72.6	Not specified	Yes	Fragkou *et al*., 2019
Meropenem + Baicalein	100	Significant	Yes	Güran *et al*., 2023

- **Repurposed Antibiotics**

Cefiderocol, a novel siderophore cephalosporin, has shown promise in the treatment of complicated infections caused by XDR and PDR *A. baumannii*. In a compassionate-use case series, Oliva *et al*. (2020) reported successful clinical and microbiological outcomes in three patients with severe infections, including bacteremia and spondylodiscitis due to PDR-AB. The favorable outcomes, even in colistin and tigecycline-resistant strains, and the absence of adverse events, underscore cefiderocol's potential as a salvage therapy for difficult-to-treat PDR infections [32].

Investigational and Novel Therapies

- **Experimental Molecules Cerastecins Targeting MsbA Transport**

Cerastecins are newly identified natural compounds that inhibit the lipooligosaccharide (LOS) flippase MsbA, a protein critical for outer membrane biogenesis in *A. baumannii*. These molecules exhibit potent bactericidal activity against carbapenem-resistant and MDR clinical isolates. Structural analyses confirmed that cerastecins uncouple ATP hydrolysis from LOS transport, thereby stalling MsbA function and disrupting membrane integrity. An optimized analog demonstrated therapeutic efficacy in murine

models of pulmonary and bloodstream infections. Though clinical translation is pending, cerastecins represent a novel antibacterial class that circumvents traditional resistance mechanisms through noncanonical target engagement [33]

Antisense Peptide Nucleic Acids (PNAs)

Peptide nucleic acids (PNAs) represent a cutting-edge genetic interference approach against *A. baumannii*. These synthetic molecules, when conjugated with cell-penetrating peptides, can silence essential bacterial genes such as acpP, ftsZ, and rne, inducing rapid bacterial killing. Nejad *et al.* (2021) [34] showed that PNAs achieve significant bactericidal activity at concentrations as low as 2–4 μM with high specificity, sparing host cells and commensal microbiota. This programmable strategy provides a promising platform for precision antimicrobials, particularly for targeting carbapenem-resistant and PDR strains

Dihydroorotate Dehydrogenase Inhibitors

Dihydroorotate dehydrogenase (DHODH), an enzyme essential for pyrimidine biosynthesis, has emerged as a validated drug target in *A. baumannii*. Russo *et al.* (2022) [35] screened antimalarial compound libraries and identified DSM186, a potent inhibitor of *A. baumannii* DHODH (AbDHODH), with submicromolar MICs against carbapenem-resistant and XDR isolates. The compound exhibited bactericidal activity, high species selectivity (no human DHODH inhibition), and strong *in vivo* efficacy in a murine thigh infection model. Crystallographic studies confirmed AbDHODH-specific binding, supporting its development as a pathogen-targeted antibiotic.

- **Alternative Approaches**

Photodynamic-Antibiotic Adjunctive Therapy

Recent studies have demonstrated that integrating photodynamic therapy (PDT) with conventional antibiotics, particularly colistin, can effectively counteract PDR-AB. In isolates harvested from burn patients, sub-lethal PDT using toluidine blue O (TBO) activated by LED light yielded an 83.7% bacterial kill rate alone, but when combined with colistin, achieved complete eradication (9-log reduction) and an >11-fold reduction in colistin MICs[36]. Mechanistically, this combination downregulated the pmrA/pmrB two-component regulatory system key determinants of colistin resistance suggesting that PDT directly modulates resistance pathways[37]. Additionally, the generation of reactive oxygen species (ROS) and membrane permeabilization associated with PDT likely enhances colistin uptake, reinforcing its bactericidal action and preventing regrowth [38]. By merging physical membrane disruption and gene-level sensitization with pharmacological antibiotic action, this approach addresses both structural and genetic resistance mechanisms, highlighting a promising, multidimensional strategy against intractable *A. baumannii* infections.

Phage-Based Therapies

Phage therapy has also emerged as a promising alternative approach for targeting MDR and potentially PDR-AB. This strategy includes monophage applications, phage cocktails, and phage–antibiotic combination therapies, all of which have shown efficacy in both in vitro and in vivo models. Several bacteriophages, such as vB_AbaP_AGC01 and ϕKM18P, demonstrated the ability to reduce bacterial load and biofilm formation, enhance survival in animal models, and synergize with antibiotics like ciprofloxacin and meropenem [39,40]. Additionally, phage-derived enzymes, including endolysins and depolymerases, have been shown to degrade bacterial cell walls and biofilm matrices, further potentiating antibacterial action. Though clinical application remains limited, phage therapy offers a highly specific, adaptable, and potentially resistance-breaking solution in the fight against *A. baumannii* [40]

Jelleine-I Therapies

Jelleine-I, a short cationic peptide originally isolated from royal jelly, has emerged as a promising antimicrobial agent against *A. baumannii* strains exhibiting MDR, XDR, and PDR phenotypes. The peptide demonstrated potent in vitro activity, with

MIC values ranging from 8 to 32 µM and bactericidal effects even against polymyxin-resistant isolates. Time-kill assays confirmed rapid bacterial clearance within hours, comparable to polymyxin B. Mechanistic investigations revealed strong peptide membrane interactions, leading to membrane disruption and cell lysis. Notably, Jelleine-I exhibited minimal hemolytic and cytotoxic effects on mammalian cells, underscoring its therapeutic potential. These findings highlight Jelleine-I as a valuable candidate in the development of novel antimicrobial strategies to combat life-threatening PDR-AB infections [41].

Synergistic Nanocomposite Strategies

Synergistic nanocomposite approaches have demonstrated potent antibacterial activity against PDR-AB. Chen *et al*. (2021) [42] reported that a nanocomposite of casein-stabilized silver nanoparticles (AgNPs) combined with tigecycline achieved a significant reduction in MIC and MBC values compared to either agent alone. The combination showed a synergistic effect (CI = 0.59) and complete bacterial clearance in a murine wound infection model, outperforming tigecycline monotherapy. Mechanistically, the AgNPs disrupted the bacterial membrane structure and increased its permeability, allowing enhanced intracellular accumulation of tigecycline. Additionally, the nanoparticles generated ROS, which contributed to oxidative damage of cellular components, leading to rapid cell death and preventing regrowth.[42,43]

In a related study, Britz *et al*. (2025) [44] demonstrated that AgNPs combined with conventional antibiotics induced dose-dependent membrane leakage, depolarization, and morphological disintegration in *A. baumannii*. These effects were linked to increased ROS production and DNA damage, effectively compromising bacterial survival pathways even in resistant strains. Enhanced efficacy was evident across multiple clinical isolates, including those resistant to colistin and carbapenems.[44]

Moreover, a silver–colistin–imipenem hybrid nanocomposite described by Khaled *et al*. (2021) [45] reduced the MICs of imipenem and colistin by 4- to 8-fold in resistant isolates. The mechanism involved synergistic membrane destabilization, electrostatic interactions enhancing antibiotic uptake, and oxidative stress–mediated cell lysis. These multimodal effects enabled the formulation to bypass resistance pathways such as efflux pumps and target-site modifications.[45]

Collectively, these synergistic nanocomposite systems act through combined physical membrane damage, ROS-mediated stress, and improved antibiotic penetration, enabling them to bypass classical resistance mechanisms and restore efficacy against PDR-AB.

Natural plant-based compounds

Baicalein, a plant-derived flavonoid compound, demonstrated by Güran *et al*. (2023) [46] exhibits synergistic antibacterial and anti-biofilm activity when combined with meropenem against both XDR and PDR *A. baumannii* clinical isolates. In their study, the checkerboard assay and time-kill analysis revealed either synergistic or additive effects in all 15 tested strains. The combination significantly reduced the MIC of meropenem and inhibited biofilm formation more effectively than either agent alone.

Mechanistically, molecular docking analysis showed that baicalein can interact with OXA-type β-lactamases and penicillin-binding proteins. This suggests that baicalein may inhibit enzymatic degradation of meropenem and disrupt bacterial cell wall synthesis, thereby restoring the antibiotic's activity and facilitating better penetration into bacterial cells. These findings emphasize the therapeutic potential of natural compound–antibiotic combinations in re-sensitizing highly resistant *A. baumannii* strains, especially in infections where conventional treatment options are exhausted [46].

- **Emerging Therapeutics**

Zosurabalpin (RG6006), a first-in-class macrocyclic antibiotic developed by Roche, is currently undergoing Phase III clinical trials for the treatment of carbapenem-resistant and PDR-AB. It targets the $LptB_2FGC$ transporter, inhibiting

lipopolysaccharide translocation and outer membrane biogenesis. Preclinical and early-phase clinical data indicate potent in vitro activity, bactericidal efficacy in murine models, and a favorable safety profile. Although not yet approved, zosurabalpin stands for one of the most promising late-stage candidates for addressing infections caused by XDR *A. baumannii* [47].

Conclusion

PDR-AB has become a serious global health problem due to it is resistant to all available antibiotics. This review shows that using combinations of different antibiotics can help fight these infections more effectively. Studies have found that combinations such as fosfomycin with meropenem or tigecycline, and colistin with apramycin or rifampicin, can reduce resistance and improve treatment outcomes. In addition to these drug combinations, new methods such as nanoparticles, light-based treatments (photodynamic therapy), and natural plant compounds such as baicalein also show promise in killing resistant bacteria. Other new approaches, such as gene-targeting molecules (peptide nucleic acids), special enzyme blockers (DHODH inhibitors), and new types of antibiotics like zosurabalpin, are being tested and could become part of future treatments.

Overall, combining traditional antibiotics with new or supportive agents may offer better results against PDR-AB. More research, clinical testing, and careful antibiotic use are needed to ensure these options work safely and effectively in patients.

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Ethical Considerations

This review did not involve any studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not needed.

Authors' Contributions

Murtadha Nabeel Abdulgani: Primary author and responsible for writing the manuscript. Ziad Tarik Noman: Collected and organized data on current treatments for PDR-AB. Bareq Nihad Al-Nuaimi and Ammar Basim Abdul-kareem: Contributed by collecting and reviewing data related to novel and experimental treatment strategies.

Conflict of Interests

The authors declare no conflict of interest.

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References

[1] Pal N, Sujatha R. Evaluation of Acute Physiology and Chronic Health Evaluation Score II in Acinetobacter baumannii Infection/Colonization and its Antimicrobial Resistance Profile in Kanpur, India. Int J Curr Microbiol Appl Sci 2017;6:1056–61. https://doi.org/10.20546/ijcmas.2017.607.127.

[2] Abdulhussein NM, Mahdi MS. Isolation and identification of multi-drug resistance Acinetobacter baumannii isolated from clinical samples at Baghdad, Iraq. Journal of Applied and Natural Science 2023;15:663–71. https://doi.org/10.31018/jans.v15i2.4499.

[3] Scoffone VC, Trespidi G, Barbieri G, Arshad A, Israyilova A, Buroni S. The Evolution of Antimicrobial Resistance in Acinetobacter baumannii and New Strategies to Fight It. Antibiotics 2025;14. https://doi.org/10.3390/antibiotics14010085.

[4] Khalid HM. Molecular study of blaVIM and blaIMP genes in Acinetobacter baumannii strains isolated from burn patients in Duhok City, Iraq. J Infect Dev Ctries 2024;18:101–5. https://doi.org/10.3855/jidc.18570.

[5] Zampaloni C, Mattei P, Bleicher K, Winther L, Thäte C, Bucher C, et al. A novel antibiotic class targeting the lipopolysaccharide transporter. Nature 2024;625:566–71. https://doi.org/10.1038/s41586-023-06873-0.

[6] Poulikakos P, Tansarli GS, Falagas ME. Combination antibiotic

treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant Acinetobacter infections: a systematic review. European Journal of Clinical Microbiology and Infectious Diseases 2014;33:1675–85. https://doi.org/10.1007/s10096-014-2124-9.

[7] Eissa ME. Resistance mechanisms and treatment burdens for A. baumannii infections: Current challenges and future opportunities. JOURNAL OF BASIC AND CLINICAL MICROBIOLOGY 2024;1. https://doi.org/10.5455/JBCM.20240115081736.

[8] Alzaidi JR. Prevalence of OXA Genes Responsible for Carbapenem-Resistance among Acinetobacter baumannii Isolated from Clinical Samples in Iraq. Medical Journal of Babylon 2023;20:632–7. https://doi.org/10.4103/MJBL.MJBL_828_23.

[9] Rastegar Lari A. CHARACTERIZATION OF AMINOGLYCOSIDE RESISTANCE MECHANISMS IN ACINETOBACTER BAUMANNII ISOLATES FROM BURN WOUND COLONIZATION. Ann Burns Fire Disasters 2019:115–21.

[10] Khurshid M, Rasool MH, Ashfaq UA, Aslam B, Waseem M, Ali MA, et al. Acinetobacter baumannii sequence types harboring genes encoding aminoglycoside modifying enzymes and 16srRNA methylase; a multicenter study from Pakistan. Infect Drug Resist 2020;13:2855–62. https://doi.org/10.2147/IDR.S260643.

[11] Atasoy AR, Ciftci IH, Petek M. Modifying enzymes related aminoglycoside: analyses of resistant Acinetobacter isolates. Int J Clin Exp Med 2015;8:2874.

[12] Jouybari MA, Ahanjan M, Mirzaei B, Goli HR. Role of aminoglycoside-modifying enzymes and 16s rRNA methylase (ArmA) in resistance of Acinetobacter baumannii clinical isolates against aminoglycosides. Rev Soc Bras Med Trop 2021;54:1–10. https://doi.org/10.1590/0037-8682-0599-2020.

[13] Sharma S, Kaushik V, Kulshrestha M, Tiwari V. Different efflux pump systems in Acinetobacter baumannii and their role in multidrug resistance. Advances in Microbiology, Infectious Diseases and Public Health: Volume 17 2023:155–68.

[14] Zack KM, Sorenson T, Joshi SG. Types and mechanisms of Efflux Pump Systems and the potential of Efflux Pump Inhibitors in the restoration of Antimicrobial susceptibility, with a special reference to Acinetobacter baumannii. Pathogens 2024;13:197.

[15] Rahi AA, Al-Hasnawy HH. Expression of Genes Associated with Efflux Pump and Porins in Acinetobacter baumannii Isolates Recovered from Different Clinical Specimens. Biomedical and Biotechnology Research Journal (BBRJ) 2024;8:464–73.

[16] K Bhardwaj A, Mohanty P. Bacterial efflux pumps involved in multidrug resistance and their inhibitors: rejuvinating the antimicrobial chemotherapy. Recent Pat Antiinfect Drug Discov 2012;7:73–89.

[17] Gedefie A, Demsis W, Ashagrie M, Kassa Y, Tesfaye M, Tilahun M, et al. Acinetobacter baumannii biofilm formation and its role in disease pathogenesis: a review. Infect Drug Resist 2021:3711–9.

[18] Roy S, Chowdhury G, Mukhopadhyay AK, Dutta S, Basu S. Convergence of biofilm formation and antibiotic resistance in Acinetobacter baumannii infection. Front Med (Lausanne) 2022;9:793615.

[19] Chukamnerd A, Saipetch N, Singkhamanan K, Ingviya N, Assanangkornchai N, Surachat K, et

al. Association of biofilm formation, antimicrobial resistance, clinical characteristics, and clinical outcomes among Acinetobacter baumannii isolates from patients with ventilator-associated pneumonia. Clin Respir J 2024;18:e13732.

[20] Falagas ME, Vouloumanou EK, Samonis G, Vardakasa KZ. Fosfomycin. Clin Microbiol Rev 2016;29:321–47. https://doi.org/10.1128/CMR.00068-15.

[21] Quraini MAL, Jabri ZAL, Sami H, Mahindroo J, Taneja N, Muharrmi ZAL, et al. Exploring Synergistic Combinations in Extended and Pan-Drug Resistant (XDR and PDR) Whole Genome Sequenced Acinetobacter baumannii. Microorganisms 2023;11. https://doi.org/10.3390/microorganisms11061409.

[22] Leite GC, Oliveira MS, Perdigão-Neto LV, Rocha CKD, Guimarães T, Rizek C, et al. Antimicrobial combinations against pan- resistant Acinetobacter baumannii isolates with different resistance mechanisms. PLoS One 2016;11. https://doi.org/10.1371/journal.pone.0151270.

[23] Assimakopoulos SF, Karamouzos V, Eleftheriotis G, Lagadinou M, Bartzavali C, Kolonitsiou F, et al. Efficacy of Fosfomycin-Containing Regimens for Treatment of Bacteremia Due to Pan-Drug Resistant Acinetobacter baumannii in Critically Ill Patients: A Case Series Study. Pathogens 2023;12. https://doi.org/10.3390/pathogens12020286.

[24] Manioglu S, Modaresi SM, Ritzmann N, Thoma J, Overall SA, Harms A, et al. Antibiotic polymyxin arranges lipopolysaccharide into crystalline structures to solidify the bacterial membrane. Nat Commun 2022;13. https://doi.org/10.1038/s41467-022-33838-0.

[25] Galani I, Souli M, Katsala D, Karaiskos I, Giamarellou H, Antoniadou A. In vitro activity of apramycin (EBL-1003) in combination with colistin, meropenem, minocycline or sulbactam against XDR/PDR Acinetobacter baumannii isolates from Greece. Journal of Antimicrobial Chemotherapy 2024;79:1101–8. https://doi.org/10.1093/jac/dkae077.

[26] Peterson LR. A review of tigecycline - the first glycylcycline. Int J Antimicrob Agents 2008;32. https://doi.org/10.1016/S0924-8579(09)70005-6.

[27] Assimakopoulos SF, Karamouzos V, Lefkaditi A, Sklavou C, Kolonitsiou F, Christofidou M, et al. Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant Acinetobacter baumannii: a case series study. Infez Med 2019;27:11–6.

[28] Mohammed HA, Monem SMA, Hassan AM, Abdallah AL. In vitro comparison of colistin-versus tigecycline-based combinations against carbapenem resistant Acinetobacter baumannii intensive care unit clinical isolates. Microbes and Infectious Diseases 2021;2:333–42. https://doi.org/10.21608/MID.2021.62397.1120.

[29] Fragkou PC, Poulakou G, Blizou A, Blizou M, Rapti V, Karageorgopoulos DE, et al. The role of minocycline in the treatment of nosocomial infections caused by multidrug, extensively drug and pandrug resistant acinetobacter baumannii: A systematic review of clinical evidence. Microorganisms 2019;7. https://doi.org/10.3390/microorganisms7060159.

[30] Halim J, Carr RA, Fliorent R, Jonnalagadda K, Kurbonnazarova

M, Kaur M, et al. Combinations of Antibiotics Effective against Extensively- and Pandrug-Resistant Acinetobacter baumannii Patient Isolates. Microorganisms 2024;12. https://doi.org/10.3390/microorganisms12071353.

[31] McLeod SM, O'Donnell JP, Narayanan N, Mills JP, Kaye KS. Sulbactam–durlobactam: a β-lactam/β-lactamase inhibitor combination targeting Acinetobacter baumannii. Future Microbiol 2024;19:563–76. https://doi.org/10.2217/fmb-2023-0248.

[32] Oliva A, Ceccarelli G, De Angelis M, Sacco F, Miele MC, Mastroianni CM, et al. Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively and pan-resistant Acinetobacter baumannii. J Glob Antimicrob Resist 2020;23:292–6. https://doi.org/10.1016/j.jgar.2020.09.019.

[33] Wang H, Ishchenko A, Skudlarek J, Shen P, Dzhekieva L, Painter RE, et al. Cerastecins inhibit membrane lipooligosaccharide transport in drug-resistant Acinetobacter baumannii. Nat Microbiol 2024;9:1244–55. https://doi.org/10.1038/s41564-024-01667-0.

[34] Nejad AJ, Shahrokhi N, Nielsen PE. Targeting of the essential acpp, ftsz, and rne genes in carbapenem-resistant Acinetobacter baumannii by antisense pna precision antibacterials. Biomedicines 2021;9. https://doi.org/10.3390/biomedicines9040429.

[35] Russo TA, Umland TC, Deng X, Mazouni F El, Kokkonda S, Olson R, et al. Repurposed dihydroorotate dehydrogenase inhibitors with efficacy against drug-resistant Acinetobacter baumannii. Proc Natl Acad Sci U S A 2022;119. https://doi.org/10.1073/pnas.2213116119.

[36] Pourhajibagher M, Kazemian H, Chiniforush N, Bahador A. Evaluation of photodynamic therapy effect along with colistin on pandrug-resistant Acinetobacter baumannii. Laser Ther 2017;26:97–103. https://doi.org/10.5978/islsm.17-OR-7.

[37] Boluki E, Kazemian H, Peeridogaheh H, Alikhani MY, Shahabi S, Beytollahi L, et al. Antimicrobial activity of photodynamic therapy in combination with colistin against a pan-drug resistant Acinetobacter baumannii isolated from burn patient. Photodiagnosis Photodyn Ther 2017;18:1–5. https://doi.org/10.1016/j.pdpdt.2017.01.003.

[38] Wozniak A, Rapacka-Zdonczyk A, Mutters NT, Grinholc M. Antimicrobials are a photodynamic inactivation adjuvant for the eradication of extensively drug-resistant Acinetobacter baumannii. Front Microbiol 2019;10. https://doi.org/10.3389/fmicb.2019.00229.

[39] Grygorcewicz B, Roszak M, Golec P, Śleboda-taront D, Łubowska N, Górska M, et al. Antibiotics act with vb_abap_agc01 phage against Acinetobacter baumannii in human heat-inactivated plasma blood and galleria mellonella models. Int J Mol Sci 2020;21:1–14. https://doi.org/10.3390/ijms21124390.

[40] Zhang Y, Lin Y, Galgano S, Houdijk J, Xie W, Jin Y, et al. Recent Progress in Phage Therapy to Modulate Multidrug-Resistant Acinetobacter baumannii, including in Human and Poultry. Antibiotics 2022;11. https://doi.org/10.3390/antibiotics11101406.

[41] Pieve de Castro A, Brito JCM, Candido WAB, Félix AS, Verly RM, Resende JM, et al. Jelleine-I Membrane Interaction-related

Biological Properties and Antimicrobial Activity against MDR, XDR, and PDR-Acinetobacter baumannii Clinical Isolates. ACS Omega 2025;10:10938–48. https://doi.org/10.1021/acsomega.4c09073.

[42] Chen Y-H, Wang W-H, Lin S-H, Yang-Wang Y-T, Tseng S-P, Chien C-S, et al. Synergistic Antibacterial Effect of Casein-AgNPs Combined with Tigecycline against Acinetobacter baumannii 2021. https://doi.org/10.3390/polym.

[43] Chernousova S, Epple M. Silver as Antibacterial Agent: Ion, Nanoparticle, and Metal. Angewandte Chemie International Edition 2013;52:1636–53. https://doi.org/10.1002/anie.201205923.

[44] Britz LS, Elbagory AM, David OM, Meyer M, Africa CWJ. Investigating the Synergistic Effect of Silver Nanoparticles With Third-Generation Cephalosporins Against Acinetobacter baumannii. J Nanotechnol 2025;2025. https://doi.org/10.1155/jnt/8899989.

[45] Khaled JM, Alharbi NS, Siddiqi MZ, Alobaidi AS, Nauman K, Alahmedi S, et al. A synergic action of colistin, imipenem, and silver nanoparticles against pandrug-resistant Acinetobacter baumannii isolated from patients. J Infect Public Health 2021;14:1679–85. https://doi.org/10.1016/j.jiph.2021.09.015.

[46] Güran M, Çakıral K, Teralı K, Kandemir T, Sanlıtürk G, Öcal MM, et al. Meropenem in combination with baicalein exhibits synergism against extensively drug resistant and pan-drug-resistant Acinetobacter baumannii clinical isolates in vitro. Pathog Dis 2023;81. https://doi.org/10.1093/femspd/ftad007.

[47] Zampaloni C, Mattei P, Bleicher K, Winther L, Thäte C, Bucher C, et al. A novel antibiotic class targeting the lipopolysaccharide transporter. Nature 2024;625:566–71. https://doi.org/10.1038/s41586-023-06873-0.