Journal of Molecular Biosciences and Engineering

Review Article

Molecular Mechanisms of Bacterial Antibiotic Resistance

Allahverdi U. Shahveranov[1], Ayaz M. Mammadov[2], and Nigar M. Hamidova[3]

[1]Department of Internal Medicine, Helios Dr. Horst-Schmidt Kliniken, Ludwig-Erhard-Straße 100, 65199 Wiesbaden, Germany
[2]Department of Natural Sciences, School of Advanced Technologies and Innovation Engineering, Western Caspian University, 17 A, Ahmad Rajabli Street, III Parallel, AZ1072 Baku, Azerbaijan
[3]Department of Vascular Medicine, St. Josefs-Hospital, Beethovenstraße 20, 65189 Wiesbaden, Germany

Received: 02.02.2026 Accepted: 22.04.2026 Published: 29.05.2026

https://doi.org/10.54414/CLFK4027

Abstract

Antibiotic resistance is a prevalent threat to global health and humankind, guided by varied bacterial adaptations that reduce the efficiency of currently available and in-use antibacterial drugs. In 2021, we estimated 4.71 million deaths were associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR. Trends in AMR mortality over the past 31 years varied substantially by age and location. From 1990 to 2021, deaths from AMR decreased by more than 50% among children younger than 5 years, yet increased by over 80% for adults 70 years and older. In this mini review, we present an effective interpretation of the major molecular systems of resistance, including target alteration, drug inactivation mechanisms, horizontal gene transfer, clinical implications, and strategic solutions. Apart from these classical mechanisms, we also acknowledge adaptive physiological pathways, similar to biofilm formation and persistence, that contribute to antimicrobial treatment failures. Comprehending these mechanisms is crucial for conducting an improvement of modern antibiotics and stewardship programs.

Keywords: antimicrobial resistance, biofilm formation, horizontal gene transfer, multidrug resistance

1. Introduction

Bacterial antimicrobial resistance (AMR) is actually one of the most critical challenges in clinical management of many infectious diseases. The common resistance mechanisms arise from both genetic and epigenetic pathologies, such as mutations and molecular injuries, and the addition of resistance genes from different organisms, frequently under selective pressure from antibiotic exposure (Figure 1). AMR mortality decreased for children younger than 5 years in all super-regions, whereas AMR mortality in people 5 years and older increased in all super-regions. For both deaths associated with and deaths attributable to AMR, meticillin-resistant Staphylococcus aureus increased the most globally (from 261 000 associated deaths and 57 200 attributable deaths in 1990, to 550 000 associated deaths and 130 000 attributable deaths in 2021) [1]. By 2050, around 2 million people, the majority aged 70 and over, could die from drug-resistant infections each year [2]. Antibiotics and antibiotic biosynthetic pathways are believed to have evolved over millions of years, suggesting that antibiotic resistance is an equally ancient phenomenon (Figure 2) [3], [4]. The increase of multidrug-resistant organisms continues to affect the effectiveness of clinically essential drugs, which leads to serious morbidity and mortality and also to healthcare burdens.

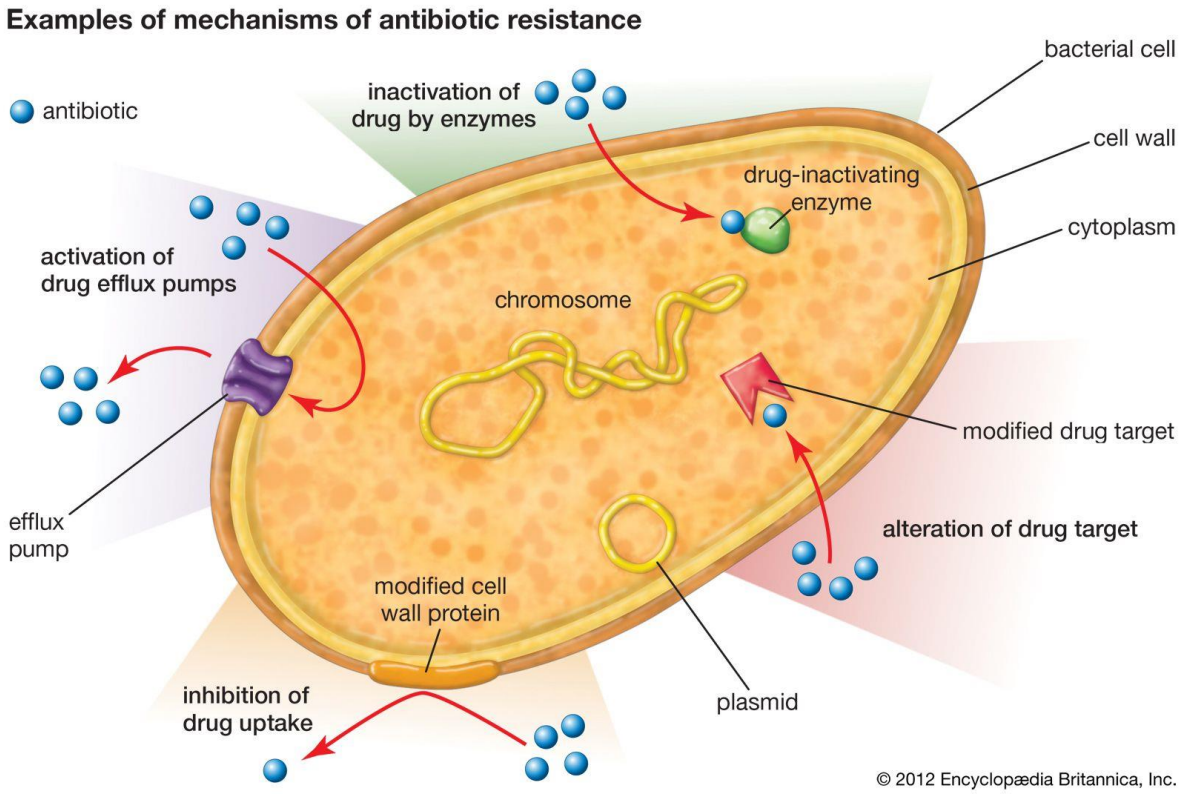

Figure 1. Mechanisms of antibiotic resistance in bacteria.
Source: Adapted from Encyclopaedia Britannica [5].

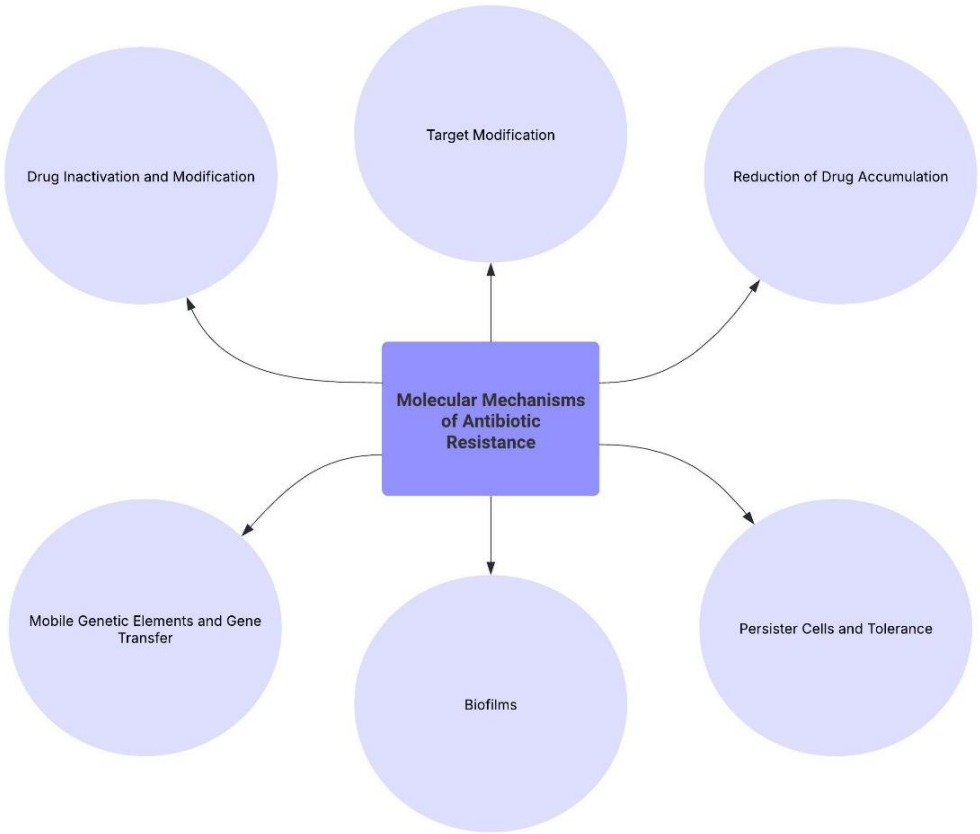

Figure 2. Six mechanisms of AMR.
Source: Created with Lucid.

2. Classical Molecular Resistance Mechanisms

2.1. Antibiotic Inactivation

One of the most common mechanisms is the enzymatic inactivation of drugs. One of the most pervasive ways is the production of beta-lactamases, which hydrolyse the beta-lactam ring crucial to penicillins, cephalosporins, and carbapenems. Correspondingly, enzymes that modify aminoglycosides through acetylation, phosphorylation, or adenylation reduce antibiotic binding to ribosomal targets. Antibiotic-inactivating enzymes can accomplish this task by one of two means: by eradicating the essential reactive center of the antibiotic or by modifying the drug in a manner that impairs target binding [6].

2.2. The Modification of Target

The alterations by bacteria in antibiotic targets that affect drug affinity. Mutations and unknown molecular alterations in ribosomal RNA and proteins confer resistance to aminoglycosides and macrolides, while changes in DNA gyrase or topoisomerase IV can lead to fluoroquinolone resistance. These modifications may originate through mutation or be carried on mobile gene elements. Modification of the antibiotic target is a resistance strategy that is increasingly prevalent among pathogens. Examples include resistance to glycopeptide and polymyxin antibiotics that occurs via chemical modification of their molecular targets in the cell envelope. Similarly, many ribosome-targeting antibiotics are impaired by methylation of the rRNA [7].

2.3. Decreasing of Antibiotic Accumulation

Decreased intracellular antibiotic concentration is another important resistance mechanism. For example, Gram-negative bacteria carry an outer membrane that inherently restricts the entry of multiple antibiotics. Alterations of porin expression can further limit uptake. There are two main ways in which porin changes can limit drug uptake: a decrease in the number of porins present, and mutations that change the selectivity of the porin channel [8]. Members of the Enterobacteriaceae are known to become resistant by reducing the number of porins (and sometimes stopping production entirely of certain porins). As a group, these bacteria reduce porin number as a mechanism for resistance to carbapenems [9]. Furthermore, efflux pumps actively eliminate a broad range of antibiotics from the cytosol, leading to multidrug resistance phenotypes.

3. Gene Transfer and Mobile Genetic Elements

The resistance genes are extensively disseminated via transposons, integrons, and plasmids. The complex process of antibiotic resistance genes (ARG) transmission via horizontal gene transfer (HGT) conjugation, transformation, transduction, and the more recently identified vesiduction is given in a review by Liu et al. [10]. Horizontal Gene Transfer (HGT) permits these elements to shift between different bacterial species, enabling rapid distribution of resistance genes within microbial strains. By examining how mobile genetic elements (MGEs) in Klebsiella pneumoniae serve as carriers of both virulence and resistance genes, Han et al. [11] summarize MGE types and how they contribute to the establishment of harmful strains such as carbapenem-resistant hypervirulent K. pneumoniae (CR-hvKP). Plasmid resistance determinants are often associated with multiple drug resistance phenotypes, presenting essential clinical problems.

4. Biofilms, Persister Cells, and Tolerance

4.1. Biofilms

Biofilms are organised bacterial communities that stick together and are embedded in an extracellular matrix, supplying resistance to antibiotics. For acute and chronic infections, underlying health conditions such as immunodeficiencies, diabetes, and cystic fibrosis can lead to commensal biofilm organisms becoming opportunistic pathogens, often manifesting as polymicrobial biofilm infections of the lungs, foot ulcers, bone and deep tissues, and indwelling medical devices [12], [13], [14], [15], [16]. These infections are refractory to treatment due to species diversity, variability of the infectious microenvironment [17], and the upregulation of virulence and resistance pathways via quorum sensing and metabolic interaction [17], [18], [19]. Furthermore, antimicrobial resistance is promoted through limiting drug penetration, the presence of dormant “persister”

cells, and the enhancement of horizontal gene transfer [20]. These result in either chronic, recurring disease or systemic life-threatening infection [21], [22].

4.2. Persister Cells and Tolerance

The multiple bacterial populations can produce persister cells that do not die and do not respond to the therapy of antimicrobial regimens. Persisters are largely responsible for high levels of biofilm tolerance to antimicrobials, but virtually nothing was known about their biology. Tolerance of Escherichia coli to ampicillin and ofloxacin was tested at different growth stages to gain insight into the nature of persisters. The number of persisters did not change in the lag or early exponential phase, and increased dramatically in the mid-exponential phase. Similar dynamics were observed with Pseudomonas aeruginosa (ofloxacin) and Staphylococcus aureus (ciprofloxacin and penicillin). This shows that the production of persisters depends on the growth stage [23].

5. Clinical Implications and Strategic Solutions

Antibiotic resistance mechanisms lead to a significant threat to global healthcare, resulting in severe medical therapeutic implications. This results in increased mortality and extended hospitalisations. Physicians could use second- and third-line agents, which can be more toxic medications. Infectious treatments could be delayed. Strategic solutions for healthcare systems in all countries are improving the programs of antibiotic stewardship, early diagnostics, and development of novel antibiotics and alternatives like bacteriophages and antimicrobial peptides.

6. Conclusion

Antibiotic resistance (AR) in bacteria is a crucial global health crisis and arises from massive overuse of antimicrobial drugs and a combination of ineffective structural, enzymatic, and physiological processes. These molecular mechanisms span from antibiotic inactivation, target modification, mobile gene transfers, biofilms, and persister cells to organised bacterial communities such as biofilms. Critical effective responses require a variety of approaches integrating molecular insights, clinical practice, and stewardship programs.

Author Contributions

All authors contributed to the conception, literature review, writing, editing, and final approval of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This research received no external funding.

Acknowledgment

The authors acknowledge the valuable scientific resources and literature databases used in conducting this study.

Abbreviations

Antimicrobial Resistance (AMR), Ribonucleic Acid (RNA), Deoxyribonucleic Acid (DNA), Antibiotic Resistance Genes (ARG), Horizontal Gene Transfer (HGT), Mobile Genetic Elements (MGEs), Carbapenem-Resistant Hypervirulent K. Pneumoniae (CR-hvKP), Antibiotic Resistance (AR).

References

[1] Naghavi M, Vollset SE, Ikuta KS, Swetschinski LR, Gray AP, Wool EE, Aguilar GR, Mestrovic T, Smith G, Han C, Hsu RL. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. The Lancet. 2024 Sep 28;404(10459):1199-226. https://doi.org/10.1016/s0140-6736(24)01885-3

[2] Naddaf M. 40 million deaths by 2050: toll of drug-resistant infections to rise by 70%. Nature. 2024;633(8031):747-8. https://doi.org/10.1038/d41586-024-03033-w

[3] Barlow M, Hall BG. Phylogenetic analysis shows that the OXA b-lactamase genes have been on plasmids for millions of years. Journal of molecular evolution. 2002 Sep;55(3):314-21. https://doi.org/10.1007/s00239-002-2328-y

[4] Hall BG, Barlow M. Evolution of the serine β-lactamases: past, present and future. Drug resistance updates. 2004 Apr 1;7(2):111-23. https://doi.org/10.1016/j.drup.2004.02.003

[5] Morier D. Antibiotic resistance [Internet]. Encyclopedia Britannica; 2026 May 5 [cited 2026 January 19]. Available from: https://www.britannica.com/science/antibiotic-resistance?utm_source

[6] D'Costa VM, Wright GD. Biochemical logic of antibiotic inactivation and modification. In Antimicrobial Drug Resistance: Mechanisms of Drug Resistance, Volume 1 2017 Jun 21 (pp. 97-113). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-46718-4_8

[7] Schaenzer AJ, Wright GD. Antibiotic resistance by enzymatic modification of antibiotic targets. Trends in molecular medicine. 2020 Aug 1;26(8):768-82. https://doi.org/10.1016/j.molmed.2020.05.001

[8] Kumar A, Schweizer HP. Bacterial resistance to antibiotics: active efflux and reduced uptake. Advanced drug delivery reviews. 2005 Jul 29;57(10):1486-513. https://doi.org/10.1016/j.addr.2005.04.004

[9] Cornaglia G, Mazzariol A, Fontana R, Satta G. Diffusion of carbapenems through the outer membrane of enterobacteriaceae and correlation of their activities with their periplasmic concentrations. Microbial drug resistance. 1996 Jun;2(2):273-6. https://doi.org/10.1089/mdr.1996.2.273

[10] Liu F, Luo Y, Xu T, Lin H, Qiu Y, Li B. Current examining methods and mathematical models of horizontal transfer of antibiotic resistance genes in the environment. Frontiers in microbiology. 2024 Apr 4;15:1371388. https://doi.org/10.3389/fmicb.2024.1371388

[11] Han B, Feng C, Jiang Y, Ye C, Wei Y, Liu J, Zeng Z. Mobile genetic elements encoding antibiotic resistance genes and virulence genes in Klebsiella pneumoniae: Important pathways for the acquisition of virulence and resistance. Frontiers in Microbiology. 2025 Feb 24;16:1529157. https://doi.org/10.3389/fmicb.2025.1529157

[12] Coburn B, Wang PW, Diaz Caballero J, Clark ST, Brahma V, Donaldson S, Zhang Y, Surendra A, Gong Y, Elizabeth Tullis D, Yau YC. Lung microbiota across age and disease stage in cystic fibrosis. Scientific reports. 2015 May 14;5(1):10241. https://doi.org/10.1038/srep10241

[13] Rossana C, Meloni M, Giurato L, Lazaro-Martinez JL, Aikaterini A, Valeria R, Bellia A, Lauro D, Uccioli L. Microbiological and clinical characteristics of infected diabetic foot ulcers managed in a tertiary level diabetic foot service. The International Journal of Lower Extremity Wounds. 2026 Mar;25(1):74-80. https://doi.org/10.1177/15347346231178642

[14] Naamany E, Shiber S, Duskin-Bitan H, Yahav D, Bishara J, Sagy I, Granat N, Drescher M. Polymicrobial and monomicrobial necrotizing soft tissue infections: comparison of clinical, laboratory, radiological, and pathological hallmarks and prognosis. A retrospective analysis. Trauma Surgery & Acute Care Open. 2021 Oct 7;6(1). https://doi.org/10.1136/tsaco-2021-000745

[15] Carbonell-Rosell C, Lakhani K, Lung M, Nadal P, Rodriguez-Pardo D, Corona PS. Etiology and antimicrobial resistance patterns in chronic osteomyelitis of the tibia: an 11-year clinical experience. Archives of Orthopaedic and Trauma Surgery. 2024 Feb;144(2):773-81. https://doi.org/10.1007/s00402-023-05095-3

[16] Caldara M, Belgiovine C, Secchi E, Rusconi R. Environmental, microbiological, and immunological features of bacterial biofilms associated with implanted medical devices. Clinical microbiology reviews. 2022 Apr 20;35(2):e00221-20. https://doi.org/10.1128/cmr.00221-20

[17] Bjarnsholt T, Whiteley M, Rumbaugh KP, Stewart PS, Jensen PØ, Frimodt-Møller N. The importance of understanding the infectious microenvironment. The Lancet Infectious Diseases. 2022 Mar 1;22(3):e88-92. https://doi.org/10.1016/s1473-3099(21)00122-5

[18] Paul S, Todd OA, Eichelberger KR, Tkaczyk C, Sellman BR, Noverr MC, Cassat JE, Fidel Jr PL, Peters BM. A fungal metabolic regulator underlies infectious synergism during Candida albicans-Staphylococcus aureus intra-abdominal co-infection. Nature communications. 2024 Jul 9;15(1):5746. https://doi.org/10.1038/s41467-024-50058-w

[19] Ciofu O, Moser C, Jensen PØ, Høiby N. Tolerance and resistance of microbial biofilms. Nature Reviews Microbiology. 2022 Oct;20(10):621-35. https://doi.org/10.1038/s41579-022-00682-4

[20] Liu HY, Prentice EL, Webber MA. Mechanisms of antimicrobial resistance in biofilms. npj Antimicrobials and Resistance. 2024 Oct 1;2(1):27. https://doi.org/10.1038/s44259-024-00046-3

[21] Zhong L, Dong Z, Liu F, Li H, Tang K, Zheng C, Wang L, Zhang K, Cai J, Zhou H, Cui W. Incidence, clinical characteristics, risk factors and outcomes of patients with mixed Candida/bacterial bloodstream infections: a retrospective study. Annals of clinical microbiology and antimicrobials. 2022 Nov 1;21(1):45. https://doi.org/10.1186/s12941-022-00538-y

[22] Sidhu MS, Cooper G, Jenkins N, Jeys L, Parry M, Stevenson JD. Prosthetic fungal infections: poor prognosis with bacterial co-infection. The bone & joint journal. 2019 May 1;101(5):582-8. https://doi.org/10.1302/0301-620x.101b5.bjj-2018-1202.r1

[23] Keren I, Kaldalu N, Spoering A, Wang Y, Lewis K. Persister cells and tolerance to antimicrobials. FEMS microbiology letters. 2004 Jan 1;230(1):13-8. https://doi.org/10.1016/s0378-1097(03)00856-5