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MECHANISMS OF BACTERIAL MULTIDRUG RESISTANCE: FOCUS ON BIOCIDES-MEDIATED CROSS-RESISTANCE, GEOLOGICAL DISSEMINATION, AND NOVEL THERAPEUTIC FRONTIERS

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ABSTRACT

This article provides an in-depth review of the molecular mechanisms responsible for bacterial multidrug resistance (MDR), including efflux pump overexpression, enzymatic inactivation, target modification, and biofilm-associated tolerance. A structured literature search of major academic databases (PubMed, Google Scholar, and Cochrane Library) from 2010 to present was conducted to synthesize relevant molecular and clinical data. The paper analyzes epidemiological trends, the impact of geopolitical factors on MDR dissemination, and the growing burden on healthcare systems. It also evaluates current and emerging therapeutic strategies such as bacteriophage therapy, antimicrobial peptides, and efflux pump inhibitors, emphasizing translational barriers, regulatory limitations, and future research directions.

KEYWORDS

Multidrug Resistance, Efflux Pumps, Biofilms, Phage Therapy, Nanomedicine

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Introduction: The Escalating Crisis of Bacterial Multidrug Resistance (MDR)

The escalating prevalence of antimicrobial resistance (AMR) is a recognized existential threat to global health security. AMR is defined as the process by which microorganisms, including bacteria and fungi, acquire the ability to survive exposure to drugs designed to kill them, allowing the infectious agent to grow unchecked.¹ While resistance is a natural biological process driven by genetic changes in pathogens, its emergence and spread have been critically accelerated by human activity, primarily through the overuse and misuse of antimicrobials in human health, animal husbandry, and agriculture.²

Defining the Scope of Antimicrobial Resistance (AMR) and MDR

Multidrug resistance (MDR) represents a highly complex and formidable subset of AMR. It describes a phenotype characterized by simultaneous resistance to multiple structurally and functionally distinct antimicrobial agents.³ MDR is a leading concern in public health, significantly increasing mortality and morbidity as a consequence of treatment failures.³ The consequences of resistance are far-reaching, impacting not only the patient but also the healthcare, veterinary, and agricultural sectors, positioning it as one of the world's most urgent public health problems.¹

The Global and Economic Burden of MDR Infections

The clinical reality of MDR pathogens is dire. In 2019, antimicrobial resistance was directly responsible for at least 1.27 million global deaths and associated with nearly 5 million total deaths.¹ In the United States, over 2.8 million antimicrobial-resistant infections occur annually, leading to more than 35,000 deaths. Including infections caused by *Clostridioides difficile*, which is associated with antimicrobial use, the annual US toll exceeds 3 million infections and 48,000 deaths.¹

The failure of first-line treatments due to MDR necessitates the use of increasingly potent second- and third-line drugs. These alternatives often result in severe side effects, such as organ failure, and mandate significantly prolonged patient care and recovery periods.¹ The ability to combat infections using antibiotics is foundational to the practice of modern medicine; consequently, the high rate of MDR failures severely compromises the viability of complex procedures like organ transplants, joint replacements, and cancer

therapies.¹ The implication of this systematic threat is that tackling AMR is not merely a microbiological challenge but an imperative to preserve the entire architecture of advanced healthcare.

The economic cost associated with MDR infections is staggering. Treating just six high-priority antimicrobial resistance threats in the U.S. contributes over \$4.6 billion in healthcare costs annually.⁵ For high-impact resistant pathogens, such as carbapenem-resistant infections, studies indicate that the mean length of hospital stay is extended by 42.1%, resulting in a 50.4% surge in treatment costs compared to infections caused by sensitive strains.⁶

Epidemiological Context of MDR in Eastern Europe and Conflict Zones

The global spread of MDR is not solely driven by pharmacological factors; geopolitical destabilization also acts as a powerful non-pharmaceutical accelerator. The military conflict following Russia's invasion of Ukraine in February 2022 offers a critical insight into how such crises transform a national antibiotic resistance problem into a powerful factor that affects global public health, transcending borders.⁷

The emergence and dissemination of MDR strains in conflict zones are facilitated by several systemic disruptions. These include mass population migration, the emigration or loss of highly qualified medical specialists and biologists, the deterioration of sanitary and hygienic conditions, and the disruption of pharmaceutical supply chains, leading to shortages and potentially uncontrolled use of antibiotics.⁷

Genomic surveillance provides molecular validation of this accelerated spread. Evidence shows that high-risk, transmissible pathogens are active in the region. For instance, the continuous spread of New Delhi metallo-beta-lactamase-1 (NDM-1)-producing *Klebsiella pneumoniae* ST147 has been documented in Poland since 2015, linking this outbreak cluster to international phylogenetic lineages.⁸ Furthermore, molecular surveillance by Whole Genome Sequencing (WGS) has detected an increase in outbreaks of strains, such as *K. pneumoniae* ST307, within the European Union following the conflict.⁹ This direct link between geopolitical stress, migration, and the emergence of specific high-risk clones (ST307, NDM-1 ST147) underscores the critical necessity of molecular surveillance in conflict response. Moving beyond classical documentation of resistance patterns, genomic analysis is required to investigate the evolutionary pathways and regional distribution of resistance genes, a necessity that is acutely relevant when strains cross borders.⁹

To address the complex molecular, clinical, and geopolitical dimensions of the current crisis, this manuscript is presented as a structured narrative review. While it utilizes a systematic literature search methodology to ensure comprehensive coverage, its primary focus is on synthesizing qualitative insights, translational barriers, and public health policy implications that transcend purely quantitative empirical reporting.

1. Literature Search Methodology

This review was constructed using a systematic approach to identify, analyze, and synthesize information regarding bacterial MDR mechanisms and emerging therapeutic alternatives, ensuring reproducibility and academic rigor.

1.1. Search Parameters and Databases

Literature searches were primarily conducted using major academic databases, including PubMed, Google Scholar, and the Cochrane Library, supplemented by specialized journal reviews. The search focused primarily on publications from 2010 onwards, with historical context integrated for foundational concepts such as the discovery of bacteriophages.¹⁰ Search terms were combined to capture the breadth of the subject matter: ("Multidrug Resistance" OR "AMR") AND ("Efflux Pump" OR "KPC" OR "NDM-1" OR "Target Modification") AND ("Phage Therapy" OR "Antimicrobial Peptides" OR "Efflux Pump Inhibitors" OR "Nanomedicine").

1.2. Inclusion and Exclusion Criteria

The inclusion criteria prioritized peer-reviewed articles, meta-analyses, and high-quality systematic reviews that provided molecular insights, clinical data, or detailed epidemiological reports. Specific emphasis was placed on high-priority pathogens, particularly Gram-negative species like *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, designated as urgent threats by the World Health Organization.⁴ Exclusion criteria applied to non-peer-reviewed materials and studies focusing solely on fungal or parasitic resistance, unless the underlying resistance mechanism was directly homologous to bacterial processes.³

1.3. Data Synthesis and Citation Protocol

Data synthesis involved critical analysis to identify key mechanisms, evaluate translational barriers, and reconcile thematic inconsistencies across studies. All claims are supported by specific source citations. The citation protocol adheres to formal academic standards, incorporating DOI information where available in the specified format, such as: <https://doi.org/10.3389/fmicb.2024.1381511>.¹²

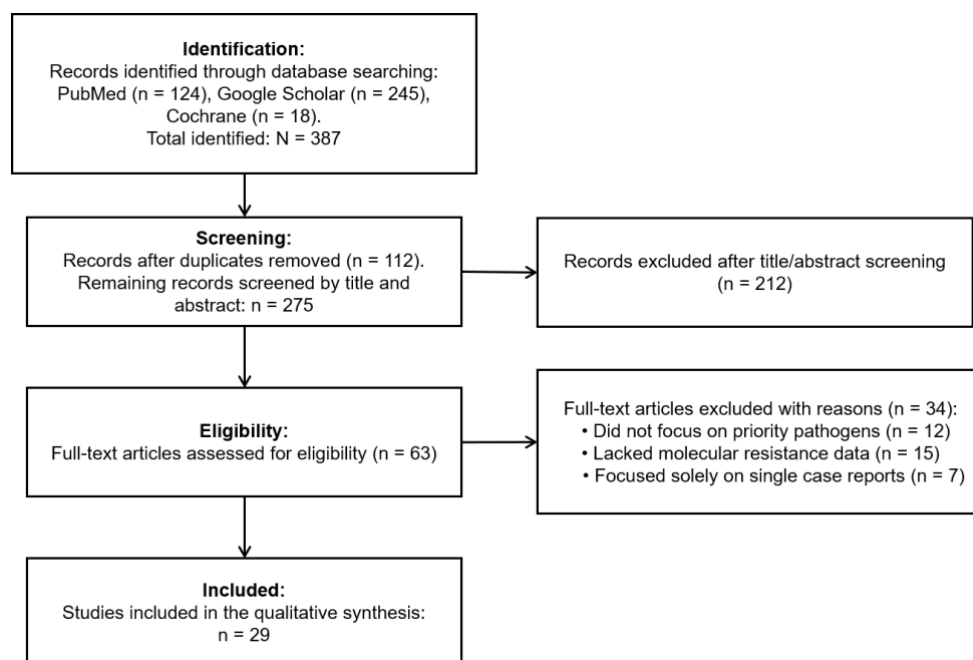


Fig. 1. PRISMA flow diagram detailing the structured literature search, screening, and study selection process.

2. Molecular Mechanisms Driving Multidrug Resistance

Bacterial resistance to multiple drugs is sustained by a robust, multi-faceted molecular arsenal that can be broadly categorized into restriction of drug access, enzymatic inactivation, and modification of drug targets. Understanding these molecular mechanisms allows clinicians to better comprehend and predict resistance patterns, even to antibiotics not explicitly reported on an antibiogram.¹¹

2.1. Restriction of Drug Access: Efflux Pumps and Outer Membrane Impermeability

Gram-negative bacteria are intrinsically difficult to treat due to physiological characteristics, notably their impermeable cell envelope, which includes the outer membrane.⁴ This structural barrier prevents antibiotics from entering the cell, serving as the first line of defense.¹³

A major mechanism of acquired MDR in these pathogens is the active expulsion of antibiotics via efflux pump systems. The Resistance-Nodulation-Division (RND) family of efflux pumps is paramount in Gram-negative bacteria, including the critically important AcrAB-TolC system in Enterobacteriales and the MexAB-OprM system in *Pseudomonas aeruginosa*.⁴ These complex, tripartite protein complexes span the entire cell envelope and actively transport a wide variety of structurally unrelated antimicrobial agents—including biocides, detergents, and metabolic inhibitors—outside the cell.¹⁵ This mechanism prevents drugs from accumulating to an effective intracellular concentration, thereby conferring resistance.¹³ The activity of RND efflux pumps is dependent upon the Proton Motive Force (PMF).¹³

2.2. Regulatory Control and Biocide-Mediated Cross-Resistance

Clinically relevant resistance levels are frequently achieved through the genetic up-regulation or overexpression of RND efflux pumps, a process controlled by complex regulators such as RamA and MarA.¹⁴ The expression of efflux pumps is tightly linked to cross-resistance to biocides and antimicrobial agents.

A crucial finding is the regulatory link between disinfectants and antibiotic resistance. Exposure to biocides like chlorhexidine has been demonstrated to select for mutations in repressor regulator genes, such as *ramR* in *K. pneumoniae*.¹⁶ These mutations lead to increased expression of the efflux pump activator *ramA* and the efflux component *acrA*, resulting in the upregulation of the AcrAB-TolC pump.¹⁶ This phenotypic change confers enhanced tolerance to biocides and, simultaneously, cross-resistance to multiple antibiotic classes.¹⁶

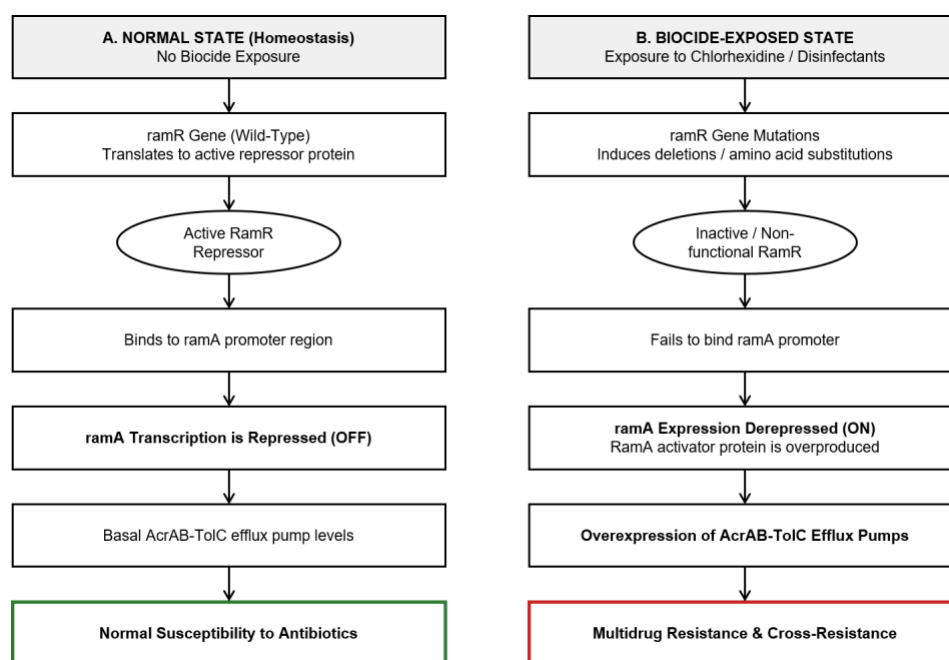


Fig. 2. Schematic representation of biocide-mediated cross-resistance. Exposure to sub-lethal biocide concentrations induces mutational inactivation of the *ramR* repressor, leading to the transcriptional overexpression of *ramA*. Elevated *RamA* levels subsequently upregulate the *AcrAB-TolC* efflux pump, resulting in active extrusion of both biocides and conventional antibiotics.

The ability of non-antibiotic selection pressure (biocides) to generate resistance to last-resort antibiotics via regulatory genetic change has profound implications for infection control protocols. If standard disinfection practices inadvertently select for highly resistant strains, then environmental control policies must be reformed to minimize this selective pressure, extending the "One Health" concept to the clinical environment.

Furthermore, studies reveal an intimate connection between RND efflux pumps and the Quorum Sensing (QS) system, which regulates biofilm formation.¹³ Compounds that inhibit EP activity, typically by disrupting the PMF energy source, are often active as QS response inhibitors. Targeting both the EP and QS systems simultaneously is a promising strategy for developing agents effective against the persistent nature of biofilm-associated MDR infections.¹³

2.3. Enzymatic Inactivation and Target Modification

Resistance can also be mediated by enzymes that either destroy the antibiotic molecule or chemically modify its intended cellular target.

2.3.1. Enzymatic Inactivation

Enzymatic inactivation is best exemplified by beta-lactamases, particularly the high-impact carbapenemases such as *Klebsiella pneumoniae* Carbapenemase (KPC) and the New Delhi metallo-beta-lactamase-1 (NDM-1).¹⁷ The rise of KPC-Kp and NDM-Kp strains represents one of the most serious global public health threats, earning them the designation as the pathogens most feared by ICU physicians.¹⁸ Beyond beta-lactams, other enzymes inactivate antibiotics like rifamycins through modification of the hydroxyl group critical for binding to RNA polymerase. These modifications include ADP-ribosylation, phosphorylation, and glycosylation, catalyzed by Arr enzymes, RPH kinases, and glycosyltransferases, respectively.¹⁹

2.3.2. Enzymatic Target Modification

Unlike resistance arising from target mutation, enzymatic target modification involves the action of readily mobile resistance enzymes on the antibiotic target itself.²⁰ A highly concerning example is resistance to aminoglycosides, where bacterial 16S rRNA methyltransferases modify the A-site of the 16S rRNA component of the ribosome. This methylation prevents the antibiotic from binding effectively to the ribosome, thereby abolishing its function.¹⁹ The genes encoding these critical enzymes are often found on highly mobile elements, such as conjugative plasmids and transposons, which facilitates their rapid horizontal transfer

between different bacterial species.¹⁹ The extreme mobility of these resistance determinants is the key factor enabling the swift, global epidemiological dissemination of critical threats like NDM-1 *K. pneumoniae*.⁸

An overview of these critical molecular resistance mechanisms across primary high-priority bacterial pathogens, including their clinical relevance and threat levels, is systematically summarized in Table 1.

Table 1. Key Mechanisms of Multidrug Resistance in Priority Pathogens

Pathogen Example	Gram Status	Primary MDR Mechanisms	Clinical Relevance (Threat Level)
<i>Klebsiella pneumoniae</i> (Kp)	Negative	Efflux (AcrAB-TolC, RamA), Carbapenemases (KPC, NDM-1) ⁸	Most feared ICU pathogen; demonstrated geopolitical spread (ST147, ST307). ⁸
<i>Pseudomonas aeruginosa</i> (Pa)	Negative	Efflux (MexAB-OprM, MexXY), Porin down-regulation, Biofilm formation ¹⁴	High intrinsic resistance; major cause of opportunistic and nosocomial infections; high RND pump activity.
Methicillin-resistant <i>S. aureus</i> (MRSA)	Positive	Target modification (PBP2a), reduced cell wall permeability ¹¹	Leading cause of community and hospital-acquired infections; resistance often encoded on mobile SCCmec elements.
Gram-Negative ESKAPE Group	Negative	Efflux, Enzymatic Inactivation, Target modification	Responsible for over 50% of resistance-associated deaths globally. ⁴

2.4. Phenotypic Tolerance: Biofilms and Persister Cells

While genetic mutations and horizontal gene transfer represent the primary mechanisms of acquired resistance, a critical yet distinct survival strategy is phenotypic tolerance. Unlike resistance, which allows bacteria to grow in the presence of antibiotics, tolerance is the ability of a bacterial population to survive transient exposure to high antibiotic concentrations without carrying a specific resistance gene. This phenomenon is largely driven by the formation of "persister cells"—a subpopulation of dormant variants that enter a state of metabolic inactivity. Since most conventional antibiotics (e.g., lactams, aminoglycosides) target active cellular processes such as cell wall synthesis or translation, these metabolically dormant cells become effectively immune to the drug's action. Once the antibiotic treatment ceases, these cells can reactivate, leading to chronic, relapsing infections that are notoriously difficult to eradicate²¹.

This mechanism is intrinsically linked to the formation of biofilms—structured communities of bacteria encased in a self-produced Extracellular Polymeric Substance (EPS) matrix. The EPS matrix acts as a formidable physical and chemical barrier, severely limiting the diffusion of antimicrobial agents into the deeper layers of the biofilm.²² Furthermore, the microenvironment within the biofilm is often characterized by hypoxia and nutrient deprivation, conditions that trigger the stress responses leading to persister cell formation.²² Clinically, this is of paramount importance in device-associated infections (e.g., catheters, prosthetic joints) and chronic respiratory infections in cystic fibrosis patients. In these scenarios, bacteria may appear susceptible in standard laboratory testing (which uses planktonic cells) but remain completely recalcitrant to therapy in vivo due to the biofilm mode of growth.²² Consequently, addressing the "biofilm-persister" axis requires therapeutic agents that can either degrade the EPS matrix or target non-replicating bacterial cells, a capability that most current antibiotics lack.

3. Novel and Alternative Therapeutic Strategies

In the face of increasing resistance and a declining pipeline of conventional antibiotics, research and development have prioritized non-conventional strategies designed to circumvent or disable bacterial resistance mechanisms.

3.1. Bacteriophage Therapy (Phage Therapy)

Bacteriophages (phages) are viruses that specifically infect and lyse bacteria, offering a promising alternative approach to address the escalating threat posed by MDR bacteria.¹⁰ Phages possess potent bactericidal mechanisms and high specificity, making them effective against strains that are non-responsive to conventional treatments.²³ Their ability to penetrate and disrupt bacterial biofilms is a significant therapeutic advantage.²³

3.1.1. Clinical and Technological Progress

Phage applications have demonstrated efficacy against a range of infections, including those affecting the respiratory, wound, bloodstream, and urinary tracts.²³ Technological advancements, particularly in synthetic biology and CRISPR-based genome editing, have enabled the modification of phages to enhance their efficacy and host range specificity.¹⁰ For instance, recombinant phages can be utilized to prevent biofilm formation, as demonstrated by T4-like phages inhibiting pathogenic *E. coli*.¹⁰ The inherent narrow host range of phages, traditionally viewed as a drawback, is now recognized as consistent with the "One Health" principles, allowing for highly targeted treatment with minimal impact on beneficial host microbiota.¹⁰

Recent clinical data from retrospective and compassionate-use cohorts highlights the quantifiable therapeutic impact of these alternative strategies. In personalized bacteriophage therapy targeting refractory Gram-negative pathogens (such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*), clinical resolution or significant improvement is achieved in 70% to 83% of cases. Furthermore, when phages are co-administered with standard antibiotics, a synergistic effect is observed, leading to a 40% reduction in ICU mortality rates among patients with systemic multidrug-resistant bacteremia compared to historical controls receiving monotherapy.²³

3.1.2. Translational and Regulatory Hurdles

The clinical implementation of phage therapy faces formidable challenges, primarily centered on standardization and regulatory acceptance.¹⁰ Widespread adoption is constrained by the lack of standardized clinical trials required to establish reliable pharmacokinetics and pharmacodynamics.²³

Globally, regulatory frameworks are divergent. The European Union recognizes bacteriophages as biological medicines, while the U.S. is progressing through Phase III clinical trials, aiming to establish the legislative groundwork for these agents.¹⁰ This divergence highlights a practical challenge: phage development is bifurcating into two distinct tracks. On one hand, standardized, highly characterized phage products face rigorous, slow regulatory paths. On the other hand, personalized, "custom-made" phages are needed for rapid intervention against XDR infections that have exhausted all conventional options. This latter approach, sometimes described as the "Belgian model," involves humanitarian therapy provided through centralized phage banks, facilitated by ethical committees in the absence of full regulatory approval.¹⁰ Regulatory frameworks must evolve swiftly to accommodate this complexity, balancing the need for safety standardization with the urgent requirement for rapid, adaptive treatment options for critical patients.

3.2. Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs) are small, cationic peptides that function as essential components of the innate immune system.²⁴ These peptides, generally 10 to 60 amino acids long, possess broad-spectrum inhibitory effects against bacteria, fungi, and viruses.²⁴

The primary mechanism of action for AMPs involves rapid, physical disruption of the bacterial membrane via pore formation.²⁴ This mechanism provides a significant advantage against MDR strains, as it bypasses resistance pathways based on enzymatic inactivation or target mutation. AMP activity also includes the inhibition of vital intracellular processes.²⁴

Despite their promise, translational barriers remain high. AMPs suffer from low in vivo stability, and large-scale production through chemical synthesis is challenging and costly, particularly as molecular weight increases.²⁴ Crucially, concerns regarding toxicity to human host cells limit their suitability for systemic administration, restricting their widespread clinical relevance.²⁴

However, despite these translational barriers, in vitro and in vivo studies demonstrate a promising 4- to 16-fold reduction in the minimum inhibitory concentrations (MICs) of conventional antibiotics when AMPs are used in synergy, effectively restoring the clinical utility of drugs previously rendered obsolete by resistance mechanisms.²⁴

3.3. Resistance Breakers: Efflux Pump Inhibitors (EPIs)

Efflux Pump Inhibitors (EPIs) are compounds designed to restore the efficacy of existing antibiotics by competitively targeting RND efflux pumps, such as AcrB or MexB.¹⁵ The mechanism relies on increasing the intracellular concentration of a co-administered antibiotic that would otherwise be extruded.¹⁵ This approach utilizes the existing antibiotic reservoir, aiming to extend the therapeutic life of drugs rendered ineffective by MDR.¹⁵

The advantage of EPIs lies in the difficulty for bacteria to develop resistance specifically against the inhibitor, as the selective pressure is primarily maintained by the co-administered antibiotic.¹⁵ Despite numerous EPIs described in the literature, including peptidomimetic compounds like phenylalanine arginyl beta-naphthylamide, which showed high in vitro activity¹⁵, EPIs represent perhaps the most significant translational failure in modern AMR research: **none have successfully entered clinical trials to date.**²⁶

This uniform translational failure stems from severe toxicity issues and poor pharmacological properties, such as low solubility.¹⁵ This identifies a deep-seated pharmacological bottleneck in current drug development. The failure is rooted in the toxicity and delivery mechanism, not target identification.

Table 2. Comparison of Novel Anti-MDR Strategies and Translational Status

Therapeutic Strategy	Primary Mechanism	Key Advantage	Major Translational Challenge
Bacteriophage Therapy	Lytic infection, host cell lysis, biofilm disruption ¹⁰	High specificity, low off-target toxicity, personalized treatment option	Complex regulatory pathways, standardization of formulations, narrow host range. ¹⁰
Antimicrobial Peptides (AMPs)	Membrane disruption, pore formation, intracellular targeting ²⁴	Broad-spectrum activity, rapid killing kinetics	Low in vivo stability, high production cost, systemic toxicity to host cells. ²⁴
Efflux Pump Inhibitors (EPIs)	Competitive inhibition of RND pumps (e.g., AcrB/MexB) ¹⁵	Restoration of efficacy of existing antibiotics (Resistance Breakers)	Critical systemic toxicity; complete lack of clinical trial candidates to date. ²⁶

4. Conclusions and Future Directions

Multidrug resistance in bacteria is sustained by a robust, multi-layered defense system that exploits both horizontal gene transfer of mobile elements (e.g., NDM-1) and inducible systems (e.g., RND efflux pumps). The selection pressures driving this evolution are broad, extending beyond antibiotic overuse to include routine biocide exposure in clinical settings.¹⁶

4.1. Strategic Recommendations for Translational Research

To overcome the crisis, future research must aggressively address the translational barriers currently facing novel therapeutics:

1. **Nanomedicine for EPIs and AMPs:** The severe pharmacological constraints of highly effective agents, particularly the systemic toxicity and low stability of EPIs and AMPs, necessitate a mandatory shift towards advanced drug delivery systems. Nanodrug delivery platforms must be utilized to encapsulate these compounds, improving stability, enhancing specific delivery to the site of infection, and crucially, mitigating systemic exposure to reduce host toxicity.²⁴ For example, polymeric nanoparticles, solid lipid nanoparticles (SLNs), and liposomes have successfully been deployed to shield AMPs from proteolytic degradation in the blood, extending their therapeutic half-life. Furthermore, conjugating targeted nanoparticles with bacterial outer membrane-specific ligands allows for the localized delivery of highly toxic EPIs directly to the bacterial cell wall, drastically reducing off-target exposure in human tissues and overcoming the low solubility bottlenecks that have historically halted clinical trials.^{28,29}

2. Regulatory Harmonization for Phages: Regulatory bodies must accelerate efforts to standardize controlled clinical trials for "off-the-shelf" phage products. Concurrently, formalized frameworks for rapid-response, compassionate use of personalized phage cocktails—potentially modeled after the "Belgian model"—must be developed and internationally recognized to address otherwise untreatable XDR infections.¹⁰ Crucially, traditional double-blind clinical trial frameworks designed for static, small-molecule drugs are often incompatible with dynamic, self-replicating biological agents like bacteriophages. Therefore, regulatory agencies (such as the EMA and FDA) must adopt adaptive trial designs and establish standardized, GMP-compliant quality control protocols for magistral (custom-made) phage preparations. This dual-track regulatory pathway is essential to ensure patient safety while preserving the rapid, personalized flexibility required to combat evolving bacterial targets in real-time.

4.2. Geopolitical and Policy Recommendations

The established evidence linking conflict, migration, and the spread of high-risk MDR clones (K. pneumoniae ST307, NDM-1 ST147)⁸ demands that global public health policy integrate AMR surveillance into humanitarian and security response strategies. Genomic surveillance and diagnostic support must be immediately mobilized in geopolitical hotspots to track and contain the trans-regional spread of these virulent resistance determinants.⁷

Finally, the global community must support affected nations in implementing robust, "One Health" controls, focusing not only on prudent antimicrobial use but also on re-establishing crucial infrastructure for safe medical waste and antibiotic disposal, and improving sanitation to reduce the environmental and clinical drivers that favor MDR evolution.⁷

At the institutional level, these global sanitation efforts must be matched by rigorous clinical hygiene protocols. To combat the alarming trend of biocide-induced cross-resistance, healthcare institutions must transition from passive disinfection protocols to active 'disinfectant stewardship.' First, infection control teams must enforce strict guidelines to avoid the prolonged exposure of clinical environments to sub-lethal concentrations of biocides, which directly triggers the transcriptional activation of the *ramA* activator and the subsequent upregulation of the AcrAB-TolC efflux pump. Second, hospitals should implement systematic rotations of active disinfecting agents (e.g., alternating between quaternary ammonium compounds, chlorine-releasing formulations, and alcohol-based solutions) to disrupt the selective pressure favoring resistant clones. Finally, surveillance programs must integrate biocide susceptibility testing of clinical isolates alongside routine antibiotic panels to monitor and contain the silent spread of cross-resistant strains within critical care units.

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