Article
JOURNAL OF UNIVERSITY OF BABYLON
For Pure and Applied Sciences (JUBPAS)
Vol. 34 ; No. 2 | 2026

Biofilm Formation and Antibiotic Resistance Are Regulated by Quorum Sensing in Bacterial Pathogenicity.

[1]Rana T. Mohsen, [2]Kawther Mohammed Nasir
[1]Department of Biotechnology, College of Science, University of Anbar
[2]Department of Biology, College of Education for Women, University Of Anbar,
*Corresponding Author: Rana Talib Mohsen
Email: rana2011@uoanbar.edu.iq

الإمراضية البكتيرية من خلال التنظيم المتوسَّط باستشعار النصاب لتكوين الأغشية الحيوية ومقاومة المضادات الحيوية

رنا طالب محسن [1], كوثر محمد ناصر [2]
قسم علوم الحياة ،كلية التربية بنات ،جامعة الانبار
قسم التقنيات الاحيائية، كلية العلوم، جامعة الأنبار

Accepted: 16/6/2026 **Published:** 30/6/2026

ABSTRACT

Background:

Quorum sensing (QS) is a multifaceted and tightly orchestrated cell-to-cell communiqué network that lets microorganisms to detect their cell mass and coordinate the appearance of a group of genes by secreting, releasing and detecting small molecules called autoinducers. This regulatory network enables bacterial populations to perform as a multi-cellular system by coordinating physiological activity only at a critical cell density. Gram-negative bacteria typically use N-acyl homoserine lactones (AHLs) as the mediators of QS, whereas Gram-positive bacteria mainly rely on processed oligopeptides. The complexity and adaptability of microbial social behavior is further highlighted by the fact that the same microbial signaling molecule, called autoinducer-2 (AI-2), is involved in interspecies communication. This matrix provides physical and chemical barrier to antibiotic penetration, poor immune system recognition and heterogeneous microenvironments, which allows for bacterial persistence. The metabolic state of the microbial cells changes in biofilms, such as sluggish increasing or inactive “persister” cells that stand very resilient to antimicrobials and promote chronic and recurrent infections. The development and growth of biofilms are strictly regulated by genes associated with adhesion factors, EPS production, motility and stress response by QS systems. Importantly, QS also regulates the expression of virulence factors (toxins, enzymes, secretion systems etc.) which increases pathogenicity during infection. QS networks have been found to be central to the establishment of persistent infections, especially in the hospital environment where device-associated infections (e.g., catheters, ventilators, implants) are prevalent. The dense cellular agglomeration and extracellular DNA in the EPS matrix can contribute to processes of horizontal gene transfer (HGT) by transformation, transduction, and conjugation. QS can also trigger efflux pump systems, alter membrane permeability and induce activation of stress response pathways, all of which contribute to increasing the broadmindedness and confrontation of bacteria to antimicrobial agents. These mechanisms are especially a problem in multidrug-resistant (MDR) infections, in which traditional antibiotics are unable to kill biofilm-associated bacteria.

Keywords: Quorum sensing, biofilm, antibiotic resistance genes, MDR bacteria, horizontal gene transfer

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com
مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

INTRODUCTION

Antibiotic resistance has arisen as one of the greatest significant threats to public health in the 21st century, especially in healthcare-associated infections (HAI), where high levels of adaptability and multidrug resistance among microorganisms are found. With the rise and spread of antibiotic-resistant bacteria (ARB), the use of conventional antimicrobials has become less effective, resulting in enlarged morbidity and mortality Antimicrobial resistance (AMR) has been consistently documented by the (WHO) as a "silent pandemic" that threatens the effectiveness of treating routine infections, as well as the success of modern medicine and the eradication of neglected diseases[1].Biofilm formation is a large biological process that helps to cause chronic and difficult-to-treat infections. Biofilms are microbial communities with a complex structure, consisting of discrete groups of cells, which are attached to biotic or abiotic surfaces and surrounded by a self-produced extracellular polymeric substance (EPS) matrix made of polysaccharides, proteins, lipids and extracellular DNA. This matrix will provide a protective barrier against antibiotic penetration, impede immune system penetration and provide heterogeneous microenvironments in which bacteria survive under stress conditions. In biofilms, bacteria have different phenotypes – they can grow slowly and have "persisted cells", which are genetically non-resistant, but highly resistant to antibiotics. In humans, it has been estimated that about 80% of chronic and recurrent infections are related to biofilms, such as chronic wounds, infections in the lungs in people with cystic fibrosis, urinary tract infections in the presence of urinary catheters and implant-associated infections. The clinical relevance of biofilms is especially evident in hospital environments where medical devices such as intravascular catheters, prosthetic joints and ventilators offer optimal surfaces for microbial attachment and maturation of the biofilm. Biofilms are hard to treat with typical antibiotic treatment, and can cause chronic infection and failure to treat. Quorum sensing (QS) systems are a highly orchestrated mode of bacterial communication that tightly regulates the development, maturation and dispersal of biofilms. When the density of bacteria is high, they produce, release and detect small molecules, called auto inducers, which are responsible for QS. When they reach a threshold concentration they induce coordinated changes in the expression of the genes of the entire bacterial population. Furthermore, autoinducer-2 (AI-2) makes communications between different species easier, showing that QS is universal in microbial ecosystems[4,5].QS regulates genes related to surface adhesion, EPS production, motility and biofilm architecture, playing a key regulatory role in biofilm formation. It also is involved in controlling the expression of virulence factors such as toxins, enzymes and secretion systems, and thus increases the pathogenicity of the bacteria during infection. Importantly, QS is not only involved in the regulation of biofilm but also in bacterial stress response and adaptive behavior in hostile environments, such as antibiotics. Recently, it has been shown that there is a close relationship between QS and the mechanisms of antibiotic resistance in clinical pathogens like *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli and Acinetobacter baumannii*[6]. There are several ways in which QS contributes to antibiotic resistance, such as increased biofilm formation, increased horizontal gene transfer (HGT), activation of efflux pump systems, and modulation of membrane permeability. Biofilms have a well-organized cell structure that makes

ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

transformation, transduction, and conjugation of genetic material such as ARGs a possibility. Healthcare-associated infections (HAI) are strongly associated with QS-mediated biofilms, multidrug resistance (MDR) and clinical failure[4]. However, the coordinated behaviour of bacterial communities enables them to resist the effects of an antibiotic treatment and escape the host's immune system; in many cases, they are just as effective without antibiotic treatment as with it[4,2]. Disruption of QS systems has been demonstrated to have a profound effect on reducing the formation and virulence of biofilms, suggesting that QS is a potential therapeutic target. In general, QS is a molecular hub for biofilm formation, bacterial cooperation and distribution of antibiotic resistance genes. Knowing this interconnected network is critical for the expansion of new antimicrobial agents, such as quorum sensing inhibitors (QSIs), anti-biofilm agents and agents that inhibit bacterial communication without killing the cells, which limits the selective pressure for antimicrobial resistance development[7].

MOLECULAR MECHANISM OF QUORUM SENSING

In Gram-negative bacteria, N-acyl homoserine lactones (AHLs) are the primary particles involved in QS, which can freely enter and exit the cell and are found in the extracellular environment. Gram-positive bacteria are different as they use active secretion of processed oligopeptides which are recognized by the membrane bound two-module regulatory systems. Moreover, the autoinducer-2 (AI-2) system is a general communication process that enables intra- and interspecies bacterial communication. The QS regulatory process is sequential, with four important steps. Bacteria produce and secrete signaling molecules (signal production). These autoinducers accumulate around them more and more as the number of bacteria grows (signal accumulation)[8,9]. This is known as gene regulation activation and is triggered by detection of these signals at the appropriate concentration by special receptors (threshold detection), which then activates or represses the appropriate target genes. This regulation by density enables bacteria to function as multicellular organisms, which maximizes their survival and ability to adapt to different conditions. QS are known to control many physiological and pathogenic events, including infection and persistence[8]. These include genes involved in biofilm formation, including adhesion factors (regulated by QS), extracellular polymeric substance (EPS) manufacture and maturation of the biofilm matrix structure. Moreover, QS controls the expression of efflux pumps that is responsible for elimination of antibiotics and a lower concentration of the drug inside the cell. It also regulates the expression of virulence factors such as toxins, enzymes, secretion systems that increase the ability of the bacteria to be pathogenic. Importantly, QS has been directly, or indirectly, associated with the regulation of antibiotic resistance genes (ARGs) by favoring horizontal gene transmission and/or the

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

activation of stress-response mechanisms that improve the bacterial survival under the action of antimicrobial agents[10]as shown in figure 1.

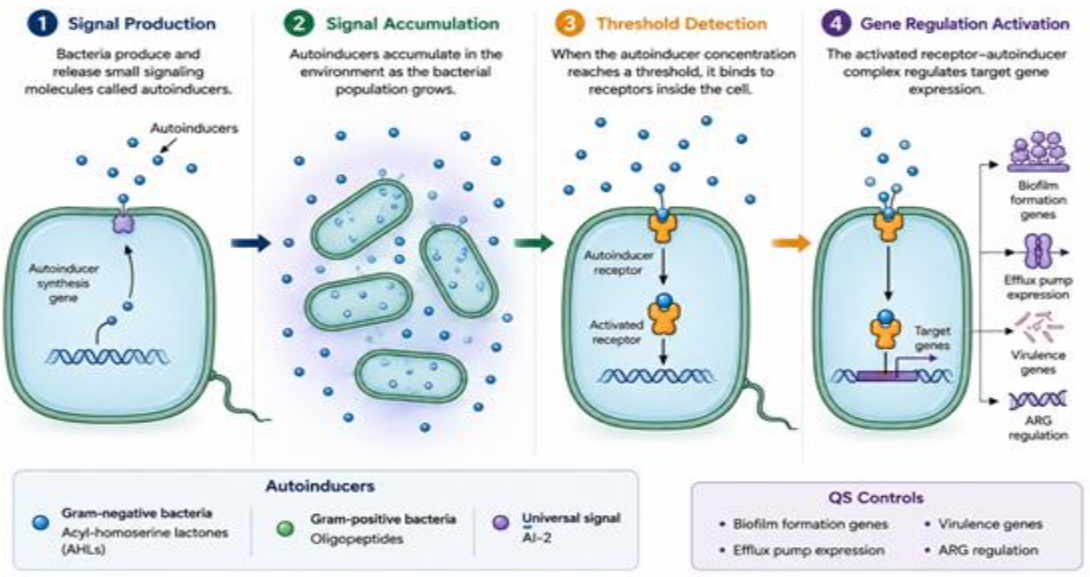

Figure 1 Regulation of bacterial communication via autoinducers that are produced as a function of cell density and that activate genes when they reach a critical concentration that promote biofilm formation, virulence and antibiotic resistance)**[11].**

BIOFILM FORMATION AND STRUCTURE

Biofilms are highly organized microbial communities, in which the bacterial cells are encased in an EPS matrix, an exopolymer produced by the community. The polysaccharides, proteins, lipids and extracellular DNA (eDNA) are the main components of this matrix, which are responsible for the structural stability and functional protection of the microbial community. Biofilms are a lifestyle of predominant bacteria living in natural, environmental and clinical settings, and they are strongly related to chronic and device-related infections because they are more resistant to antimicrobials and host immune responses. [13]. The development of a biofilm is a dynamic and sequential process which has several well-defined stages. Initial Adhesion – the first stage of adhesion is initial, in which planktonic (free-floating) bacteria interact with a biotic or abiotic surface in a reversible manner, done weak physicochemical interactions such as electrostatic forces and Van Der Waals forces. This is followed by irreversible attachment which involves the production of adhesins and early EPS which helps the association be stable and permanent.Microcolony formation occurs during the third stage, when bacteria attach and start to grow in small clusters. Intercellular signaling systems, such as quorum sensing (QS), are now

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

more active and help regulate group behavior. This results in the formation of a mature biofilm with its complex, three-dimensional structure and water channels to allow nutrients to be distributed, wastes to be excreted, and chemical signals to be exchanged. The mature biofilm is very structurally heterogeneous and different bacterial subpopulations are able to survive in different oxygen and nutrient gradients[14].Dispersion involves the release of cells or clusters from the biofilm and the return to a planktonic state that facilitates the establishment of new biofilms on new surfaces and the spread of infection in the host or environment. This dispersal is important for the dissemination of infection and is highly controlled by environmental signals and QS signaling pathways. From a functional standpoint, biofilms are a very strong defense against antimicrobial agents. The EPS matrix slows down the penetration of antibiotics, limits the antibiotic diffusion and can inactivate some antimicrobial compounds. Moreover, biofilm-associated bacteria have changed metabolic rates such as reduced growth rate and dormant persister cells, which also contribute to the resistance to antibiotics. Biofilms also play an important role in antibiotic resistance, through horizontal gene transfer and the transfer of ARGs, which makes infections difficult to treat and can result in chronic/disease recurrence[3,14].

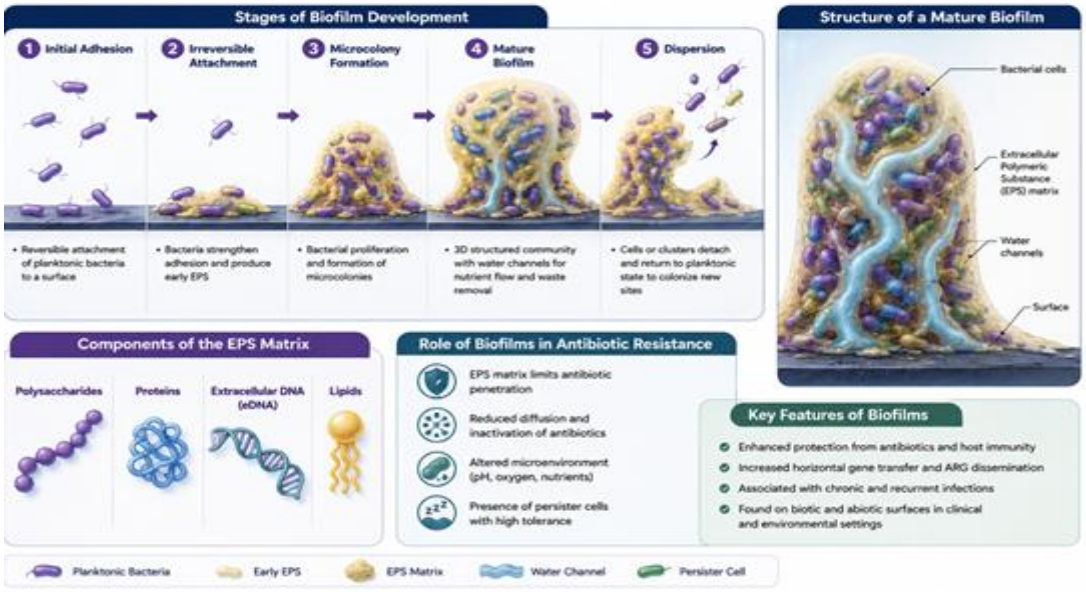

Figure 2. Biofilm formation and architecture, with emphasis on sequential stages of biofilm development, composition of extracellular polymeric substance (EPS) matrix and role of biofilms in antimicrobial resistance. [14].

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

ANTIBIOTIC RESISTANCE GENES (ARGS) IN BIOFILM-FORMING BACTERIA

Modelling and field studies have shown that the dissemination and emergence of antibiotic resistance genes (ARGs) in multidrug resistant (MDR) infections is greatly facilitated by the presence of multiple ARGs in the genomes of the biofilm forming bacteria. Clinical isolates from chronic wounds and medical device-associated infections frequently harbor a large number of ARGs, which makes them resistant to various classes of antimicrobial agents (15 ,16). The presence of ESBL-producing bacteria with these genes has spread to other countries around the world and is a serious threat in the hospital and community environments.The carbapenemase genes blaNDM-1 and blaOXA-48 are particularly clinically significant as they provide resistance to carbapenems (16). Such genes are usually found in biofilm-producing *Klebsiella pneumoniae*, *Escherichia coli* and *Acinetobacter baumannii*, and are responsible for the widespread dissemination of carbapenem resistance around the world in these microorganisms (15,16). Similarly, the aminoglycoside acetyltransferase, which renders the aminoglycoside antibiotics enzymatically inactive and therefore less effective against bacteria (16). The presence of these resistance determinants in the same bacteria in the biofilm makes the bacteria more difficult to treat. Biofilms can promote the acquisition, preservation and transfer of ARGs through several mechanisms. One is the reduced penetration of antibiotics through the extracellular polymeric substance (EPS) matrix that actually forms a physical barrier that restricts the diffusion of antimicrobial agents and lowers their concentration in deeper layers of the biofilm (10,14). Furthermore, parts of the EPS matrix can interact with antibiotics prior to their introduction to their cellular targets, which can reduce their antimicrobial efficacy (10). Another important mechanism by which ARGs are spread among bacterial populations is horizontal gene transfer (HGT), which is facilitated by biofilms. Biofilms are characterized by a high cell density and close cell-cell contact, which can promote the transfer of plasmids, transposons, integrons, etc. with the acquisition of resistance genes (15,17). The extracellular DNA in the biofilm matrix is also a reservoir for genetic material that can be taken up by neighboring cells, and can serve as a structure that helps to increase the spread of the ARG (10, 17). Another reason for resistance developing is that the bacteria that grow in a biofilm have a higher mutation rate. Genetic variation and adaptive mutations that lead to increased resistance phenotypes can be induced through environmental stresses, including oxidative stress, nutrient limitation, and extended periods of antibiotic use (16,18). Such mutations may be selectively preserved in the biofilm and contribute to the formation of bacterial subpopulations that are extremely resistant.In addition,

ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

mature biofilms contain special, dormant cells called persister cells that are extremely resistant to antimicrobial therapy even when they do not have specific resistance mechanisms (18). Persister cells are not metabolically active or metabolize at a decreased rate, making them more resistant to antibiotics that target cellular processes. After antibiotic treatment, these cells can re-populate the biofilm and cause recurrent and persistent infections (18,20).All together, limited antibiotic penetration, increased horizontal gene transfer, increased mutation rates, and persisted cells, make biofilm major reservoirs of antibiotic resistance genes. The combination of these properties plays a pivotal role in the maintenance of chronic infections and in the global dissemination of antimicrobial resistance, thus highlighting the importance of developing new therapeutic approaches targeting biofilm formation and ARG dissemination (14,15,20).

Interconnection Between Quorum Sensing (QS), Biofilm Formation, and Antibiotic Resistance Genes (ARGs)

Quorum sensing (QS), biofilm formation, and antibiotic resistance genes (ARGs) are all highly connected and important regulators of bacterial persistence and the development of multidrug resistance. These processes are not independent processes, but rather work together to provide bacteria with greater survival under environmental stress and antibiotic pressure. More and more, it is becoming clear that QS acts as a hub for central regulation that connects biofilm development with acquisition, maintenance, and dissemination of ARGs, which are responsible for chronic and recurrent infections (18,21).Regulation of genes that contribute to extracellular polymeric substance (EPS) synthesis is one of the main mechanisms of antibiotic resistance that QS promotes. When activated, QS signaling pathways generate polysaccharides, proteins and extracellular DNA that create the structural matrix of biofilms (10,21). The increased EPS production leads to a more dense and stable biofilm structure, shielding bacterial cells from the host immune system and greatly reducing antibiotic penetration. This means that bacteria inside the biofilm are under sublethal doses of antibiotics and conditions are optimal for using and keeping resistant populations (14,20).Also, one of the most important means of ARGs dissemination is horizontal gene transfer (HGT), which is favored by biofilm environment. Bacteria within mature the biofilms are in close physical proximity and at high densities, which promotes plasmid and transposon transfer, as well as the transfer of integrons and other mobile genetic elements containing resistance determinants (15,22). QS systems have been demonstrated to stimulate conjugative plasmid transfer and competence development in a number of bacterial species, speeding up the transfer of ARGs in microbial communities (21,22). Therefore, biofilms can serve as a source of resistance genes that are easily shared between bacteria.Another significant feature of this association is the stability and longevity of ARGs in biofilm communities. The protective biofilm matrix will minimize environmental fluctuations and selective pressures which could otherwise kill off the resistant strains. This stable condition

ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

provides bacteria with ARG the ability to survive, grow, and keep the ARG determinants for a long time (17, 22). Furthermore, extracellular DNA in EPS matrix not only acts as a structural part of EPS but also provides genetic material, which can be transferred to adjacent cells by natural transformation, and further promotes the dissemination of ARG (10,17).QS is also directly involved in the regulation of some resistance associated mechanisms such as multidrug resistance efflux pumps and stress response genes. Bacterial resistance is promoted by efflux pumps which actively remove antibiotics from the bacterial cell, thereby lowering the antibiotic concentration in the bacterial cells (16,21). At the same time, QS also activates stress response pathways, which will improve bacterial survival under challenging conditions, such as antimicrobial treatment, nutrient limitation and oxidative stress (21,23).This interplay of QS, biofilm and ARG dissemination forms a vicious cycle that leads to chronic infection and therapeutic resistance. The QS activation increases EPS production and consequently biofilm formation. The dissemination and persistence of resistance genes increase the chances of survival for the bacteria and sustained infections. Chronic infections, in turn, generate further chances for QS activation and maturation of biofilm, thus perpetuating the cycle of resistance and persistence (20–23).

Clinical Isolates: Global and Iraq Context

Multidrug-resistant (MDR) bacterial pathogens have become an important challenge in clinical settings, particularly in the healthcare sector. Many studies have illustrated that it is a common phenomenon that biofilm-producing bacteria cause a significant amount of hospital-acquired infections (HAIs) such as chronic wound infections, urinary tract infections, burn infections, respiratory tract infections and indwelling medical device infections. *Pseudomonas aeruginosa*, Escherichia coli and Staphylococcus aureus are among the most common pathogens isolated, and are known to have the ability to form biofilms and to gain multiple antibiotic resistance determinants (26,27). *Pseudomonas aeruginosa*, is known as one of the most troublesome opportunistic pathogens worldwide because of its inherent resistance mechanisms, effective quorum sensing (QS) and ability to form biofilm. In the intensive care unit, in burn units and in ventilator-associated pneumonia patients, clinical isolates often have multidrug resistance and high biofilm production, which helps to cause chronic infection and lead to a low cure rate (27,28). Likewise, E. coli strains that form biofilm are frequently found in UTIs, and are frequently ESBL-positive, specifically blaCTX-M, blaTEM, and blaSHV, which substantially limit the efficacy of β-lactam antibiotics (29). It has been found to easily form biofilms on medical devices and damaged tissues, allowing it to survive long-term and evade antibiotic treatment and host immune responses. Recurrent infections are due to the occurrence of the mecA gene along with other factors responsible for tolerance associated with biofilm formation (30).In Iraq, recent clinical studies have revealed similar patterns to that seen worldwide, with a high incidence of MDR bacterial isolates being recovered from healthcare facilities and hospitals. *P. aeruginosa*, *E. coli* and S. aureus are consistently reported as the most prevalent and resistant pathogens in burn units, wound infections, urinary tract infections and intensive care, and possess high abilities to form biofilms (31,32). Burn wound isolates of P. aeruginosa have

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

exhibited high rates of resistance to cephalosporins, fluoroquinolones and carbapenems, and have also exhibited increased virulence and biofilm production (31).There are also multiple Iraqi studies that show the presence of ESBL-producing Enterobacteriaceae (32,33) with resistance genes like blaCTX-M, blaSHV and blaTEM, which are often found in clinical isolates that form biofilm. Moreover, carbapenem-resistant variants with blaNDM and blaOXA genes have also been increasingly reported, and this is a matter of concern due to the limited treatment options available (33). These resistance factors can reside on mobile genetic elements that enable the spread of resistance genes in and out of bacterial populations in biofilms. A remarkable thing that can be noted in both global and Iraqi studies is the correlation between biofilm and antimicrobial resistance. Biofilm-forming isolates are typically highly resistant to β-lactams, carbapenems, aminoglycosides and fluoroquinolones (28,31). These pathogens are able to persist in clinical environments in large part because of the protective effects of the extracellular polymeric substance (EPS) matrix, QS-regulated resistance mechanisms and improved horizontal gene transfer (23,28).Together, this shows that QS is an important mechanism for persistence and dissemination of antibiotic resistant pathogens in both developed and developing nations. The high prevalence of MDR biofilm-forming isolates and the common occurrence of ARGs like blaCTX-M, blaSHV, blaTEM, mecA, and carbapenemase genes emphasize that new therapeutic approaches that disrupt bacterial communication systems and the mechanisms that drive biofilm formation are essential. Without action on these interrelated parameters, the ongoing high rates of antibiotic treatment failure, hospitalization and mortality in infected individuals are likely to persist (23,27,33).

Therapeutic Strategies: Quorum Quenching (QQ)

Quorum quenching (QQ) is a novel antimicrobial strategy that disrupts quorum sensing (QS) systems without disrupting bacterial growth or killing bacterial cells. The advantage of QQ over conventional antibiotics is that it disrupts bacterial communication systems that control virulence, biofilm development and resistance-related behaviours, which minimizes the selection of resistance while decreasing pathogenicity (34,35).There are a few mechanisms demonstrated that affect the disruption of QS signaling. Examples of these are the enzymatic degradation of autoinducers, which causes a breakdown of the signal and prevents its accumulation in the cell and eliminates any communication between bacterial cells; receptor inhibition, where signaling molecules bind to receptors or to other molecules in the bacteria and are not absorbed by the target receptors; and inhibition of signal synthesis which stops the production of quorum molecules in the bacteria (35,36). Besides, numerous natural products such as extracts of plants, essential oils and flavonoids, have been shown to have quorum quenching capabilities by disrupting the different steps of the QS signaling pathways (37).QQ disrupts bacterial communication and can dramatically inhibit the production of virulence factors, inhibit biofilm formation and make bacterial pathogens more susceptible to conventional antibiotics (34,36). Importantly, unlike traditional antimicrobial therapy, QQ does not directly kill bacteria, and will, therefore, be less likely to cause the emergence of resistant strains (35). Thus, quorum quenching has become a novel approach to manage chronic biofilm-associated infections and to overcome the alarming issue of antimicrobial resistance.

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

CONCLUSION

Bacterial pathogens are remarkable for their adaptability and ability to survive under the stress of antibiotics, making antibiotic resistance one of the biggest challenges for today's healthcare. The evidence is growing that quorum sensing (QS), biofilm formation, and antibiotic resistance genes (ARGs) are interlinked and integral to a regulatory network that improves the persistence, virulence and resistance of bacteria. QS is a central communication system which allows bacteria to coordinate the expression of collective behaviours by producing and detecting molecules of communication. Bacteria can quickly adapt and adjust their growth in response to environmental fluctuations and maximize their survival in adverse conditions like in the presence of antibiotics through QS-mediated regulation.Biofilms also help bacteria to be more resilient by creating an environment that is very protective for them. The extracellular polymeric substance (EPS) matrix, which hinders antibiotic diffusion, protects bacterial cells from host immune systems, and increases the survival of metabolically dormant persister cells. Moreover, biofilms are excellent vehicles for HGT, which enables the spread and persistence of ARGs within bacterial communities. This means that biofilm infections can also be very tolerant to some antimicrobial agents and are often associated with chronic, recurrent and difficult-to-treat conditions. The prevalence and dissemination of clinically relevant ARGs such as blaTEM, blaSHV, blaCTX-M, blaNDM and blaOXA variants, mecA and aac(6′)-Ib genes have significantly contributed to the global surge in multidrug resistant (MDR) pathogens. These genes are frequently found in clinical isolates that can form a biofilm, and are frequently spread through mobile genetic elements in biofilm populations. The interplay between QS-controlled biofilm development and ARG proliferation results in an ongoing loop that leads to bacterial persistence, therapy failure, lengthened hospital stays and higher mortality rates. Numerous clinical studies have been performed globally, including in Iraq, and have consistently shown a high proportion of MDR P. aeruginosa, E. coli, and S. aureus clinical isolates with high biofilm-forming ability and with broad resistance phenotypes. This widespread occurrence of ESBLs and CRs emphasizes the need to find alternative therapeutic options that can overcome the limitations of conventional antibiotics.

Conflict of interests.

There are non-conflicts of interest.

References

[1] J. W. Costerton, P. S. Stewart, and E. P. Greenberg, “Bacterial biofilms: a common cause of persistent infections,” *Science*, vol. 284, no. 5418, pp. 1318–1322, 1999.

[2] D. Davies and G. G. Geesey, “Why are bacteria refractory to antimicrobials?” *Nature Reviews Microbiology*, vol. 1, no. 2, pp. 114–120, 2003.

[3] N. Høiby, T. Bjarnsholt, M. Givskov, S. Molin, and O. Ciofu, “Antibiotic resistance of bacterial biofilms,” *International Journal of Antimicrobial Agents*, vol. 35, no. 4, pp. 322–332, 2010.

[4] H.-C. Flemming and J. Wingender, “The biofilm matrix,” *Nature Reviews Microbiology*, vol. 8, no. 9, pp. 623–633, 2010.

[5] L. Hall-Stoodley, J. W. Costerton, and P. Stoodley, "Biofilms: from environment to infectious diseases," *Nature Reviews Microbiology*, vol. 2, no. 2, pp. 95–108, 2004.
[6] R. M. Donlan and J. W. Costerton, "Biofilms: survival mechanisms of clinically relevant microorganisms," *Clinical Microbiology Reviews*, vol. 15, no. 2, pp. 167–193, 2002.
[7] K. Lewis, "Persister cells, dormancy and infectious disease," *Nature Reviews Microbiology*, vol. 5, no. 1, pp. 48–56, 2007.
[8] M. B. Miller and B. L. Bassler, "Quorum sensing in bacteria," *Annual Review of Microbiology*, vol. 55, pp. 165–199, 2001.
[9] C. M. Waters and B. L. Bassler, "Cell-to-cell communication in bacteria," *Annual Review of Cell and Developmental Biology*, vol. 21, pp. 319–346, 2005.
[10] W. L. Ng and B. L. Bassler, "Bacterial quorum-sensing network architectures," *Annual Review of Genetics*, vol. 43, pp. 197–222, 2009.
[11] M. Whiteley, S. P. Diggle, and E. P. Greenberg, "Quorum sensing research progress," *Nature*, vol. 551, no. 7680, pp. 313–320, 2017.
[12] S. T. Rutherford and B. L. Bassler, "Quorum sensing in virulence and control," *Cold Spring Harbor Perspectives in Medicine*, vol. 2, no. 11, 2012.
[13] K. Papenfort and B. L. Bassler, "Quorum sensing signal-response systems," *Nature Reviews Microbiology*, vol. 14, no. 9, pp. 576–588, 2016.
[14] T. Bjarnsholt, "Chronic infections and biofilms," *APMIS*, vol. 121, Suppl. 136, pp. 1–58, 2013.
[15] R. M. Donlan, "Biofilms: microbial life on surfaces," *Emerging Infectious Diseases*, vol. 8, no. 9, pp. 881–890, 2002.
[16] H.-C. Flemming, U. Szewzyk, et al., "Biofilms as bacterial life form," *Nature Reviews Microbiology*, vol. 14, no. 9, pp. 563–575, 2016.
[17] P. Krzyżek, "Anti-biofilm therapy limitations," *Frontiers in Microbiology*, vol. 13, 2022.
[18] D. Sharma, L. Misba, and A. U. Khan, "Antibiotics vs biofilm," *Antimicrobial Resistance & Infection Control*, vol. 8, 2019.
[19] J. M. A. Blair et al., "Molecular mechanisms of antibiotic resistance," *Nature Reviews Microbiology*, vol. 13, no. 1, pp. 42–51, 2015.
[20] S. R. Partridge et al., "Mobile genetic elements," *Clinical Microbiology Reviews*, vol. 31, no. 4, 2018.
[21] J. S. Madsen et al., "Biofilms and gene transfer," *FEMS Immunology & Medical Microbiology*, vol. 65, no. 2, pp. 183–195, 2012.
[22] W. C. Chiang et al., "eDNA shields biofilms," *Antimicrobial Agents and Chemotherapy*, vol. 57, no. 5, pp. 2352–2361, 2013.
[23] K. Lewis, "Persister cells and resistance," *Nature Reviews Microbiology*, vol. 5, no. 1, pp. 48–56, 2007.
[24] J. Botelho et al., "Pseudomonas aeruginosa resistance," *Drug Resistance Updates*, vol. 44, 2019.
[25] Z. Pang et al., "Pseudomonas resistance mechanisms," *Biotechnology Advances*, vol. 37, no. 1, pp. 177–192, 2019.
[26] S. Y. C. Tong et al., "Staphylococcus aureus infections," *Clinical Microbiology Reviews*, vol. 28, no. 3, pp. 603–661, 2015.
[27] S. S. Magill et al., "Healthcare-associated infections," *New England Journal of Medicine*, vol. 379, pp. 1732–1744, 2018.
[28] N. S. Al-Khafaji and A. B. Al-Lami, "Biofilm formation in burn infections," *Iraqi Journal of Medical Sciences*, vol. 19, no. 2, pp. 145–153, 2021.
[29] A. A. J. Aljanaby and A. R. Medhat, "ESBL E. coli in Iraq," *Gene Reports*, vol. 27, 2022.
[30] M. T. Abdulwahid, J. S. Hassan, and A. H. Mohammed, "Carbapenemase genes in Iraq," *Journal of Infection and Public Health*, vol. 16, no. 5, pp. 742–749, 2023.
[31] C. Grandclément et al., "Quorum quenching developments," *FEMS Microbiology Reviews*, vol. 40, no. 1, pp. 86–116, 2016.

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

[32] V. C. Kalia, "Quorum sensing inhibitors overview," *Biotechnology Advances*, vol. 31, no. 2, pp. 224–245, 2013.
[33] B. LaSarre and M. J. Federle, "QS interference strategies," *Microbiology and Molecular Biology Reviews*, vol. 77, no. 1, pp. 73–111, 2013.
[34] D. A. Vattem et al., "Phytochemicals as QS inhibitors," *Fitoterapia*, vol. 78, no. 4, pp. 302–310, 2007.
[35] H. Z. Asfour, "Anti-quorum sensing compounds," *Journal of Microscopy and Ultrastructure*, vol. 6, no. 1, pp. 1–10, 2018.
[36] K. Krzyżek, "Biofilm resistance strategies," *Frontiers in Microbiology*, vol. 13, 2022.
[37] D. Sharma et al., "Biofilm-antibiotic battle," *Antimicrobial Resistance & Infection Control*, vol. 8, 2019.

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com
مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

الخلاصة

يُعد استشعار النصاب (Quorum Sensing, QS) نظامًا معقدًا ومنظمًا بدقة للتواصل بين الخلايا البكتيرية، يتيح للكائنات الحية الدقيقة استشعار كثافتها الخلوية والتنسيق في التعبير عن مجموعة من الجينات من خلال إفراز وإطلاق واستقبال جزيئات صغيرة تُعرف بالمحفزات الذاتية (Autoinducers). وتمكّن هذه الشبكة التنظيمية التجمعات البكتيرية من العمل كنظام متعدد الخلايا من خلال تنسيق الأنشطة الفسيولوجية عند الوصول إلى كثافة خلوية حرجة. تستخدم البكتيريا سالبة الغرام عادةً جزيئات N-acyl homoserine lactones (AHLs) كوسائط لاستشعار النصاب، في حين تعتمد البكتيريا موجبة الغرام بصورة رئيسية على الببتيدات قليلة الوحدات المعالجة (Processed Oligopeptides). كما تتجلى درجة التعقيد والقدرة التكيفية للسلوك الاجتماعي الميكروبي في حقيقة أن جزيئًا إشاريًا واحدًا يُعرف باسم المحفز الذاتي-2 (Autoinducer-2, AI-2) يشارك في التواصل بين الأنواع البكتيرية المختلفة.تُعد الأغشية الحيوية (Biofilms) مجتمعات ميكروبية منظمة للغاية تنمو على الأسطح الحية وغير الحية، وتُحاط بمصفوفة تنتجها الخلايا ذاتيًا تُعرف بالمادة البوليمرية خارج الخلوية (Extracellular Polymeric Substance, EPS)، والتي تتكون من السكريات المتعددة والبروتينات والدهون والحمض النووي خارج الخلية (eDNA). وتوفر هذه المصفوفة حاجزًا فيزيائيًا وكيميائيًا يحد من اختراق المضادات الحيوية، ويقلل من قدرة الجهاز المناعي على التعرف على البكتيريا، كما يخلق بيئات دقيقة غير متجانسة تساعد على بقاء الكائنات الدقيقة واستمرارها.تخضع الخلايا البكتيرية داخل الأغشية الحيوية لتغيرات في حالتها الأيضية، حيث تتواجد بعض الخلايا في حالة نمو بطيء أو في صورة خلايا كامنة تُعرف بخلايا الاستمرار (Persister Cells)، والتي تتميز بمقاومة عالية للعوامل المضادة للميكروبات وتسهم في حدوث العدوى المزمنة والمتكررة. ويتم تنظيم تكوين الأغشية الحيوية ونموها بشكل صارم بواسطة أنظمة استشعار النصاب من خلال التحكم في الجينات المرتبطة بعوامل الالتصاق، وإنتاج مصفوفة EPS، والحركة البكتيرية، والاستجابة للإجهاد البيئي.ومن الأهمية بمكان أن استشعار النصاب ينظم أيضًا التعبير عن عوامل الضراوة (Virulence Factors) مثل السموم والإنزيمات وأنظمة الإفراز المختلفة، مما يؤدي إلى زيادة القدرة الإمراضية للبكتيريا أثناء العدوى. وقد أظهرت الدراسات أن شبكات استشعار النصاب تلعب دورًا محوريًا في إحداث العدوى المستمرة لدى العديد من الممرضات ذات الأهمية السريرية، مثل الزائفة الزنجارية (Pseudomonas aeruginosa)، والمكورات العنقودية الذهبية (Staphylococcus aureus)، والإشريكية القولونية (Escherichia coli)، والراكدة البومانية (Acinetobacter baumannii)، وخاصةً في البيئات الاستشفائية التي تنتشر فيها العدوى المرتبطة بالأجهزة الطبية مثل القساطر وأجهزة التنفس الصناعي والزرعات الطبية.كما يسهم التراكم الكثيف للخلايا البكتيرية ووجود الحمض النووي خارج الخلية داخل مصفوفة EPS في تعزيز عمليات النقل الأفقي للجينات (Horizontal Gene Transfer, HGT) من خلال التحول (Transformation)، والنقل بالعاثيات (Transduction)، والاقتران البكتيري (Conjugation). بالإضافة إلى ذلك، يمكن لأنظمة استشعار النصاب أن تحفز تشغيل مضخات القذف الخلوي (Efflux Pumps)، وتُحدث تغيرات في نفاذية الأغشية الخلوية، وتُفعّل مسارات الاستجابة للإجهاد، وهي جميعها آليات تسهم في زيادة قدرة البكتيريا على تحمل ومقاومة العوامل المضادة للميكروبات.وتبرز خطورة هذه الآليات بشكل خاص في حالات العدوى الناتجة عن البكتيريا متعددة المقاومة للمضادات الحيوية (Multidrug-Resistant, MDR)، حيث تصبح المضادات الحيوية التقليدية غير قادرة على القضاء على البكتيريا المرتبطة بالأغشية الحيوية، مما يجعل علاج هذه العدوى أكثر صعوبة وتعقيدًا

الكلمات المفتاحية: استشعار النصاب، الأغشية الحيوية، جينات مقاومة المضادات الحيوية، البكتيريا المقاومة للأدوية المتعددة، النقل الجيني الأفقي