e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 13, Issue 5; 2025, 26-33

Antibiotics: Classification, Mechanism of Action, Resistance, and Future Perspectives

Akshat Sharma[1], Suresh Poonia[1], Danish Khan[1], Chandra Prakash Mishra[2], Pawan Kumar Basniwal[3]

[1]Scholars, Sri Balaji College of Pharmacy, Jaipur
[2]Assistant Professor, Sri Balaji College of Pharmacy, Jaipur
[3]Professor & Principal, Sri Balaji College of Pharmacy, Jaipur

Received: 10-08-2025 / Revised: 24-08-2025 / Accepted: 23-09-2025
Corresponding author: Chandra Prakash Mishra
Conflict of interest: No conflict of interest.

Abstract:

Antibiotics are powerful chemotherapeutic agents used to prevent and treat bacterial infections. Antibiotics have revolutionized medicine, saving countless lives since their discovery in the early 20th century. However, the origin of antibiotics is now overshadowed by the alarming rise in antibiotic resistance. This global crisis stems from the relentless adaptability of microorganisms, driven by misuse and overuse of antibiotics. This article explores the origin of antibiotics and the subsequent emergence of antibiotic resistance. It delves into the mechanisms employed by bacteria to develop resistance, highlighting the dire consequences of drug resistance, including compromised patient care, increased mortality rates, and escalating healthcare costs. The article elucidates the latest strategies against drug-resistant microorganisms, encompassing innovative approaches such as phage therapy, CRISPR-Cas9 technology, and the exploration of natural compounds. Moreover, it examines the profound impact of antibiotic resistance on drug development, rendering the pursuit of new antibiotics economically challenging. The limitations and challenges in developing novel antibiotics are discussed, along with hurdles in the regulatory process that hinder progress in this critical field. Proposals for modifying the regulatory process to facilitate antibiotic development are presented. The withdrawal of major pharmaceutical firms from antibiotic research is examined, along with potential strategies to re-engage their interest. The article also outlines initiatives to overcome economic challenges and incentivize antibiotic development, emphasizing international collaborations and partnerships. Finally, the article sheds light on government-led initiatives against antibiotic resistance, with a specific focus on the Middle East. It discusses the proactive measures taken by governments in the region, such as Saudi Arabia and the United Arab Emirates, to combat this global threat. In the face of antibiotic resistance, a multifaceted approach is imperative. This article provides valuable insights into the complex landscape of antibiotic development, regulatory challenges, and collaborative efforts required to ensure a future where antibiotics remain effective tools in safeguarding public health.

Keywords: antibiotic resistance, drug designing, bacterial mutation, bacterial evolution, horizontal gene transfer, public and agricultural health.

Introduction

Antibiotics are chemical substances produced naturally, semi-synthetically, or synthetically that inhibit the growth of or destroy microorganisms, especially bacteria. The term antibiotic was first coined by Selman Waksman in 1942 to describe substances produced by microorganisms that suppress the growth of other microbes. The discovery of penicillin by Alexander Fleming in 1928 marked a revolutionary milestone in medical history. Subsequent discoveries of streptomycin, tetracycline, erythromycin, and many others further expanded the arsenal of antimicrobial agents. However, the irrational and extensive use of antibiotics has led to the emergence of antibiotic resistance (ABR), now recognized as a global health crisis by the World Health Organization (WHO).[1]

The history of using antimicrobial agents to combat infections is rich, dating back to ancient civilizations where various natural extracts were employed for their healing properties. Some of these extracts, originating from plants and molds, exhibited antibacterial properties, even before the term “antibiotics” was coined [2]. The introduction of the term “antibiotics” was the result of pioneering work by American microbiologist Selman Waksman and his team, who successfully isolated chemical substances from microorganisms capable of inhibiting the growth of other microbes [3]. While the concept of using microorganisms to combat infections has ancient roots, it was Alexander Fleming’s serendipitous discovery of penicillin in 1928 that marked the inception of modern antibiotic therapy [4]. Fleming’s discovery bridged the gap between ancient knowledge, such as the Egyptians’ use of moldy bread to treat infection, and the era of antibiotics [5]. The post-World War II period, often referred to as the “golden era” of antibiotic discovery, witnessed the identification of numerous antibiotic classes that continue to be used today [6]. The advent of penicillin rapidly propagated the belief that infections could be effectively controlled with antibiotics, despite earlier use of sulfonamides as the first antimicrobials, which faced limitations due to emerging resistance mechanisms that persist to this day [7]. Interestingly, the penicillin discovery team identified penicillinase, a bacterium capable of degrading penicillin, even before widespread access to the antibiotic [8]. Subsequent decades brought forth remarkable progress, marked by the development of antibiotics like streptomycin, chloramphenicol, tetracyclines, erythromycin, vancomycin, cephalosporins, and others. This expansion of the antibiotic arsenal made previously fatal diseases treatable, cementing the antibiotic age [9]. The post-World War II era also saw the emergence of semi-synthetic antibiotics like amoxicillin and quinolones, notable for their enhanced stability and broader antibacterial spectra. Antibiotics such as vancomycin played pivotal roles in combating drug-resistant bacterial strains, particularly methicillin-resistant Staphylococcus aureus (MRSA). Innovations continued with the development of macrolides, third-generation cephalosporins, daptomycin, and linezolid, addressing Gram-negative resistance and enhancing antibiotic pharmacokinetics [10]. However, despite these advancements, antibiotic-resistant bacterial strains have proliferated in recent decades [11], leading to a reassessment of antibiotic usage, increased awareness of antibiotic resistance, and the implementation of antibiotic stewardship programs, alongside the exploration of novel strategies like phage therapy, combination therapies, and precision-medicine approaches to combat drug-resistant bacteria [12].

The global scenario regarding antibiotic resistance remains a pressing issue for public health, with a consistent upward trend in resistance prevalence over the past few decades. This phenomenon extends its reach to a broad spectrum of bacteria, rendering many antibiotics less effective or entirely impotent against infections. Consequently, once easily treatable common infections have become more formidable adversaries, resulting in prolonged hospitalizations, elevated healthcare expenses, and heightened mortality rates.

One of the paramount challenges associated with antibiotic resistance is the sluggish pace of new antibiotic development. Several pharmaceutical companies have withdrawn from antibiotic research and development, due to the low profitability of these drugs. Crafting a novel antibiotic is a protracted and costly endeavor, which has led to diminished enthusiasm for innovation in this vital medical domain.[13]

The unwarranted and incorrect use of antibiotics continues to be a substantial contributor to resistance development. Antibiotics are frequently prescribed when unnecessary, both in healthcare settings and for common community illnesses. Furthermore, the use of antibiotics in agriculture and animal husbandry exacerbates resistance dissemination, particularly through practices such as using antibiotics as growth promoters in livestock, potentially transmitting resistance to humans through the food chain.[14]

Efforts to combat antibiotic resistance have gained momentum through global initiatives and organizations like the World Health Organization (WHO). These entities work diligently to heighten awareness about antibiotic resistance, champion responsible antibiotic use, and advocate for innovative antibiotic research. The One Health approach, acknowledging the interconnectedness of human, animal, and environmental health, has gained traction as a comprehensive strategy for addressing antibiotic resistance. This approach recognizes that the application of antibiotics in any one sector can have repercussions on resistance in other sectors. Notably, regional variations exist in antibiotic resistance rates and trends, contingent on dissimilar healthcare practices, antibiotic usage patterns, and regulatory frameworks. In summary, antibiotic resistance remains a formidable global public health concern. While significant strides have been made in raising awareness and promoting responsible antibiotic use, the inexorable ascent of antibiotic resistance and the dearth of new antibiotic development underscore the imperative need for continuous efforts to combat this critical issue. The collaborative endeavors of healthcare professionals, researchers, policymakers, and the public remain pivotal to mitigating the impact of antibiotic resistance on global health.[15]

The primary objectives and aims of this comprehensive review article are to address the global challenge of antibiotic resistance, explore innovative strategies against drug-resistant microorganisms, examine economic challenges in antibiotic development, and propose strategies to re-engage pharmaceutical firms. It emphasizes the importance of international collaborations and government-led initiatives in combating antibiotic resistance.[16]

Classification of Antibiotics

Antibiotics can be classified in several ways:

Based on Spectrum of Activity

- **Broad-spectrum antibiotics:** Active against a wide range of Gram-positive and Gram-negative bacteria (e.g., tetracyclines, chloramphenicol).

- **Narrow-spectrum antibiotics:** Effective against specific groups of bacteria (e.g., penicillin G for Gram-positive cocci).

Based on Chemical Structure

1. **β-lactam antibiotics:** Penicillins, cephalosporins, carbapenems, monobactams.
2. **Aminoglycosides:** Streptomycin, gentamicin, amikacin.
3. **Macrolides:** Erythromycin, clarithromycin, azithromycin.
4. **Tetracyclines:** Tetracycline, doxycycline, minocycline.
5. **Fluoroquinolones:** Ciprofloxacin, levofloxacin, moxifloxacin.
6. **Sulfonamides:** Sulfamethoxazole, sulfadiazine.
7. **Glycopeptides:** Vancomycin, teicoplanin.[17]

Table 1: Based on Mode of Action

Mechanism	Example Antibiotics	Target Site
Inhibition of cell wall synthesis	Penicillins, Cephalosporins	Peptidoglycan synthesis
Inhibition of protein synthesis	Aminoglycosides, Macrolides, Tetracyclines	Ribosomal subunits
Inhibition of nucleic acid synthesis	Fluoroquinolones, Rifamycins	DNA gyrase, RNA polymerase
Inhibition of metabolic pathways	Sulfonamides, Trimethoprim	Folic acid synthesis
Disruption of cell membrane	Polymyxins	Cell membrane integrity

Mechanism of Action of Antibiotics

Each class of antibiotic targets a specific bacterial process or structure:

Inhibitors of Cell Wall Synthesis

β-lactam antibiotics (Penicillins, Cephalosporins) inhibit the transpeptidation reaction by binding to Penicillin-Binding Proteins (PBPs), preventing cell wall cross-linking.

Vancomycin, a glycopeptide, binds to the D-Ala-D-Ala terminus of peptidoglycan precursors, blocking polymerization.[18]

Inhibitors of Protein Synthesis

- **Aminoglycosides** bind irreversibly to the 30S ribosomal subunit, causing misreading of mRNA.
- **Macrolides** and **chloramphenicol** bind to the 50S subunit, inhibiting peptide bond formation.
- **Tetracyclines** prevent attachment of aminoacyl-tRNA to the ribosomal A-site.

Inhibitors of Nucleic Acid Synthesis

- **Fluoroquinolones** inhibit **DNA gyrase** and **topoisomerase IV**, blocking DNA replication.
- **Rifampicin** inhibits **RNA polymerase**, suppressing RNA synthesis.[19]

Inhibitors of Metabolic Pathways

Sulfonamides compete with para-aminobenzoic acid (PABA) for dihydropteroate synthase, and trimethoprim inhibits dihydrofolate reductase, both blocking folate synthesis.

Disruptors of Cell Membrane

Polymyxins interact with phospholipids of the bacterial cell membrane, causing leakage of intracellular contents.[20]

Mechanisms of Antibiotic Resistance: Resistance mechanisms can be intrinsic (natural) or acquired through mutation or gene transfer (via plasmids, transposons, or bacteriophages).

Enzymatic Degradation or Modification

Production of β-lactamases that hydrolyze β-lactam rings (e.g., TEM, SHV, ESBL, NDM-1 enzymes).

Alteration of Target Sites

Mutation or modification in PBPs, ribosomal proteins, or DNA gyrase reduces drug binding (e.g., MRSA altering PBPs).

Efflux Pumps

Active expulsion of antibiotic molecules out of the bacterial cell (common in tetracycline resistance).

Reduced Permeability

Alteration or loss of porin channels in Gram-negative bacteria reduces drug uptake.

Biofilm Formation

Bacteria in biofilms exhibit higher resistance due to limited antibiotic penetration and metabolic dormancy.[21]

Factors Responsible for Antibiotic Resistance

1. **Overuse and misuse** of antibiotics in humans and animals.
2. **Incomplete courses** of antibiotic therapy.
3. **Self-medication** without prescription.
4. **Use of antibiotics in animal feed** and agriculture.
5. **Lack of infection control** in hospitals and communities.
6. **Insufficient research** and investment in new antibiotics.[22]

Global Impact of Antibiotic Resistance

According to WHO (2024), antibiotic resistance is among the top 10 global public health threats. Infections such as tuberculosis, gonorrhea, and urinary tract infections are becoming increasingly difficult to treat. The economic burden is also significant due to prolonged hospital stays, need for expensive drugs, and increased mortality.

Strategies to Combat Antibiotic Resistance

Rational Use of Antibiotics

- Prescribe antibiotics only when necessary and based on culture-sensitivity results.
- Avoid broad-spectrum antibiotics when narrow-spectrum agents are effective.

Antibiotic Stewardship Programs

- Implementation of hospital-based policies to optimize antibiotic use.
- Monitoring and surveillance of resistance patterns.

Development of New Therapeutic Approaches

- Discovery of novel antimicrobial agents targeting new pathways.
- Use of β-lactamase inhibitors (e.g., clavulanic acid).
- Exploration of bacteriophage therapy, antimicrobial peptides, and CRISPR-based systems.

Public Awareness and Education

- Educating healthcare professionals and the public about the risks of misuse.
- Promoting hygiene, vaccination, and infection control practices.[23]

Future Perspectives

The future of antibiotic therapy depends on innovation and global collaboration.

Research into nanotechnology-based drug delivery, phage therapy, synthetic biology, and AI-guided drug discovery offers promising solutions.

Preventing resistance also requires coordinated international efforts through surveillance, stewardship, and strict policy implementation. Future research endeavors must prioritize innovative drug design, explore alternative antimicrobial approaches like phage therapy, and delve into the environmental aspects of antibiotic resistance. The adoption of the One Health approach, which acknowledges the interconnectedness of human, animal, and environmental health, will be central in tackling antibiotic resistance holistically. Finally, by harnessing the full potential of AI and incorporating the latest developments, the healthcare sector is better equipped to combat antibiotic resistance while ensuring responsible antibiotic use. As the threat of antibiotic resistance looms large, global cooperation and innovative solutions are essential to ensure the continued effectiveness of antibiotics in safeguarding public health.[24]

Conclusion

Antibiotics remain one of the most valuable medical discoveries in history. However, their effectiveness is diminishing due to increasing resistance. A combined effort involving rational drug use, continuous research, strict policy enforcement, and global cooperation is essential to preserve these life-saving drugs for future generations. The antibiotic era has witnessed a complex journey, marked by pivotal shifts in both global evolutionary and human historical contexts.

The advent of antibiotics heralded a medical revolution, empowering the medical community with potent tools to combat bacterial infections. However, the widespread and often indiscriminate use of antibiotics precipitated a swift and concerning rise in antibiotic resistance, as bacteria developed mechanisms to resist the drugs' effects. A pressing challenge in this era is the need to curtail the indiscriminate use of antibiotics, seeking more targeted approaches to address pathogens with precision. Research efforts must be dedicated to identifying potential causes of antibiotic resistance, enabling the development of early warning systems and preventive measures to preserve the efficacy of antibiotics. The looming crisis of antibiotic resistance necessitated a fundamental shift in drug development strategies, necessitating the exploration of novel compounds, innovative drug combinations, and alternative therapeutic approaches.

The profound impacts of antibiotic resistance underscore the urgency of developing new therapies capable of tackling multidrug-resistant infections. Future trends in drug development embrace the principles of precision medicine, tailoring treatments according to individual patient profiles. Leveraging cutting-edge technologies like genomics and artificial intelligence, scientists are poised to design more effective antibiotics. Collaboration among scientists, healthcare professionals, policymakers, and the pharmaceutical industry is indispensable in the battle against antibiotic resistance, ensuring long-term solutions for infectious disease management and reshaping the landscape of drug development for the years to come.[25]

References

1. Gould K. Antibiotics: From prehistory to the present day. J. Antimicrob. Chemother. 2016;71:572–575. doi: 10.1093/jac/dkv484.
2. Clardy J., Fischbach M.A., Currie C.R. The natural history of antibiotics. Curr.

Biol. 2009;19:R437–R441. doi: 10.1016/j.cub.2009.04.001

3. Fleming A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. influenzæ. Br. J. Exp. Pathol. 1929;10:226–236. doi: 10.1093/ clinids/2.1.129.
4. Hodgkin D.C. The X-ray analysis of the structure of penicillin. Adv. Sci. 1949;6:85–89.
5. Sheehan J.C., Henery-Logan K.R. The Total Synthesis of Penicillin, V.J. Am. Chem. Soc. 1959;81:3089–3094. doi: 10.1021/ja01521a044.
6. Von Döhren H. Antibiotics: Actions, Origins, Resistance, by C. Walsh. 2003. Volume 13. ASM Press; Washington, DC, USA: 2009. p. 345.
7. Abraham E.P., Chain E. An Enzyme from Bacteria able to Destroy Penicillin. Nature. 1940;146:837. doi: 10.1038/146837a0.
8. Aminov R.I. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. Front. Microbiol. 2010;1:134. doi: 10.3389/fmicb.2010.00134
9. Durand G.A., Raoult D., Dubourg G. Antibiotic discovery: History, methods and perspectives. Int. J. Antimicrob. Agents. 2019;53:371–382. doi: 10.1016/j.ijantimicag.2018.11.010.
10. Iskandar K., Murugaiyan J., Hammoudi Halat D., Hage S.E., Chibabhai V., Adukkadukkam S., Roques C., Molinier L., Salameh P., Van Dongen M. Antibiotic Discovery and Resistance: The Chase and the Race. Antibiotics. 2022;11:182. doi: 10.3390/antibiotics11020182.
11. .Christensen S.B. Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and β-Lactams. Molecules. 2021;26:6057. doi: 10.3390/ molecules26196057.
12. Chait R., Vetsigian K., Kishony R. What counters antibiotic resistance in nature? Nat. Chem. Biol. 2012;8:2–5. doi: 10.1038/nchembio.745.
13. Blair J.M.A., Webber M.A., Baylay A.J., Ogbolu D.O., Piddock L.J.V. Molecular mechanisms of antibiotic resistance. Nat. Rev. Microbiol. 2015;13:42–51. doi: 10.1038/nrmicro3380.
14. Livermore D.M., Blaser M., Carrs O., Cassell G., Fishman N., Guidos R., Levy S., Powers J., Norrby R., Tillotson G., et al. Discovery research: The scientific challenge of finding new antibiotics. J. Antimicrob. Chemother. 2011;66:1941–1944. doi: 10.1093/jac/dkr262.
15. Saga T., Yamaguchi K. History of antimicrobial agents and resistant bacteria. Japan Med. Assoc. J. 2009;52:103–108.
16. Hwang I.Y., Tan M.H., Koh E., Ho C.L., Poh C.L., Chang M.W. Reprogramming Microbes to Be Pathogen-Seeking Killers. ACS Synth. Biol. 2014;3:228–237. doi: 10.1021/sb400077j.
17. Orfali R., Perveen S., AlAjmI M.F., Ghaffar S., Rehman M.T., AlanzI A.R., Gamea S.B., Essa Khwayri M. Antimicrobial Activity of Dihydroisocoumarin Isolated from Wadi Lajab Sediment-Derived Fungus Penicillium chrysogenum: In Vitro and In Silico Study. Molecules. 2022;27:3630. doi: 10.3390/molecules27113630.
18. Davies J., Davies D. Origins and Evolution of Antibiotic Resistance. Microbiol. Mol. Biol. Rev. 2010;74: 417–433. doi: 10.1128/MMBR.00016-10.
19. Bartlett J.G., Gilbert D.N., Spellberg B. Seven Ways to Preserve the Miracle of Antibiotics. Clin. Infect. Dis. 2013;56:1445–1450. doi: 10.1093/cid/cit070.

20. .Velez R., Sloand E. Combating antibiotic resistance, mitigating future threats and ongoing initiatives. J. Clin. Nurs. 2016;25:1886–1889. doi: 10.111 1/jocn.13246.
21. D'Costa V.M., McGrann K.M., Hughes D.W., Wright G.D. Sampling the Antibiotic Resistome. Science. 2006;311:374–377.
22. Peterson E., Kaur P. Antibiotic Resistance Mechanisms in Bacteria: Relationships between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. Front. Microbiol. 2018;9: 2928. doi: 10.3389/fmicb.2018.02928.
23. Vega N.M., Gore J. Collective antibiotic resistance: Mechanisms and implications. Curr. Opin. Microbiol. 2014;21: 28–34. doi: 10.1016/j.mib.2014.09.003.
24. Darby E.M., Trampari E., Siasat P., Gaya M.S., Alav I., Webber M.A., Blair J.M.A. Molecular mechanisms of antibiotic resistance revisited. Nat. Rev. Microbiol. 2023;21:280–295. doi: 10.1038/s41579-022-00820-y
25. Chellat M.F., Raguž L., Riedl R. Targeting Antibiotic Resistance. Angew. Chemie Int. Ed. 2016;55:6600–6626. doi: 10.1002/anie.201506818
26. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. Virulence. 2016;7:252–266. doi: 10.1080/21505594.2016.1159366