

## Recent Advances in Anti-Biofilm Strategies to Combat Antimicrobial Resistance

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### Abstract

Antimicrobial resistance (AMR) is a significant global health challenge, hindering bacterial infection treatment and contributing to rising hospitalization and death rates. Many pathogenic bacteria can form biofilms, complex communities protected by extracellular polymeric materials, which make them resistant to antimicrobial drugs and immune system attacks. Biofilm-forming bacteria exhibit persistence, leading to recurring infections. Limited drug penetration, low metabolic activity of sessile cells, and increased gene transfer within biofilms contribute to the failure of conventional antibiotic treatments.

Recent progress has been made in strategies aimed at preventing biofilm growth and making biofilms more susceptible to antimicrobial treatments. While in vitro results are promising, translating these strategies into clinical applications remains challenging. This review explores the molecular mechanisms underlying biofilm-associated AMR and highlights recent advances in anti-biofilm strategies, such as quorum sensing inhibitors, nanotechnology, bacteriophage therapies, and biofilm-degrading enzymes and peptides. The review also discusses the clinical challenges impeding progress and suggests future research directions for effective and environmentally friendly anti-biofilm treatments.

A literature search was conducted using PubMed and Scopus databases, covering studies published between 2015 and 2025. This study is a narrative review synthesizing recent advances in anti-biofilm strategies, aimed at improving treatment outcomes and developing more environmentally friendly solutions.

**Keywords :** Bacterial biofilms; Antimicrobial resistance; Quorum sensing inhibition; Nanoparticles; Multidrug-resistant bacteria

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## 1. Introduction

Antimicrobial resistance (AMR) has emerged as one of the most serious global public health threats because it renders traditional antibiotics ineffective while multiplying the number of bacterial infections that occur worldwide [1]. The rapid rise of multidrug-resistant (MDR) bacteria occurs because several factors combine to create this situation, which includes improper antibiotic usage and the insufficient development of new antimicrobial drugs and the exceptional ability of bacterial pathogens to adapt through selective pressure [2]. The medical field now faces difficulties because infections that doctors once treated successfully have turned into persistent diseases that cause more health problems and death [1–3].

The process of building bacterial biofilms shows special importance among the multiple methods which create antimicrobial resistance. Biofilms establish structured microbial communities which develop protective systems through EPS matrix production to establish their connection with living organisms and nonliving surfaces [4]. Hospital environments see biofilm-related bacteria as the main cause of chronic diseases and infections from medical equipment and healthcare facilities because these bacteria show greater resistance to both antimicrobial treatments and immune system defenses. The epidemiological research shows that human bacterial infections mainly involve biofilm-associated bacteria instead of their planktonic counterparts [4–6].

The mechanisms that enable biofilm-associated microorganisms to resist antimicrobial agents come from three main sources which include physical attributes and physiological functions and genetic composition. The EPS matrix restricts the ability of antimicrobial agents to move through biofilms which leads to the existence of slow-growing and inactive bacterial subpopulations that show reduced vulnerability to antibiotics which target active cellular functions. Bacterial communities develop resistance to drugs because biofilms enable bacteria to transfer resistance genes through their tightly packed cell structures which allow for horizontal gene transfer. The features of biofilms create challenges for standard antimicrobial treatments which stem from planktonic bacterial models because these treatments fail to eliminate biofilms successfully [7–9].

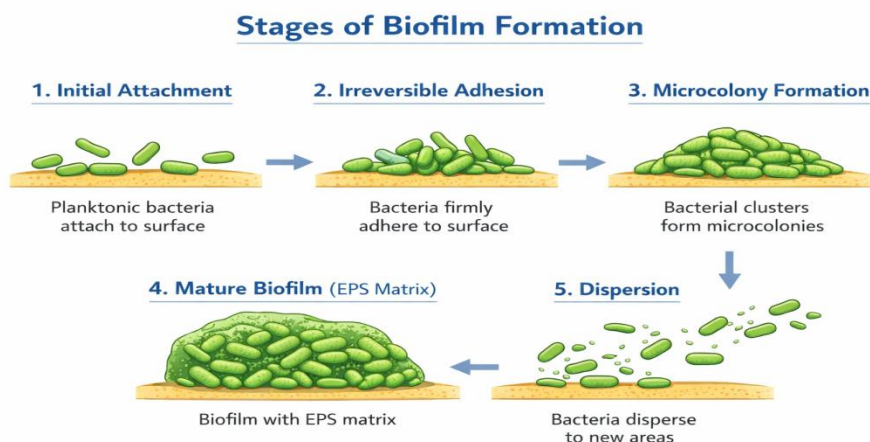
Standard antibiotic treatments cannot fully eliminate biofilms which results in persistent infections while creating stronger bacterial strains that become resistant to treatment. The existing limitations create a pressing requirement for new treatment methods which will attack biofilm formation and structural integrity and lasting presence in systems. Researchers have developed new anti-biofilm methods that use quorum sensing inhibition and nanoparticle-based antimicrobial delivery systems and bacteriophage therapy and biofilm-disrupting enzymes and peptides [10–13].

The goal of this review is to critically examine the role of bacterial biofilms in antimicrobial resistance, summarize recent advances in anti-biofilm strategies, discuss current limitations, and highlight future perspectives for developing effective and environmentally friendly therapeutic approaches.

## 2. Biofilm Formation and Its Role in Antimicrobial Resistance

### 2.1 Stages of Biofilm Development

Bacteria use biofilm formation as a regulated process to develop their survival skills which work against harmful environmental conditions and antimicrobial treatments [14]. The process starts when planktonic bacteria start to attach to surfaces with temporary connections which use weak physicochemical forces like hydrophobicity and electrostatic attraction to form their first bonds with biotic and abiotic surfaces (Figure 1) [14,15].



**Figure 1.** Schematic representation of the stages of bacterial biofilm development, beginning with initial attachment and progressing through irreversible adhesion, microcolony formation, and extracellular polymeric substance (EPS) production, followed by maturation and eventual dispersal of bacterial cells. Created by the author.

Bacteria begin their adhesion process through initial attachment but permanently stick to surfaces when they use their surface structures which include pili and fimbriae and adhesins to create EPS. The EPS matrix creates stable bonds to surfaces which enable microcolony development that results in mature biofilms which display complex three-dimensional structures and strong nutrient and oxygen distribution patterns [16,17].

The final stage of biofilm development is dispersion, a process which enables bacterial cells to leave established biofilms and spread to new habitats through its controlled mechanisms. The dispersed cells maintain their adaptive traits which they developed during their time in the biofilm territory because they developed enhanced abilities to resist antimicrobial drugs. This increase in adaptive abilities leads to infection persistence and recurrence [18].

### 2.2 Mechanisms of Antimicrobial Resistance within Biofilms

Bacteria that live inside biofilms develop much stronger resistance against antimicrobial treatment than their planktonic equivalents because they need doctors to use antibiotics at levels which exceed all

permitted medical limits for successful treatment. The enhanced tolerance of these organisms emerges from their ability to combine multiple resistance mechanisms which protect them better than any single defensive element [19].

The EPS matrix functions as a major biofilm resistance element because it establishes physical and chemical barriers which prevent antimicrobials from reaching biofilm depths while decreasing drug effectiveness to penetrate subsequent biofilm stages. The dynamic nutrient and oxygen distribution within biofilms creates metabolic diversity which produces bacterial subpopulations that grow slowly or stop metabolic activity, making them less vulnerable to antibiotics that attack active cells [20].

The presence of different cell types allows bacteria to create persister cells, which form a dormant bacterial group that survives against high antimicrobial doses but does not pass on genetic resistance traits to future generations [21]. The compact nature of biofilms with their numerous cells situated closely next to each other creates a situation that allows bacteria to share genetic material, which helps them spread and maintain their antimicrobial resistance genes [22,23].

Biofilm bacteria develop extreme tolerance through their combination of physical, physiological, and genetic attributes, which reduces the success rate of standard antimicrobial treatments.

### **3. Conventional Strategies for Biofilm Control and Their Limitations**

The standard treatment methods for bacterial infections linked to biofilms depend on antibiotic treatments which doctors use in two ways. The first method involves administering antibiotics as single drugs while the second method uses multiple antibiotics together at high doses for extended periods. The treatment methods successfully kill free-floating bacterial cells but they fail to eliminate established biofilms which contain bacteria that naturally resist treatment because of their biofilm-based defense system. The incomplete removal of biofilms results in ongoing infections which emerge as recurrent cases [24].

The common treatment method uses high-dose antibiotic treatment to defeat biofilm bacteria because their bacteria have low metabolic rates and the antibiotics have difficulty reaching them. The use of higher antibiotic doses leads to severe systemic toxicity problems which create negative health effects but these increased doses do not consistently succeed in destroying biofilms. The bacteria in biofilms develop survival abilities which enable them to survive better after they experience nonlethal antibiotic treatment [25].

Doctors use combination antibiotic treatment to extend their ability to kill bacteria while fighting against treatment-resistant infections. Combination treatment systems provide certain advantages but they create strong selective pressure which leads to bacteria developing multidrug-resistant characteristics. The standard treatment approach fails to treat patients because it does not tackle the fundamental biofilm structure which protects bacteria from all antimicrobial treatments [26].

Doctors use drugs together with physical and mechanical methods to treat device-related infections which include surgical debridement and catheter replacement and removal of infected medical devices. The methods temporarily decrease biofilm levels but they fail to stop bacteria from returning to the area because bacteria can easily attach to surfaces which leads to biofilm development. The methods face

challenges because they need invasive procedures which require expensive resources that doctors cannot apply to every case in hospitals dedicated to treating critically sick and immunocompromised patients [27].

The traditional methods for controlling biofilm growth face a serious challenge because they depend on methods that test antibacterial effectiveness against floating bacteria. The standard susceptibility tests incorrectly assume that biofilm bacteria have the same resistance as free-floating bacteria which leads to a significant underestimation of the required antimicrobial doses needed to eliminate biofilms. The medical tests based on these testing methods result in poor treatment results which lead to treatment failure while bacterial resistance keeps growing [28–30].

Antimicrobial treatments show several shortcomings when treating infections which biofilms cause and these limitations create an urgent need for new drug development which will fight specific biofilm structures and biofilm-based metabolic changes and resistance signaling pathways.

These multifactorial mechanisms and the major limitations of conventional biofilm control strategies are integrated and summarized in **Table 1**, highlighting the need for biofilm-targeted therapeutic approaches.

**Table1. Biofilm-Associated Antimicrobial Resistance: Integrated Mechanisms and Limitations of Conventional Control Strategies**

Domain	Specific Mechanism / Strategy	Underlying Scientific Basis	Impact on Antimicrobial Efficacy	Clinical Implications	References
<b>Biofilm structure</b>	Restricted antimicrobial penetration	The EPS matrix limits diffusion and may bind antimicrobial agents, creating concentration gradients across biofilm layers	Reduced drug availability within deeper biofilm regions	Incomplete eradication and persistence of infection	[7,8,20,23]
<b>Biofilm physiology</b>	Metabolic heterogeneity	Nutrient and oxygen gradients generate slow-growing or metabolically inactive bacterial subpopulations	Decreased susceptibility to antibiotics targeting active cellular processes	Prolonged treatment duration and therapeutic failure	[5,9,17,19]
<b>Phenotypic adaptation</b>	Persister cell formation	Dormant, non-replicating bacterial subpopulations survive lethal antimicrobial exposure without acquiring genetic resistance	Survival of biofilm bacteria after antibiotic treatment	High recurrence rates following therapy	[21,23,25]
<b>Genetic mechanisms</b>	Horizontal gene transfer	High cell density and close cell-to-cell contact facilitate plasmid exchange and dissemination of resistance genes	Rapid spread of antimicrobial resistance determinants	Emergence of multidrug-resistant biofilm-associated infections	[7,22,26]

<b>Pharmacological strategy</b>	High-dose antibiotic therapy	Increased antimicrobial exposure intended to overcome diffusion barriers	Systemic toxicity with limited improvement in biofilm eradication	Adverse drug reactions and suboptimal clinical outcomes	[24,25,28]
<b>Therapeutic strategy</b>	Combination antibiotic therapy	Broadening antimicrobial spectrum and bactericidal activity	Strong selective pressure favoring resistant strains	Acceleration of multidrug resistance development	[11,26,28]
<b>Physical intervention</b>	Mechanical or surgical removal	Temporary reduction of biofilm biomass on infected surfaces or medical devices	Rapid recolonization of treated surfaces	Invasive procedures with high recurrence risk	[6,27]
<b>Diagnostic limitation</b>	Planktonic-based susceptibility testing	Standard assays fail to reflect biofilm-associated tolerance	Underestimation of effective antimicrobial concentrations	Inappropriate therapy selection and persistent infections	[19,23,30]

#### 4. Emerging Strategies Targeting Bacterial Biofilms

Researchers have dedicated extensive efforts to develop new approaches that target biofilm structures and their development and survival due to traditional antimicrobial methods which lack effectiveness against biofilm-related infections. The new anti-biofilm methods differ from traditional antibiotics which work by killing bacteria that are actively multiplying because they aim to destroy biofilm structures and block bacterial communication and break down protective barriers while increasing the effectiveness of antimicrobial agents. The treatment methods which focus on biofilm-specific mechanisms can enhance patient outcomes while decreasing the risk of developing antimicrobial resistance through their selective pressure on bacteria [31].

##### 4.1 Quorum Sensing Inhibition

Bacteria use quorum sensing (QS) as their communication method between cells to control the development of biofilms and the production of virulence factors together with all bacterial activities that depend on their population density. Researchers consider QS pathway inhibitors to be an effective anti-biofilm method because these inhibitors decrease both pathogenicity and biofilm formation while not killing bacteria. The use of QS inhibitors leads to reduced biofilm creation and increased bacterial resistance against standard antibiotics. The clinical effectiveness of these treatments as standalone options remains restricted because bacteria possess multiple QS signaling pathways that operate through similar functions and bacteria can activate backup regulatory systems [32].

##### 4.2 Nanoparticles and Nanotechnology-Based Approaches

Researchers have gained interest in nanotechnology-based solutions because they improve the effectiveness of antimicrobial agents in reaching and penetrating biofilms. Multidrug-resistant bacteria can be treated with various nanomaterials because they include metallic nanoparticles and polymeric nanoparticles and liposomal systems which show strong anti-biofilm properties. The systems enable precise drug delivery while they increase local antimicrobial levels and the systems themselves produce antimicrobial activity. The technology has clinical application limitations because its benefits are

disrupted by major issues which include toxic effects on cells and environmental damage and long-term use safety and production capacity [33].

### 4.3 Bacteriophage-Based Therapies

Bacteriophages provide an advanced method that precisely targets biofilm bacteria through their ability to self-replicate. Phages invade biofilms to reproduce at infection sites and their depolymerase enzymes break down the EPS matrix. The combined actions of this treatment result in more effective bacterial destruction and better antibiotic distribution throughout the body. Phage-based therapies face obstacles because their treatment possibilities remain restricted due to host range limitations and immune response challenges and the need for regulatory processes to be established [34].

### 4.4 Enzymes and Anti-Biofilm Peptides

Enzymatic degradation of biofilm matrix components, such as extracellular DNA and polysaccharides, represents another promising anti-biofilm strategy. Additionally, antimicrobial and anti-biofilm peptides can disrupt bacterial membranes and destabilize biofilm structure, thereby enhancing antimicrobial efficacy. While these agents demonstrate broad-spectrum activity and direct biofilm-disrupting effects, issues related to stability, delivery, immunogenicity, and production costs pose challenges for clinical development [35].

A comparative summary of these emerging strategies, including their mechanisms of action, advantages, and major limitations, is provided in **Table 2**.

**Table 2. Emerging Strategies Targeting Bacterial Biofilms: Mechanisms, Advantages, and Limitations**

Strategy	Primary Target / Mechanism	Key Advantages	Major Limitations and Challenges	References
Quorum sensing inhibition	Disruption of bacterial cell–cell communication pathways regulating biofilm formation and virulence	Reduces biofilm formation and pathogenicity without exerting strong selective pressure for resistance; preserves beneficial microbiota	Limited efficacy as monotherapy; potential pathway redundancy among bacterial species	[10,11,32]
Nanoparticles and nanomaterials	Enhanced penetration of biofilm matrix and targeted delivery of antimicrobial agents to embedded bacteria	Improved drug delivery; activity against multidrug-resistant biofilms; synergistic effects with antibiotics	Cytotoxicity concerns; environmental impact; challenges in large-scale production and long-term safety	[29,33,31]
Bacteriophage-based therapies	Phage replication at infection sites and enzymatic degradation of EPS via phage-derived depolymerases	High specificity; self-amplifying at infection sites; restoration of antibiotic susceptibility	Regulatory hurdles; narrow host range; immune system interactions	[12,34,23]
Enzymes and anti-biofilm peptides	Degradation of biofilm matrix components (e.g., eDNA, polysaccharides) and disruption of bacterial membranes	Direct biofilm destabilization; enhanced antibiotic penetration; broad-spectrum activity	Stability issues; delivery challenges; high production costs	[13,35,36]

## 5. Clinical Challenges and Future Perspectives

The latest anti-biofilm research shows positive developments yet new clinical applications face major obstacles to becoming successful. The main problem exists because *in vitro* tests show effective results before they bring actual results through human testing since existing biofilm models do not match the exact conditions found in real medical infections which involve immune system responses and multiple types of bacteria and changing body states [37,38].

The development of nanoparticle-based and peptide-based treatments encounters obstacles created by safety and toxicity concerns which act as extra hindrances. The medical evaluation process requires complete examination of all long-term biocompatibility issues and biodistribution patterns and tissue buildup and off-target effects before clinical approval can proceed for this product. Bacteriophage therapy shows potential yet clinical use faces multiple obstacles because of host-specificity challenges and immune system neutralization problems and issues with manufacturing consistency and regulatory standards which need to be achieved. The research process needs standardized biofilm infection models plus standardized susceptibility testing protocols to evaluate treatment methods. Standard antimicrobial susceptibility tests help detect planktonic bacteria yet these tests fail to determine adequate antimicrobial levels needed to kill biofilms. The existing disparities between actual and expected therapeutic performance create decision-making problems which require developing testing methods and biofilm-specific diagnostic tools for clinical treatment needs.

The development of anti-biofilm therapies requires researchers to bridge multiple existing knowledge gaps which need investigation. This area requires scientists to study how molecular mechanisms control biofilm dispersion and how two microbial species interact in mixed biofilm populations and how antivirulence and anti-biofilm methods drive long-term evolutionary changes. The discovery that bacteria can evolve resistance against new anti-biofilm compounds demonstrates why scientists need to monitor bacterial resistance patterns through extended research on how bacteria gain resistance against anti-biofilm treatment. The research field needs to develop new treatment methods which combine traditional antibiotics with biofilm-disrupting compounds because this combination creates stronger treatment effects while decreasing the risk of developing therapy resistance. The introduction of omics technologies with bioinformatics and artificial intelligence will help researchers discover new biofilm targets and create effective anti-biofilm solutions which will benefit from rational design processes. The experimental discoveries need multidisciplinary strategies to transform into medical procedures which provide effective and sustainable healthcare benefits [38–40].

## 6. Conclusion

Bacterial biofilms play a significant role in making infections chronic by increasing AMR. The structural complexity of biofilms and the physiological diversity within them contribute to heightened antimicrobial resistance. This complexity facilitates the spread of resistance genes, making bacterial infections harder to treat. For instance, the EPS matrix restricts the ability of antimicrobial agents to penetrate the biofilm, allowing bacteria to persist and grow in environments where treatments fail.

Despite significant advances in biofilm-targeted therapies, many studies rely heavily on *in vitro* models, which do not fully capture the real-world dynamics of *in vivo* infections. *In vitro* models often show promising results in early stages, but they fail to account for immune system responses and the

interaction of multiple bacterial species in human infections. This represents a limitation in translating laboratory-based findings into effective clinical treatments, highlighting the gap between experimental success and clinical application.

A key strength of this study is its focus on practical applications within living systems (in vivo) rather than solely relying on laboratory models. The multidisciplinary approach employed, incorporating strategies like bacteriophage therapy and nanotechnology, positions this research ahead of many studies that focus purely on in vitro testing. This broadens the scope of potential real-world applicability, where traditional antibiotics may not be as effective.

Ultimately, the primary challenges remain the safety, efficacy, and regulatory approval of these new treatments. Expanding these strategies requires a deeper understanding of biofilm biology, as well as the development of specialized diagnostic tools capable of assessing treatment effectiveness in living systems. Additionally, as bacteria may evolve resistance against new anti-biofilm treatments, continuous monitoring of resistance patterns will be crucial.

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There Is No Conflict Of Interest To Declare.

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