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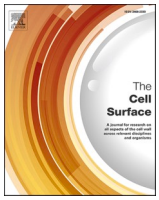

Combatting biofilm-mediated infections in clinical settings by targeting quorum sensing

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ABSTRACT

Biofilm-associated infections constitute a significant challenge in managing infectious diseases due to their high resistance to antibiotics and host immune responses. Biofilms are responsible for various infections, including urinary tract infections, cystic fibrosis, dental plaque, bone infections, and chronic wounds. Quorum sensing (QS) is a process of cell-to-cell communication that bacteria use to coordinate gene expression in response to cell density, which is crucial for biofilm formation and maintenance.. Its disruption has been proposed as a potential strategy to prevent or treat biofilm-associated infections leading to improved treatment outcomes for infectious diseases. This review article aims to provide a comprehensive overview of the literature on QS-mediated disruption of biofilms for treating infectious diseases. It will discuss the mechanisms of QS disruption and the various approaches that have been developed to disrupt QS in reference to multiple clinical pathogens. In particular, numerous studies have demonstrated the efficacy of QS disruption in reducing biofilm formation in various pathogens, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Finally, the review will discuss the challenges and future directions for developing QS disruption as a clinical therapy for biofilm-associated infections. This includes the development of effective delivery systems and the identification of suitable targets for QS disruption. Overall, the literature suggests that QS disruption is a promising alternative to traditional antibiotic treatment for biofilm-associated infections and warrants further investigation.

Introduction

The emergence of antimicrobial resistance (AMR) makes the treatment of bacterial infections increasingly difficult in clinical settings (Llor and Bjerrum, 2014). Several antibiotic-resistant pathogens such as *Enterococcus faecium*; *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* species, commonly abbreviated as ESKAPE pathogens, pose an increasing risk of infectious diseases (De Oliveira et al., 2020). Vancomycin-resistant (VRSA), methicillin-resistant *Staphylococcus aureus* (MRSA), fluoroquinolone-resistant strains of *Pseudomonas aeruginosa*, and multiple drug-resistant (MDR) strains of *Mycobacterium tuberculosis* in particular, are on the rise. The worldwide spread of antibiotic-resistant bacteria in hospitals, especially in immunocompromised patients and in low-resource settings, increases the burden of infectious diseases with implied costs in healthcare (Antimicrobial Resistance C, 2022; Ventola, 2015). Thus, alternative therapeutic strategies are required to combat bacterial pathogens that have developed resistance to antibiotics (Mc et al., 2020).

The development of antibiotic resistance is a complex process that can arise due to a variety of factors, including natural selection and human behavior, and it is a growing problem that poses a significant threat to public health. When antibiotics are present in an environment, they create selective pressures that significantly alter the structure of microbial communities. This leads to a reduction in biodiversity and promotes the proliferation of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs). The ecological consequences of this shift are considerable, especially when compared to antibiotic-free environments, where microbial communities tend to be more stable, diverse, and capable of performing essential ecological functions without the pressure to develop resistance.

Bacteria can survive in the presence of antibiotics by acquiring drug-resistance genes through several mechanisms, including intrinsic resistance, random spontaneous mutation, hypermutation, adaptive mutation, and horizontal transfer of resistance genes from other bacteria. Mutations that confer antibiotic resistance are typically advantageous under selective pressures from antibiotics. When antibiotics are present, even weak selective pressures can favor the survival and proliferation of

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resistant strains, often through mutations that alter drug targets or efflux mechanisms. These resistance mutations tend to persist because they directly improve bacterial fitness in an antibiotic-laden environment (Pereira et al., 2023). In environments without antibiotics, resistance mutations can come with fitness costs, such as slower growth or increased metabolic burdens. As a result, these mutations may be less likely to be favored. Numerous studies have shown that in the absence of antibiotic pressure, the prevalence of resistance traits often declines due to these associated disadvantages (Vanacker et al., 2023) However the fitness impact of resistance mutations could be context-dependent, varying with both the specific genetic makeup of the bacteria and the environmental conditions (Hinz et al., 2024).These mechanisms can result in the development of genetic changes that allow bacteria to evade the effects of antibiotics and continue to grow and reproduce. It is important to note that not all bacteria are capable of developing antibiotic resistance through these mechanisms, and some may require a combination of factors to become resistant. Additionally, the overuse or misuse of antibiotics can increase the selective pressure for bacteria to develop resistance, making it a growing concern for public health (Blair et al., 2015; Maclean et al., 2010; Wright, 2011).

Conventional mechanisms of antibiotic resistance include the inactivation of active molecules, alteration of target sites, reduction of drug concentration through restricted uptake, and the action of efflux systems that expel antibiotics from bacterial cells (Rouveix, 2007; Wright, 2005). However, additional resistance mechanisms such as target modification, biofilm formation, and bacterial communication (quorum sensing) also play critical roles in enhancing resistance, especially in persistent and multidrug-resistant infections (Romero et al., 2011; Schillaci et al., 2017; Lewis, 2001; Stewart and Costerton, 2001).

A biofilm refers to a community of bacterial species that are attached to a surface or to each other encased in an exopolysaccharide-based matrix (Donlan, 2002). Biofilm formation is a complex process where bacteria transition from a free-living state to a structured community attached to surfaces and embedded in an extracellular polymeric substance (EPS) matrix. This biofilm enhances cellular adhesion and provides protection, increasing resistance to antimicrobials and environmental stresses (Donlan, 2002). Biofilms form when bacteria adhere to a surface, aided by specific surface proteins and extracellular DNA essential for their stability (Whitchurch et al., 2002). Mechanosensing and quorum sensing regulate biofilm development by promoting gene expression changes that enhance maturation and maintenance (Remis et al., 2010). Surface-associated growth allows bacterial cells to thrive in various environments. Consequently, biofilms pose significant challenges in healthcare and industry due to their role in persistent infections and biofouling (Zhao et al., 2023). Biofilms can be found in diverse environments in nature. Importantly, a diverse range of microbial infections is associated with biofilm formation ranging from cystic fibrosis, dental caries, endocarditis, wound infections, medical implant device infections, etc (Del Pozo, 2018). Resistance to conventional antibiotics in biofilm state is 10 to 1000 fold higher as compared to that observed in free-floating or planktonic cells. Such high levels of resistance to antibiotics in biofilms make treatment of biofilm-associated infections makes it difficult if not impossible, even with the highest dose of antibiotics. Several alternative mechanisms have been proposed for biofilm-induced resistance (Stewart and Costerton, 2001; Mah and O'Toole, 2001; Li et al., 2020).

One major mechanism for the resistance of biofilms is the extracellular matrix that surrounds the biofilm (Uruén et al., 2020). The extracellular matrix acts as a physical barrier that can prevent antibiotics from penetrating the biofilm and reaching the bacterial cells within. The extracellular matrix also contains enzymes that can degrade antibiotics and render them inactive before they can reach their target. This can lead to much higher concentrations of antibiotics being required to effectively penetrate the biofilm and eliminate the bacterial cells (Karygianni et al., 2020; Goodman and Bakaletz, 2022). Another mechanism for the resistance of biofilms is the presence of persister cells. Persister cells are a small subpopulation of bacterial cells that are dormant and can tolerate high levels of antibiotics (Roberts and Stewart, 2005). These cells can "switch off" their metabolic activity and enter a dormant state, which makes them less susceptible to antibiotics. This allows the persister cells to survive antibiotic treatment and then "wake up" when the antibiotic is no longer present, potentially leading to recurrences of infection (Yan and Bassler, 2019). Bacteria within biofilms can grow more slowly than planktonic cells, leading to a reduced susceptibility to antibiotics that target actively growing cells. Biofilms can also exhibit altered gene expression patterns that can lead to changes in metabolism and increased antibiotic resistance. This can be due to environmental cues within the biofilm, such as changes in pH, oxygen concentration, and nutrient availability. Biofilms can contain more efflux pumps, which are protein complexes that pump antibiotics out of bacterial cells. The increased number of efflux pumps in biofilms can contribute to higher levels of antibiotic resistance. Biofilms can facilitate horizontal gene transfer, which allows bacteria to exchange genetic material and acquire antibiotic resistance genes from other bacteria within the biofilm or the environment (Liu et al., 2024). Finally, bacteria within biofilms can communicate with each other using quorum sensing, which allows them to coordinate gene expression and behavior. Quorum sensing can lead to the upregulation of genes involved in antibiotic resistance and the formation of a more robust biofilm. This can lead to the spread of antibiotic resistance within the biofilm and beyond, making treatment more difficult (Ghasemi et al., 2018) (see Fig. 1).

Quorum sensing

The development of bacterial biofilms requires self-organization, cooperation, and communication among members of the biofilm community to switch from free-floating planktonic cells to a three-dimensional well-organized biofilm mode of existence. Biofilm formation requires several environmental cues: stress, nutrient limitation and cell-to-cell communication. Bacterial adaptation to a changing environment requires sensing and responding by coordinated gene expression. A form of bacterial cell-to-cell communication, Quorum Sensing (QS) coordinates and regulates gene expression via the release, detection, and uptake of small diffusible molecules called autoinducers (AI) in a cell-density-dependent manner. QS can occur within a given species of bacteria (intraspecies) or among different species (interspecies) and regulates several physiological processes such as DNA transfer, expression of virulence factors, secondary metabolites such as antibiotics, motility, and biofilm formation (Mukherjee and Bassler, 2019). Quorum sensing systems are very well dissected in several gram-positive and gram-negative bacteria. In gram-negative bacteria, N-acyl homoserine lactone (AHL), furanosyl borate diester termed autoinducer 2 (AI-2), and autoinducer 3 (AI-3) are major autoinducers. Quorum sensing (QS)

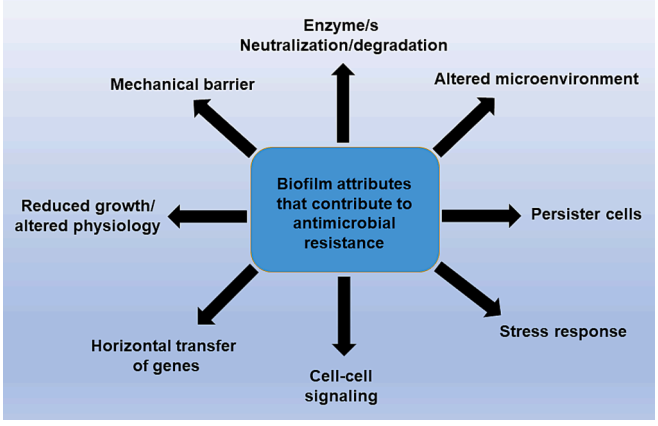

Fig. 1. Key biofilm characteristics that enhance antimicrobial resistance mechanisms.

regulates several stages of biofilm formation by controlling processes like motility, the production of adhesins, extracellular polysaccharides, DNA release, and biosurfactants, which collectively aid in both biofilm maturation and the release of cells from biofilms in various pathogens (Quadriya et al., 2018). Through these regulatory mechanisms, QS enhances the structural integrity of biofilms while also facilitating detachment and dispersion, which are essential for bacterial survival and spread in new environments (Muhammad et al., 2020). The regulation of QS on biofilm formation can be both positive and negative; for example, QS represses and induces biofilm in *Vibrio cholerae* and *Vibrio anguillarum* respectively (Hammer and Bassler, 2003; Croxatto et al., 2004).

QS plays a critical role in regulating biofilm formation in many bacterial species, including *Pseudomonas aeruginosa* and *Staphylococcus aureus. P. aeruginosa* is a gram-negative bacterium commonly found in soil and water, but it can also infect humans. *P. aeruginosa* uses a complex QS system to regulate its virulence and biofilm formation. The QS system in *P. aeruginosa* involves the production and sensing of multiple signaling molecules called acyl-homoserine lactones (AHLs) (Chadha et al., 2022). The production of AHLs is regulated by the LasI/R and RhlI/R systems, which interact to form a hierarchical network. The LasI/R system is responsible for the production and detection of the AHL molecule, 3-oxo-C12-HSL, while the RhlI/R system is responsible for the production and detection of the AHL molecule, C4-HSL (Lee and Zhang, 2015). These two systems work together to regulate the expression of genes involved in virulence and biofilm formation. In *P. aeruginosa*, QS regulates the production of extracellular polysaccharides (EPS), which are essential for biofilm formation. The LasI/R system is responsible for the production of EPS, while the RhlI/R system is responsible for the regulation of EPS synthesis (Pearson et al., 1997; Schuster et al., 2023).

S. aureus is a gram-positive bacterium that can colonize human skin and mucosal surfaces. It is also an important opportunistic pathogen that can cause a range of infections. *S. aureus* uses a QS system involving the production and sensing of autoinducing peptides (AIPs). The production of AIPs is regulated by the *agr* locus, which is a quorum-sensing regulator. The *agr* locus produces and detects AIPs, which regulate the expression of genes involved in virulence and biofilm formation (MDowell et al., 2001; Williams et al., 2023). In *S. aureus*, QS regulates the expression of genes involved in biofilm formation, such as *icaA*, which encodes a protein involved in the synthesis of the polysaccharide intercellular adhesin (PIA), an important component of the biofilm matrix (see Fig. 2).

Quorum sensing development of biofilm occurs in several other gram-positive bacteria, such as *Bacillus subtilis* (Omer Bendori et al., 2015; Mielich-Suss and Lopez, 2015);; *Enterococcus* (Hancock and Perego, 2004), and *Streptococcus mutans* (Jimenez and Federle, 2014). In case of gram-negative bacteria, such as *Vibrio cholerae,* high cell density biofilm formation is repressed and at low cell density biofilm formation is induced (Hammer and Bassler, 2003; Zhu and Mekalanos, 2003). However, for other pathogens such as *Acinetobacter* spp., use of N-acyl homoserine lactone have been shown to induce biofilm formation (Anbazhagan et al., 2012). Understanding the molecular mechanisms of QS in these organisms may lead to the development of novel strategies for controlling biofilm formation and improving the treatment of bacterial infections (Gray et al., 2013; Vasquez et al., 2017).

Quorum sensing inhibition as a target to disrupt biofilm formation

Targeting quorum sensing is an alternative and effective strategy to disrupt biofilm-associated infections and the genetics of quorum sensing circuits of several bacterial pathogens have been well characterized. Quorum Sensing Inhibitors (QSIs) disrupt bacterial QS and can aid in combatting bacterial infections by mitigating virulence without imposing selective pressure associated with traditional antibiotics (Rasmussen and Givskov, 2006; Vashistha et al., 2023). QSI are neither bacteriostatic nor bactericidal agents, their mode of action can vary including degradation of auto-inducers, regulating the expression of autoinducer synthase or QS receptors (Chen et al., 2018; Shaaban et al., 2019; Bzdrenga et al., 2017). QSI can interfere with bacterial communication and prevent the formation of coordinated bacterial communities, such as biofilms, which are often more resistant to antibiotics and host immune responses and will likely increase susceptibility to both the host immune response and to antibiotics that are less effective for bacteria that have formed a biofilm. Without the ability to communicate effectively, bacterial species may become more vulnerable to the host immune response, as they are unable to coordinate their defenses and evade host immune cells. Additionally, QSI can reduce the production of virulence factors and enhance the efficacy of the host immune response, leading to better outcomes for the host. Many chemicals have been identified that can disrupt quorum sensing in Gram-positive and Gram-negative bacterial pathogens. Inhibition of QS pathways permits the use

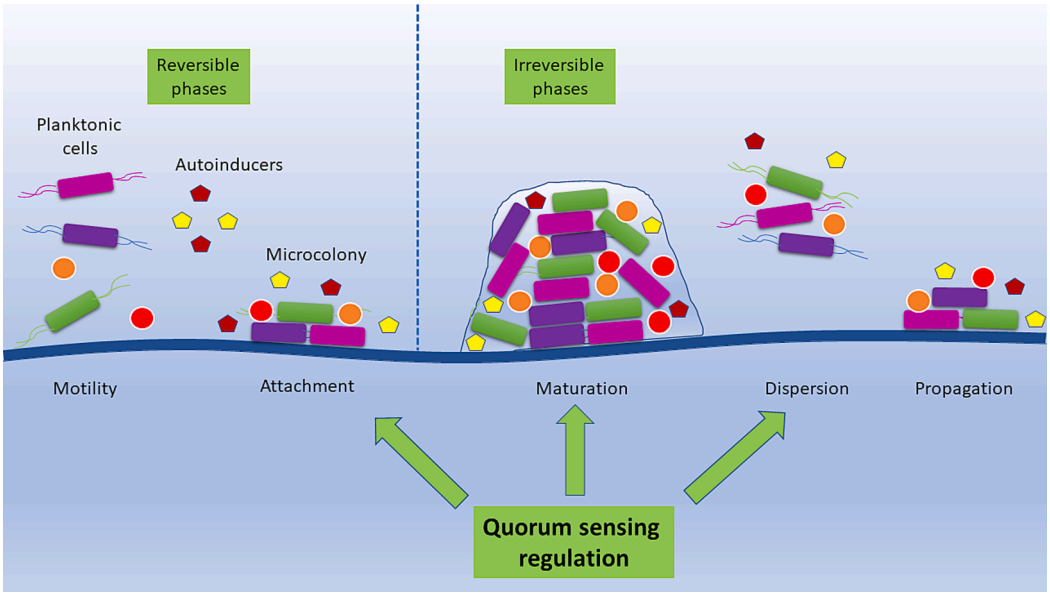

Fig. 2. Role of quorum sensing in the regulation of biofilm formation, maturation, and dissemination.

of lower doses of antibiotics to treat bacterial infections as antibiotics might be more effective at lower concentrations in biofilm deficient cells. Furthermore, QSI usage is less likely to develop antimicrobial resistance as it targets alternative pathways for virulence without the use of antibiotics. QS can be blocked at the stage of signal generation, transmission, or reception using inhibitors and the use of QSI has been shown to disrupt different stages of biofilm formation or the expression of virulence factors (see Fig. 3).

It is thought that microbes may have developed mechanisms to inhibit QS in response to environmental pressures or to compete with other bacterial species. Studies have shown that many bacteria produce natural QSI, such as enzymes or small molecules, which can interfere with QS systems even in other species. QSI are of interest for their potential applications in developing new antibiotics and anti-biofilm agents and thereby could potentially influence the outcome of a clinical condition. The use of QSI is an attractive target for many biofilm-associated bacterial infections. Table 1 highlights characteristic quorum-sensing inhibitors that disrupt biofilm formation in clinical environments while Table 2 lists some mechanisms of quorum quenchers targeting biofilm formation in clinical pathogens.

Therapeutic potential of QSI in cystic fibrosis

For the clinical manifestation of QS in clinical biofilms, a very well-studied example is Cystic Fibrosis (CF), which affects both children and adults. CF is a genetic disorder that affects the respiratory, digestive, and reproductive systems. CF is characterized by mucus secretion in the respiratory epithelium, leading to colonization of various pathogens in the lungs and dysregulation of innate immune functions and inflammation. Biofilm formation is a common feature of bacterial infections in the lungs of CF patients and people with CF are more susceptible to respiratory infections. QS is known to play a critical role in the formation and maintenance of biofilms in the lungs of CF patients and disrupting QS has been proposed as a potential therapeutic approach for treating CF-associated infections (Bjarnsholt et al., 2009). Common pathogens associated with CF include *Pseudomonas aeruginosa*; *Staphylococcus aureus*, *Burkholderia cepacia complex*, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Aspergillus fumigatus*. Associated with chronic infections in the CF lungs, *Pseudomonas aeruginosa*, a resident opportunistic pathogen switches from nonmucoid, planktonic cells to alginate-producing mucoidy biofilms. Key reference strains for cystic fibrosis (CF) include Pseudomonas aeruginosa PAO1, a commonly used laboratory reference strain in CF research (Salunkhe et al., 2005). These biofilms are difficult to treat as they are resistant to various antibiotics such as β-lactams and to the -host's innate immune defense mechanism such as the action of macrophages. The triggering of this phenotypic switch is likely due to the excessive secretion of mucus, which decreases bacterial motility in CF patients. Additionally factors such as hypoxia and the release of secreted proteins contribute to an apparent increase in the concentration of bacterial cells.. Autoinducers 3O-C12-homoserine lactone and C4-homoserine lactone have been detected in the sputum of cystic fibrosis patients. Several compounds have been identified that can disrupt biofilm formation. For the treatment of cystic fibrosis, one target is quorum sensing mediated biofilm disruption. Small molecule QSI has been demonstrated to inhibit biofilm formation of CF- associated bacteria. A study found that a synthetic QS-inhibiting compound called N-acyl homoserine lactone could inhibit biofilm formation by *Pseudomonas aeruginosa*, which is a common bacterial pathogen in CF patients (Malesevic et al., 2019). In *Pseudomonas aeruginosa* PA14, a compound *meta*-bromo-thiolactone has been identified from a screen of quorum sensing dependent production of pyocyanin production, a virulence factor. The compound has been found to inhibit both pyocyanin production and biofilm formation (O'Loughlin et al., 2013).

Another study found that an AHL analogue, a halogenated furnanone inhibits AHL mediated Quorum sensing and affecting biofilm architecture and dispersal in flow chambers (Hentzer et al., 2002). Other studies have explored the role of enzymatic QSI such as lactonases to degrade QS molecules. Studies have found that the expression of a lactonase called SsoPox, from the bacterium *Sulfolobus solfataricus*, could disrupt biofilms formed by *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*, which are both common CF pathogens (Ng et al., 2011). Mode of action of azithromycin, a macrolide antibiotic is thought to act by disruption of quorum sensing (Hoffmann et al., 2007). Other studies suggest the use of acidified sodium nitrite to remove mucoid *P. aeruginosa* in CF patients (Major Tiffany et al., 2010). Some studies have investigated the use of combination therapies that target both QS and other bacterial processes. For example, a study found that a combination of the antibiotic tobramycin and a QS-disrupting molecule, 6-gingerol analog, could enhance the efficacy of tobramycin against *Pseudomonas aeruginosa* biofilms (Ham et al., 2021). Another study explored the use of combined enzymes with antibiotics to disrupt QS pathways and biofilm formation in multiple drug-resistant *P aeruginosa* (Zhang et al., 2023). Such a combination of QSI with antibiotics could

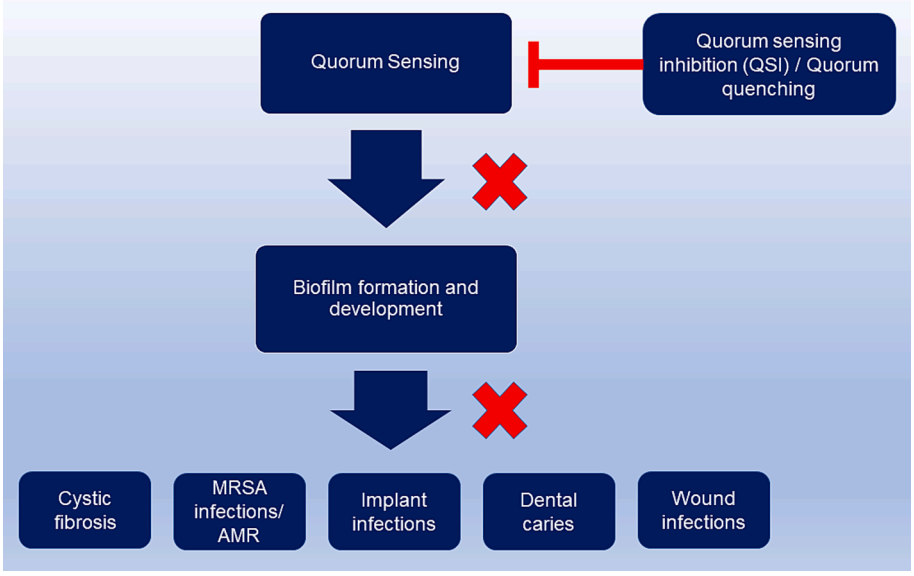

Fig. 3. Quorum sensing disruption as a strategy to interfere with biofilm-associated infections.

Table 1
Representative quorum sensing inhibitors for biofilm disruption in clinical conditions.

Infectious disease or infection	Causative agent or pathogen	Quorum sensing genes	Qurum sensing inhibitors	References
Cystic fibrosis	*Pseudomonas aeruginosa*	*las I*, *lasR*, *rhlI*, *rhlR*	Dimetridazole or Ribavirin	Yuan et al. (2022)
Urinary tract infections	*Escherichia coli*	*fimA*, *pap A*	PPK1 inhibitors	Peng et al. (2020)
Implant infections	Coagulase-negative staphylococci	RNAIII, *agr*	RNA III inhibiting peptide (RIP)	de Oliveira et al. (2021)
Dental Caries	*Streptococcus mutans*	*comA*, *comB*, *com DE*	Antimicrobial photodynamic therapy	Pourhajibagher et al. (2022)
Nosocomial infections	Methicillin-resistant *Staphylococcus aureus* (MRSA)	*norA, agrA* *hlyA*, *hlA*	Benzylaniline 4K	Zheng et al. (2022)
Wound infections	*Pseudomonas aeruginosa*	*lasB*, *rhlA*, *pqsA*	Sodium salicylate	Gerner et al. (2020)
Periodontitis	*Porphyromonas gingivalis*	*luxS*, *rgp*, *kgp*, *hagB*	Coumarin	He et al. (2022)
Skin infection	*Chromobacterium violaceum*	*cviR*	Imidazole derivaties	Arendse et al. (2022)
Luminescent vibriosis	*Vibrio campbellii*	*luxR*, *pl-1*, *pl-2*, *pl-3*	Sodium Ascorbate	Han et al. (2020)

Table 2
Representative mechanisms of quorum quenchers targeting biofilm formation in clinical pathogens.

Pathogen	Quorum quencher	Effect on biofilms	References
Pseudomonas aeruginosa	Chlorogenic acid	Reduces pyocyanin and elastase production	Xu et al. (2022)
Escherichia coli	Ginkgetin (Gin)	Reduces expression of curli, flagella, exopolysaccharide production	Bai et al. (2022)
Salmonella typhimurium	Terazosin	Downregulates *sdiA* gene encoding QS receptor	Hegazy et al. (2022)
Staphylococcus aureus	Terpenes combination	Reduced expression of *agr* (*accessory gene regulator),* and *hld* encoding hemolysin	Salinas et al. (2022)
Klebsiella pneumoniae	Silver nanoparticles	Downregulates *mrkA*, encoding type 3 fimbriae and *luxS* gene	Foroohimanjili et al. (2020)
Acinetobacter baumanii	Nervonic acid and oleic acid	Binds to acylhomoserine lactone synthase	Khadke et al. (2021)
Multi-drug resistant *Pseudomonas aeruginosa*	Methanol extract of *E. globulus* leaves	Regulates swarming, and exopolysaccharide synthesis	Sagar et al. (2022)

potentially reduce the emergence of antimicrobial resistance. Burkholderia cepacia complex (BCC) is a group of bacterial pathogens that can cause respiratory infections in CF patients. One study found that cis-14-methylpentadec-2-enoic acid, a structural analog of Burkholderia diffusible signal factor [BDSF]) QS could disrupt BCC biofilms and virulence (Cui et al., 2019).

Therapeutic potential of QSI for MRSA and other resistant pathogens

Even though *Staphylococcus aureus* is part of normal flora in humans, a large number of infections including skin, respiratory, blood, and soft tissue infections are caused by the microbe. Alternative strategies are required for infections caused by Methicillin and Vancomycin resistance strains of *Staphylococcus* infections as they are extremely difficult to treat, even with broad-spectrum antimicrobial agents. Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to multiple antibiotics, making it difficult to treat infections caused by this pathogen. It can cause a wide variety of infections varying from skin to systemic infections leading to bacteremia and sepsis. A quorum sensing system in *Staphylococcus* includes a RNAI activating peptide (RAP) and its conserved target protein, TRAP (Balaban et al., 2001). A small linear peptide, RIP (RNAIII inhibiting peptide) antagonizes TRAP by inhibiting its phosphorylation leading to a reduction in cellular adhesion. Because TRAP is conserved among various species of *Staphylococcus*, RIP could potentially block infections caused by MRSA or VRSA. Synthetic RIP is active both *in vitro* and in animal models of infection (Balaban et al., 2005). A compound, benzylaniline 4 K, downregulated QS-related genes and eradicated biofilm formation in MRSA strains (Zhang et al., 2019). An antimicrobial peptide LL37 was investigated for both its antibiofilm and antimicrobial activity against Methicillin-resistant *Staphylococcus aureus* and Methicillin-sensitive *Staphylococcus aureus*. The study found that quorum sensing and virulence-related genes including *atlA*; *agrA,* and RNAIII were affected by LL-37 at suboptimal range and the compound inhibited biofilm formation of both MRSA and MSSA (Demirci et al., 2022). Analogues of AI-2 have been investigated as potential QSIs for MRSA. One study found that a compound called (S)-4,5-dihydroxy-2,3-pentanedione (DPD) could inhibit QS and reduce biofilm formation in MRSA (Fteita et al., 2018). Aza derivatives of Diflunisal in combination with or without clindamycin have shown to be effective in reducing MRSA infections regulated by quorum sensing mediated agr system. One derivative, Azan 7 in particular, demonstrated reduced cytotoxicity, did not affect bacterial growth, and reduced expression of virulence genes such as *agrA*, *hla*, *hysA*, among others. Besides, the compound also repressed hemolysis, improved killing by macrophages and reduced survival of pathogen at low pH. In combination with clindamycin, Azan 7 improved the susceptibility of MRSA both in planktonic and biofilm mode and did not induce resistance (Bernabe et al., 2021). Octopromycin, an antimicrobial peptide, can inhibit quorum sensing pathways, prevent biofilm formation, and effectively kill resistant strains of *Acinetobacter baumannii*, an opportunistic pathogen (Rajapaksha et al., 2023).

Therapeutic potential of QSI in dental caries

The oral cavity is diverse in microbial composition and can fluctuate depending on health and disease conditions. Dental caries is a chronic infectious disease that causes irreversible demineralization of teeth.

Dental caries is primarily caused by the bacterium *Streptococcus mutans*, which forms biofilms in the mouth. This process involves virulence factors and quorum sensing, likely through the production of glucans that aid in colonizing tooth surfaces. Antimicrobial photodynamic therapy (aPDT) using nano-quercetin in combination with blue light has been shown to reduce biofilm formation of *S. mutans* via increased reactive oxygen species generation, reduced metabolic activity, and inhibition of QS-related genes such as *comA*, *comB*, *comDE* among others (Pourhajibagher et al., 2022). *Ligustrum robustum* extract (LRE), a component of herbal tea has been tested for its impact on reducing the biofilm formation of *S. mutans*, which also downregulated *comD* and *comE* (Zhang et al., 2021). Yet, another study exhibited that gecko cathelicidin Gj-CATH2 has been shown to inhibit *S. mutans* biofilm formation and also represses quorum sensing genes including *luxS*

and *comD/E*. Rhodiola rosea extract (RE) was found to be effective in reducing biofilm formation, and EPS synthesis with reduced expression of quorum sensing and virulence-related genes in *S. mutans* (Zhang et al., 2020). Relapse of dormant persisters of *S. mutans* is thought to be crucial for recurrent infections or developing resistance and has been studied in the presence of novel quaternary ammonium: dimethylaminododecyl methacrylate (DMADDM). The resumption of persisters in the presence of a lethal dose of DMADDM via induction of quorum sensing and VicRK pathways and hence such pathways could also serve as potential targets for the pathogen (Lu et al., 2019). A quorum sensing inhibitor, furanone C-30, inhibits biofilm formation in both *S. mutans* and its *luxS* mutant strain, without affecting its growth (He et al., 2012).

Therapeutic potential of QSI for infections of indwelling medical devices

In clinical settings, implanted medical devices such as indwelling and urinary catheters provide surfaces for microbes to adhere and form biofilms. Hence, therapeutic approaches for reduction of infections associated with implanted medical devices include steps to minimize biofilm formation. Novel Thiazolinyl-picolinamide based palladium(II) complexes are effective against biofilm formation and quorum sensing processes such as pilli and exopolysaccharide production in *Acenitobacter baumanii*. Such coating could offer protection against various pathogens by inhibiting of biofilm formation and reducing infections on the surfaces of implants (Jothipandiyan et al., 2022). Another study investigated the combination of photothermal therapy with quorum sensing inhibition strategy as a modification of a Ti-based implant surface to reduce biofilm formation in medical settings (Hu et al., 2022). A combination of nanorods responsive to near-infrared laser, QSI, and ROS has been shown to reduce *S. aureus* biofilms rapidly from Titanium surfaces at a moderate temperature of 45 °C (Zhang et al., 2021). Nanofibers have also been incorporated with antibiofilm compounds such as PLGA, which was effective in BALB-C mice (Geremias et al., 2021). Flufenamic acid, a nonsteroidal anti-inflammatory drug, also inhibited the quorum sensing genes and biofilm formation of MRSA and improved local MRSA infections in mice. The drug also acted synergistically with oxacillin and exhibited reduced resistance and could serve as useful coating on implants (Zhang et al., 2020). A QSI has been demonstrated to reduce biofilm formation by *Streptococcus pneumoniae* and highly efficacious in minimizing infection or otitis media in guineapigs (Cevizci et al., 2015). Perillaldehyde, a flavoring agent, inhibited biofilm formation of a common catheter-associated pathogen, *Pseudomonas aeruginosa*, via disruption of quorum sensing systems, possibly by binding to QS receptors (Benny et al., 2022). Indole extract from rhizobium Enterobacter sp. Zch127 inhibits biofilm formation by Proteus mirabilis, a common cause of catheter-associated urinary tract infections. The extract also down-regulated swarming activity and quorum sensing genes, *luxS* at sub-minimum inhibitory concentrations, and exhibited reduced toxicity in human fibroblasts (Amer et al., 2022). Using scanning electron microscopy, the role of RNAIII inhibiting peptide, a peptide that phosphorylates TRAP and interferes with the QS system of Staphylococcus spp., was investigated (de Oliveira et al., 2021). When grown in the presence of the peptide on catheter surfaces, biofilm formation is significantly impaired in coagulase-negative *Staphylococci* (de Oliveira et al., 2021). Quercitin in combination with commonly used antibiotics could inhibit quorum sensing and subsequently impair biofilm formation in *Pseudomonas aeruginosa* (Vipin et al., 2020).

Therapeutic potential of QSI in wound infections

Chronic wounds are difficult to heal due to the persistence of bacteria within biofilms. Targeting of biofilms within wounds by disruption of quorum sensing can speed up the recovery and healing of wound infections. Such an approach can also reduce the incidences of antimicrobial resistance. Furanone C-30, a QS-disrupting compound, significantly reduced quorum sensing gene expression in Pseudomonas aeruginosa and disrupted its biofilms *in vitro* and in a mouse model of infected wounds, resulting in improved healing (Proctor et al., 2020). A heterologously expressed lactonase targeting AHL-mediated QS in Gram-negative bacteria inhibited biofilm formation of *Pseudomonas aeruginosa* PAO1 and multidrug-resistant clinical strains. When a lactonase lactonase-expressing strain was combined with Tobramycin or Gentamycin, the survival of the zebrafish post-infection with the PAO1 strain improved greatly (Djokic et al., 2022). Sodium salicylate reduces the expression of QS genes including *lasB*; *rhlA,* and *pqsA,* and other virulence factors in *P. aeruginosa*, however, presence of serum increased expression of QS-related genes and decreased biofilm formation (Gerner et al., 2020). Sodium salicylate, in the presence of silver, significantly inhibits the biofilm formation of *P. aeruginosa*, a bacterium that hinders wound healing. This combination could effectively target quorum sensing and treat wound infection (Gerner et al., 2021). Diabetic foot infections are chronic wound infections caused by a commonly occurring pathogen, *P. aeruginosa*. Hypertonic glucose reduced expression of QS-related genes such as *lasI* and *lasR* and reduced swimming motility, growth, and biofilm formation in multi-drug resistant strain of *P. aeruginosa*, PAO1. Besides, the administration of hypertonic glucose also facilitated the survival of Galleria mellonella larvae infected with *P. aeruginosa* which suggested the potential use of hypertonic glucose for the treatment of chronic wound infections (Chen et al., 2020). A wireless electroceutical dressing (WED) model, which generates a weak electrical field, was evaluated for the treatment of polymicrobial infections caused by *P. aeruginosa* and *A. baumanni* and its potential use as a wound dressing. WED was found to disrupt biofilm formation in wounds as evident by scanning electron microscopy, accelerated wound healing and disrupted QS genes including *pqsR*, *rhlR*, and *lasR* and E-cadherin silencing and opened the possibility of using electroceuticals for treatment of wound infections (Barki et al., 2019).

Discussions

As biofilms are resistant to many antibiotics, an alternative therapeutic approach is required to combat biofilm-mediated infections. Because biofilm formation requires quorum sensing-dependent regulation in certain clinical pathogens, targeting QS is increasingly becoming an attractive choice for those pathogens. Since there is very little selective pressure from the QSI, they are less likely to develop resistance. While several QSI appear effective *in vitro*, very few have been tested *in vivo*, and only a limited number of candidates have shown promise in animal models.. A number of clinical trials have been conducted to assess the efficacy of QSI; however, much work remains to be done in this area.Inhibition of quorum sensing may have an insignificant effect on the infectivity of certain pathogens; however, for others, disruption of QS systems can increase their virulence.. Combined use of genomics, metagenomics, and other approaches can help identify newer targets, which can facilitate designing novel antimicrobials. QSI alone or in combination with antimicrobials might be used together to target different QS in different bacterial pathogens causing infectious diseases in clinical settings.

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Impact statement

This review highlights recent work on strategies to disrupt quorum sensing mediated biofilm formation in clinically relevant pathogens. Thus, these strategies can be used as an antibiofilm and potential antivirulence strategy, particularly for pathogens that are biofilm formers which may be challenging to treat due to antimicrobial resistance in

clinical settings.

CRediT authorship contribution statement

Arindam Mitra: Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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