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REVIEW ARTICLE

Multidrug Resistant Microorganisms (MDR) and Biofilm Producers: A Challenge for Hospital Infectious Control

Daniel Lucio[1], Elizabeth Proaño[2], Alberto Bustillos[3,4]*

[1]Faculty of Health Sciences, Universidad Técnica de Ambato, Ambato, Ecuador
[2]Faculty of Health Sciences, NutrigenX Research Group, Universidad Técnica de Ambato, Ambato, Ecuador
[3]Facultad de Ciencias Agropecuarias, Universidad Técnica de Ambato, Ecuador
[4]Carrera de Medicina, Universidad Regional Autónoma de los Andes, Ambato, Ecuador

*Corresponding Author: aa.bustillos@uta.edu.ec

Abstract: Antimicrobial Resistance (AMR) now represents a major threat to contemporary health care, especially in hospitals, where repeated antimicrobial exposure selects for and facilitates the dissemination of Multidrug-Resistant (MDR) microorganisms. Biofilm growth adds another layer of persistence by increasing microbial tolerance, supporting long-term colonization of medical devices, and worsening clinical and economic outcomes. This narrative review synthesizes evidence on MDR biofilm-forming microorganisms, focusing on resistance mechanisms, epidemiological relevance, and developing therapeutic options. Frequently reported agents include Methicillin-Resistant Staphylococcus Aureus (MRSA), Vancomycin-Resistant Enterococcus (VRE), Pseudomonas aeruginosa, Acinetobacter baumannii, β-lactamase-producing Klebsiella pneumoniae, and Candida spp. Available evidence supports reciprocal reinforcement between antimicrobial resistance and biofilm physiology; organisms growing in sessile communities may tolerate antimicrobial concentrations 10–1000 times higher than comparable planktonic cells. In Latin America, mortality associated with MDR infections has approached 45%. Although nanotechnology, phytochemicals, bacteriophages, and combination regimens show promising antibiofilm effects, most supporting data remain experimental or preclinical. Meaningful reduction of MDR biofilm-associated infection will require coordinated antimicrobial stewardship, stronger epidemiological surveillance, and therapeutic interventions with demonstrated clinical antibiofilm effectiveness.

Keywords: Antimicrobial Resistance, Multidrug Resistant Bacteria, Biofilm, Hospital Acquired Infections, ESKAPE Pathogens, Nanoparticles

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Introduction

Antimicrobial Resistance (AMR) is now a central threat to contemporary health care because it progressively reduces the effectiveness of antimicrobial therapy and places global public health at risk. The World Health Organization (WHO) estimates that bacterial antimicrobial resistance directly accounts for approximately 1.27 million deaths annually and is associated with

nearly 4.95 million deaths worldwide, illustrating its growing clinical and socioeconomic consequences [1-3]. If containment measures are not strengthened, the health burden attributable to AMR is likely to rise markedly in the coming decades. Hospitals are particularly affected because infections acquired during health care remain a frequent complication of medical treatment. In developing countries, these infections affect up to 10% of hospitalized patients, with resistant microorganisms responsible for a substantial share of cases [4-6].

From an epidemiological perspective, Multidrug Resistant (MDR) microorganisms contribute substantially to the burden of disease by increasing morbidity and mortality, extending hospital stays, and raising health-care costs [6]. The Centers for Disease Control and Prevention (CDC) attributes hundreds of thousands of health-care-associated infections among hospitalized patients each year to antimicrobial-resistant pathogens. Clinically important MDR organisms include Methicillin Resistant Staphylococcus Aureus (MRSA), Vancomycin-Resistant Enterococcus spp. (VRE), Extended-Spectrum B-Lactamase (ESBL) producing Enterobacterales, Carbapenem-Resistant Enterobacterales (CRE), carbapenem-resistant Acinetobacter baumannii, and multidrug resistant Pseudomonas aeruginosa [2-4, 6-8]. These organisms are associated with severe hospital infections such as ventilator-associated pneumonia, bloodstream infection, catheter-associated urinary tract infection, and sepsis. Their management frequently requires last resort antimicrobials, which may carry greater toxicity, higher costs, and less favorable clinical outcomes [1, 9].

Antimicrobial resistance refers to the ability of a microorganism to remain viable or continue growing despite exposure to an antimicrobial agent that would ordinarily inhibit or eliminate it. When reduced susceptibility extends across multiple antimicrobial classes, the microorganism is considered Multidrug Resistant (MDR). MDR phenotypes arise through several adaptive routes, including acquisition of resistance determinants on plasmids and other mobile elements, enzymatic destruction or modification of antimicrobial compounds such as β-lactams, changes in drug targets, reduced membrane permeability, and increased activity of efflux systems that lower intracellular antimicrobial concentrations [10-12].

Biofilm production is another major determinant of the persistence of health-care-associated infections. Instead of remaining as individual planktonic cells, microorganisms in a biofilm develop surface-associated communities enclosed within an extracellular material that they produce themselves and that contains polysaccharides, proteins, lipids, and extracellular DNA [5, 13]. The resulting three-dimensional structure restricts antimicrobial access, lowers metabolic activity in part of the population, favors tolerant physiological states, and increases opportunities for horizontal gene exchange, thereby promoting survival under antimicrobial pressure [5, 13]. In hospitals, these communities readily establish on intravascular and urinary catheters, prosthetic joints, cardiac valves, and other implanted devices, where they can function as persistent infectious reservoirs that are difficult to clear [14]. Estimates suggest that biofilms participate in approximately 65–80% of human infections and are associated with recurrence, therapeutic failure, longer hospitalization, and increased health-care expenditure [1, 3, 15].

Given the growing overlap between antimicrobial resistance and biofilm-associated persistence, this narrative review critically evaluates MDR biofilm-forming microorganisms in hospital environments, emphasizing the mechanisms that sustain resistance, their epidemiological consequences, and emerging treatment options. The synthesis is intended to clarify how current evidence can inform more effective prevention of health-care-associated infection and contribute to strategies for reducing the expanding global impact of AMR.

Materials and Methods

The work was conducted as a structured narrative review guided by PRISMA principles for the identification, screening, and reporting of the literature. Its purpose was to examine the association between Multidrug Resistant (MDR) microorganisms and biofilm formation in hospital settings and to assess how this interaction contributes to persistent health-care-associated infection. Literature was retrieved from PubMed, Scopus, and Google Scholar, databases chosen for their broad coverage of biomedical, microbiological, and clinically oriented research relevant to the review question.

Relevant studies were located using English-language terms corresponding to the main review variables, including multidrug-resistant bacteria, antimicrobial resistance, biofilm formation, biofilm-producing microorganisms, and hospital infections. The descriptors were combined with the Boolean connectors and OR so that the search could capture complementary combinations of the concepts while maintaining relevance to the review objective. The principal search queries were as follows:

- ("multidrug-resistant bacteria" OR "MDR bacteria") AND biofilm
- ("antimicrobial resistance" AND "biofilm formation") AND hospital
- ("nosocomial infections" OR "hospital infections") AND biofilm AND "multidrug resistance
- ("biofilm-producing microorganisms") AND ("antibiotic resistance")

These search strategies allowed the identification of studies addressing antimicrobial resistance, biofilm formation capacity, and their impact on infections associated with hospital environments.

Study selection proceeded in two steps. Titles and abstracts were examined first to identify records with potential relevance; subsequently, the complete articles that remained after this screening were assessed against the objectives of the review.

Eligible evidence consisted of articles from indexed journals that investigated the relationship between Multidrug-Resistant (MDR) microorganisms and biofilm production, with particular attention to health-care-associated infections. Original investigations, systematic reviews, and meta-analyses were all considered to obtain a broad and current synthesis of the evidence. Publications written in English or Spanish during the preceding ten years were considered, and preference was given to work addressing antimicrobial resistance, biofilm-forming capacity, and clinically important microorganisms involved in nosocomial infection.

Studies were excluded when duplicate records were identified during the screening process, when the full text was unavailable, or when their content was not directly related to antimicrobial resistance and biofilm formation or lacking sufficient information for qualitative analysis. Additionally, documents without scientific peer review, including blogs, non-academic websites, and other non-scientific publications, were not considered eligible for inclusion. Priority was given to studies published in indexed journals classified within Q1 and Q2 quartiles to ensure the quality, rigor, and relevance of the selected evidence.

Finally, the included studies were critically analyzed to extract information on key MDR microorganisms, antimicrobial resistance mechanisms, biofilm formation, and their impact on healthcare-associated infections. The extracted data were organized and synthesized into thematic sections to facilitate the analysis and discussion of the findings reported in the scientific literature

Results

Figure 1 depicts the PRISMA-based selection pathway, from identification and screening of records through eligibility evaluation to the set of studies ultimately retained for this review.

Biofilm Producing MDR Microorganisms in Hospital Settings

MDR microorganisms that also produce biofilms are particularly relevant to persistent health-care-associated infection because the biofilm state improves survival under unfavorable conditions and diminishes the effectiveness of antimicrobial treatment [16]. In contrast to planktonic growth, these organisms assemble into surface-associated communities on living or inert substrates and become enclosed in an Extracellular Polymeric Substance (EPS) that contains mainly polysaccharides, proteins, lipids, and extracellular DNA. This extracellular framework provides both mechanical protection and biological support, reducing exposure to antimicrobials and host immune mechanisms [13, 17, 18].

Biofilm formation develops through an ordered but dynamic sequence: initial adhesion to a surface, formation of small cellular aggregates, architectural maturation, and eventual release of cells from the mature community. During these stages, microorganisms undergo phenotypic and metabolic shifts that support quorum-sensing activity, alter expression of genes involved in biofilm biology, and improve survival during antimicrobial exposure [5, 8, 16, 18, 19]. Figure 2 illustrates the principal stages of this developmental process.

In hospitals, the frequent use of invasive devices further favors biofilm establishment. Intravascular and urinary catheters, prosthetic implants, and endotracheal tubes offer artificial surfaces on which microorganisms can attach, mature into biofilms, and maintain long-term colonization. This favors recurrent infection and makes complete microbial elimination more difficult even when antimicrobial therapy is administered [20].

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Microbiologically, the organisms most often associated with this phenomenon span several groups, including Gram-positive bacteria, non fermenting Gram-negative bacilli, Enterobacterales, and opportunistic yeasts [2].

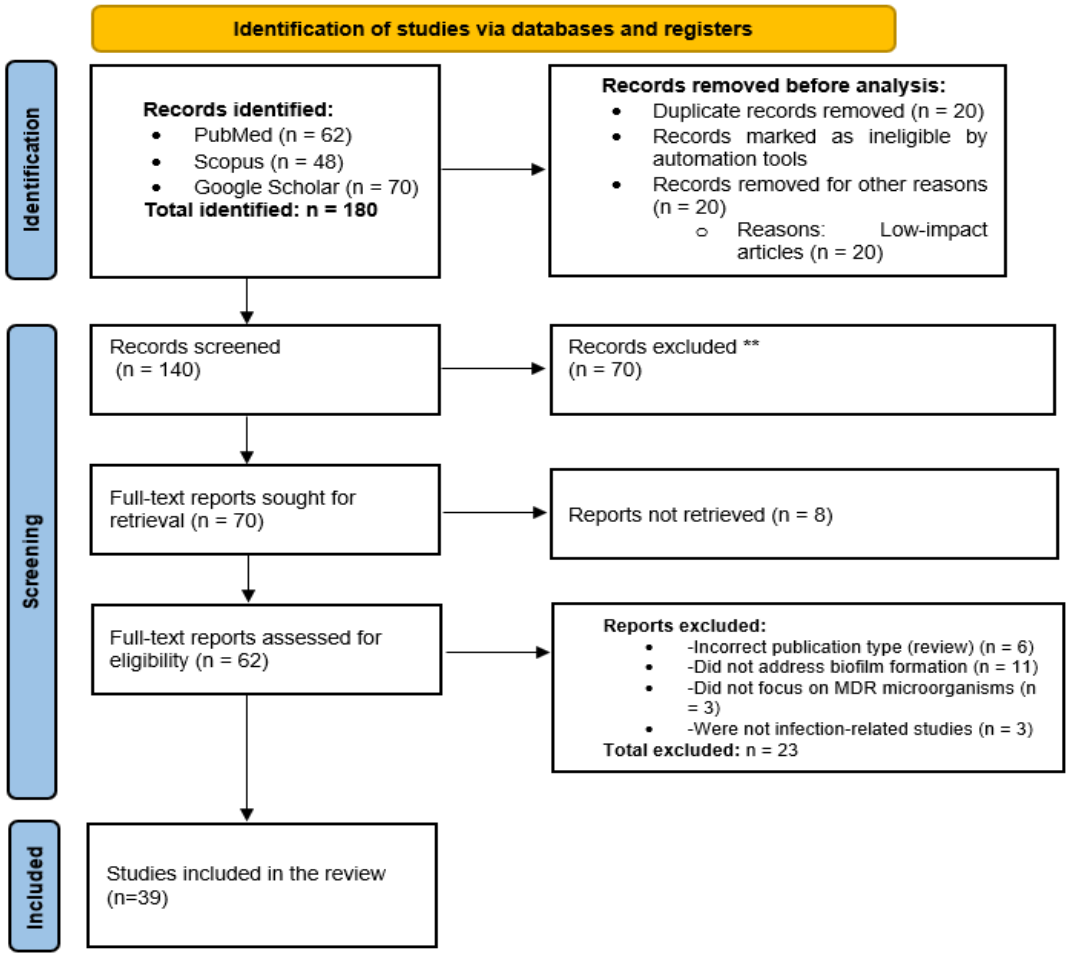

Fig. 1: PRISMA flow diagram

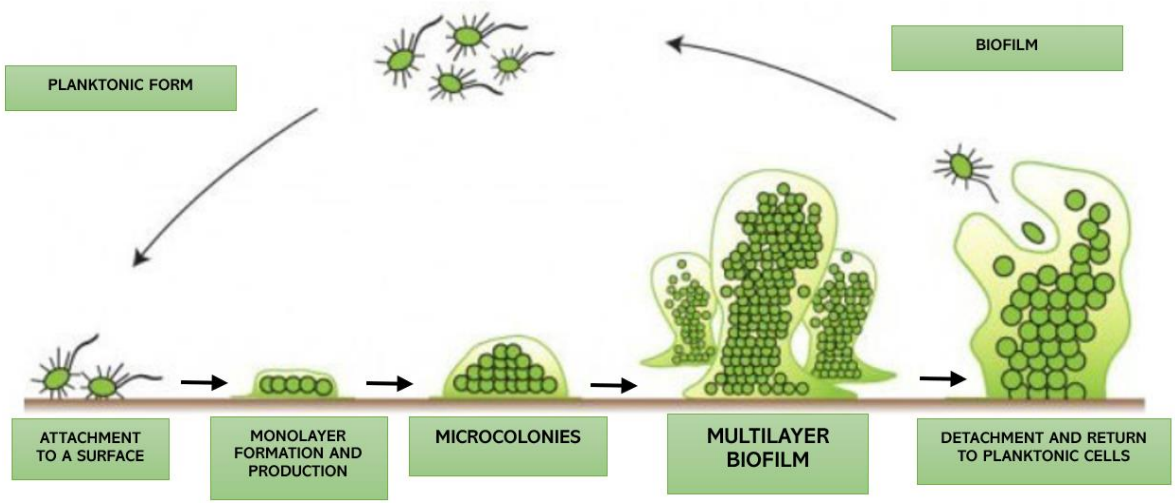

Fig. 2: Stages of bacterial biofilm formation

Gram Positive Bacteria

Within the Gram-positive group, Staphylococcus aureus is a prominent cause of health-care-associated infection because it combines numerous virulence traits with broad antimicrobial resistance and an efficient capacity to form biofilms. This member of the Staphylococcaceae commonly colonizes cutaneous and mucosal sites, especially the anterior nasal cavity, thereby creating a reservoir for transmission in both community and hospital environments. Pathogenicity is mediated by diverse factors, including toxins, secreted enzymes, adhesins, and proteins that interfere with host immunity. Protein A, for example, impairs opsonization, whereas surface adhesins promote binding to host tissues and implanted materials, facilitating stable colonization [21-22].

Infection with S. aureus may present as localized disease of the skin or soft tissues or progress to severe conditions such as bacteremia, osteomyelitis, pneumonia, and infective endocarditis. Its importance in hospitals is further amplified by Methicillin-Resistant Staphylococcus Aureus (MRSA) and by the organism's ability to establish biofilms on medical devices. Together, these characteristics reduce treatment effectiveness and favor infections that persist or recur despite therapy [21-23].

The ability of S. aureus to persist on biomaterials begins with adhesion. Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) bind extracellular-matrix constituents such as fibrinogen, fibronectin, and collagen that coat prosthetic surfaces. After attachment, the organism produces a matrix rich in Polysaccharide Intercellular Adhesin (PIA), proteins, and extracellular DNA, creating mature biofilms that hinder antimicrobial access and shield bacteria from immune clearance. For this reason, prosthetic-joint infections, central-line infections, and endocarditis involving biofilm-forming S. aureus often show prolonged persistence and may require removal of the infected device in addition to antimicrobial therapy [16, 20].

Vancomycin-Resistant Enterococcus (VRE) is likewise an important hospital pathogen whose persistence extends beyond resistance to glycopeptides. In addition to intrinsic and acquired resistance affecting several antimicrobial classes, VRE can adhere to inert surfaces and generate biofilms on urinary catheters and intravascular devices. These properties support sustained bacteremia and repeated episodes of infection, especially in critically ill and oncohematological patients [13, 19, 24].

Taken together, the clinical behavior of Gram-positive MDR pathogens reflects the combined effects of antimicrobial resistance and biofilm-mediated persistence. Their interaction favors long-lasting colonization, reduces antimicrobial performance, and promotes chronic infection of indwelling devices, supporting the need for treatment strategies that address both resistance determinants and the biofilm state.

Non-Fermenting Gram-Negative Bacilli

Non-fermenting Gram-negative bacilli are especially troublesome in hospitals because their genomic plasticity supports rapid acquisition of resistance traits and persistence under environmental stress. Pseudomonas aeruginosa is among the most important members of this group and is a frequent cause of health-care-associated infection, particularly in critically ill patients and individuals with lengthy hospital stays [25, 26].

The success of P. aeruginosa as a pathogen is closely linked to its capacity to form mature biofilms under the control of interconnected quorum-sensing circuits, notably Las, Rhl, and Pqs. These systems coordinate biofilm behavior while regulating multiple virulence determinants. Clinically, the organism is associated with ventilator-associated pneumonia, infected burns, and bloodstream infection [25]. In mature biofilms, metabolic heterogeneity generates slowly growing or persister subpopulations and reduces the activity of agents such as carbapenems and fluoroquinolones, thereby supporting chronic infection and treatment failure [3-8].

Accordingly, persistence of P. aeruginosa cannot be explained by intrinsic drug resistance alone. Biofilm-related physiological changes act together with classical resistance mechanisms to improve survival and make eradication difficult even when an appropriate antimicrobial regimen is used.

Acinetobacter baumannii is also classified as a critical-priority pathogen because carbapenem resistance is widespread and the organism can remain viable for prolonged periods on dry surfaces in the hospital environment. Biofilm formation on ventilators, catheters, and other equipment supports environmental survival, patient-to-patient spread, and health-care-associated outbreaks [3, 27-29]. These combined properties help explain the difficulty of controlling A. baumannii with conventional infection-prevention measures.

Enterobacterales Producing Broad Spectrum Enzymes

Among Enterobacterales, Klebsiella pneumoniae strains that produce Extended-Spectrum B-Lactamases (ESBLs) or carbapenemases are important causes of complicated urinary infection, hospital-acquired pneumonia, and sepsis. Their pathogenic potential is reinforced by a polysaccharide capsule and by biofilm growth on uroepithelium and medical devices, conditions that sustain persistence, favor recurrence, and reduce antimicrobial susceptibility. The simultaneous presence of enzymatic resistance and biofilm-mediated protection is therefore associated with less favorable outcomes and higher mortality in invasive infection [3].

Opportunistic Yeasts

Candida albicans and other members of the Candida complex are frequent fungal causes of catheter-related candidemia. Their biofilms contain blastoconidia and hyphal forms within an extracellular matrix rich in β-glucans, which restricts antifungal access. The biofilm environment also modifies expression of determinants related to azole and echinocandin susceptibility, further decreasing treatment effectiveness and promoting persistent infection in critically ill patients [4].

Molecular Basis of Antimicrobial Resistance

Bacterial survival during antimicrobial treatment reflects multiple genetic and physiological adaptations that diminish drug activity. Repeated antibiotic exposure in health-care environments imposes strong selection that favors MDR organisms and their dissemination. When resistance mechanisms occur in organisms that can also establish biofilms, persistence is further strengthened and health-care-associated infections become more difficult to eliminate and contain [4].

Bacteria rarely depend on a single resistance pathway. Instead, MDR phenotypes usually emerge from several mechanisms acting together, including drug inactivation or modification by enzymes, alteration of antimicrobial targets, reduced permeability of the cell envelope, increased efflux activity, and horizontal acquisition of resistance determinants [1, 23].

Enzymatic Inactivation or Modification of Antibiotics

Extended-Spectrum B-Lactamases (ESBLs) and carbapenemases are clinically important because they hydrolyze the β-lactam structure and thereby neutralize many β-lactam agents. This mechanism is common among Enterobacterales, including Escherichia coli and Klebsiella pneumoniae, and contributes substantially to hospital infections with restricted therapeutic options. Aminoglycoside modifying enzymes act differently: acetylation, phosphorylation, or adenylation of the drug reduces its capacity to interact effectively with bacterial targets [18].

Alteration of Antibiotic Target Sites

Resistance may also arise when the bacterial target is altered in a way that reduces antimicrobial binding while preserving its essential cellular function. In Methicillin Resistant Staphylococcus Aureus (MRSA), for instance, mecA specifies the alternative penicillin-binding protein PBP2a, whose poor affinity for β-lactams permits peptidoglycan synthesis to proceed during drug exposure. Fluoroquinolone resistance can similarly emerge from mutations in the Quinolone Resistance Determining Regions (QRDRs) of DNA gyrase and topoisomerase IV, which decrease drug-target interaction in both Gram-positive and Gram-negative bacteria [20].

Reduced Membrane Permeability

Reduced outer-membrane permeability provides Gram-negative bacteria with another means of lowering antimicrobial susceptibility. Instead of chemically inactivating the drug, these organisms can decrease porin abundance or alter porin structure, limiting entry of hydrophilic antimicrobials. The resulting intracellular concentrations may remain below effective levels. This mechanism is particularly important in opportunistic pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, where it often operates together with additional resistance determinants and contributes to the MDR phenotype.

Active Efflux Systems

Efflux systems are active resistance mechanisms that expel antibiotics from the bacterial cell through energy-dependent transport pumps. These systems, belonging to families such as RND, MFS, ABC, and MATE, can simultaneously remove multiple antimicrobials, promoting MDR phenotypes. Their overexpression reduces therapeutic efficacy and enhances bacterial survival within biofilms, where antibiotic diffusion is already limited [30].

Horizontal Gene Transfer

The spread of antimicrobial resistance among bacterial populations depends heavily on the movement of genetic information. Resistance is not generated only by spontaneous mutation; it can also be acquired through conjugation, transformation, or transduction. Plasmids, transposons, and integrons serve as vehicles that transfer resistance determinants across strains, species, and even genera. In hospitals, intense antimicrobial selection combined with continuous exchange of these elements favors the accumulation of multiple resistance genes in individual isolates and accelerates the appearance and long-term maintenance of MDR pathogens [1].

Biofilm Formation Capacity

The reviewed evidence indicates that biofilm production is common among major pathogens responsible for health-care-associated infection, especially in Intensive Care Units (ICUs). These communities consist of surface-attached or otherwise sessile microorganisms enclosed in a complex matrix containing proteins, lipids, nucleic acids, and polysaccharides. The Extracellular Polymeric Substance (EPS) promotes adhesion, retains nutrients, buffers environmental stress, and decreases antimicrobial susceptibility [2] Biofilms have been detected widely in hospital environments, including on areas that undergo terminal cleaning, with persistence reported on more than 90% of ICU surfaces. Medical devices are particularly important substrates: urinary and central venous catheters, endotracheal tubes, and other indwelling devices provide sites for initial attachment, progressive maturation, and sustained reservoirs of health-care-associated infection during prolonged hospitalization [16].

Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae are repeatedly identified as strong biofilm producers in different hospital environments. Their persistence depends on more than the physical shielding conferred by the EPS matrix. Reduced metabolic activity and formation of persister subpopulations within biofilms further decrease susceptibility to antibiotics and disinfectants, favoring chronic colonization and repeated infection [8].

Although biofilm-mediated antimicrobial tolerance is well established experimentally, its translation to patient care remains incomplete. Much of the available evidence comes from simplified in vitro systems dominated by single-species biofilms and therefore does not reproduce the polymicrobial interactions, host responses, or environmental complexity of infections in hospitalized patients. The clinical contribution of biofilm-associated resistance may consequently be underestimated and should be investigated in models that more closely resemble real infections.

Polymicrobial Biofilms and Microbial Interactions

Although most antimicrobial resistance studies have traditionally focused on single-species biofilms, increasing evidence indicates that clinically relevant biofilms are frequently composed of complex polymicrobial communities. These microbial consortia exhibit cooperative interactions that enhance persistence, virulence, and therapeutic failure compared with monospecies biofilms.

In polymicrobial biofilms, different microbial species interact through metabolic cross-feeding, intercellular signaling, and continuous remodeling of the Extracellular Polymeric Substance (EPS). These cooperative processes create a highly protective microenvironment that restricts antimicrobial diffusion and enhances microbial survival. These interactions represent an additional layer of complexity in MDR infections because therapeutic strategies effective against individual pathogens may fail when microorganisms coexist within structured communities [23].

[11] A clinically important example of polymicrobial cooperation involves Candida albicans and Staphylococcus aureus: components produced by the fungal matrix can support bacterial attachment and biofilm maturation, whereas bacterial products may enhance persistence of the mixed community. Similar cooperative behavior has been described among MDR bacteria including Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii. In such communities, exchange of genetic material together with local adaptive responses may accelerate the appearance and spread of multidrug-resistant phenotypes.

Therefore, future antibiofilm strategies should move beyond pathogen-specific approaches and consider the ecological characteristics of polymicrobial communities. Understanding microbial interactions within biofilms may provide new opportunities for designing targeted therapies capable of disrupting cooperative mechanisms that sustain chronic infections.

Relationship Between MDR and Biofilm

The literature reviewed here supports a reciprocal association between Multidrug Resistance (MDR) and biofilm formation. Compared with susceptible isolates, MDR strains often generate thicker, more mature, matrix-rich biofilms; in the opposite direction, residence within a biofilm increases antimicrobial tolerance and can also favor resistance even when no new resistance determinant has been acquired. This behavior reflects biofilm-specific phenotypic changes, including its spatial architecture and the altered physiology of microorganisms growing in a sessile state [13, 17, 18, 31].

The Extracellular Polymeric Substance (EPS) surrounding a biofilm slows the movement of antibiotics and biocides into the community. At the same time, local conditions within the biofilm favor persister cells and metabolically quiescent subpopulations, reducing the effect of agents that depend on active bacterial metabolism. Consequently, microorganisms in mature biofilms can display Minimum Inhibitory Concentration (MIC) values approximately 10 to 1000 times those measured for the same organisms in planktonic growth [5, 16, 18, 30, 32].

The close spatial organization of biofilms also increases opportunities for horizontal transfer of genetic material. Mobile elements carrying carbapenemase determinants such as blaOXA, blaNDM, and blaKPC, together with multidrug efflux systems such as mexAB-oprM, can therefore circulate more readily among neighboring bacteria. Under the intense antimicrobial selection typical of hospitals, this genetic exchange contributes to the appearance and maintenance of highly resistant MDR populations [18].

MDR and biofilm formation can thus reinforce one another: resistant organisms may be better able to establish mature biofilms, while biofilm growth further improves survival during antimicrobial exposure. This feedback favors chronic and recurrent infection, treatment failure, and prolonged persistence of ESKAPE pathogens on devices and hospital surfaces, making control within health-care facilities more difficult [18, 19, 33, 34].

Extensive antimicrobial use selects for MDR organisms and may simultaneously favor populations that persist within biofilms. Once a mature matrix is present, embedded cells are partially shielded from antimicrobial compounds and host defenses, permitting survival over long periods and increasing the probability of persistent health-care-associated infection [19, 33, 34, 35].

Biofilm Tolerance and Antimicrobial Resistance

Because biofilm formation and antimicrobial resistance frequently occur together, they are sometimes treated as if they were the same biological phenomenon; however, they represent different modes of survival. Antimicrobial resistance is based on stable heritable changes, including chromosomal mutation, acquisition of resistance genes by horizontal transfer, and incorporation of mobile elements such as plasmids or transposons. These genetic traits are transmitted during cell division and allow reduced antimicrobial susceptibility to persist across generations.

Conversely, biofilm-associated tolerance represents a transient physiological adaptation in which microorganisms survive antimicrobial exposure without necessarily acquiring additional resistance determinants. This adaptive response is primarily driven by restricted antimicrobial diffusion across the Extracellular Polymeric Substance (EPS), together with reduced cellular metabolism, physicochemical gradients within the biofilm, and the accumulation of dormant persister cells, all of which enhance microbial survival during antimicrobial exposure.

The coexistence of resistance and tolerance creates a major therapeutic challenge, as antimicrobial treatments may eliminate susceptible planktonic populations while allowing tolerant biofilm communities to persist. Consequently, successful therapeutic approaches should not only target resistance mechanisms but also disrupt the physiological adaptations that enable long-term biofilm survival.

Despite extensive knowledge of resistance mechanisms, current therapeutic strategies remain insufficient because they frequently target bacterial viability rather than the biofilm-associated processes responsible for persistence.

Table 1 summarizes the major resistance mechanisms described in MDR bacteria and indicates how they can interact with biofilm-associated persistence to sustain health-care-associated infections in hospitals.

Table 1: Antimicrobial resistance mechanisms employed by different bacteria

Resistance mechanism	Bacteria using it (relevant examples)	Type of antimicrobial resistance conferred
β-lactamase production (ESBLs, AmpC, carbapenemases)	Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Pseudomonas aeruginosa, Acinetobacter baumannii	Resistance to penicillins, 3rd–4th generation cephalosporins, and carbapenems
Modification of penicillin-binding proteins (PBP)	Staphylococcus aureus (MRSA), Streptococcus pneumoniae	Resistance to β-lactams (methicillin, penicillins, cephalosporins)
Target site alteration (mutations in DNA gyrase and topoisomerase IV)	Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus	Resistance to fluoroquinolones
Ribosomal RNA methylation (erm, cfr genes)	Staphylococcus spp., Enterococcus spp., Streptococcus spp., E. coli	Resistance to macrolides, lincosamides, and streptogramins
Aminoglycoside-modifying enzymes (acetylation, phosphorylation, adenylation)	Enterococcus spp., Staphylococcus aureus, Pseudomonas aeruginosa	Resistance to aminoglycosides (gentamicin, amikacin, tobramycin)
Reduced permeability due to porin loss or modification	Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae	Resistance to β-lactams, carbapenems, and fluoroquinolones
Active efflux systems (RND, MFS, ABC, MATE)	Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, Staphylococcus aureus	Multidrug resistance (β-lactams, macrolides, fluoroquinolones, tetracyclines)
Folate metabolism modification (sul, dfr genes)	Escherichia coli, Streptococcus pneumoniae, Staphylococcus aureus	Resistance to sulfonamides and trimethoprim
Horizontal gene transfer (plasmids, transposons, integrons)	Enterobacterales, Enterococcus spp., Staphylococcus aureus	Emergence of MDR/XDR strains and accumulation of multiple resistance determinants
Biofilm-associated protection	Staphylococcus epidermidis, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae	Antimicrobial tolerance and therapeutic failure against multiple antibiotics

ESBLs: Extended-Spectrum β-Lactamases; PBP: Penicillin-Binding Proteins; MRSA: Methicillin-Resistant Staphylococcus Aureus; QRDR: Quinolone Resistance-Determining Region; RND: Resistance-Nodulation-Division Family; MFS: Major Facilitator Superfamily; ABC: ATP-Binding Cassette Transporters; MATE: Multidrug And Toxic Compound Extrusion family; AmpC: AmpC β-Lactamase

Epidemiology of Antimicrobial Resistance in Hospital Settings

Across Latin America and the Caribbean, Antimicrobial Resistance (AMR) has developed into a major public-health problem, with MDR infections associated with high mortality and increasingly difficult clinical management. A systematic review and meta-analysis covering 54 observational studies published from 2000 through 2022, mainly from Brazil, Argentina, and Colombia, estimated an overall unadjusted case-fatality rate of about 45% among patients infected with MDROs [23]. This substantial burden should be interpreted in light of differences among countries in health-care resources, microbiology capacity, access to antimicrobials, and infection-prevention practices, because each of these conditions may influence outcomes.

Adjusted analyses demonstrated that AMR was independently associated with increased mortality compared with infections caused by susceptible microorganisms (adjusted OR = 1.93; 95% CI 1.58–2.37), indicating that resistance significantly contributes to unfavorable clinical outcomes [23]. However, the impact of AMR cannot be attributed exclusively to the presence of resistance determinants. The clinical consequences of MDR infections are also influenced by additional factors, including delayed effective therapy, limited treatment options, pathogen virulence, and the ability of resistant microorganisms to persist through biofilm-associated survival mechanisms.

Mortality was also higher when patients did not receive an appropriate empirical antimicrobial regimen (OR = 2.27; 95% CI 1.44–3.56), emphasizing the clinical value of early effective treatment where resistance is common [23]. At the same time, this association illustrates a central therapeutic dilemma: empiric coverage must be sufficiently rapid and effective without promoting unnecessary use of broad-spectrum agents that can intensify selection pressure. Better outcomes therefore depend on pairing antimicrobial stewardship with rapid diagnostic tools that support timely, pathogen-directed therapy.

Methicillin Resistant Staphylococcus Aureus (MRSA) is one of the best-characterized resistant pathogens, but an organism-by-organism view alone does not adequately describe current AMR epidemiology. Many health-care-associated infections involve the ESKAPE organisms Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp. which are notable for accumulating multiple resistance mechanisms that markedly narrow therapeutic options.

These pathogens demonstrate that resistance is not a single biological event but rather the result of the accumulation and interaction of different adaptive mechanisms, including β-lactamase production, porin alterations, efflux pump activation, horizontal gene transfer, and biofilm formation [2]. Importantly, the presence of resistance genes alone does not completely explain treatment failure, as bacterial persistence within biofilm communities may provide additional protection against antimicrobial exposure. Consequently, epidemiological surveillance based only on resistance rates may underestimate the real clinical threat posed by MDR pathogens.

Overall, the regional burden of AMR reflects an interaction among microbial adaptation, limitations within health-care systems, and constraints on effective therapy rather than a single causal factor. More informative control strategies will require stronger surveillance, more rational antimicrobial use, and epidemiological assessments that also consider biofilm-associated persistence when estimating infection severity and the threat posed by MDR organisms [7].

Impact on Device Associated Infections

The widespread use of invasive medical devices is a major contributor to healthcare-associated infections (HAIs), especially in highly specialized hospital environments such as Intensive Care Units (ICUs). According to current evidence, approximately 50–70% of hospital-acquired infections are linked to the use of invasive devices, with intravascular catheters, mechanical ventilation systems, and implanted prosthetic materials representing the most common sources of device-related infections [13-17].

Intravascular Catheters

Central Venous Catheters (CVCs) are an important source of device-related bloodstream infection because they remain in direct contact with the circulation and can support sustained microbial colonization. Biofilm development is central to this process: it helps maintain catheter-associated infection, favors persistence of MDR microorganisms, and reduces the likelihood that antimicrobial therapy alone will eradicate the infection.

A systematic review of CVC-associated clinical isolates found biofilm-forming ability in 59% to 100% of recovered microorganisms, a characteristic that can support persistence and reduce antimicrobial responsiveness. Frequently isolated organisms include Staphylococcus epidermidis, Methicillin-Resistant Staphylococcus Aureus (MRSA), Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, and Candida spp.; several of these commonly display MDR phenotypes.

After colonizing a catheter surface, biofilm communities develop a structured microenvironment in which antimicrobial penetration is restricted and microorganisms occupy metabolically diverse states. Close proximity within the community also favors horizontal transfer of resistance determinants and prolonged microbial survival. Clinically, these processes increase the likelihood of persistent bacteremia, sepsis, treatment failure, and hospital mortality [13].

Mechanical Ventilation

Mechanical ventilation increases the risk of Ventilator-Associated Pneumonia (VAP), a frequent and clinically important infection among critically ill patients. Evidence synthesized in systematic reviews indicates that endotracheal tubes, ventilator circuits, and internal components of ventilation equipment create surfaces suitable for microbial attachment and subsequent biofilm maturation. These communities are commonly dominated by MDR Gram-negative organisms, especially Pseudomonas aeruginosa and Acinetobacter baumannii [14].

Mature biofilms on respiratory equipment and airways can serve as persistent reservoirs from which pathogens remain in the lower respiratory tract despite antimicrobial treatment. Their presence is linked to repeated VAP, longer periods of mechanical ventilation, extended hospitalization, and greater mortality. Biofilm-associated cells may tolerate antimicrobial concentrations as much as 1000 times those affecting planktonic cells, which helps explain why therapeutic response may be poor in critically ill patients [14].

Prostheses and Other Implantable Devices

Orthopedic prostheses, cardiac valves, dialysis devices, and other medical implants provide an ideal substrate for bacterial adhesion and chronic biofilm development. Evidence from systematic reviews indicates that these infections are often present insidiously, with persistent clinical manifestations and high recurrence rates following conventional antimicrobial therapy [32].

When a biofilm develops on an implanted device, resident microorganisms become less accessible to immune defenses and to antimicrobial treatment. Standard broad-spectrum therapy may consequently fail to clear the infection, and removal or replacement of the device is often necessary for definitive management. Such infections can produce substantial morbidity, greater health-care costs, and an increased probability of persistent functional limitation [32, 38].

Table 2 brings together the principal MDR biofilm-producing microorganisms associated with medical devices and the main clinical consequences reported in hospital settings.

Novel Therapeutic Strategies Against MDR Biofilms in Healthcare Settings

Infections caused by MDR microorganisms growing in biofilms are particularly difficult to treat in current clinical practice. This difficulty has stimulated the development of therapies that aim not only to kill the pathogen but also to prevent biofilm establishment, disrupt its architecture, or interfere with its maintenance. Approaches under active investigation include antimicrobial nanoparticles, bioactive compounds of natural origin, agents that degrade or destabilize the matrix, and bacteriophages; experimental evidence suggests that these strategies can enhance antimicrobial activity and reduce persistence of chronic infection [18, 36, 37].

Table 2: Impact of biofilm-producing multidrug-resistant microorganisms in device-associated infections

Invasive device	Predominant pathogens	Microbiological determinants of MDR and biofilm	Clinical consequences
Central venous catheter (CVC)	MDR/XDR Acinetobacter baumannii, Staphylococcus epidermidis, methicillin-resistant Staphylococcus aureus (MRSA), ESBL-producing Klebsiella pneumoniae	Initial adhesion mediated by outer membrane proteins (OmpA, Csu pili); structured biofilm formation; efflux pump overexpression and β-lactamase production	Catheter-associated bloodstream infection, sepsis, increased hospital mortality, prolonged hospital stays
Urinary catheter	Acinetobacter baumannii, ESBL-producing Enterobacterales, vancomycin-resistant Enterococcus faecium	Persistent intraluminal biofilm formation; antimicrobial tolerance; horizontal gene transfer of resistance determinants	Catheter-Associated Urinary Tract Infection (CAUTI), recurrent infections, progression to bacteremia
Mechanical ventilation (endotracheal tube)	Acinetobacter baumannii, Pseudomonas aeruginosa, carbapenem-resistant Klebsiella pneumoniae	Polymicrobial biofilm formation on endotracheal surfaces; carbapenem resistance; induction of low-metabolic activity states (persister cells)	Ventilator-Associated Pneumonia (VAP), increased ICU mortality, prolonged mechanical ventilation
Prostheses and implantable medical devices	Acinetobacter baumannii, Staphylococcus epidermidis, Staphylococcus aureus	Mature biofilm formation on metallic and polymeric surfaces; immune evasion; sustained antimicrobial tolerance	Chronic prosthetic infections, frequent relapses, functional impairment
Devices in intensive care units (ICUs)	MDR/XDR Acinetobacter baumannii (predominant)	Prolonged environmental persistence; high survival capacity; synergistic interaction between biofilm formation and multidrug resistance	Nosocomial outbreaks and cross-transmission among critically ill patients

When emerging antibiofilm approaches are combined with conventional antimicrobials, synergistic activity has been observed in experimental models and may improve outcomes in MDR health-care-associated infection. However, the available evidence remains largely preclinical; adequately designed clinical trials are still necessary before these combinations can be adopted as routine therapeutic practice [34, 37, 38, 39].

Nanotechnology Based Strategies for Biofilm Eradication

Nanotechnology is increasingly recognized as an innovative therapeutic platform capable of addressing many of the shortcomings of conventional antimicrobial treatments used against MDR biofilm-associated infections. Unlike traditional antibiotics, which frequently exhibit reduced activity against metabolically inactive biofilm-associated cells, nanomaterials can provide multifunctional antimicrobial effects by simultaneously targeting bacterial membranes, inducing oxidative stress, and interfering with Extracellular Polymeric Substance (EPS) organization. Recent studies have shown that metal–phenolic network nanoparticles can effectively destabilize mature biofilms while improving antimicrobial activity against resistant microorganisms. These findings indicate that nanotechnology-based systems may offer an effective alternative for eliminating bacterial populations that exhibit limited susceptibility to conventional antimicrobial therapies [40].

However, the current evidence supporting nanotechnology-based antibiofilm strategies remains largely dependent on in vitro studies, and their clinical relevance is still uncertain. Despite encouraging results obtained under experimental conditions, the performance of nanoparticles in vivo may be influenced by multiple biological factors, including interactions with host tissues, immune system activity, and physiological barriers that are difficult to reproduce in laboratory models. In addition,

several challenges continue to limit their clinical implementation, such as potential cytotoxic effects, long-term tissue accumulation, large-scale manufacturing, product standardization, and regulatory requirements. Consequently, future investigations should prioritize not only the optimization of antimicrobial efficacy but also rigorous safety assessment and validation in clinically relevant models to determine whether these nanotechnology-based approaches provide meaningful advantages over currently available therapeutic options [41].

Phage Therapy as a Targeted Alternative Against MDR Biofilms

Bacteriophages have regained attention as a potential treatment for MDR infections in which biofilms contribute to persistence. Their narrow bacterial tropism allows them to infect susceptible target bacteria while having relatively little effect on the commensal microbiota. Some phages also encode depolymerases or other enzymes that degrade components of the biofilm matrix, which can improve penetration and increase access to bacteria located deep within mature communities. These features make phage-based treatment a potential adjunct when conventional antimicrobials are compromised by biofilm growth [42].

Important obstacles still limit routine clinical use of bacteriophages. High host specificity, although beneficial for sparing commensal bacteria, may restrict coverage because a given phage often acts against only a narrow subset of strains. Other concerns include the selection of phage resistant variants, neutralization by host immunity, difficulties in manufacturing reproducible formulations, and regulatory requirements for clinical products. These unresolved issues have slowed incorporation of phage therapy into standard practice [42-43].

Despite advances in antibiofilm technologies, no current strategy has demonstrated sufficient clinical evidence to replace conventional antimicrobial therapy. Therefore, future approaches should prioritize combination therapies capable of simultaneously targeting resistance mechanisms and biofilm persistence.

Discussion

The literature evaluated in this review supports the view that MDR and biofilm formation interact to sustain health-care-associated infection. [12] describe biofilms as organized microbial communities in which restricted antimicrobial penetration coexists with conditions that favor expression and maintenance of resistance mechanisms, thereby promoting chronic infection that is difficult to treat. [16] similarly found that biofilm-producing isolates from intensive care units are linked with greater persistence and poorer therapeutic response.

With respect to the organisms involved, the pattern observed here agrees with [2, 3], who identify the ESKAPE group as major contributors to MDR infection in hospitals. [20] further emphasize that the clinical success of these organisms reflects not only antimicrobial resistance but also their adaptability, environmental survival, and capacity for biofilm growth.

From a pathophysiological standpoint, the reviewed evidence is compatible with the mechanisms described by [18, 31]: the biofilm matrix generates heterogeneous microenvironments in which antimicrobial penetration is reduced and low-metabolic states are favored, conditions that promote persister-cell formation. [30] also report a high prevalence of biofilm-forming Acinetobacter baumannii, reinforcing the importance of this phenotype for persistence and reduced susceptibility in hospitals.

At the level of individual pathogens, [13] emphasize the contribution of biofilms to infections involving indwelling devices, particularly intravascular catheters. [14] similarly report that Pseudomonas aeruginosa in ventilator-associated pneumonia has a pronounced ability to form biofilms, a property that can support chronic infection and reduce antimicrobial effectiveness.

The epidemiological evidence considered in this review is also consistent with [23], who document the continuing contribution of MDR infection to mortality in Latin America. These findings support stronger surveillance and more effective antimicrobial-stewardship programs as components of infection control. [9] reached a comparable conclusion, identifying these measures as central to limiting dissemination of resistant organisms within health-care institutions.

For treatment, the evidence reviewed here parallels reports by [34, 35] describing the capacity of nanomaterials and antimicrobial nanoparticles to interfere with biofilm integrity. [10] additionally indicate that some natural compounds can affect several bacterial targets and may therefore influence both biofilm production and antimicrobial susceptibility. Nevertheless, [18] note that much of the evidence for these alternatives remains experimental and is not yet sufficient to support broad clinical implementation.

A further conclusion from this synthesis is that promising experimental findings have not yet translated consistently into clinical practice. This agrees with [15], who call for well-designed clinical investigations capable of determining whether emerging antibiofilm therapies provide meaningful benefits in patients.

Conclusion

This review shows that the combination of Multidrug Resistance (MDR) and biofilm growth strongly influences persistence, disease severity, and treatment failure in health-care-associated infection. Biofilm-forming MDR microorganisms employ several adaptive mechanisms that improve survival during antimicrobial exposure. Clinically, these infections tend to be accompanied by less favorable outcomes, including greater morbidity and mortality and longer periods of hospitalization.

This work contributes to the scientific community by providing a comprehensive and integrative analysis of the microbiological, epidemiological, and pathophysiological mechanisms underlying MDR and biofilm-associated infections in hospital settings. Additionally, it consolidates current evidence on emerging therapeutic strategies, offering a framework for future research focused on targeted and more effective interventions.

MDR biofilm-associated infections also place considerable financial pressure on health-care systems through prolonged admission, greater treatment expenditure, use of advanced therapies, and increased complications and readmissions. Reducing this burden will require coordinated antimicrobial stewardship, reinforced infection-prevention and control practices, and continued development of therapies that directly target biofilm biology. Together, these measures may reduce both the clinical consequences and the economic costs of MDR infection.

Overall, bridging the gap between experimental advances and clinical implementation remains a critical priority to effectively combat MDR biofilm-associated infections and improve patient outcomes in hospital environments.

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Author’s Contributions

Daniel Lucio López and Alberto Bustillos: Participated in conceptualization, literature assessment, data analysis, manuscript preparation, and final revision.
Elizabeth Proaño: Contributed to the study design, critically reviewed the manuscript, and supervised the research process. All authors reviewed and approved the final version of the manuscript.

Ethics

This work synthesizes previously published literature and did not include direct research involving human participants or animals; therefore, institutional ethical approval and informed consent were not applicable. the authors declare that the publication raises no ethical concerns.

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