MULTIDRUG-RESISTANT BACTERIAL INFECTIONS

An Examination of Innovative Drug Strategies to Address Multidrug-Resistant Bacterial Infections

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Abstract

Infections due to multidrug-resistant (MDR) bacteria present a major challenge to modern healthcare since resistance can weaken the effectiveness of multiple antibiotic classes, resulting in greater complexity, length, and cost of treatment. Resistance develops through mechanisms such as enzymes that deactivate antibiotics, altered drug targets, reduced membrane permeability, active efflux, metabolic changes, and biofilm creation. This review examines new pharmacological strategies aimed at preventing, addressing, or improving conventional antibacterial therapies. It includes the latest combinations of β-lactam/β-lactamase inhibitors, antibiotics associated with siderophores, substances aimed at resistant Acinetobacter, antimicrobial peptides, phage therapy, anti-virulence substances, techniques to break down biofilms, antibiotic boosters, immunotherapy approaches, and CRISPR-based antimicrobials. Examples include cefiderocol, ceftazidime-avibactam, aztreonam-avibactam, and durlobactam-sulbactam.

Keywords: multidrug resistance; resistance to antimicrobials; innovative antibiotics; β-lactamase inhibitors; bacteriophage treatment; biofilm; adjuvants for antibiotics

1 Introduction

Antimicrobial resistance (AMR) represents a critical and escalating global health problem, as emphasized by the World Health Organization (WHO, 2015). The significant increase and distribution of MDR bacterial pathogens have greatly compromised the efficacy of existing antimicrobial therapies. These pathogens acquire resistance through various methods, including horizontal gene transfer and random mutations driven by selective pressure due to exposure to antimicrobials [1]. The natural biological process of developing resistance occurs rapidly primarily because of the misuse and overuse of antibiotics, inadequate monitoring and testing practices, and the unregulated use of antimicrobials in healthcare, agriculture, and veterinary settings. Together, these factors contribute to the persistent and global spread of MDR organisms, underscoring the urgent need for innovative strategies in antimicrobial development, regulation, and policy reforms [2] Antibiotic resistance has emerged as a major public health concern, resulting in considerable global deaths. In the United States, it results in over 23,000 deaths annually, as reported by the Centers for Disease Control and Prevention. In Europe, the anticipated death toll exceeds 33,000 each year, highlighting the urgent need for coordinated international efforts to address this growing crisis. Despite alarming current figures, predictive models indicate that antimicrobial resistance could lead to more than 10 million fatalities globally by 2050.

The increasing threat of multidrug-resistant (MDR) bacteria poses a significant challenge to global health. Infections caused by MDR pathogens can lead to standard therapies being ineffective, extended illness durations, higher mortality rates, and increased healthcare costs. The alarming rise in antimicrobial resistance underscores the urgent need for a comprehensive evaluation of antibacterial agents that demonstrate efficacy against MDR strains. The major bacteria known for their ability to withstand the impact of antibiotics are categorized under the acronym "ESKAPEE" (which includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacter species, and *Escherichia coli*) [3] Furthermore, the World Health Organization (WHO) has classified important bacterial pathogens into critical, high, and medium priority tiers, highlighting the pressing need for new antibiotics and steering research towards novel antibacterial agents. These "priority" pathogens represent a major health threat due to their disease effects, antibiotic resistance, and potential to lead to severe infections.

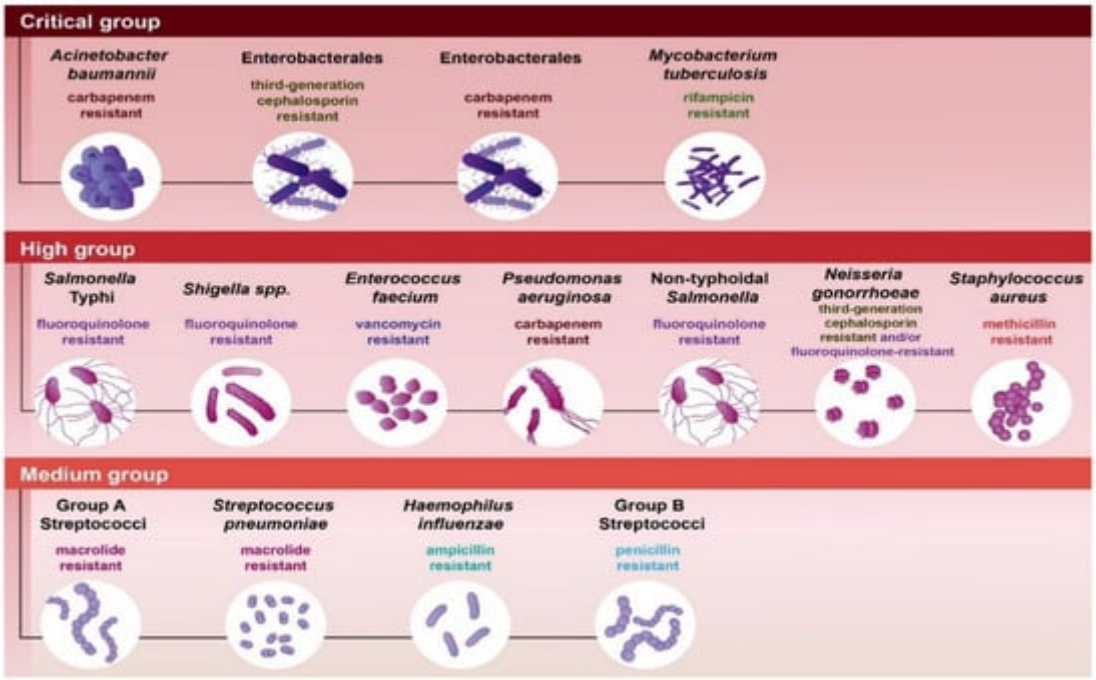


Figure 1. List of priority bacterial pathogens [3].

In 2021, it was estimated that 4.71 million deaths were associated with bacterial antimicrobial resistance (AMR), including 1.14 million fatalities directly resulting from bacterial AMR. In 2020, over 800,000 infections due to MDR bacteria occurred in the European Union/European Economic Area (EU/EEA), resulting in more than 35,000 deaths, according to the European Antimicrobial Resistance Surveillance Network [4] In 2015, it was estimated that methicillin-resistant *Staphylococcus aureus* (MRSA) caused more than 148,000 infections and resulted in 7,000 deaths In the United States of America (USA), the incidence of healthcare-associated infections (HAIs) caused by MDR bacteria increased by 20% during the COVID-19 pandemic, peaking in 2021. In 2022, the rates for all major MDR pathogens, except for MRSA, remained above pre-pandemic levels. In 2019, MRSA and vancomycin-resistant *Enterococcus* (VRE) accounted for 323,700/10,600 and 54,500/5400 cases/deaths, respectively. In 2022, *Mycobacterium tuberculosis* was the second leading cause of death from a single infectious agent worldwide, leading to around 1.3 million fatalities. In 2022, the tally of newly diagnosed tuberculosis (TB) cases hit 7.5 million, representing the highest count since the WHO

began global TB surveillance. In 2019, approximately 500,000 people were identified with rifampicin-resistant tuberculosis, obstructing global efforts to control the disease [5]

1.1 Strategies and measures for preventing antibiotic resistance

Antibiotic resistance jeopardizes modern medicine, mainly affecting the effectiveness of a swift and efficient global health response to infectious diseases due to the widespread misuse and overuse of antibiotics in healthcare and food production. Undoubtedly, the widespread or inappropriate use of these medications in humans, animals, or agriculture results in the emergence of drug-resistant microorganisms that have adapted due to this significant selective pressure. In 2015, acknowledging the major challenge of antibiotic resistance, the WHO decided to launch the Global Action Plan on Antimicrobial Resistance, based on five key objectives: to increase understanding and awareness of antimicrobial resistance; to improve knowledge and data access; to reduce infection rates through proper hygiene practices; to optimize the use of antimicrobial drugs in human and animal health; and to enhance funding for new medications, diagnostic techniques, vaccines, and other interventions [7]

In addition to the WHO, various organizations such as the United Nations Food and Agriculture Organization and the World Organisation for Animal Health highlight the fight against antibiotic resistance. The use of antibiotics in veterinary medicine is vital: Strengthening the regulatory guidelines for medicated food and feed, mostly used in intensive farming, is necessary to prevent the development of infections due to the high concentration of animals in restricted spaces. To achieve this, monitoring and surveillance systems for resistant bacteria and the indiscriminate use of antibiotics have risen, not only in human healthcare but also in veterinary medicine. It is usually recommended to avoid repetitive use of the same molecule and to improve patient adherence with appropriate drug dosages and timing.

In 2013, the European Centre for Disease Prevention and Control (ECDC) released a document assessing protocols and recommendations to enhance adherence among health professionals concerning the timing, dosage, and duration of peri-operative antibiotic prophylaxis aimed at preventing infections in operating rooms. Consequently, novel molecules are essential for addressing the resistances that have emerged, along with the necessity to enhance the application of current antibiotics and to encourage the development of more reliable diagnostic tests for recognizing resistant bacteria and for assessing antibiotic sensitivity [8]

1.2 Molecular mechanisms of antibiotic deactivation

Bacteria can deactivate antibiotics via various molecular mechanisms:

- Synthesis of inactivating enzymes: The antibiotic's biological function is diminished as it is specifically neutralized by enzymes generated by the bacterium. This occurs, for instance, with β-lactam antibiotics that are broken down by β-lactamases. *Enterobacter spp.* generate extended-spectrum β-lactamases (ESBL) with identical inactivating properties, making them challenging to eliminate. Additional enzymes that can inactivate specific antibiotics include acetyltransferase, phosphotransferase.
- Modifications and variations in the antibiotic target: This occurs, for instance, in erythromycin resistance, where the methylation of an adenine nucleotide in the 23S rRNA peptidyl-transferase reduces its binding affinity for the antibiotic without impairing protein synthesis. A significant instance is the alteration of penicillin binding proteins (PBPs) by MRSA.

- Decreased cellular permeability: Structural alterations in the cell's surface membranes can diminish the uptake of an antibiotic. In Gram-negative bacteria, the resistance could be attributed to a change or a reduced quantity of porins, which are proteins that facilitate the entry of various antibiotics. They hinder the influx of a variety of antibiotics through various mechanisms, such as restrictions on molecular size, hydrophobicity, and charge repulsion, thereby aiding in the inherent resistance of many microorganisms. *Pseudomonas aeruginosa* demonstrates resistance to imipenem [9]

2 Multidrug resistance: categorization and key pathogens

2.1 Classification

The terms MDR, XDR and PDR describe increasing patterns of antimicrobial non-susceptibility. The original international proposal by Magiorakos and colleagues provides standardized definitions for acquired resistance in selected bacterial groups. Laboratory interpretation must use current organism-specific breakpoints and local standards (Table 1) [10].

Table 1. Classification of antimicrobial resistance.

Term	General meaning	Clinical significance
MDR	Non-susceptibility to at least one agent in three or more antimicrobial categories.	Several usual treatment options may be unavailable.
XDR	Non-susceptibility to all but one or two antimicrobial categories.	Very few active treatment options remain.
PDR	Non-susceptibility to all agents in all relevant antimicrobial categories.	Treatment options may be extremely limited.

2.2 Important MDR pathogens

Table 2. Important MDR pathogens [11].

Pathogen	Significant resistance characteristic	Key issue
Escherichia coli and Klebsiella pneumoniae	ESBL production; carbapenem resistance (CRE)	Urinary, bloodstream, and infections related to hospitals.
Acinetobacter baumannii	Carbapenem resistance (CRAB)	Pneumonia related to ventilators and infections in the bloodstream.
Pseudomonas aeruginosa	Hard-to-treat resistance; changes in efflux and porins	Nosocomial pneumonia, bloodstream infection, and wound infections.
Staphylococcus aureus	MRSA; lowered susceptibility to certain agents	Infections of the skin, soft tissue, bones, and those that are invasive.
Enterococcus faecium	Vancomycin-resistant (VRE)	Healthcare-related bloodstream and urinary infections.

3 Mechanisms of antibiotic resistance

3.1 Enzymatic drug inactivation

Bacteria have the capability to generate enzymes that alter or eliminate antibiotics. β-lactamases break down the β-lactam ring found in penicillins, cephalosporins, and, depending on the specific enzyme, carbapenems. ESBLs, AmpC enzymes, and carbapenemases like KPC, NDM, and OXA-48-like enzymes hold significant clinical relevance. Aminoglycoside-modifying enzymes can additionally render their drug substrates inactive.

3.2 Alteration of drug target

Mutations or newly acquired genes can alter the structure of the antibiotic target, hindering drug binding. Instances include modified penicillin-binding proteins in MRSA, alterations in ribosomal targets, mutations in DNA gyrase/topoisomerase linked to fluoroquinolone resistance, and variations in cell-wall precursor pathways [12]

3.3 Reduced permeability

Alterations in outer-membrane porins may decrease antibiotic uptake in Gram-negative bacteria. A loss or decrease in OprD expression in *P. aeruginosa* correlates with diminished susceptibility to carbapenems. Decreased permeability can combine with β-lactamase production to create significant resistance [13]

3.4 Active efflux pump

Efflux pumps actively move antimicrobial substances out of bacterial cells. Elevated levels of pumps like MexAB-OprM in *P. aeruginosa* can lower intracellular drug levels and lead to multidrug resistance. Efflux systems can also affect bacterial fitness and virulence.

3.5 Biofilm formation

Biofilms consist of organized bacterial populations enclosed in an extracellular matrix that adheres to either living or inert surfaces. Bacteria in biofilms can exhibit decreased antibiotic effectiveness due to restricted penetration, sluggish growth, modified metabolism, and the development of persister cells. Biofilms play a significant role in chronic wounds, catheters, implants, and respiratory infections [14]

3.6 Horizontal gene transfer

Resistance genes can transfer among bacteria via conjugation, transformation, and transduction. Plasmids, transposons, and integrons enable the transfer and buildup of various resistance factors. This process may speed up the development of organisms that are resistant to multiple classes of antibiotics [15]

4 Creative antibacterial medication approaches

4.1 β-lactam/β-lactamase inhibitor combinations

A β-lactam antibiotic disrupts bacterial cell-wall formation by attaching to PBPs. A β-lactamase inhibitor safeguards the accompanying antibiotic from specific β-lactamases. Recent combinations

aim to target specific enzyme families, yet no single inhibitor encompasses all β-lactamases. Choice relies on the resistance mechanism and lab sensitivity outcomes. Pharmacological strategy combination Essential aspects Ceftazidime–avibactam Meropenem–vaborbactam Ceftazidime targets PBPs; avibactam blocks various class A, class C, and certain class D β-lactamases. Meropenem blocks cell-wall formation; vaborbactam targets specific serine β-lactamases, such as KPC. Effective against certain KPC- and OXA-48-like CRE; not effective on its own against metallo-β-lactamases. Created for specific carbapenem-resistant Enterobacterales. Imipenem–cilastatin–relebactam Relebactam obstructs certain class A and C β-lactamases; imipenem serves as the antibacterial agent. Aztreonam–avibactam Aztreonam is resistant to hydrolysis by metallo-β-lactamases, while avibactam inhibits the serine β-lactamases that are produced alongside it. Might regain effectiveness against certain resistant Gram-negative bacteria. Examined for severe infections resulting from resistant Gram-negative bacteria; REVISIT was a phase 3 trial Sulbactam–durlobactam Sulbactam possesses inherent efficacy against *A. baumannii*; durlobactam obstructs key class A, C, and D β-lactamases. A focused approach for severe *A. baumannii* infections; assessed in the ATTACK trial.Key limitation: inhibitor effectiveness is specific to enzymes. Metallo-β-lactamases like NDM, VIM, and IMP necessitate varied strategies; susceptibility assessment and expert analysis are crucial [16]

4.2 Siderophore-linked antibiotics: cefiderocol

Cefiderocol is a cephalosporin that functions as a siderophore. Its catechol side chain attaches to ferric iron, enabling the drug to exploit bacterial iron-transport mechanisms to penetrate Gram-negative bacteria—the 'Trojan horse' approach. After entering the periplasmic space, cefiderocol blocks PBPs and interferes with cell-wall construction. It exhibits efficacy against various hard-to-treat Gram-negative bacteria, depending on susceptibility. The phase 3 CREDIBLE-CR trial assessed cefiderocol for severe infections resulting from carbapenem-resistant Gram-negative bacteria The research emphasized the importance of analyzing results based on pathogen and infection type; cefiderocol should not be viewed as universally effective against all resistant strains [17]

4.3 Agents aimed at *Acinetobacter* resistant to carbapenems

CRAB is a significant pathogen found in hospitals. Sulbactam-durlobactam was created to tackle this issue. Sulbactam attaches to the PBPs of *A. baumannii*, whereas durlobactam safeguards sulbactam from various β-lactamases. In the phase 3 ATTACK trial, sulbactam-durlobactam was evaluated against colistin, with imipenem-cilastatin used as adjunct therapy [18] Current recommendations suggest a regimen containing sulbactam for CRAB, with the choice of regimen influenced by availability, susceptibility, and expert opinion.

4.4 Novel targets and antibiotic categories

Studies are investigating bacterial mechanisms beyond traditional cell wall, protein, and nucleic acid production. Possible targets consist of lipid A production, bacterial energy metabolism, protein balance, riboswitches, quorum sensing, and crucial metabolic pathways. The 2025 literature review outlines novel targets and combination strategies; however, numerous candidates still exist in preclinical or early clinical phases. A significant challenge in development is making sure that new agents target pathogens that have few treatment options, rather than merely introducing another drug with similar effects. WHO pipeline analyses highlight the necessity for truly innovative treatments targeting priority pathogens [19]

5 Alternative and biological approaches

5.1 Antimicrobial peptides

Antimicrobial peptides are brief, biologically active substances present in living beings from bacteria to humans. Numerous substances are cationic and amphipathic, enabling them to engage with negatively charged bacterial membranes. Certain peptides compromise membrane integrity through pore creation or destabilization of membranes; others disrupt intracellular functions or adjust host immune reactions. Instances examined in antimicrobial studies comprise defensins, cathelicidins, bacteriocins, and modified peptide variants. Their possible benefits encompass swift membrane actions and effectiveness against certain resistant pathogens. Challenges encompass proteolytic breakdown, toxicity, inadequate pharmacokinetic characteristics, production expenses, and the potential for resistance. Recent evaluations address peptide modification, administration methods, and combined applications [20]

5.2 Bacteriophage therapy

Bacteriophages are viruses that target bacteria. Lytic phages bind to particular bacterial receptors, deliver their genetic information, reproduce inside the bacterial cell, and trigger lysis, releasing new phages. Phage mixtures can expand host range and lower the chances of developing resistance to an individual phage [21]

Phage therapy might be viewed as an experimental or compassionate-use method for specific challenging infections, frequently in conjunction with antibiotics. Its constraints consist of a limited host range, immune responses that neutralize, resistance to phages, manufacturing and quality-control demands, and complex regulations. Testing for phage susceptibility and the meticulous choice of only strictly lytic phages are crucial [22]

5.3 CRISPR-based antimicrobials

CRISPR-Cas systems can be engineered to identify particular bacterial DNA sequences. Studies investigate the use of engineered bacteriophages or alternative vectors for delivering CRISPR components to specifically target and disrupt bacteria that possess resistance genes or critical genomic elements. This approach might, in principle, target resistant strains for removal while leaving susceptible microbiota unharmed. Nonetheless, challenges such as delivery into specific bacteria, variations in sequence, escape mutations, safety concerns, and regulatory issues continue to pose significant obstacles [23]

5.4 Anti-virulence therapy

Anti-virulence agents focus on diminishing the capacity of bacteria to induce illness instead of directly eliminating them. Possible targets consist of adhesins, toxins, secretion systems, quorum-sensing pathways, and enzymes necessary for tissue invasion. By reducing virulence, these agents might impose less direct selective pressure on bacterial survival compared to traditional bactericidal medications. However, the clinical effectiveness and the potential for compensatory adaptation need additional assessment.

5.5 Immunotherapeutic approaches

Monoclonal antibodies, vaccines, and immune-modulating agents can enhance antibiotics by neutralizing toxins, preventing bacterial attachment, or improving opsonophagocytic clearance. These

approaches target specific pathogens and do not substitute for antibiotics in serious active infections. Their progression is constrained by antigen variability, immune evasion, and the requirement to show clinical advantage [24]

5.6 Nanotechnology-based delivery

Nanocarriers, liposomes, polymeric nanoparticles, and surface coatings are under exploration to enhance drug stability, targeted delivery, biofilm infiltration, or cytoplasmic concentration. Nanotechnology could facilitate the combined delivery of antibiotics and adjuvants. Implementing translation to clinical practice necessitates thorough assessment of toxicity, biodistribution, manufacturing consistency, and long-term safety [25]

6 Combined therapy and targeted antimicrobial treatment

Combination therapy could be suitable when backed by clinical evidence, particularly for targeted resistant pathogens with few effective options. The objectives might involve additional mechanisms, wider initial coverage, or decreased development of resistance. Nonetheless, combinations may enhance toxicity, drug interactions, and ecological strain. Not all combinations produce synergy, and standard combination therapy isn't inherently better than an effective singular agent. Accurate antimicrobial therapy starts with collecting suitable clinical samples, recognizing the pathogen, and assessing susceptibility. Molecular assays can quickly identify specific resistance genes, yet they do not consistently substitute for phenotypic susceptibility tests. Reducing treatment to the minimal effective agent, suitable dosage and duration, along with source management, are crucial components of responsible care [26]

7 Clinical development and evidence

Clinical development encompasses laboratory discoveries and animal research, followed by phase I safety assessments, phase II dosage and initial efficacy evaluations, phase III comparative studies, and post-marketing monitoring. A hopeful in-vitro outcome does not confirm clinical efficacy. Key outcomes encompass death, clinical recovery, microbiological elimination, recurrence, side effects, and development of resistance. Clinically evaluated innovations include cefiderocol in CREDIBLE-CR sulbactam-durlobactam in ATTACK, and aztreonam-avibactam in REVISIT. These trials demonstrate the significance of pathogen-targeted development and the necessity of assessing both effectiveness and safety. New biological methods like phage therapy and CRISPR-based antimicrobials need additional standardization and regulated clinical proof The WHO indicated that there were 97 antibacterial drugs in clinical development in 2023, up from 80 in 2021, yet highlighted that the pipeline still fell short of global demand and that only a small portion included genuinely innovative medications [27]

8 Difficulties in creating new antibacterial medications

1. Scientific intricacy: bacteria have the ability to merge multiple resistance strategies, and resistance might arise during treatment.
2. Challenges in clinical trials: resistant infections vary widely, patient availability may be restricted, and timely effective treatment might be ethically required.

3. Safety and pharmacokinetics: novel agents should achieve effective concentrations at the infection site without causing unacceptable toxicity.
4. Economic obstacles: antibiotics are typically prescribed for brief durations and must be preserved, which may lead to decreased financial gains.
5. Availability and cost: new treatments might not be accessible or affordable in areas with significant AMR challenges.
6. Regulatory and manufacturing challenges: biologics, phages, peptides, and precision treatments might necessitate unique production and quality assurance processes.
7. Surveillance deficiencies: inadequate microbiology information may postpone the identification of resistance trends and diminish [28]

9 Function of antibiotic stewardship

Antimicrobial stewardship encourages the correct choice, dosage, administration method, and length of antimicrobial treatment. Its goal is to enhance patient results while minimizing preventable toxicity and the emergence and transmission of resistance. Stewardship programs achieve maximum effectiveness when backed by clinicians, pharmacists, microbiologists, infection-control teams, and hospital administrators.

1. Administer antibiotics solely when there is a suspicion or confirmation of a bacterial infection and when clinical treatment is warranted.
2. Gather relevant cultures prior to initiating antibiotics when this does not postpone urgent care.
3. Reassess therapy when culture and susceptibility findings are accessible.
4. Reduce or halt unwarranted broad-spectrum therapy.
5. Administer the appropriate dosage, method, and duration according to patient characteristics, infection location, and existing recommendations.
6. Instruct patients on avoiding the sharing of antibiotics or using unused medications.
7. Track the usage of antibiotics and regional resistance patterns [29]

Pharmacists play a vital role in antimicrobial stewardship by reviewing prescriptions, optimizing dosages, assessing renal dosing, screening for interactions, counseling patients, evaluating IV-to-oral conversions, and participating in multidisciplinary antimicrobial stewardship teams.

10 Prevention and infection control

Avoiding infections diminishes antibiotic use and curtails the spread of resistant pathogens. Essential measures encompass hand hygiene, cleaning of environments, sterilization and disinfection processes, correct application of personal protective gear, isolation precautions when necessary, safe injection methods, device-care bundles, vaccination, and monitoring. In hospitals, prompt identification of clusters and sharing laboratory results are crucial. The One Health framework acknowledges the link between human health, animal health, food systems, and the environment. Proper use of antimicrobials across all sectors, effective sanitation, management of wastewater, and coordinated monitoring are essential elements in controlling AMR [30]

11 Conclusion

Infections caused by multidrug-resistant bacteria jeopardize contemporary medical practices and necessitate synchronized efforts in science and public health. Resistance occurs via enzymatic drug degradation, alteration of targets, decreased permeability, efflux mechanisms, biofilm production, and gene transfer related to resistance. Novel antibacterial combinations, siderophore antibiotics, and agents directed at resistant Acinetobacter have broadened treatment possibilities for specific infections. Antimicrobial peptides, bacteriophages, CRISPR-derived antimicrobials, anti-virulence compounds, biofilm-targeted therapies, nanocarriers, and immunotherapeutics offer further research pathways, though many are still under investigation. No one approach can conquer all types of resistance. The most efficient response combines precise diagnosis, treatment based on susceptibility, antimicrobial stewardship, infection prevention, monitoring, and ongoing advancement of truly innovative therapies.

References

[1] Giurazza R, Mazza MC, Andini R, Sansone P, Pace MC, Durante-Mangoni E. Emerging treatment options for multidrug-resistant bacterial infections. *Life (Basel)*. 2021;11(6):519. https://doi.org/10.3390/life11060519

[2] Vitiello A, Rezza G, Silenzi A, Salzano A, Alise M, Boccellino MR, et al. Therapeutic strategies to combat increasing rates of multidrug resistant pathogens. *Pharm Res*. 2024;41(8):1557–71. https://doi.org/10.1007/s11095-024-03756-5

[3] Jacobowski AC, Boleti APA, Cruz MV, Santos KFDP, Andrade LRM, Frihling BEF, et al. Combating antimicrobial resistance: innovative strategies using peptides, nanotechnology, phages, quorum sensing interference, and CRISPR-Cas systems. *Pharmaceuticals (Basel)*. 2025;18(8):1119. https://doi.org/10.3390/ph18081119

[4] Rathored J, Budhbaware T. Integrative strategies against multidrug-resistant bacteria: synthesizing novel antimicrobial frontiers for global health. *Microb Pathog*. 2025;208:108018. https://doi.org/10.1016/j.micpath.2025.108018

[5] Geng S, Tang Q, Shi N. Antibiotic-sparing strategies for multidrug-resistant organism (MDRO) infections. *Front Pharmacol*. 2025;16:1653424. https://doi.org/10.3389/fphar.2025.1653424

[6] Vázquez-López R, et al. A comprehensive overview of antibacterial agents for combating multidrug-resistant bacteria: the current landscape, development, future opportunities, and challenges. *Antibiotics (Basel)*. 2025;14(3):221. https://doi.org/10.3390/antibiotics14030221

[7] Novel antibacterial approaches and therapeutic strategies. *Antibiotics (Basel)*. 2025;14(4):404. https://doi.org/10.3390/antibiotics14040404

[8] Imran M, Ahmad MN, Dasgupta A, Rana P, Srinivas N, Chopra S. Novel approaches for the treatment of infections due to multidrug-resistant bacterial pathogens. *Future Med Chem*. 2022;14(15):1133–48. https://doi.org/10.4155/fmc-2022-0029

[9] El-Sayed SE, Messiha AA, Zafer M. Effective alternative strategies to combat challenges associated with MDR bacterial infections: drug repurposing, role of artificial intelligence, and novel therapeutic options. *J Infect Public Health*. 2026;19(2):103058. https://doi.org/10.1016/j.jiph.2025.103058

[10] Acharya A, Singh AK, Tiwari S, Kaushal B, Ghosh J, Kumar A, et al. Combatting antibiotic resistance: challenges and emerging therapeutic strategies. *Future Microbiol*. 2026;21(1):87–103. https://doi.org/10.1080/17460913.2026.2627823

[11] Peng H, Chen IA, Qimron U. Engineering phages to fight multidrug-resistant bacteria. *Chem Rev*. 2025;125(2):933–71. https://doi.org/10.1021/acs.chemrev.4c00681

[12] Abdelkader K, Gerstmans H, Saafan A, De Vos D, Briers Y. The preclinical and clinical progress of bacteriophages and their lytic enzymes: the parts are easier than the whole. *Viruses*. 2019;11(2):96. https://doi.org/10.3390/v11020096

[13] Bhale B, Shirodkar S, Sawarkar S, Omri A. Phage therapy: innovations, challenges, and future directions in combating superbugs and antibiotic resistance. *Expert Rev Anti Infect Ther*. 2026;24(2):213–37. https://doi.org/10.1080/14787210.2026.2632669

[14] Alzahrani AJ. Bacteriophage therapy against multidrug resistant bacterial infections demonstrates clinical advances and engineering innovations between 2020–2026. *Front Microbiol*. 2026;17:1865548. https://doi.org/10.3389/fmicb.2026.1865548

[15] Sahu P, Satapathy T. Beyond new pills: integrative strategies to overcome multidrug-resistant bacteria. *Arch Microbiol*. 2026;208(6). https://doi.org/10.1007/s00203-026-04817-6

[16] Yan B, Yan C, Ding Y, Cai S, Wang Y, Agbo E, et al. Multidrug-resistant Pseudomonas aeruginosa infections: current status, challenges, and prospects of phage therapy. *Front Microbiol*. 2026;16:1723885. https://doi.org/10.3389/fmicb.2025.1723885

[17] Piracha ZZ, Saeed U. Next-generation bacteriophage therapeutic systems: CRISPR-based engineering, near-infrared bioimaging, and precision strategies for treating multidrug-resistant and extensively drug-resistant bacterial infections. *Front Microbiol*. 2026. https://doi.org/10.3389/fmicb.2026.1748742

[18] Innovative strategies in the fight against bacterial infections: phage therapy, nanotechnology, and new antimicrobial agents for multidrug-resistant pathogens. *Results Chem*. 2025;15:102304. https://doi.org/10.1016/j.rechem.2025.102304

[19] Combating antibiotic resistance: mechanisms, multidrug-resistant pathogens, and novel therapeutic approaches: an updated review. *Pharmaceuticals (Basel)*. 2025;18(3):402. https://doi.org/10.3390/ph18030402

[20] Effective alternative strategies to combat challenges associated with MDR bacterial infections: drug repurposing, role of artificial intelligence, and novel therapeutic options. *J Infect Public Health*. 2026;19(2):103058. https://doi.org/10.1016/j.jiph.2025.103058

[21] Machado E, Sousa JC. New antibiotics for treating infections caused by multidrug-resistant bacteria. *Antibiotics (Basel)*. 2025;14(10):997. https://doi.org/10.3390/antibiotics14100997

[22] Tängdén T, Carrara E, Hellou MM, Yahav D, Paul M. Introducing new antibiotics for multidrug-resistant bacteria: obstacles and the way forward. *Clin Microbiol Infect*. 2025. https://doi.org/10.1016/j.cmi.2024.09.025

[23] Windham S, Kollef MH. How to use new antibiotics in the therapy of serious multidrug resistant Gram-negative infections? *Curr Opin Infect Dis*. 2022;35(6):561–7. https://doi.org/10.1097/QCO.0000000000000858

[24] Macesic N, Uhlemann AC, Peleg AY. Multidrug-resistant Gram-negative bacterial infections. *Lancet*. 2025;405(10474):257–72. https://doi.org/10.1016/S0140-6736(24)02081-6

[25] Delroba K, Alaei M, Khalili H. Treatment options for infections caused by multidrug-resistant Gram-negative bacteria: a guide to good clinical practice. *Future Microbiol*. 2023;18:287–94. https://doi.org/10.2217/fmb-2022-0160

[26] Jhalora V, Bist R. A comprehensive review of molecular mechanisms leading to the emergence of multidrug resistance in bacteria. *Indian J Microbiol*. 2025;65(2):844–65. https://doi.org/10.1007/s12088-024-01384-6

[27] Birlutiu V, Birlutiu RM. An overview of the epidemiology of multidrug resistance and bacterial resistance mechanisms: what solutions are available? A comprehensive review. *Microorganisms*. 2025;13(9):2194. https://doi.org/10.3390/microorganisms13092194

[28] Temesgen AB, Shiferaw SA. Antimicrobial multidrug resistance and mechanisms of action: an overview. *Biomed Res Int*. 2025;2025:8847267. https://doi.org/10.1155/bmri/8847267

[29] Elshobary ME, Badawy NK, Ashraf Y, Zatioun AA, Masriya HH, Ammar MM, et al. Combating antibiotic resistance: mechanisms, multidrug-resistant pathogens, and novel therapeutic approaches: an updated review. *Pharmaceuticals (Basel)*. 2025;18(3):402. https://doi.org/10.3390/ph18030402

[30] Phages as antimicrobials against multi-drug resistant bacteria. *Front Microbiol*. 2026;17:1747240. https://doi.org/10.3389/fmicb.2026.1747240