Targeting microbial virulence factors: potential alternative to evade the antimicrobial resistance threats

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1. Brief history of microorganisms and the needs for antibiotics

The search for antibiotics began in the 18th century, when the germ theory of disease linked bacteria and other microorganisms to the causation of a variety of ailments. Consequently, scientists began to search for antimicrobial agents that would kill the diseases-causing microorganisms. The aim of such exploration was to find so-called “magic bullets” that would destroy microorganisms without toxicity to the person taking the antimicrobial agent [1, 2].

“Antibiotics are probably one of the most successful forms of chemotherapy in the history of medicine” [3]. Needless to say how many lives they have saved and how meaningfully they have contributed to the management and control of microbial infectious diseases that were the leading causes of human illness and death. As oppose to the common belief that the exposure to antibiotics is limited to the contemporary “antibiotic era,” researches have revealed that this is not the case. The traces of some antibiotics such as tetracycline have been discovered in human skeletal remains from ancient Sudanese Nubia dated 350 to 550 AD [4]. The distribution of tetracyclines in skeleton is only justifiable after exposure to tetracycline-containing materials in the meals of these ancient people [3,5].

Likewise, antimicrobial activity seems present in a number of other herbs used in traditional Chinese medicine [6] and the discovery of active compounds in the ancient remedies may enrich the arsenal of antimicrobials used by the conventional medicine. Simultaneously, selective pressures exerted by these antimicrobial activities during the long-term history of traditional Chinese medicine may have been one of the factors that contributed to the accumulation of antibiotic resistance genes in modern human medicine. Microorganisms just like any other living entities evolve and thus obey the Darwinian Theory of Evolution “survival of the fittest” [7]. Therefore, in order to survive microorganisms have been re-inventing better mode of invading their hosts.

2. Modes of microbial invasion of the host

Microbial pathogenicity has been well-defined as the physical and biochemical mechanisms through which microorganisms cause disease. Microbial pathogenicity, particularly in bacteria may be associated with structural components of the cells such as capsules, pili, fimbiae, lipopolysaccharides or other cell wall components and active production of substances that either protect the bacteria against host defences or damage host tissues [8,9]. Hence, there are two broad merits of pathogenic bacteria that underlie the mechanisms by which they cause disease: invasiveness and toxigenesis. The former is centre of discussion in this chapter.

The earliest stage of microbial infection is colonization that is the establishment of the pathogenic microorganism at the portal of entry. Pathogenic microorganisms usually colonize host tissues that are in contact with the external environment [10]. Sites of entry in human hosts include the respiratory tract, the urogenital tract, the digestive tract, and the conjunctiva. Microorganisms that infect these regions have usually developed tissue adherence mechanisms (Table 1) and some ability to overcome or endure the perpetual pressure of the host defences at the surface [11,12].

2.1 Microbial attachment to mucosal surfaces

Microbial adherence or attachment to a eukaryotic cell or tissue surface requires the participation of two features viz. a ligand and a receptor (Table 1). The microbial ligands are also known as adhesin, is a macromolecular component of the bacterial cell surface that interacts with the host cell receptor, which are usually specific carbohydrate or peptide residues on the eukaryotic cell surface. Adhesins and receptors usually interact in a harmonizing and specific fashion with specificity comparable to enzyme-substrate relationships and antigen-antibody reactions.
Table 1  Some specific attachments of bacteria host cell or surfaces.

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Adhesin</th>
<th>Receptor</th>
<th>Attachment site</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Cell-bound protein</td>
<td>Amino terminus of fibronectin</td>
<td>Mucosal epithelium</td>
<td>Various</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>N-methylphenylalanine</td>
<td>Fucose and mannose carbohydrate</td>
<td>Intestinal epithelium</td>
<td>Cholera</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Fibronectin, Flagella, type I pili-mediated motility</td>
<td>Antigen 85 complex cell binding domain (CBD) CR1, CR3 mannose-receptor, transferin receptor CD4+ scavenger</td>
<td>Alveolar macrophages</td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>flagella and type IV pili (Tfp) Aliginate</td>
<td>Toll-like receptor 5 glycosphingolipids Cell surface glycoproteins, glycolipids</td>
<td>Tracheal epithelium</td>
<td>Opportunistic infections (Urinary tract and Respiratory infections, bacteremia)</td>
</tr>
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</table>

Some of the indirect evidences for specificity of adherence of bacteria to host cells or tissues include:

- **Organ or tissue tropism** - Particular bacteria are known to have an obvious preference for some tissues over others, for example *Neisseria gonorrhoea* colonize genital tract, and *N. Meningitidis* colonize/infect human oropharynx, though spread to the brain, produce type IV pili (Tfp) that mediate adherence to host tissues [13]. *Neisseria gonorrhea* infects its host using the Tfp that binds to glucosmane-galactose-containing adhesion on surface of cervical and urethral cells [14]. While *Corynebacterium diphtheriae* solely colonizes the throat [15, 16], *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophillus influenza* and other haemolytic streptococci are human upper respiratory tract commensal flora [10].

- **Species specificity** - Some pathogenic bacteria infect only a few species of animals, such as *Bordetella pertussis* and *N. gonorrhoea* infections are confined to humans; *Escherichia coli* K-99 strains infect calves while enteropathogenic *E. coli* K-88 cause infections in pigs; *E. coli* CFA I and CFA II infect humans; *E. coli* K-99 strains infect calves and Group A streptococcal are only pathogenic in human beings. Moreover, some indigenous species and symbionts are animal species specific in their associations [17].

- **Intra-species genetic specificity** - Genetic specificity is common in a number of host–parasite systems. Every host can harbor and resist only a few parasites; on the other hand each parasite can survive in particular hosts. Biochemical recognition patterns determine the appropriate matching host and parasite genotypes that may result in resistance or disease [18]. The recognition systems regularly correlate with well-known genetic polymorphism in the host and parasite populations [18,19].

### 2.2 Host-microorganism communication

There is some kind of a dialogue between microorganisms and their hosts and that chemical signal is the means of inter-kingdom communication. Because of their long coexistence animals and plants, microorganisms have evolved receptors for eukaryotic hormones, which the microorganisms use to detect the presence of a suitable host and to timely express genes necessary for host colonization. Different mammalian hormones are recognized by pathogenic microorganisms; such as *Burkholderia pseudomallei* specifically bind with high affinity to insulin, which explain why in diabetic patients the progression of melioidosis has been shown to be predisposed by serum insulin levels [20]. The above observations might justify the establishment of microorganism on the surfaces of their specific hosts and explain the existence of specific interactions between microorganisms and eukaryotic tissue surfaces.

### 3. Modes of microbial evasion of host immune responses

In order to evade sophisticated defence mechanisms of their hosts, microorganisms have evolved counter attack and efficient mechanisms that permit them to circumvent both the innate and adaptive immune responses. Regardless that a number of virulence factors are employed by the pathogens, there are some universal mechanisms that are used to subvert and exploit immune systems that are shared between these diverse pathogenic microorganisms [21].

Virulence mechanisms are necessary to overcome the host defence systems, and the development of antimicrobial resistance is essential to enable pathogenic microorganisms to overcome antimicrobial therapies and to adapt to and survive in competitive and new niches. The immune systems and antimicrobial pressure hinder the survival of the microorganisms, as they considerably limit the capacity for growth and lead to decreased microbial diversity [22]. The virulence and resistance factors are often transmitted between species or genera by horizontal gene transfer (HGT); the transfer of mobile genetic elements (MGEs) is doubtless the main genetic mechanism of collection and spread of
virulence and resistance genes, though other mechanisms such as compensatory or adaptive mutations may also be involved [23].

Antibiotic resistance is often associated with infection and is therefore also related to virulence, such as in biofilm-producing microorganisms or intracellular infections [24,25]. Other characteristics that are common to virulence and resistance include the direct involvement of efflux pumps, porins, cell wall alterations, and two-component systems (TCS) that activate or repress the expression of various genes such as CbrA-CbrB[22]. In addition to the role of CbrA as a sensor kinase that functions in conjunction with its cognate regulator CbrB in virulence and virulence related processes such as biofilm formation, cytotoxicity, swarming and antibiotic resistance in a number of bacteria [26], it also controls the use of multiple carbon and nitrogen in some potentially pathogenic bacteria [27].

3.1 Strategies for microbial escape from innate defence mechanisms

Microorganisms may produce some peptides that prevent opsonization that is essential for microbial colonization of host surfaces [28], secrete toxin that paralyze the host’s defences and disrupt its mucosal integrity [29]. Microbial recognition and host responses such as the secretion of antimicrobial peptides or chemokine production can be impaired by modification of pathogen-associated molecular pattern (PAMP) or pattern-recognition receptors (PRR) or interference with intracellular signalling or cell trafficking [30]. Microorganisms escape from the phagosome along with inhibition of intracellular recognition or persistence in modified endosomes can then impede removal by host defence mechanisms[31].

3.2 Microbial defence strategies against the adaptive immune response/mechanisms

An arsenal of strategies are employed, including the induction of immunosuppressive cytokines, such as interleukins (IL): IL-10, IL-6 and TGF-β (1); inhibition of pro-inflammatory cytokine production; and surface expression of costimulatory molecules such as CD86, CD28, CD40, CD40L, CD80, cytotoxic T lymphocytes antigen-4 (CTLA-4) and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-antigen (DC-SIGN) by antigen presenting cells (APC)- [32]. Some bacteria, such as Mycobacteria spp and Listeria monocytogenes can survive and replicate intracellularly, particularly in macrophages while inducing the IL-10 [33]. Interference with phagosome maturation, major histocompatibility complex (MHC) class I and II expression also lead to diminished antigen presentation and antigen processing [34]. Inhibiting tyrosine phosphorylation of the T and B lymphocyte receptors and activating the inhibitory carcinoembryonic antigen-related cell adhesion molecule-1 (CEA-CAM1) receptor on T lymphocytes further decreases the effector cell function [35]. Certain bacteria can also induce regulatory T lymphocytes that dampen the immune response [36] or induce T lymphocyte apoptosis by enhancing FasL expression on T lymphocytes [37]. For example S. aureus secretes three proteins: staphylococcus protein A (SpA), staphylococcus binder of immunoglobulin (Sbi) and adenoside synthase A (AdsA). When it forms a complex VH3-type IgM on surface of B lymphocytes, SpA functions as a superantigen and modulates antibody response to staphylococcal infection. But also SpA and Sbi capture staphylococcus-specific antibodies by binding their Fcγ portion, associated with complement factors D and factor H to promote the depletion of complement [38].

3.3 Quorum sensing of potentially pathogenic microorganisms

In nature, bacteria are frequently found encased in a polysaccharide matrix attached to a solid surface that also offers protection from environmental agents that would otherwise threaten their planktonic counterparts [39]. These vibrant microbial communities are known as biofilms; in which transition between planktonic and sessile modes of growth occur interchangeably in response to diverse environmental signs. In fact, bacteria within the biofilms are times more resistant to antibiotics than their planktonic counterparts [40].

Biofilms formed on medical devices and in bacterial infections can inflict havoc, principally due to the fact that bacteria growing as a biofilm are refractile to host defences including phagocytes, antibodies, and complement components [41]. It has been shown that deposition of C3b, binding of C-reactive protein and the complement component C1q to the S. pneumoniae surface are reduced during the biofilm formation [42]. Moreover, these microorganisms are highly resistant to antibiotics, because of the position of extracellular matrix that make their eradication by using conventional chemotherapy virtually ineffectual. The ability to synchronize behaviour in a cell-density-dependent manner has numerous advantages. In the case of pathogenic microorganisms, the regulation of virulence factors during the infection process is believed to play a principal role in pathogenicity. Evasion of the host defences is a major goal of pathogens; hence quorum sensing is an imperative asset since it enables microorganisms to amass a sufficient cell density prior to expression of virulence factors, thus are able to make a concerted invasion and produce enough virulence determinants to defeat the host defences [43].

3.4 The SOS response

The SOS response is a global response system of the cell to respond to numerous DNA damages in which the cell cycle is arrested and DNA repair and mutagenesis are induced. The SOS responses can be induced by antibiotics, ultraviolet
radiation or ionizing radiation [44]. Usually heavily damaged DNA is no longer able to replicate and leads to interruption of the cell cycle. Bernier et al. demonstrated in vitro that SOS stress response induced in heterogeneous and nutrient-deprived biofilm microenvironments is a molecular mechanism leading to biofilm-specific high tolerance to fluoroquinolone ofloxacin [45].

During normal cell growth, the SOS genes are negatively regulated by LexA repressor protein dimers. Activation of the SOS genes (RecA) occurs after DNA damage by the accumulation of single stranded DNA regions generated at replicatin sites, where DNA polymerase is blocked [22]. LexA and RecA control the SOS genes that encode functions required for DNA damage repair. DNA damage activates RecA to stimulate autocatalytic cleavage of LexA so that the SOS genes are derepressed and expressed for repair. However, this response is also involved in the following:

1. Transmission of virulence factors such as Shiga-like-toxin in E. coli
2. Dissemination of mobile elements such as pathogenicity islands in E. coli and S. aureus
3. Increased expression of genes necessary to transfer the integrating conjugative element SXT of Vibrio cholerae, which is involved in multi-antibiotic resistance [22].

The cell division is suppressed and/or delayed resulting filamentation to allow repair before cell division (Fig. 1).

Moreover, Mellies et al. observed that the SOS response by itself can induce the expression of virulence factors since the virulence factor type III secretion system in enteropathogenic E. coli (EPEC), which is encoded by the locus of enterocyte effacement (LEE), exhibited LexA-dependent regulation. The EPEC inflict intestinal lesions, mediated by a type III secretion system, and some effector molecules, which are injected into the host cell [46].

4. Targeting the virulence factors of the pathogenic bacteria

Habitually, antibiotics have been obtained as compounds that prevent the proliferation of both pathogenic and non-pathogenic bacteria. Since most of the available antimicrobial agents can’t discriminate between members of the human normal flora and the disease-causing bacteria, this might have significantly contributed to the development of antimicrobial resistance. "The use of antimicrobial agents specifically targeting the pathogenic bacteria could be a safer approach for patients and contribute to alleviation of antimicrobial resistance spread. Many bacterial pathogens have a number of virulence factors that apparently are absent in commensal microorganisms, as they are necessary for the pathogenesis, and that, if blocked, could allow the selective inhibition of the pathogens without affecting other bacteria" [47].

Bacteria use cell-to-cell communication based on chemical signal molecules to coordinate their behaviour within the population. The chemical communication involves production, release, detection and response to peptides-like molecules called inducers. This process is popular as quorum sensing (QS) system. These QS systems are potential targets for antivirulence therapies, because many pathogenic bacteria control the expression of virulence determinants through the QS networks [48]. The matter of fact that is biofilm maturation is also influenced by QS systems, quenching the systems may contribute to combat biofouling [48].

The individual bacterium is not physically aware of the presence and the number of other bacteria, but senses the concentration of the signalling molecules, which also depends on the cell population density [49]. The principles behind QS signal-mediated gene expression in both Gram-positive and Gram-negative bacteria are shared, but the molecular mechanisms and signal molecules differ [50]. The Gram-positive QS systems typically make use of small post-translationally processed peptide signal molecules. These peptide signals interact with the sensor element of a histidine kinase TCS transduction system. Several bacteria such as S. aureus, Bacillus sublitis and S. pneumoniae causes a wide range of disease states that range from mild to life-threatening through such systems and/or production of virulence factors [51,52]. For instance, the virulence of S. aureus is dependent on the sequential expression of several virulence determinants, including both cell-associated substances, such as collagen, protein A and fibronectin-binding protein, and secreted products including proteases, lipases, alpha-toxin, beta-hemolysin, toxin-1, and enterotoxin. Gram-negative bacteria signalling QS systems is via the N-acylhomoserine lactone (AHL) signal molecules, are the most widely investigated examples of QS [53,54]. AHL secretion is considered indicative of the presence of functional QS regulatory circuits.

Most diseases in which QS regulation plays an important role are from infections caused by opportunistic microorganisms. These infections often become chronic as a consequence of the bacterium adopting the sessile, biofilm

![Fig. 1 The Bacterial SOS response.](image-url)
mode of growth [54]. For example, apart from using an arsenal of virulence factors, *Pseudomonas aeruginosa* also uses fibre-like motorized appendages called type IV pili, which not only uses for attachment and movement, but also for sensing mechanical features of the environment and regulate cellular processes [55]. The following Gram negative bacteria namely *P. aeruginosa*, *Vibrio cholerae* and *E. coli* as well as Gram positive and acid fast bacteria *S. aureus* and *Mycobacterium tuberculosis* respectively will be a centre of discussion in the next sections.

### 4.1 *Escherichia coli*

Virulence factors enable *E. coli* to colonise selectively the mucosal epithelium, evoke an inflammatory reaction and ultimately proceed to tissue invasion and/or damage. The capacity of *E. coli* to produce numerous virulence factors contributes to its pathogenicity. These virulence factors enable some members of the normal flora such as *E. coli* to elicit an infection by overcoming the host defence mechanisms. Pilus is the main virulent factor involved in adhesion of pathogenic *E. coli* to the host cells, including type 1 pili, pylonephritis associated pili (pap) also known as P- pilus or P-fimbriae, and curli [56]. The subunit of type 1 pilus encoded by fimH gene is located at the tip of the fimbria as well as laterally in the fimbrial structure. FimH binds to mannose-containing glycoprotein receptors and can mediate bacterial attachment to a variety of different host cell types [56,57].

Currently, extraintestinal pathogenic *E. coli* (ExPEC) are of significant health concern. Not only the emergence of drug resistant *E. coli* with high virulence potential is a great threat, but also lack of sufficient data on transmission dynamics, and spectrum of antimicrobial resistance of uropathogenic *E. coli* (UPEC) from developing countries with high infection burden hinders the infection control and management efforts [58].

UPEC harbour numerous virulence factors, including α-hemolysin, adhesions, cytotoxic necrotizing factor and iron acquisition machineries. These factors support adherence to uroepithelial cells, help to resist the microbicidal effect of serum and augment cell surface hydrophobicity thereby leading ultimately to endothelial cells damage [56, 59]. Adherence to the urinary tract mucosa might protect bacteria from urinary lavage and in turn augment their ability to survive and invaze renal tissues [60]. Specific adhesion is mediated by certain adhesins which can be differentiated based on their receptor binding specificity and affinity. P-fimbriae are the most important mannose-resistant adhesins, even though they are expressed by only a few *E. coli* serotypes. The most vehement P-fimbriated serotypes of the UPEC strains revealed one of the ten groups O1, O2, O4, O6, O7, O8, O16, O18, O25 and O75 that are associated with UPEC strain [61]. Hemolysin production is another important virulence determinant of UPEC that inflict direct cytotoxic effects on renal epithelium resulting in necrosis and scaring. Hemolysins cause deadly effects on endothelial cells by synergizing among themselves. Likewise, hemolysins are toxic to a number of host tissues and cells including erythrocytes, leucocytes, epithelial and endothelial cells. Alpha-hemolysin is described to be a lethal factor with demonecrotic effects and is antigenic in nature and contributes to ExPEC *E. coli* infections [61].

The importance of cell surface hydrophobicity (CSH) is a common feature of a number of bacteria that also acts as virulence attribute. The CSH is an important factor that helps *E. coli* to adhere to different surfaces for colonization mechanisms via which bacteria are lysed by normal serum. Bacterial resistance to killing by serum results from individual or combined effects of lipopolysaccharides, capsular polysaccharides and other surface proteins [62].

Jadhav et al. conducted phenotypic and biochemical characterization of 19 mucoid UPEC isolates and found that all clinical isolates were encapsulated. About 58% of the mucoid UPEC was encapsulated and serum resistant [58]. Capsule confers serum and phagocyte resistance and this could be ascribed to sialic acid residues that disrupt the ability of bacterial surface to activate complement by the alternative pathway thereby augmenting the virulence potential of such pathogens. Moreover, haemolytic phenotype seems to be associated with extended beta lactamase (ESBL) production as 65.6% isolates were beta lactamase producers relatively higher than in non-ESBL-producing UPEC strains [58].

### 4.2 *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* has emerged as a potential human pathogen, probably from the development of available niches as a result of successful eradication of other pathogens by antibiotics and disinfectants. *Pseudomonas aeruginosa* produces a wide range of virulence factors (Fig. 2), which makes it highly pathogenic for susceptible patients [63]. The bacterium causes both invasive and toxigenic infections. The bacterium is capable of producing both cell-associated and extracellular products. The outer membrane proteins are of given interest because of its cell-surface exposure and involvement in transport of antibiotics, export of extracellular virulence factors and anchoring features that mediate adhesion and motility [64].

Moreover, *P. aeruginosa* is an opportunistic pathogen that uses three interwoven QS circuits-Las, Rhl, and Pqs-to control the global expression of innumerable virulence-associated genes [65]. Intervention of these signalling networks with small molecules denotes an emerging strategy for the development of anti-infective agents against this bacterium. Several of the extracellular virulence factors include siderophores pyochelin and pyoverdine; exotoxin A, a haemolytic and a non-haemolytic phospholipase C, pyocyanin and proteases (exoproteases, exoenzyme S and alkaline protease), which are controlled by QS and allow the bacterium to secrete these factors in cell-density dependent manner [64]. The
surface-associated polysaccharide, alginate and pilus-associated adhesins are responsible for binding to specific epithelial cell receptors]. These exosacharides are self-secreted substances that serve as biofilm formation signals [55].

Pyocyanin and rhamnolipid are the main virulence factors that are coordinated by the Las-Rhl-Pqs-QS enzyme systems. Therefore the modulation of Rhl receptor activity can induce inverse regulation of pyocyanin and rhamnolipid. Moreover, some RhlR agonists strongly repress Pqs signalling, resulting into disruption of Rhl-Pqs cross-regulation that is an indication of novel mechanism for QS inhibition [67]. The QS of P. aeruginosa just like in other bacteria is a complex system that requires interactions of several enzyme systems. Apart from the Las-Rhl-Pqs-QS enzyme systems [66], P. aeruginosa uses two AHL-based QS systems comprise LasR and LuxI homologues with specific signal preference, 3-oxo-C12-HSL for the Las system and N-butanoylhomoserine lactone (C4-HSL) for the Rhl system; and the 3-oxo-C12-HSL play a major role in modulation of host immunity [67]. The complexity and flexibility of QS in P. aeruginosa is exemplified by the fact that over 77 genes have been identified and that the QS regulon are undoubtedly non-conditionally expressed [68].

Investigation on the effects of cbrA deletion mutant of P. aeruginosa showed that biofilm formation and in vitro cytotoxicity in human bronchial epithelial cells are enhanced. This fact was associated with defective swarming motility. This suggests that since the cbrA-cbrB gene is part and parcel of the TCS that is involved in a complex process of adaptation, and in different virulence genes; then indeed, this system can regulate the expression of other TCS genes viz. PmrA-PmrB and PhoP-PhoQ in P. aeruginosa, which control resistance to several antimicrobial compounds [68].

4.3 Staphylococcus aureus

Staphylococcus aureus fundamentally harbours two types of exotoxins, pyrogenic toxin superantigens (PTSAgs) and hemolysins. The molecular basis of PTSAg toxicity is reflected in the two diseases that are caused by these exotoxins: toxic shock syndrome and staphylococcal food poisoning. The family of staphylococcal PTSAgs currently includes toxic shock syndrome toxin-1 (TSST-1) and most of the staphylococcal enterotoxins (SEs) (SEA, SEB, SEC, SED, SEE, SEG, and SEH). As the name suggests, the PTSAgs are multifunctional proteins that perpetually are associated with fatal activity, superantigenicity, pyrogenicity and the capacity to trigger lethal hypersensitivity to endotoxin [69].

Like other two shortly described bacteria, Staphylococcus aureus have a number of virulence factors involved in different invasive and evasive mechanisms:

- Binding protein used for binding to host protein such as vitronectin, collagen type II, fibrinogen and fibronectin.
- Enzymes used for invasion such as clumping factors, staphylokinase, coagulase, hyaluronidase and lipase.
- Microcapsule containing protein A that bind to Fc portion of immunoglobulin G.
- Exotoxins such as TSST-1, SE, ET-A, ET-B and hemolysins.

Some of those virulence factors facilitate tissue adhesion, immune evasion, and host cell injury. Additionally, in the bloodstream, these factors stimulate inflammatory mediators, impair immune cell function, alter the coagulation process and compromise vascular integrity. S. aureus also produces a number of membrane damaging toxins that allow the microorganism to further invade and hurt the host, of which the α-toxin is the most renowned and is the protein responsible for septic shock. The alpha- toxin also binds to a specific receptor in platelets and monocytes in humans, forming pores that ultimately obliterate the cell [70]. Gamma- toxin (leukotoxin) is the other toxin that works in combination with leukocidin in causing human infection. These two proteins work in synergy though, are products of two different genes. Only a few (2%) of all of S. aureus isolates express leukocidin, while about 90% of the strains isolated from severe skin lesions usually express this toxin [71]. The bacterium also possesses a surface protein (Protein A) which binds to IgG in the erroneous orientation, interrupting the body’s regular phagocytic activity by secreting Chemotaxis Inhibitory Protein of Staphylococci (CHIPS) and Staphylococcal Complement Inhibitor (SCIN)- [72]. Likewise, S. aureus secretes six enterotoxin-like antigens that cause diarrhea and vomiting upon ingestion [73].

The function machinery of the innate immune system can successfully be circumvented by S. aureus through the production of anti-chemotactic signals using the cell-wall–anchored Staphylococcal protein A (SpA) by preventing antibody-driven opsonophagocytic clearance. The SpA binds to the Fc and Fab portions of the host immunoglobulin
antibodies, preventing staphylococcal antigen recognition and Fc-mediated effector functions. SpA also engages the B lymphocyte receptor and initiates activation-induced apoptotic death of Vβ3+ B lymphocytes [74]. The staphylococcal virulence factors coagulase (Coa) and von Willebrand factor binding protein (vWbp) promote the non-catalytic activation of prothrombin, yielding cleavage of soluble fibrinogen to stimulate fibrin clot formation in the absence of an stirring injury [74,75]. Fibrin clots promote clumping factor protein-mediated (ClfA and ClfB) aggregation of staphylococci thus promoting bacterial survival. Moreover, alpha-toxin disrupt the endothelial barrier by promoting the untimely cleavage of vascular endothelial (VE)-cadherin using its cellular receptor A Disintegrin and Metalloprotease 10 (ADAM10) (Fig. 3); thus destroying the intercellular connexion that is necessary for vascular integrity [75].

Another component of the TCS in S. aureus, is theWalK-WalR gene system that is implicated in the regulation of cell wall synthesis though work differently in regulation of Staphylococcus autolysis [76]. It has been shown that a single amino acid mutation in both genes of vancomycin-susceptible S. aureus (VSSA) strains is associated with resistance to vancomycin and daptomycin. Moreover, the virulence decreased vividly in both an in vivo model of S. aureus infection, and the in vitro biofilm formation [22].

Kaplan et al. analyzed the effect of subminimal inhibitory concentrations of methicillin, ampicillin, amoxicillin, and cloxacillin antibiotics on possible induction of biofilm formation by phylogenetically different methicillin-resistant S. aureus and methicillin-sensitive S. aureus isolates; and found that the rate biofilm formation was 10 times higher and was inversely proportional to the rate of biofilm production of the isolates in absence of antibiotics [77]. Biofilm formation induced by low-level methicillin was subdued by DNase that in turn induced extracellular DNA (eDNA) release, which is essential for attachment, aggregation, and stabilization of microcolonies [78]. Bacteria deficient in autolysin (atl) could not induce biofilm formation; which led to conclusion that possibly suboptimal concentrations of β-lactam antibiotics notably induce autolysin-dependent eDNA release and biofilm formation in some isolates of S. aureus [77] as shown in Fig. 4.

**Fig. 3** The ADAM10-dependent endothelial gap formation.Adopted from Berube & Wardenburg [71].

**Fig. 4** Extracellular DNA and stressful conditions as cause of virulence.

Usually there is an induction of eDNA release in a multispecies community and antibiotic tolerance (Fig. 4). This figure shows how two bacteria (P. aeruginosa and S. aureus) co-existing in the same microenvironment, when subjected to stressful conditions can develop tolerance to the stressors and subsequently increase in virulence [79]. Similarly, Jenkins et al. using two model systems of S. aureus to represent asymptomatic colonizer to an invasive pathogen stages of the bacterium analyzed about 23 virulence factors of S. aureus ranging from protein and carbohydrate secreted toxins, adhesins and proteins involved in metal cation acquisition and immune evasion. Constant upregulation of sdrC, fnbA, fhuD, sstD, and hla was observed in the shift between colonization and invasive stages that indicates an important role of these genes in staphylococcal pathogenesis [80].

### 4.4 Vibrio cholera

*Vibrio cholerae* is a facultative Gram-negative bacillus bacterium that causes cholera. This disease is characterized by enormous fluid loss through stools, which can be fatal. The bacillus resides between two main environments either in aquatic habitats or in the intestine of a human host. Because the bacterium has to be adapted both kind of environments; a number of the bacterium features, such as their flagella and pili, have to be securely genetically regulated [81]. Although only two strains of *V. cholerae* namely the O1 and O139 are linked with epidemics, other groups are usually reservoirs for virulence determinants that may horizontally transmit the genetic traits of toxicity to another strains. Most notably the O1 and O139 strains contain cholera toxin (CT), coregulated pilus (TCP), which is a pilus that is required
for colonization and ToxR that is a membrane complex responsible for regulation of TCP production [82]. Fig.5 illustrates some of the potential virulence determinants of the bacterium.

![Fig. 5 Schematic representation of virulence determinants of V. cholera.](image)

The virulence factors, CT and TCP are indispensable for enterotoxicity and colonization of the host, respectively. The virulence factors are under genetic control of ToxT, an AraC/XylS family protein that triggers transcription of the genes encoding TCP and CT. The ToxT is under the control of a virulence regulatory cascade that is the ToxR regulon, which responds to various environmental stimuli to ensure maximal virulence-factor induction within the human intestine [83].

Numerous studies have investigated on the potentially pathogenic O1 and O139 strains to study effects their components and establish any association [84-86]. Two previous studies determined the effects of rugose, vibrio polysaccharides (VPS), and vibrio polysaccharides regulator (VpsR), components of V. cholerae on the pathogenesis of the bacterium [87]. Production of rugose resulted in wrinkled, tiny colonies due to overproduction of EPS, which resulted in increased biofilm formation, and increased resistance to stressful conditions [87]. This led to assumption that rugose was promoting pathogenesis and that the VpsR upregulated VPS genes and genes involved in the synthesis of EPS, and therefore it was hypothesized that rugose can be involved in regulation of virulence factors [84].

Recently, two teams of researchers [84, 88] demonstrated that the extracellular matrix components of V. cholerae including VPS induce in vivo biofilm formation and pathogenicity since biofilm serve as strategy for survival and persistence. However, researchers also found that excessive VPS production resulted in inhibition of colonizing ability, though the ability to produce VPS was negatively affected.

### 4.5 Mycobacterium tuberculosis

Mycobacteria are some of the well characterized species of bacteria. They are Gram positive acid fast microorganisms with a very complex cell wall envelope that is responsible for the extraordinary low permeability of their cells as well as the characteristic differential staining procedure. Both features are due to the presence of long chain α-alkyl, β-hydroxy fatty acids in their cell wall. The Mycobacterium genus is usually separated into two major groups on the basis of their growth rate. One group consists of slow-growing species such as Mycobacterium tuberculosis (MTB), Mycobacterium leprae and Mycobacterium bovis that are ethiological agents of human tuberculosis (TB), leprosy and bovine tuberculosis (BTB) respectively; the other group includes fast-growing species such as Mycobacterium smegmatis, which in general are non-pathogenic or opportunistic bacteria [89]. MTB can cause the disease by employing any of the following: 1) using the virulence factors to induce the host cell-bacterium adhesion, 2) by increasing the colonisation of the host body and the persistence, 3) by invading the host cells, 4) by expressing immune suppressive substances and 5) by expression of toxins [90].

A number of mycobacterial virulence compounds or genes have also been identified such as: sigma factors, proteases, lipids, secretion systems, regulators just naming a few [89]. Based on their function, the mycobacteria virulence factors can be categorized into the following groups, cellular localization or molecular features: (1) Lipid and fatty acid metabolism, including catabolism of cholesterol, (2) cell envelope proteins such as cell wall proteins, lipoproteins and secretion systems, (3) protein kinases, (4) proteases, including metalloproteases, (5) metal-transporter proteins, sub-divided into importer and exporters, (6) proteins inhibiting antimicrobial effectors of the macrophage, such as those involved in responses to oxidative and nitrosative stresses, phagosome arresting and inhibition of apoptosis, (7) gene expression regulators, including TCS, sigma factors and other transcriptional regulators, (8) proteins of unknown function, including multigene family designated as PE and PE-PGRS and (9) other virulence proteins [89].

MTB has a singular membrane structure rich in glycolipids such as trehalose 6,69-dimycolate (TDM), which is a non-fluid hydrophobic fatty acid layer. Synthesis of mycolic acid has enabled several enzymes to be studied as virulence factors, the fact that these fatty acids are also acting as diffusible factors in pathogenesis as TDM and trehalose monomycolate (TMM) led to investigate the pathways involved in the synthesis of trehalose, the major free sugar in the cytoplasm of the bacteria [91]. Given the abilities of mycobacteria to survive desiccation, freezing, drying, and other stresses; Harland et al. hypothesized that TDM alone may suffice to bestow
dehydration resistance to the membranes and thus TDM may facilitate the survival of the MTB in dry environments that punctuate their residence in "wet" host organisms [92]. Consequently, further insight into the composition of mycobacterial membranes would further the understanding of correlations between the biophysical properties of molecules such as TDM and the biology of MTB.

Moreover, although mycolic acids are a remarkable feature shared by all mycobacterial species, MTB is also characterized by a plethora of complex lipids and glycolipids present in its cell envelope. These lipids and glycolipids are sloppily associated to the cell envelope, and thus they can be diffusible factors to modulate the host's immune response or can act as infection stage signals for the pathogen. Cell wall lipids of MTB contain multiple methyl-branch fatty acids that play important roles in pathogenesis and thus offer targets for new anti-mycobacterial drugs [93].

The bacterium is made up of several lipids that are esterified with multiple methyl-branch fatty acyl substituents include sulfolipids (SL), di- and tri-acylated trehaloses (DAT and TAT), poly-acyltrehaloses (PAT) and phthiocerol dimyocerosates (PDIM). The PDIM consists of a long-chain β-diol - phthiocerol- esterified by one type of such long-chain multiple methyl-branch fatty acids called mycocerosic acids and are major virulence factors particularly during the early step of infection [89]. MTB uses mannose protein for attachment, the protein belongs to class of adhesins that contribute significantly to MTB infectiosity through binding to host innate-immune system receptors, including lung surfactant protein A (SP-A) and DC-SIGN. The proteins are considered to be the receptors preferentially used by Mycobacteria to enter target cells and evade host defence mechanisms [94].

MTB just like other intracellular pathogens use membrane vesicles (MVs) as an alternative way to deliver ligands that can be recognized by host cells via the innate immune responses [95]. The bacterium enters the host through the lungs by inhalation of bacilli where the alveolar macrophages, monocytes and dendritic cells recognize them PRR. This is followed by the internalization of the bacteria releasing MVs that provides flexibility to respond to environmental cues, secrete components (pro-inflammatory cytokines, chemokines, matrix metalloproteinases and other molecules), virulence factors and antigens, and interact with the host leading to the recruitment of neutrophils, NK cells and T lymphocytes, and granuloma formation [96]. The recognition of MTB by PRRs is mediated primarily by (toll-like receptors (TLRs), especially TLR2, TLR4, and TLR9 [97]. Since MVs release is conserved across several host organisms, MV-mediated functions are expected to be critical to microbial life. Proteomic analysis using enzymatic digestion and nano- liquid-chromatography/mass spectrometry has revealed the composition of the MVs and confirmed that they are rich in components associated with virulence and other TLR-2 lipoprotein agonists, which are released within the macrophages suggesting that they influence the outcome of the macrophage-mycobacterium interaction [98].

4.5.1 Importance of trace metallic elements in virulence development

It is well known that copper (Cu^{2+}) is vital for several physiological processes, but is only toxic once the intracellular Cu^{2+} is in excess. There is evidence that Cu^{2+} plays a central role in controlling TB. It has been demonstrated that a MTB mutant lacking the outer membrane channel protein Rv1698 accumulates 100-fold more Cu^{2+} and becomes prone to Cu^{2+} toxicity than wild type MTB [99]. Similar observations were reported for a M. smegmatis mutant lacking the homolog Ms3747, showing that there are mycobacterial Cu^{2+} transport proteins B (MctB) that are crucial for Cu^{2+} resistance in virulence of MTB [101].

The ability of copper ions to undergo reversible oxidation from Cu^{+} to Cu^{2+} plus its high redox potential makes copper an essential cofactor in aerobic enzyme systems that use electron transfer reactions. Because of the broad effects of Cu^{2+} on the growth of the mycobacteria, many of the enzymes that utilize Cu^{2+} as a cofactor are required for in vitro growth. Mutants of MTB deficient in copper resistance mechanisms are vital for MTB virulence, which means Cu^{2+} can be used by the immune system as an antitubercular agent [100].
of copper toxicity, presumably several proteins that are neither copper binding nor copper translocating, may be important in combating copper toxicity; and therefore deletion or mutations of such ostensibly irrelevant proteins can result in copper-sensitivity and virulence defects [99]. In vivo evidence show that copper-deficient diets reduce the respiratory burst and consequent microbicidal activities of macrophages, neutrophils, and T-lymphocyte dependent antibodies [102].

On the other hand, iron is another very essential micronutrient that is required by almost all living organisms on earth due to its crucial role as a redox cofactor of proteins necessary for important cellular processes and plays a major role in virulence of several microorganisms [103]. Pathogenic bacteria, MTB inclusive, have evolved an array of complex mechanisms to scavenge limited iron from the host. MTB meets its iron demands by stripping host iron stores employing two hydroxyphenylazoxaline siderophores, mycobactin (Mbt) and carboxymycobactin (cMbt). To counteract these bacterial iron acquisition processes, the alveolar macrophage in which MTB thrives, keeps phagosomal iron levels extremely low by the natural-association-mediated macrophage protein-1 (Nramp1) in particular after activation by interferon. However, Mbt and cMbt increase the physiological availability of iron within the phagosomal compartment by approximately 20-times signifying that the MTB siderophores can evade the host defence mechanisms [104].

One previous study looked into the Mycobacterial iron-dependent repressor (ideR) that shows 80% identity in the functional domains with its corynebacterial homologue, diphtheria toxin repressor (DtxR). MTB was transformed by a vector expressing an iron-independent, positive dominant, corynebacterial dtxR hyperrepressor, DtxR(E175K) using BALB/c mice as in vivo model. Then the mice were infected by tail vein injection with $2 \times 10^7$ microorganisms of wild type or MTB transformed with the dtxR mutant. At 16 weeks, there was a 1.2 log reduction in bacterial survivors in both spleen (p = 0.0002) and lungs (p = 0.006) with MTB- DtxR(E175K). The attenuation of M. tuberculosis was achieved by the insertion of a plasmid containing a constitutively active, iron-insensitive repressor, DtxR(E175K), which is a homologue of IdeR, suggesting that IdeR controls genes essential for virulence in MTB [105]. This also implies that dominant positive corynebacterial dtxR allele can attenuate the virulence of MTB in vivo animal model.

MTB acquire iron from transferrin, ferritin, and lactoferrin in the lung parenchyma by producing salicylic and citric acids and siderophores (mycobactins). Intraphagosomal pH and Fe$^{2+}$ concentration is important for MTB pathogenicity; and both the bacterium and host have evolved competing mechanisms to adjust them [105].

Lipoarabinomannan (LAM) is an abundant surface-exposed lipoglycan, which is believed to be an important virulence factor for intracellular endurance and latency of MTB. In vitro studies have shown that purified surface-exposed LAM binds to the macrophage mannose receptor and facilitates bacterium entry, inhibition of phagosome-lysosome fusion, and modulation of non-specific immune responses. It was recently shown that MTB lipoprotein (LprG), a cell envelope lipoprotein, binds to the acyl groups of lipoglycan, though the role of LprG in LAM biosynthesis and localization is unclear [106]. Nevertheless, it is suggested that LprG binding to LAM facilitates its transfer from the plasma membrane into the cell envelope, increasing surface-exposed LAM, enhancing cell envelope integrity, allowing inhibition of phagosome-lysosome fusion and enhancing the bacterium survival in macrophages; and thus LprG is essential for normal surface expression of LAM, virulence and pathogenesis of MTB [84, 106].

5. Potential antivirulence agents

Chemical or/and proteinous substances that are able to inhibit QS by interfering with the synthesis of signalling molecules from binding to specific receptors, blocking the diffusion of signalling molecules or impeding the signal transduction upon binding to the receptors, without creation of selective pressure, may be potential antivirulence agents. Such chemical or compounds are referred to as QQ, which is the interference with QS such as virulence. Because QS is indispensable for bacterial growth, inhibition of QS is encouraged as alternative strategy for antivirulence therapy. Different QQ agents have been extracted and identified from various sources and organisms [107].

5.1 Enzymatic approaches for virulence attenuation

The TCS signalling pathways represent the most common form of bacterial signal transduction, based on phosphotransfer. A phosphorus group is transferred from the CA-domain to a conserved His-residue of the histidine kinase and from there at a conserved Asp-residue of the response regulator [108]. This leads to dimerization of the phosphorylated response regulator and activates it to induce the expression of its downstream target genes. The TCS are possible targets for antibacterial drug as multiple members are found in nearly all bacteria and not exist in mammals. Moreover, many TCSs have been shown to be essential for bacterial survival [109].

Several means of interfering with bacterial QS have been proposed; the first approach is signal inactivation by enzymatic degradation or modification. Such QQ enzymes are wide-spread in the prokaryotic microenvironments and have also been found in eukaryotes [110]. Likewise, lactonases and acylases that hydrolyze AHL signalling molecules, different oxidoreductases active toward AHLs or 2-alkyl-4(1H)-quinolone signals and other signal-converting enzymes have been intensively investigated [111]. Several synthetic furanone analogues have been designed aiming at enhancing their effectivity. A structure-activity analysis of some furanones with varying side chain length and substitutions on the
furanone ring showed that compounds without side chains, but with electronegative substituents on the furanone ring, are effective in inhibiting the QS systems of *P. aeruginosa*. They are used a signalling molecule *lasB* based AHL monitor to detect the QS regulation of *in vitro* biofilms. Control over *lasB* expression is transcriptionally governed by LasR and RhlR. Then it was demonstrated by means of transcriptomic analysis that furanone C-30 specifically inhibits QS-controlled genes in both Gram positive and Gram negative bacteria [112].

In addition to that, the TCS has important role in the QseCB system that is involved in host-derived adrenergic signals and the bacterial QS signal autoinducer AI-3; AI-3 has been shown to trigger expression of virulence genes in several bacterial species. Because QseC homologues are present in most of the human and plant pathogenic bacteria; therefore targeting QseC agonists could be an ideal approach for attenuation of bacterial virulence [113]. Moreover, antibacterial agents targeting the QseC periplasmic domain will be more beneficial in comparison to the agent with intracellular targets as they only have to transverse the bacterial outer membrane to reach the target.

5.2 Natural quorum quenching sources

The earliest natural QS-blocking compounds came from the marine environment. It was shown by de Nys et al. that the Australian macroalga, *Delisea pulchra*, produces a range of halogenated furanones [114]. A characteristic of halogenated furanones is their antifouling property. Another pioneering study [115] presented the first evidences that furanones undoubtedly inhibit bacterial QS, though the exact mechanism of inhibition is not yet fully known. Western-blot analysis indicates that these secondary metabolites can promote rapid turnover of the *LuxR* protein, reducing the amount of protein available to interact with AHL and act as transcriptional regulator [116].

Generally, the natural QQ compounds may be grouped into two categories according to their molecular weights: small molecular and macromolecular QQ compounds, which are also designated as QS inhibitors and QQ enzymes, respectively [117]. Several natural QQ inhibitors with diverse structures have been discovered; and they possess inhibitory effects against Pqs, AHL, AI-2 and AIP-dependent QS [118-120]. For that matter, some dissimilarities in modes of action or interference with QS may exist. It is now well recognized that the virulence factors of various pathogenic bacteria are regulated positively by QS, which allow inhibition of QS and thus controlling the bacterial pathogenicity. On the other hand, the orphan receptor QscR of *P. aeruginosa* and CAI-1-dependent QS in *V. cholerae* are negatively correlated with virulence, hence in order to attenuate the virulence, these pathways should be activated rather than be inhibited [117, 118].

Some tumonic acids isolated from *Blennothrix cantharidomum* have demonstrated inhibitory effects against the bioluminescence of *V. harveyi* BB120 without impeding bacterial growth [119]. Two compounds viz. N-(2-phenylethyl)-isobutyramide and 3-methyl-N-(2-phenylethyl)-butyramide secreted by *Halobaccillus salinus* (a Gram-positive bacterium), have demonstrated inhibitory effects against the violacein biosynthesis of *Chromobacterium violaceum* CV026 in the presence of exogenous-AHLS; while piericidin extracted from marine actinobacteria blocks violacein biosynthesis in *C. violaceum* CV026 [117]. Diketopiperazines (DKPs) that inhibit AHL-dependent QS were isolated from *Bacillus cereus* and *Marinobacter* sp. SK-3[120].

5.3 Conventional antibiotics with antivirulence effects

Some conventional antibiotics, such as Azithromycin have been reported to inhibit QS by reducing the production of several of the virulence factors of *P. aeruginosa*, including elastase and rhamnolipids as well as reduction of *lasI* and *rhlI* expression [121].

One *in vitro* study showed that a garlic-treated *P. aeruginosa* biofilm was susceptible to both tobramycin treatment and grazing of plynomonuclear neutrophils (PMNs). The PMNs showed an increased activation when incubated on the garlic treated biofilm. The results suggest that a QS inhibitory extract of garlic is by increasing the sensitivity of the *P. aeruginosa* biofilms to tobramycin, phagocytosis and the PMN respiratory burst. When garlic extract treated mice were infected by the bacterium, resulted in a significantly improved clearing of the infecting bacteria [122].

5.4 Physical approaches for virulence attenuation

Another strategy to inhibit bacterial virulence is by physically blocking the interaction between the adhesin and the host cell, which are the primary virulence factors of many pathogenic bacteria. Almost all toxins are proteins delivered into the host to cause mass cell destruction and tissue damage [123]. Their extreme toxicity and critical role in pathogenesis makes inhibition of toxin production or binding an obvious approach for development of antivirulence antimicrobials.

A number of compounds are known to possess inhibitory effects on toxin transcription and expression. Virstatin inhibits the transcription factor ToxT that regulates expression of cholera toxin and cholera co-regulated pilus, and blocks intestinal colonization by this pathogen in murine models[117]. The undisputed QS pathways consist of secreted signal molecules known as autoinducers (AI) such as AHLs in many Gram-negative bacteria, autoinducing peptides (AIPs) in Gram-positive bacteria. When the AI molecules attain a sufficient concentrations (threshold) interact with cognate sensor receptors namely *LuxR* and *LuxS* receptors to induce the expression of virulence genes [124]. For example, a loss of motility is a consequence of the misfolding of protein FlgI, a component of the periplasmic ring of...
the flagellar motor and a DsbA substrate. These observations point to a major regulatory role in virulence and identify the DSB enzymes as key targets for the development of anti-virulence agents [125, 126].

6. Concluding remarks

The fast spreading antibacterial resistance worldwide to almost all available antibiotics calls for an urgent need for new antimicrobial agents, antibacterial/antimicrobial targets and therapeutic concept. This chapter reviewed some important strategies that can render bacteria highly susceptible to the antimicrobial machinery of the immune system by targeting bacterial immune evading mechanisms, which are conserved in a number of pathogenic bacteria with major emphasis on *P. aeruginosa, V. cholera, E. coli, M. tuberculosis* and *S. aureus*.

The QS system is a potential antibacterial target if the research findings reviewed in this chapter can be extrapolated to the human infections. The obvious synergistic activities of QQ or QS inhibitors make it even more relevant to consider QS blockade as part of early interventionist chemotherapy. Upon prophylactic administration of QQ agents, the patients would be expected to experience only recurrent acute infections which are sensitive to the host defence system and conventional antibiotics, and therefore do not reach the point of no return leading to the establishment of chronic infection. Antivirulence agents namely QQ agents, QS molecular signalling inhibitors and the like would be unlikely to affect host cells, be cross-resistant to existing therapies and induce resistance themselves. Another important approach would be to interfere with QS is signal inactivation by enzymatic degradation or modification such as lactonases and acylases that hydrolyze AHL signalling molecules that have been widely studied. Last but not least, the rational use of the existing antimicrobial agents, including avoidance of sub-optimal concentrations/dose usage, is of paramount importance as can greatly deaccelerate development and spread of antimicrobial resistance through QQ and inhibition of microbial biofilm formation and maturation. Therefore a multidisciplinary approach is necessary in order to target and attenuate the microbial virulence factors, which in turn will result in reduction of antimicrobial resistance.

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